Effect of postoperative course on midterm outcome after esophageal resection for cancer

Themistokles Chamogeorgakis, MD, Faiz Bhora, MD, Ioannis Toumpoulis, MD, Andy Nabong, MA, and Cliff Connery, MD

Esophageal resections are challenging procedures often associated with postoperative complications and a prolonged hospital stay. This study investigated the impact of postoperative course on midterm survival in 35 patients undergoing esophageal resection for malignancy between January 2002 and November 2007. The impact of preoperative and operative variables, pathology, staging, early postoperative complications, and length of hospital stay on midterm survival was determined with Cox regression analysis. During the follow-up period, 17 (48.6%) patients died. Multivariate analysis identified surgical stage and length of stay as independent predictors of midterm survival; in addition, the total number of complications reached statistical significance. In conclusion, in addition to surgical stage, postoperative course has an impact upon midterm survival after esophageal resection.

Esophagectomies are challenging procedures often associated with postoperative complications and prolonged hospital stay. Stage and radicality of resection have traditionally been reported to predict outcomes in patients with primary esophageal carcinoma (1–4). In addition, other variables such as sex, neoadjuvant treatment, and intensive care unit (ICU) length of stay have been reported to be independent predictors of long-term outcome (4–6). This study identified predictors of midterm survival in such patients and specifically investigated the potential role of postoperative complications in survival beyond patients' discharge from the hospital.

METHODS

A total of 35 consecutive patients underwent esophagectomy for primary esophageal carcinoma between January 2002 and November 2007 at the Continuum Cancer Centers of New York Thoracic Oncology Program (St Luke's–Roosevelt Hospitals and Beth Israel Medical Center) affiliated with Columbia University College of Physicians and Surgeons and the Albert Einstein College of Medicine. The mean follow-up was 32 months (range, 1.3–69.2 months).

Data collected as part of the Thoracic Surgery General Thoracic Database (7) were age, sex, any associated comorbidities, American Society of Anesthesiologists (ASA) score, Zubrod score, modeled Thoracscore (8), the type of the procedure

performed, pathology, surgical staging, and postoperative complications (*Table 1*). Midterm mortality data were obtained from the institution's cancer registry in July 2008.

Informed consent was not obtained because the data used in this study had already been collected for clinical purposes. Furthermore, the present study did not interfere with the treatment of patients, and the database was organized to prevent the identification of an individual patient.

Cases were evaluated with respect to demographic, surgical, and postoperative variables. Numerical variables were presented as mean $\pm$ standard deviation, and discrete and categorical variables were presented as percentages. The impact of preoperative and operative variables, pathology, staging, and early postoperative complications on midterm survival was determined with Cox regression analysis. A score equaling the total number of postoperative complications per patient was entered in the survival analysis. In addition, the modified Thoracscore of each patient was calculated based on the formula that has been previously published (8): Thoracscore = $-6.975 + [-0.108$ if patient age was >55 years and <65 years or 1.057 if patient age was ≥ 65 years] + $[0.402$ if patient sex was male] + $[1.909$ if ASA class was $\geq 3]$ + $[2.655$ if Zubrod score was $\geq 3]$ + $[0.975$ if priority of surgery was urgent or emergent] + $[0.063$ for esophageal malignancy] + $[0.093$ if number of comorbidities was ≤ 2 or 0.761 if number of comorbidities was $\geq 3]$. Variables were evaluated with univariate analysis and subsequently with multivariate analysis. The model selection was performed with a backward stepwise method, starting from all variables with a $P < 0.05$. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Finally, a Kaplan-Meier survival curve was generated for the entire patient population. All analyses were performed in SPSS v 15.0 (SPSS, Inc; Chicago, IL).

From the Department of Cardiothoracic Surgery, Baylor University Medical Center at Dallas (Chamogeorgakis); and the Department of Cardiothoracic Surgery, Continuum Cancer Centers, St. Luke's–Roosevelt Hospital, New York, NY (Bhora, Toumpoulis, Nabong, Connery).

Corresponding author: Themistokles Chamogeorgakis, MD, Department of Cardiothoracic Surgery, Baylor University Medical Center at Dallas, 3900 Junius Street, Suite 605, Dallas, TX 75246 (e-mail: Themistokles.Chamogeorgakis@BaylorHealth.edu).

Table 1. Characteristics of 35 patients undergoing esophageal resection for cancer

Variable	Frequency
Preoperative	
Mean age (years) (SD)	62.0 (13.5)
Male	22 (63%)
Female	13 (37%)
Type of cancer	
Squamous carcinoma	16 (46%)
Adenocarcinoma	19 (54%)
Stage	
Complete response	1 (3%)
I	14 (40%)
IIA	2 (6%)
IIB	7 (20%)
III	11 (31%)
IV	—
ASA class	
I	—
II	12 (34%)
III	22 (63%)
IV	1 (3%)
Zubrod score	
0	11 (31%)
1	20 (57%)
2	3 (9%)
3	1 (3%)
4	—
Diabetes mellitus	7 (20%)
Hypertension	18 (51%)
CAD or HF	4 (11%)
Mean Thoracscore (SD)	4.1 (1.4)
Operative	
Total esophageal resection	25 (71%)
Partial esophageal resection	10 (29%)
Postoperative	
Pulmonary complications	4 (11%)
Anastomotic leak	2 (6%)
Cardiac arrhythmia	2 (6%)
Chylothorax	1 (3%)
Recurrent laryngeal nerve paresis	2 (6%)
Empyema	1 (3%)
Mean length of stay (days) (SD)	19.5 (23.7)

ASA indicates American Association of Anesthesiologists; CAD, coronary artery disease; HF, heart failure.

RESULTS

Twenty-five patients underwent total esophagectomy: 1 with a left-sided neck anastomosis via a left thoracoabdominal incision; 20 with a combined right thoracotomy and a laparotomy; and 4 with a transhiatal approach. Ten patients had a partial esophagectomy for a lower third esophageal tumor: 7 via a left thoracoabdominal incision and 3 via a combined right thoracotomy and laparotomy. Except for the transhiatal resections, a double-lumen endotracheal tube was used to achieve selective ventilation of the contralateral lung. Frozen section analysis of the specimen's margin was performed intraoperatively, and additional resection was undertaken, if necessary, to obtain margins free of tumor. In addition, a pyloromyotomy and a feeding jejunostomy were performed in all cases.

There were no in-hospital deaths. Pulmonary complications were the most common of all complications ($n = 4$); this complication was defined as pneumonia, prolonged mechanical ventilation, or pulmonary atelectasis requiring bronchoscopy. Other postoperative complications were cardiac dysrhythmias ($n = 2$), recurrent laryngeal nerve paresis ($n = 2$), anastomotic leak that was treated medically ($n = 2$), thoracic empyema ($n = 1$), and chylothorax ($n = 1$; *Table 1*). Five patients required transfusion of blood products perioperatively. No patient developed renal failure requiring dialysis postoperatively.

During the follow-up period, 17 (48.6%) patients died, 16 from esophageal cancer and 1 from unknown cause. The Kaplan-Meier survival curve is shown in the *Figure*. Univariate analysis identified ASA score, surgical stage, total number of postoperative complications, and length of stay as independent variables for midterm survival (*Table 2*). Blood product transfusion and operative blood loss were not predictors of midterm survival. Multivariate analysis identified surgical stage and length of stay as independent predictors of midterm survival (*Table 2*).

DISCUSSION

In this retrospective analysis of patients undergoing curative resection of primary esophageal carcinoma, we identified independent predictors of survival. Despite surgical stage, the

Figure. Kaplan-Meier survival plot for 35 patients undergoing esophageal resection for cancer.

Table 2. Independent predictors of midterm mortality in 35 patients undergoing esophageal resection for cancer

Variable	Hazard ratio	95% confidence interval	P value
Univariate analysis			
Age	1.019	0.979–1.060	0.359
Female sex	0.946	0.349–2.569	0.946
American Society of Anesthesiologists score	0.324	0.125–0.840	0.020
Zubrod score	1.000	0.471–2.125	0.999
Preoperative chemotherapy or radiation therapy	1.069	0.344–3.317	0.908
Thoracoscore	0.839	0.603–1.168	0.298
Length of stay	1.023	1.002–1.044	0.032
Total number of complications (per patient)	2.065	1.114–3.826	0.021
Stage	1.579	1.067–2.337	0.022
Histology (adenocarcinoma)	1.110	0.804–1.533	0.524
Multivariate analysis			
Stage	1.691	1.096–2.610	0.018
Length of stay	1.033	1.010–1.057	0.005
Total number of complications (per patient)	1.705	0.890–3.270	0.108

postoperative course had an impact on midterm outcome; the additive effect of complications and length of stay appears to affect patients' outcome beyond the immediate postoperative period.

The concept that the postoperative course predicts patient outcome beyond the hospital stay has been shown before in cardiac surgery patients (9). In our patient group, all but one death were cancer related. One can make the hypothesis that a complicated perioperative course may suppress the immune system's ability to survey and eliminate cancer cells; the exact mechanism, however, can be only speculative at this point.

Although the effect of a prolonged ICU stay on patients' quality of life has been previously investigated (10), there is a dearth of research on the impact of prolonged postesophagectomy ICU stay on long-term survival. Cense et al, in their analysis of 109 patients undergoing transthoracic esophageal resection, concluded that the length of ICU stay using a cutoff number of 5 days did not influence long-term survival (11). The patients' median survival was 4.7 years. Two reasons may explain why their results are different: the larger number of patients and the fact that the length of stay was entered as a discrete variable in their analysis. In our analysis, the hospital length of stay was used as a continuous variable. On the other hand, van Sandick et al showed that ICU length of stay predicts long-term outcome (4).

Regarding the impact postoperative complications have on long-term survival, Junemann-Ramirez et al showed that the anastomotic leak effect does not extend beyond the hospital stay (12).

Surgical stage is an important survival prognosticator for esophageal carcinoma. As in other studies (2, 3, 13), stage was

an independent variable of midterm outcome in our analysis. In addition to stage, radicality of surgical resection improves long-term outcome (4); therefore, an effort to obtain good surgical margins beyond the neoplastic process and add a thorough lymph node dissection in the resection is advisable.

Gender and neoadjuvant treatment have also been reported to affect long-term outcome. Female patients appear to have a better outcome than male patients (5), and preoperative chemoradiation seems to improve long-term prognosis because it allows curative resection in a greater number of cases due to tumor downstaging (13). The above variables were not independent predictors of midterm outcome in our analysis.

Thoracoscore was first introduced by Falcoz et al as a multivariate model for the prediction of in-hospital mortality after general thoracic procedures (14). Furthermore, this risk prediction model can be applied beyond patient discharge (8). This variable was not an independent predictor of midterm survival after esophageal resection for cancer. This survival prediction model is more useful in the whole context of thoracic surgery patients.

Although blood loss and transfusion of packed red blood cells are reported to be independent predictors of survival in gastrointestinal malignancies, this does not appear to be the case in our study, presumably due to the small number of patients included in our analysis; borderline statistics need more patients to reach statistical significance.

There are several limitations in our study. In this retrospective study, possible factors that may have biased the results were not included in the statistical analysis, and the number of patients was small. This study referred to a single-center database, and it is likely that selection of patients for surgery may be an important determinant, which differs widely among thoracic surgery units.

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