Surgical Management of Esophageal Cancer
A Decade of Change


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Objective
To examine trends for use of transhiatal esophagectomy (THE) and to relate outcome variables to changes in use, controlling for preoperative risk.

Background
High operative morbidity and mortality rates are reported with conventional transthoracic esophagectomy (TTE). Transhiatal esophagectomy has been proposed as an alternative but is controversial.

Methods
In this retrospective study divided into early and late time periods, outcome variables were subjected to univariate and multivariate analyses.

Results
Use of THE increased significantly in the late period ($p < 0.0001$). Patients who had THE had significantly higher American Society of Anesthesiologists (ASA) risk scores ($p < 0.001$). By the late period, 92% of patients with ASA III/IV scores were resected by THE. Postoperative morbidity decreased significantly and operative mortality decreased from 15% to 0% ($p < 0.01$) between the early and late time periods. By multivariate analysis, ASA ≥ III and TTE were associated with adverse surgical outcome. Pathologic stage determined disease-free survival, which was 37% at 3 years for all survivors.

Conclusions
Increased use of THE results in better operative outcome and does not adversely affect disease-free survival.

In 1980 Earlam and colleagues$^1$ reviewed 83,783 cases of esophageal cancer reported in the surgical literature in the preceding 20 years and reported a 29% operative mortality rate, concluding that esophageal cancer resect-

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esophagectomy (THE), first performed successfully by Grey-Turner and Durr¹ in 1933 for resection of carcinoma of the thoracic esophagus, eliminating the need for combined abdominothoracic exposure and intrathoracic esophagogastrectomy. In the past 15 years, many surgeons have gained experience with the “Orringer” technique. However some surgeons are concerned because it does not provide adequate cancer staging and resection² and it may be a blind and inherently unsafe procedure. Several nonrandomized studies⁶⁻⁹ have not shown an advantage of THE over the Lewis technique.

To determine the change over time in use of THE, particularly in high-risk patients, and to determine the effect of any change in use on postoperative morbidity, length of hospital stay, operative mortality, and disease free survival, we reviewed trends in use in our hospital of the two procedures beginning in 1981, approximately 2 years after Orringer’s initial report. A second goal of our study was to compare the outcomes of the two operative procedures based on their postoperative morbidity, operative mortality, and disease free survival.

MATERIALS AND METHODS

Between January 1981 and June 1993, 82 consecutive patients had resection of carcinoma of the esophagogastric junction or thoracic esophagus at the Ochsner Medical Institutions. Gastric cancers with no gross involvement of the esophagus that could be resected and reconstructed by a subdiaphragmatic approach were excluded.

Information pertaining to clinical history, medical comorbid conditions, preoperative chemotherapy or radiotherapy, location, size and histologic type of tumor, type of operation performed, intra- and postoperative complications, and operative death rate were recorded on retrospective review. Operative death was defined as any death within 30 days of operation or during the same hospitalization as the operative procedure, even if occurring more than 30 days later.

The American Society of Anesthesiologists (ASA) physical status classification⁸ (Table 1) was assigned prospectively by a staff anesthesiologist one day before surgery independent of the surgeons’ clinical assessment. The postsurgical pathologic stage was assigned using established criteria.¹⁰

The resection technique was either transthiatal¹ (48 cases or 58.5%) or transthoracic, in most cases by the method of Lewis¹¹ (29 cases or 35.4%) or by left thoracic (2 cases or 2.4%) or left thoracoabdominal (3 cases or 3.7%) approach. Reconstruction was by gastric interposition in all but one case, in which a colon interposition was performed. Operative procedure was selected by the attending surgeon; no formal department policy existed at the time of the study.

We divided the study into an early phase (1/81 to 3/87) and a late phase (4/87 to 6/93) to permit evaluation of trends in the use of the two procedures as well as the morbidity and mortality rates and disease-free survival during the study. Statistical analysis was done using BMDP statistical package (BMDP Statistical Software, Los Angeles, CA) on a personal computer. Univariate statistics using means and standard deviations, and proportions (percentages) were used to describe the demographics, risk status, cancer stage, and the median disease-free survival for the entire sample. The analysis then proceeded to the bivariate and multivariate techniques to achieve the study objectives.

To achieve the first objective, patients’ demographic, operative morbidity, and operative mortality variables were compared for the two time periods using Pearson chi-square test or Fisher’s exact test for independent proportions. The Mantel-Haenszel chi-square test was used whenever stratified analysis was appropriate. Two-group means comparison using the t-test was done to compare continuous variables, such as age and hospital stay, for the two time periods. Similar analytic tools were used to compare the two operative procedures’ outcomes at the bivariate level to achieve the second study objective.

Development of substantial postoperative cardiopulmonary complications (defined as myocardial infarction, congestive heart failure, arrhythmia, pneumonia, or pulmonary insufficiency requiring ventilator support for more than 48 hours) was analyzed as an outcome variable using multiple logistic regression models, including the time period and operative procedures together with other potentially confounding variables as independent variables. Effect modification (statistical interaction) by time or any significant variable in the model was carefully reviewed and its significance level reported. The magnitude of the effects was reported in terms of odds ratios, their 95% confidence interval, and their significance level. Cox multivariate proportional hazards regression modeling was used to compare the 3-year disease-free survival for the two operative procedures and time periods. Modeling strategies similar to those used in the logistic regression analysis were used in

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Table 1. AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) RISK CLASSIFICATION⁹

| I. A normal, healthy patient |
| II. A patient with a mild to moderate systemic disease |
| III. A patient with a severe systemic disease that limits activity, but is not incapacitating |
| IV. A patient with an incapacitating systemic disease that is a constant threat to life |
| V. A moribund patient not expected to survive 24 hours with or without operation |
the survival analysis. However the magnitude of effects were reported in terms of relative risks rather than odds ratios.

RESULTS

Patient Population

Table 2 lists general descriptive statistics for the overall patient population and by time period. No significant differences were noted between the two time periods in mean patient age, sex, histologic type, stage distribution, tumor location, or use of preoperative chemotherapy or radiotherapy. During the late period, the percentage of patients with ASA status of III or IV increased from 31% to 49%, which was of borderline significance (p < 0.1).

Time Trends in Use of THE and TTE

The use of transhiatal esophagectomy increased significantly over time from 27% of patients in the early period to 80% of patients in the late period (p < 0.0001; Table 3). The increased use of THE occurred only for cancers of the lower esophagus and esophago gastric junction, for which the use of THE increased from 17% in the early period to 83% in the late period (p < 0.0001; Table 3). No change was noted in use of THE for cancer of the mid and upper thoracic esophagus between the two time periods. The ASA risk status was significantly worse for THE patients than for TTE patients during both the early and the late periods (p < 0.001; Table 3). Furthermore, 92% of patients with ASA risk status greater than or equal to III had THE in the late period compared with 50% of patients in the early period (p < 0.025; Table 3). In addition, 95% of patients 65 years or older had THE in the late period compared with 38% in the early period (p < 0.001; Table 3). The distribution of cancers by histologic type, stage, and location did not vary significantly according to the operative procedure for either period.

Time Trends in Morbidity, Length of Stay, and Mortality

Recurrent laryngeal nerve palsy and anastomotic leak did not vary significantly for the two periods. The anastomotic stricture rate increased from 9% to 20% in the late period; the difference, however, was not statistically significant (p > 0.2). Transhiatal esophagectomy was associated with a higher anastomotic stricture rate (21% compared with 9%); however the difference is not statistically significant (p > 0.2).

Both the intensive care unit (ICU) and the hospital length of stay significantly decreased from the early to the late period. Length of stay in the ICU decreased from a mean of 13 to a mean of 4.3 days (p < 0.05), whereas hospital length of stay decreased from 24 days to 13 days (p < 0.025).

Operative mortality decreased significantly from 15% in the early period to 0% in the late period (Fisher’s exact test; p < 0.01). The preoperative ASA risk status was a marginally significant predictor of operative death for THE (7.7% mortality for ASA I and II; 42.9% mortality for ASA III and IV; p = 0.05) but not for THE because no operative deaths were noted in patients having THE, regardless of preoperative ASA status. The type of procedure also correlated significantly with operative mortal-
ity rate (TTE operative mortality rate of 15%; THE operative mortality rate of 0%; p < 0.025). Because the proportion of high-risk cases (ASA ≥ III) was significantly higher among THE patients and changed significantly over time, we performed a stratified analysis of operative deaths after controlling for ASA risk status. This revealed an even more striking reduction in operative mortality in the late period (p < 0.00005) and with use of THE (p < 0.005). The patient’s age, tumor stage, location, histologic type, and administration of preoperative chemotherapy or radiation therapy did not correlate with operative mortality rate.

The percentage of patients suffering significant cardiopulmonary complications decreased from 48% in the early period to 30% in the late period, but this difference was not statistically significant (p > 0.4). However the percentage of patients in whom multiple cardiopulmonary complications (2+) developed decreased significantly from the early (27%) to the late (6%) period (p < 0.05). Multivariate logistic regression showed that the occurrence of cardiopulmonary complications was significantly related to the preoperative ASA risk class (odds ratio of 4.41 for ASA greater than or equal to III; 95% CI, 1.292 to 15.1; p = 0.009). The occurrence of cardiopulmonary complications was also significantly related to the operative procedure (odds ratio of 7.5 times for TTE; CI, 2.192 to 25.6; p = 0.0003). Time period of the study was not an independent variable for predicting the occurrence of cardiopulmonary complications.

**Stage and Survival**

More patients had cancers of stage IIB or greater in the early period (79% compared with 64%). However, the difference was not statistically significant (p > 0.2). Three-year disease-free survival did not vary significantly for the two periods. Cox multivariate regression analysis (Table 4, Fig. 1) revealed that disease-related survival was stage dependent; patients with tumor stage greater than or equal to IIB had a 3.8 times greater relative risk for death than did patients with tumors less than stage IIB (CI, 2.28 to 12.96; p < 0.0001). Patients with cancers of the middle third of the esophagus also did significantly worse whether resected by THE or TTE (relative risk, 2.4 times; CI, 1.09 to 5.30; p < 0.05). There was a trend toward survival advantage for patients having THE, but this was not statistically significant (p > 0.1). There was no relationship between disease-related survival and histologic type, age, sex, and whether the patient received preoperative chemotherapy and radiation therapy.

**DISCUSSION**

In our study, the preoperative ASA risk status had significant predictive ability for postoperative morbidity after either THE or TTE, and for operative mortality after

### Table 3. UTILIZATION OF OPERATIVE PROCEDURE AS A FUNCTION OF TIME PERIOD, ASA RISK STATUS, AND AGE

<table>
<thead>
<tr>
<th></th>
<th>Early Period</th>
<th>Late Period</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTE:TTE</td>
<td>72.7%:27.3%</td>
<td>20.4%:79.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>83%</td>
<td>17%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>50%</td>
<td>50%</td>
<td>ns</td>
</tr>
<tr>
<td>Upper</td>
<td>0%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>ASA risk status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>78.3%</td>
<td>44.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>17.4%</td>
<td>55.6%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>IV</td>
<td>4.3%</td>
<td>0%</td>
<td>ns</td>
</tr>
<tr>
<td>Patient with ASA risk status ≥ III (n = 34)</td>
<td>50%</td>
<td>50%</td>
<td>8%</td>
</tr>
<tr>
<td>Patients ≥ 65 yrs (n = 40)</td>
<td>62.5%</td>
<td>37.5%</td>
<td>p &lt; 0.001</td>
</tr>
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</table>

### Table 4. COX MULTIVARIATE REGRESSION MODEL FOR 3-YEAR DISEASE-FREE SURVIVAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Stage</td>
<td>0.0000</td>
<td>5.4</td>
<td>2.28, 12.96</td>
</tr>
<tr>
<td>Tumor location</td>
<td>0.0418</td>
<td>2.4</td>
<td>1.09, 5.30</td>
</tr>
<tr>
<td>Operative procedure</td>
<td>0.1321</td>
<td>1.6</td>
<td>0.89, 2.77</td>
</tr>
<tr>
<td>Histologic type</td>
<td>0.4246</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA risk status</td>
<td>0.7737</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td>0.3821</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time period</td>
<td>0.1652</td>
<td></td>
<td></td>
</tr>
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</table>
TTE. Although such a finding has not been reported specifically for esophageal cancer resection, it is consistent with several previous studies correlating operative morbidity and mortality with ASA risk status for major abdominal and thoracic surgical procedures.

Between the early and late periods of the study, use of THE for all patients increased significantly, particularly for high-risk patients who did poorly after TTE during the early period of the study.

The effect of increased THE use on operative mortality rate was dramatic, with a reduction to 0% in the late period. The mortality with TTE also decreased in the second time period (although not significantly, probably because of the small number of patients involved). This probably represents more careful selection of patients in light of the significant trend toward avoiding TTE in high-risk patients in the late period. The effect of the shift in use of the operative procedure on hospital length of stay and postoperative cardiopulmonary morbidity was also significant, and multivariate analysis revealed that the type of operative procedure and the preoperative ASA risk status were the major independent variables predictive of postoperative cardiopulmonary morbidity.

Multivariate disease-free survival analysis revealed that stage is the dominant prognostic variable for disease-free survival and that neither the type of operative procedure nor the period of study affected disease-free survival significantly. Cancers of the mid-thoracic esophagus fared significantly more poorly than did patients with tumors of the upper and lower esophagus, regardless of the type of surgical procedure used.

Several nonrandomized retrospective studies compared the efficacy of transthoracic and transhiatal esophageal cancer resection and have not noted improved short-term results with transhiatal resection as we did in this study. In those studies, coanalysis of the preoperative risk status to rule out adverse selection of patients for THE was not done. In our own study, such analysis indicates that preoperative risk status predicts the frequency of postoperative morbidity and also predicts the risk for operative death for transthoracic resection. In view of this, the significantly lower postoperative morbidity rate and nonexistent mortality after THE are even more impressive, given the significantly worse ASA risk scores for patients undergoing THE. Although we noted no correlation between ASA risk status and the risk for operative death for transhiatal patients, the number of ASA IV patients having transhiatal resection is small and we cannot conclude a lack of correlation between risk status and death after THE for these patients at high risk. If such patients were included in significant numbers in other studies, this might lead to a significantly different short-term outcome after THE than was noted in our study.

We found significant shifts in patterns of use of THE and TTE in our hospital, especially for high-risk patients (ASA ≥ III), and we noted significantly decreased postoperative complication rates, postoperative length of stay, and operative mortality rates associated with this shift in use. Together these trends represent a dramatic change in the surgical approach to and early postoperative results after esophageal cancer resection in our institution. Regrettably the increased use of THE was not associated with better long-term disease-free survival, nor did evidence show that adoption of THE compromised long-term disease-free survival. The relatively lower use of THE for mid-esophageal cancers in both periods of the study and the reduced survival of this subgroup of patients highlights the limitations of THE and any alternative surgical approach for cancers of this region.

References


Discussion

DR. JOHN L. SAWYERS (Nashville, Tennessee): Drs. Bolton and Ochsner favor transhiatal esophagectomy over transthoracic esophagectomy and report an enviable result of 62 consecutive esophagectomies for cancer without a mortality. There’s been one other change in the last decade, and that’s been an approach to the management of esophageal cancer by instituting neoadjuvant therapy. And I would like to show a slide of the approach that we have utilized in recent years of neoadjuvant regimen of two cycles of cisplatin, 5-FU, and leucovorin with or without VP-16, with concomitant 3000 microgray of radiation. This has resulted in an improved survival with the patients who underwent the neoadjuvant therapy shown here and those who underwent esophagectomy alone or underwent radiation with or without esophagectomy. The median survival time has been prolonged from 8 months without neoadjuvant therapy to more than 26 months with neoadjuvant therapy. And in fact, median survival has not yet been reached. The 2-year actuarial survival rate was 76% with neoadjuvant therapy compared to 15%. Now, there’s been an increase of adenocarcinoma of the esophagus in the past decade, and Dr. Bolton showed that in his report. This arises to more than 50% of esophageal cancers, frequently in association with Barrett’s esophagus. Most of these tumors are in the lower one third of the esophagus and can easily be removed by transhiatal esophagectomy, an operation that we are also using with increasing frequency. Transhiatal esophagectomy lends itself well to cancers in proximal and the distal esophagus but less well for tumors in the middle one third, which may be adherent to the left main stem bronchus or the distal trachea. Neoadjuvant therapy has downstaged esophageal cancers and permitted use of a transhiatal esophagectomy even in these middle one third lesions. We’ve had no mortality from esophagectomy in our last 30 patients since using neoadjuvant therapy. I’d like to ask Dr. Bolton how he stages his patients prior to operation. Does he use transesophageal ultrasound to help decide if patients should have a transhiatal or a transthoracic esophagectomy? Has either operation resulted in improved survival rate? Transthoracic esophagectomy permits a wider mediastinal dissection. Is this important? And, finally, what has been his experience with neoadjuvant therapy for esophageal cancer? I believe 13% of his patients had this.

DR. IRVING L. KRON (Charlottesville, Virginia): Dr. Bolton demonstrated that transhiatal esophagectomy is amazingly safe. A 0% mortality is certainly enviable. More importantly, there was no difference in long-term survival for the two procedures. Survival was only based on tumor stage. Tom Daniel from our group published the UVa experience last year, and we reported 101 patients that underwent esophagectomy between 1982 and 1990. The mortality for the transhiatal approach for intrathoracic esophageal lesions was 4% compared to the transthoracic of 8%. Therefore, we agree entirely with Dr. Bolton’s conclusions. I have only one question for Dr. Bolton. In this day and age, is there any indication for transthoracic esophagectomy other than inoperability from the transhiatal approach?

DR. JOHN S. BOLTON (Closing Discussion): In response to Dr. Sawyer’s questions, we have not noted as impressive a result with neoadjuvant therapy as he has, nor have we studied it as systemically as he has. We use neoadjuvant therapy primarily for the patient with a marginally resectable lesion in order to downstage them and facilitate their resection. In the absence of any clear-cut evidence otherwise that neoadjuvant improves survival, we’ve elected to take a surgical approach initially to restore swallowing in patients as quickly and as efficiently as possible. In essence then, I think our patients who are treated with neoadjuvant therapy tend to be the bulkier tumors. And while we’ve not had any indication that preoperative therapy is beneficial either in a univariate or multivariate analysis, clearly, I think we’re adversely selecting them. In terms of our preoperative staging, we rely primarily on the preoperative CT scan. We’re not using endoscopic ultrasound. And again I think our philosophy is primarily that our aim is to as quickly as possible resect the tumor to restore swallowing. The level of invasion in the esophageal wall in most cases does not determine resectability and nor does the presence of periesophageal nodes determine whether or not the surgeon can resect the tumor itself in the esophageal wall. So that we’ve not used that. It might be helpful if you were systematically studying neoadjuvant therapy, but since we’re not doing that we’ve not used the preoperative endoscopic ultrasound. In response to Dr. Kron’s question about the indications for transthoracic resection, clearly, we feel that in a good-risk patient, transthoracic resection is accompanied by relatively low operative mortality. And so in the good-risk patient, probably either technique is acceptable, although we feel strongly that the complication rate, the length of stay, and the recovery will all be better after the transthoracic resection. So that as Dr. Sawyer mentioned, the problem is the patient with the mid-esophageal tumor. That’s the one for which, I think, in many ways we don’t have a good resection by either technique. The fact is that a bulky mid-esophageal cancer in most cases will be adherent to the carina or the trachea, and even by the transthoracic route, the radial or circumferential margins around the tumor are often inadequate. I agree that those are the patients in whom the preoperative neoadjuvant therapy can be of benefit. For those patients with the mid-esophageal cancers, we will typically attempt a transthoracic resection and convert if it’s clear that we can’t make headway by that technique. And I think that in our hands that remains probably the biggest and the main indication for transthoracic resection at this time.