Esophagectomy Outcomes in the Endoscopic Mucosal Resection Era

Karen J. Dickinson, MBBS FRCS (Engl), Kenneth Wang, MD, Lizhi Zhang, MD, Mark S. Allen, MD, Stephen D. Cassivi, MD, MS, Francis C. Nichols,, III, MD, Robert Shen, MD, Dennis A. Wigle, MD, PhD, and Shanda H. Blackmon, MD, MPH

Divisions of General Thoracic Surgery, Gastroenterology, and Pathology, Mayo Clinic, Rochester, Minnesota

Background. **Endoscopic mucosal resection (EMR) and esophagectomy are treatment options for cT1 esophageal adenocarcinoma. Our aim was to study outcomes for patients undergoing EMR then esophagectomy.**

Methods. **We identified patients undergoing EMR and esophagectomy for cT1 esophageal adenocarcinoma over 10 years. EMR histology was used to predict nodal involvement with a risk-scoring tool. Patient demographics, surgical techniques, pathology, postoperative outcomes, and survival were recorded.**

Results. **Of 1,092 that esophagectomies were performed, 51 patients underwent EMR and esophagectomy for cT1 esophageal adenocarcinoma. The mean time between EMR and esophagectomy was 4 (SD,8.0) months. According to the risk-scoring tool based on EMR histology, 1 patient was low risk, 13 (25%) were at moderate risk, and 37 (73%) were at high risk for lymph node metastasis. The time between EMR and the surgical intervention was longer and more patients had multiple EMRs in the moderate-risk group (9 vs 1.4 months, $p = 0.03$) compared with the high-risk group (38% vs 11% patients, $p = 0.04$). Operative mortality was 4% and morbidity was 43%. Pneumonia occurred in 3 of 51 patients (6%), atrial fibrillation in 4 (8%), and clinical anastomotic leak in 6 (12%). Of the 51 patients, 14 (27%) were upstaged after esophagectomy. Nodal involvement was present in 3 of 13 moderate-risk patients (23%) and in 7 of 37 high-risk patients (19%). The 5-year survival was reduced in moderate-risk compared with high-risk patients (54% vs 84%, $p = 0.04$).**

Conclusions. **Studying outcomes for cT1 esophageal adenocarcinoma is important. These patients can be divided into those undergoing EMR for staging before esophagectomy and those in whom esophagectomy is a salvage procedure after therapeutic EMRs. Care should be taken to avoid upstaging of patients in the latter group, and we recommend frequent restaging and surveillance to prevent undetected progression of disease. A low threshold for esophagectomy when EMR fails to control disease should be considered.**

(Ann Thorac Surg 2016;■:■–■)

The management of early esophageal cancer is in evolution and is controversial [1]. Esophagectomy has been the traditional treatment of choice for these tumors. Although quality of life after esophagectomy can be good [2], esophagectomy is not without morbidity and mortality. Treatment of these early cancers with endoscopic mucosal resection (EMR) offers patients valuable esophageal preservation but requires extensive postprocedural surveillance. Predicting the risk of lymph node metastases for a patient is essential to avoid the risks associated with undertreating disease. EMR is currently used for cT1a and favorable cT1b tumors [3]. The Worldwide Esophageal Cancer Collaboration has demonstrated worse survival for T1b tumors compared with T1a, and this is likely because of the increased risk of nodal metastases in the latter group [4].

The key to esophageal preservation in these patients is accurate preoperative staging with identification of patients at risk of lymph node metastases. Studies, including that of the National Cancer Institute's database and a recent metaanalysis, have shown the prevalence of lymph node metastases is less than 2% in T1a adenocarcinoma of the esophagus [5] and 20% to 30% for T1b tumors [6–13]. Any infiltration into the submucosa, tumor size greater than 10 mm, and poor tumor differentiation are independently associated with the presence of nodal disease [6]. Preoperative staging involves endoscopic ultrasound (EUS) and positron emission tomography-computed tomography scans.

EMR arguably provides the best information with regard to T staging of esophageal tumors and can even establish the diagnosis of a cT2 tumor better than EUS. Studying outcomes of patients who have undergone EMR for cT1 disease with subsequent esophagectomy provides invaluable information on patient outcomes. This study describes outcomes in a challenging and poorly studied patient group undergoing EMR for cT1 esophageal adenocarcinoma and then subsequent esophagectomy.

Accepted for publication Aug 17, 2016.

Presented at the Fifty-second Annual Meeting of the Society of Thoracic Surgeons, Phoenix, AZ, Jan 23–27, 2016.

Address correspondence to Dr Blackmon, Division of General Thoracic Surgery, Mayo Clinic, 200 First ST, SW, Rochester, MN 55905; email: blackmon.shanda@mayo.edu.

Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.08.062

Patients and Methods

We retrospectively analyzed a prospectively collected database of all esophagectomies between November 2004 and November 2014. We identified patients undergoing EMR for cT1 esophageal adenocarcinoma and subsequent esophagectomy. In our institution, all cT1b esophageal adenocarcinomas are referred for surgical opinion. The analysis excluded patients who did not have esophagectomy after EMR. This work was approved by the Mayo Clinic IRB and patient consent obtained.

Scoring System

The EMR histology of patients who had cT1 esophageal adenocarcinoma was reviewed. Patients were risk stratified according to a modified established scoring system based on tumor size, differentiation, depth, and lymphovascular invasion [14]. This scoring system was developed by Lee and colleagues [14], who correlated the histologic characteristics of primary esophageal resections for T1 esophageal adenocarcinoma. They found that tumor size and the presence of lymphovascular invasion were the strongest independent predictors of lymph node metastases. They used their multivariate analysis to develop a scoring system to predict the risk of lymph node metastases in patients with T1 esophageal adenocarcinoma. Each variable was allocated a different number of points and allowed patients to be classified as low, medium, or high risk for lymph node metastases. Patients classified at low risk had a total score of 1, moderate risk patients had a score of 2 to 4m and high risk patients 5 or higher. We modified the scoring system to +2 for tumor depth if a patient with T1a disease had positive margins on EMR (Table 1). This scoring system by Lee and colleagues [14] has not previously been validated.

EMR specimens were prepared under a standard protocol in our histology laboratory. The tissue was fixed in 10% neutral-buffered formalin and then serially sectioned perpendicular to the long axis at approximately 2-mm intervals. The tissue was embedded in paraffin and sectioned at 5-μm thickness for hematoxylin and eosin staining, with three levels obtained from each paraffin block. Esophagectomy specimens were processed routinely. Tissue from the lesion site was usually totally submitted to look for residual tumors.

Table 1. Modified Risk-Scoring System for Predicting Lymph Node Involvement in Patients With T1 Esophageal Adenocarcinoma[a]

Variable	Points
Size, per cm	1
Depth	
T1a	0
T1b or + margin	2
Differentiation	
Well	0
Moderate	3
Poor	3
Lymphovascular invasion	6

[a] From and Lee colleagues [14], 2013. Republished with permission of the Journal of the American College of Surgeons, from Predicting Lymph Node Metastases in Early Esophageal Adenocarcinoma Using a Simple Scoring System, Lee L, Ronellenfitsch U, Hofstetter WL, et al, 217;2:191-9, 2013; permission conveyed through Copyright Clearance Center, Inc.

Perioperative Details

The duration between EMR and esophagectomy was recorded. Patients' preoperative T stage (cT) was defined by the T stage on EMR histology before esophagectomy. Perioperative details, such as preoperative neoadjuvant therapy, preoperative tumor stage (EMR, EUS, positron emission tomography with or without computed tomography), and type of esophagectomy were collected. Postoperative morbidity and mortality were recorded.

The pathology reports from the esophagectomy specimens were reviewed, and the following information was collected: size of tumor, presence of lymphovascular invasion, depth of tumor invasion (pT), presence and location of positive lymph nodes, and number of lymph nodes harvested in the specimen. Length of follow-up was recorded for each patient, including presence of tumor recurrence or metastasis, death in hospital, and survival.

Our surveillance protocol for those patients undergoing EMR alone for cT1a esophageal adenocarcinoma involves endoscopic biopsy specimens every centimeter throughout the previous segment of Barrett's esophagus every 3 months for a year after complete elimination of intestinal metaplasia. Subsequent endoscopy and biopsies are performed at 6 months for a year and yearly thereafter.

Statistical Analysis

Descriptive statistics are reported as frequency (percentage) or mean (SD) as appropriate. Patient characteristics and EMR histology variables were compared among risk groups (low/moderate or moderate vs high) using a two-sample *t*-test or Kruskal-Wallis, as appropriate, for continuous variables and a χ^2 or Fisher exact test where appropriate for discrete variables. The association of T-stage on EMR with positive lymph nodes at final resection was assessed using univariate logistic regression. The Kaplan-Meier method was used to estimate the overall survival at 1-year intervals up to 5 years. Univariate Cox proportional hazards models, reported as hazard ratios, were used to assess the association of risk factors with death. A p value of less than 0.05 was considered statistically significant. Statistical analyses were completed using SAS 9.3 (SAS Institute Inc, Cary, NC) and R 3.1.1 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 1,092 esophageal resections during the 10-year study period, of which 997 were performed to treat esophageal cancer. EMR was performed in 51 patients (44 men and 7 women) for cT1 esophageal adenocarcinoma with subsequent esophagectomy. Mean age at esophagectomy was 66 (SD, 10.5) years. Mean time between the