Survival After Surgical Resection of Stage IV Esophageal Cancer

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Background. **Five-year survival of stage IV esophageal cancer is rare. The treatment of advanced esophageal cancer is typically palliative and the role of surgery remains controversial. We sought to understand the impact of curative surgery on survival and identify any favorable tumor or patient characteristics that might make surgical resection appropriate when treating stage IV esophageal cancer.**

Methods. **A retrospective review of 3,500 esophagectomies performed at our institution from 1985 to 2013 identified 52 (1.5%) patients with stage IV esophageal cancer who underwent surgical resection with intent for cure. In 46 (88.5%) patients, M1 disease was discovered at the time of surgery and 6 (11.5%) patients had known M1 disease prior to surgery.**

Results. **Median age at the time of surgery was 60 years (range, 31 to 81 years). The majority of patients were men (82.7%) with adenocarcinoma (88.5%). Neoadjuvant therapy was used in 18 (34.6%) patients; all patients operated on after 1999 received neoadjuvant therapy. An Ivor Lewis esophagectomy was performed in 39 (75%) patients. Follow-up was complete in all patients for a median of 324 days (range, 4 days to 8.5 years). Overall, 1-year survival was 29% and 5-year survival was 6%. There was no significant difference in survival between patients with known preoperative versus intraoperative discovery of M1 disease. Factors associated with improved survival included neoadjuvant treatment, low T stage, and lack of alcohol use.**

Conclusions. **Few patients with stage IV esophageal cancer survive long term after surgical resection, though 5-year survival can occur. Our current recommendation is that esophagectomy should not be performed for stage IV disease.**

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Esophageal carcinoma is an aggressive malignancy and about a third of patients present with distant metastatic disease [1]. While survival is slowly improving with better diagnostic tools and therapy, the overall 5-year survival remains low at 18%. Survival of patients with stage IV esophageal adenocarcinoma is exceedingly poor, with less than 5% surviving 5 years. Current National Comprehensive Cancer Network guidelines recommend only palliative and supportive measures for patients with metastatic esophageal cancer [2]. Current surgical treatments for stage IV disease are palliative in nature, dealing with treatment of obstruction or bleeding and providing nutritional access. Treatment for stage IV disease is chemotherapy in select patients, while the role of radiation therapy and surgical resection remain controversial [3–6]. We wanted to determine if there is any survival benefit to surgical resection in highly selected patients with metastatic esophageal cancer, particularly in patients who have had a positive response to neoadjuvant therapy. The purpose of this study is to characterize the survival of patients with stage IV esophageal carcinoma after resection with a curative intent.

Patients and Methods

Data Collection

The Mayo Clinic Institutional Review Board approved this study. We retrospectively collected data including demographics, presenting symptoms, evaluation, surgical and medical management, pathology, and short-term and long-term outcome for patients who had an esophagectomy from 1985 to 2014 (Table 1). Patients with stage IV (M1) esophageal squamous or adenocarcinoma according to the American Joint Committee on Cancer Seventh Edition (2010) tumor node metastasis (TNM) staging system found either preoperatively or intraoperatively who underwent an esophagectomy with curative intent were identified. Patients with cancers other than esophageal adenocarcinoma or squamous carcinoma, as well as those who underwent palliative operations, were excluded. Variables analyzed were TNM stage, tumor grade, tumor location, age, sex, presence of

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Table 1. Demographics

Variable	Value
Gender	
Male	43 (82.7)
Female	9 (17.3)
Age at operation, years	60.8 ± 12.7 (31.0–81.0)
Hypertension	
No	34 (65.4)
Yes	18 (34.6)
Coronary artery disease	
No	47 (90.4)
Yes	5 (9.6)
Diabetes mellitus	
No	49 (94.2)
Yes	3 (5.8)
Renal disease	
No	51 (98.1)
Yes	1 (1.9)
Smoking status	
Nonsmoker	22 (42.3)
Former smoker	24 (46.2)
Current smoker	6 (11.5)
Pack years (n = 30)	40.5 ± 25.4 (2.0–100.0)
Alcohol use	
No	33 (63.5)
Yes	19 (36.5)
GERD	
No	21 (40.4)
Yes	31 (59.6)
M1 known pre-op	
No	46 (88.5)
Yes	6 (11.5)

Values are n (%) or mean ± SD (range). N = 52.

GERD = gastroesophageal reflux disease; M1 = metastasis; pre-op = preoperative.

comorbidities (hypertension, coronary artery disease, diabetes mellitus, renal insufficiency, history of smoking or alcohol use, and gastroesophageal reflux disease [GERD]), neoadjuvant and adjuvant chemotherapy or radiation therapy, date of disease recurrence, and date of death. The primary endpoint was overall survival. Date of the operation was used as time zero for the survival analysis. The secondary endpoint included progression-free survival.

Statistics

Descriptive statistics for discrete variables are reported as number and percentage. The primary outcome of patient survival was estimated using the Kaplan Meier survival method [6]. A 2-sample *t* test (with an unequal variance assumption) was used if there was a difference in age at operation. Chi-square tests were used to test if there were differences between gender, the type of cancer, and the surgical procedure. Univariate Cox proportional hazards models were used to determine survival differences between those with known M1 disease prior to surgery versus intraoperative discovery, recurrence or death over time for variables of interest, and hazard ratios were recorded. A p value less than 0.05 was considered significant.

Results

Patient Characteristics

A retrospective review of 3,500 esophagectomies performed at the Mayo Clinic from 1985 to 2014 identified 52 (1.5%) patients with stage IV esophageal cancer who underwent surgical resection with intention of cure. Thirty-seven patients (71.2%) had their operation before 2000. Median age of the patients was 60 years old with a range of 31 to 81 years. The majority of patients were men (n = 43, 82.7%) (Table 1). Comorbidities such as hypertension, coronary artery disease, renal disease, or diabetes mellitus were not prevalent in this population; however, GERD was present in 59.6% (Table 1). Approximately, 42.3% of patients were nonsmokers, 46.2% were former smokers (patient had quit smoking prior to surgical consultation), and 11.5% were current smokers. Median smoking pack-years was 40.5, with a range of 2 to 100 pack-years. Alcohol use was present in 36.5% of patients (Table 1).

Preoperative evaluation included an esophagogastroduodenoscopy in all 52 patients (100%), computerized tomography scan in 49 patients (94.2%), positron emission tomography (PET) scan in 15 (28.8%), and endoscopic ultrasound (EUS) in 15 (28.8%). The most frequent tumor location was in the lower third of the esophagus in 44 patients (84.6%), followed by tumors in the midesophagus in 5 (9.6%), Siewert type III in 2 (3.8%), and upper esophagus in 1 patient (1.9%) (Table 2).

Prior to surgery, a total of 18 patients (34.6%) received neoadjuvant therapy, 17 patients received both chemotherapy and radiation, and 1 patient received radiation therapy alone. Only 2 patients received chemoradiation prior to 1999. In 6 (11.5%) patients M1 disease was identified prior to surgery and M1 disease was discovered intraoperative in 46 (88.5%) patients (Table 2).

The most common surgical approach was an Ivor Lewis esophagectomy in 39 patients (75%). A transhiatal esophagectomy was performed in 5 (9.6%) patients, one of which was minimally invasive. McKeown and thoracoabdominal approaches were done in 3 (5.8%) patients each and the 2 (3.8%) patients with Siewert type III tumors had a gastrectomy with jejunum Roux-en-Y reconstruction. Pathology showed that 46 (88.5%) patients had adenocarcinoma of the esophagus, while 6 (11.5%) patients had squamous cell carcinoma. The pathologic T stage was ypT0 in 5 patients, T1 in 1, T2 in 6, T3 in 38, and T4 in 3. The location of the metastasis was lung in 20 (38.5%) patients, liver in 15 (28.8%) patients, abdomen (omentum, peritoneum, pancreas, spleen, small bowel, adrenal, and ovary) in 14 (26.9%) patients, and supraclavicular or cervical lymph nodes in 3 (5.7%) patients (Table 2).