

Locally advanced esophageal cancer: What becomes of 5-year survivors?

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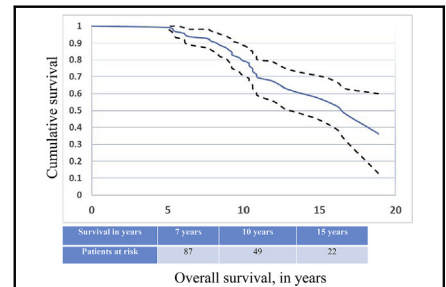
ABSTRACT

Objective: To determine the long-term outcomes of patients with locally advanced esophageal cancer (LAEC) who underwent esophagectomy and survived at least 5 years, and the predictors of disease-free survival (DFS) beyond 5 years.

Methods: This was a retrospective review of a prospective database to identify patients with clinical stage T2N0M0 or higher LAEC. Medical records were reviewed to obtain demographic, clinical, and pathological characteristics, as well as data on recurrence and survival. Multivariable analysis of predictors of DFS beyond 5 years was performed using a Cox regression model.

Results: Between 1988 and 2009, 355 of 500 patients underwent esophagectomy for cT2N0M0 or higher disease. Of these 355 patients, 126 were alive and disease-free at the 5-year follow-up, for an actuarial 5-year DFS of 33%. Recurrent esophageal cancer developed in 8 patients after 5 years. Among the 126 surviving patients, the actuarial overall survival was 94% at 7 years and 80% at 10 years. On multivariable analysis, the sole significant predictor of DFS after the 5-year time point was non-en bloc resection at the original operation ($P = .006$). Pulmonary-related deaths accounted for 10 out of 22 noncancer deaths. A second primary cancer developed in 23 of the 126 surviving patients.

Conclusions: Prolonged survival can be obtained in one-third of patients with LAEC. An en bloc resection at the original operation is the most significant predictor of prolonged survival. Survivors experience a high rate of second primary cancer and an apparently high rate of deaths from pulmonary disease. Careful follow-up is necessary for these patients, even after the 5-year mark. (*J Thorac Cardiovasc Surg* 2016;151:726-32)



Overall survival for disease-free patients after 5 years of follow-up.

Central Message

In LAEC patients who survived at least 5 years after esophagectomy, actuarial overall survival at 10 years and 15 years is 80% and 59%, respectively. Although recurrent EC is uncommon, patients remain at risk for another primary cancers and pulmonary morbidities.

Perspective

Among 5-year survivors, non-en bloc resection was the sole significant predictor of disease-free survival. Recurrent esophageal cancer, another primary cancers, and pulmonary diseases were the most common causes of death beyond 5 years postesophagectomy. Careful follow-up is mandatory for patients with locally advanced esophageal cancer even after 5 years of follow-up.

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Despite advances in surgical techniques and neoadjuvant treatment strategies, locally advanced esophageal cancer (LAEC) remains a virulent malignancy associated with poor survival.^{1,2} Advances in surgical techniques,

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Abbreviations and Acronyms

CCI	=	Charlson Comorbidity Index
CI	=	confidence interval
CT	=	computed tomography
DFS	=	disease-free survival
LAEC	=	locally advanced esophageal cancer
OS	=	overall survival
PET	=	positron emission tomography

perioperative care, and preoperative treatment strategies have improved outcomes somewhat; however, long-term survival beyond 5 years is considered uncommon. There is little published information on the outcome of patients with LAEC treated by esophagectomy with or without induction therapy beyond the 5-year mark, and whether these patients are truly cured remains unclear. The objective of the present study was to determine the outcomes of patients with LAEC clinically staged as T2N0M0 or higher who had survived at least 5 years after esophagectomy and were without disease at that time point.

PATIENTS AND METHODS**Study Design**

We conducted a retrospective review of a prospectively assembled thoracic surgery database. The Institutional Review Board of Weill Cornell Medical College and the New York–Presbyterian Hospital approved the database and the study design. Patient consent was waived. Patients were considered eligible for this review who had locally advanced carcinoma of the esophagus or gastroesophageal junction (Siewert type I or II) clinically staged as cT2N0M0 or higher and were treated by esophagectomy, with or without preoperative induction therapy, between January 1988 and September 2009. Patients undergoing esophagectomy after September 2009 were excluded, to obtain a minimum of 5 years of follow-up. Patients with clinical T1 disease were also excluded, because they were considered to have early-stage disease with a favorable long-term outcome.

A total of 355 patients met the selection criteria, of whom 126 patients were alive and disease-free at the 5-year time point. The hospital records of these 126 patients were reviewed for demographic and clinical characteristics, including age, sex, clinical stage, and use of neoadjuvant therapy. Performance status of all patients was graded according to Eastern Cooperative Oncology Group guidelines, and comorbidities were graded using the Charlson Comorbidity Index (CCI).³ Records were also reviewed for perioperative and pathological data, including surgical approach, extent of resection, fields of lymph nodes resected, pathological stage, histological cell type, and completeness of resection (R status).

Preoperative Evaluation

All patients were evaluated by history, physical examination, upper gastrointestinal endoscopy with biopsy and computed tomography (CT) of the chest and upper abdomen. Endoscopic ultrasonography and positron emission tomography (PET) were routinely obtained preoperatively only in the latter half of the cohort, from 1999 to 2009. Pulmonary function tests

were routinely obtained, and cardiac stress testing was done if risk factors were present. Patients were considered for surgical resection if preoperative evaluation revealed no evidence of distant visceral metastases or clear evidence of direct tumor invasion of the airway or major vascular structures. The presence of extensive nodal disease was not considered a contraindication to resection unless it clearly extended beyond the proposed fields of dissection.

Neoadjuvant Therapy

The majority of patients received neoadjuvant chemotherapy alone. Neoadjuvant chemotherapy included 2 to 4 cycles of a platinum-based regimen with either a taxane or epirubicin and capecitabine. Preoperative chemoradiotherapy was provided using either cisplatin/5-fluorouracil or, more commonly, carboplatin/paclitaxel delivered concurrently with radiotherapy. Esophagectomy was performed at 3 to 6 weeks after the conclusion of preoperative therapy.

Surgical Treatment

Esophagectomy was performed with either a transthoracic en bloc approach or a transhiatal approach. En bloc esophagectomy with 2- or 3-field lymphadenectomy was performed in medically fit patients aged <80 years. The basic technique of en bloc esophagectomy has been described previously.⁴ Alternatively, resection was done by either a non-en bloc conventional (Ivor-Lewis) transthoracic approach or a transhiatal approach. Regardless of surgical approach, upper abdominal and retroperitoneal node dissection was performed in all patients. Reconstruction with a greater curvature gastric tube was done in most of cases. Pathological staging was done according to the TNM classification of the seventh edition of the American Joint Committee for Cancer staging manual.⁵

Follow-up

After hospital discharge, patients were seen at 3-month intervals for the first 12 months, then every 6 months up to year 3, and annually thereafter. Patients from distant geographic locations were followed by contacting their treating physician and/or by direct telephone contact. CT scans of the chest and upper abdomen were done postoperatively every 6 months for 3 years and annually thereafter. Other studies, such as endoscopy and PET scanning, were done only if clinically indicated. All data were collected, entered into a prospective database, and updated at regular intervals until the patient's last follow-up or death.

Recurrence

Local recurrence was defined as recurrence within the wall or the lumen at or close to the anastomotic site. Regional recurrence was defined as nodal recurrence at any site within the operative field. Distant recurrence was defined as any tumor recurrence in nodal basins outside the field of surgical dissection or in distant organs. The operating surgeon reported recurrence data based on review of findings on CT, PET, endoscopy, or relevant biopsy analyses whenever possible.

Statistical Analysis

The database was queried to identify relevant clinical and pathological characteristics, which were represented by descriptive statistics (frequency and percentage, median and interquartile range). Cox proportional hazards regression analysis was performed to identify predictors of disease-free survival (DFS) at 5 or more years after esophagectomy. Univariate analyses examined age, sex, performance status,

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