

CLINICAL—ALIMENTARY TRACT

Endoscopic and Surgical Treatment of Mucosal (T1a) Esophageal Adenocarcinoma in Barrett's Esophagus

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See CME quiz on page 1161.

BACKGROUND & AIMS: Endoscopic therapy is emerging as an alternative to surgical therapy in patients with mucosal (T1a) esophageal adenocarcinoma (EAC) given the low likelihood of lymph node metastases. Long-term outcomes of patients treated endoscopically and surgically for mucosal EAC are unknown. We compared long-term outcomes of patients with mucosal EAC treated endoscopically and surgically. **METHODS:** Patients treated for mucosal EAC between 1998 and 2007 were included. Patients were divided into an endoscopically treated group (ENDO group) and a surgically treated group (SURG group). Vital status information was queried using an institutionally approved internet research and location service. Statistical analysis was performed using Kaplan–Meier curves and Cox proportional hazard ratios. **RESULTS:** A total of 178 patients were included, of whom 132 (74%) were in the ENDO group and 46 (26%) were in the SURG group. The mean follow-up period was 64 months (standard error of the mean, 4.8 mo) in the SURG group and 43 months (standard error of the mean, 2.8 mo) in the ENDO group. Cumulative mortality in the ENDO group (17%) was comparable with the SURG group (20%) ($P = .75$). Overall survival also was comparable using the Kaplan–Meier method. Treatment modality was not a significant predictor of survival on multivariable analysis. Recurrent carcinoma was detected in 12% of patients in the ENDO group, all successfully re-treated without impact on overall survival. **CONCLUSIONS:** Overall survival in patients with mucosal EAC when treated endoscopically appears to be comparable with that of patients treated surgically. Recurrent carcinoma occurs in a limited proportion of patients, but can be managed endoscopically.

The incidence of esophageal adenocarcinoma (EAC) continues to increase faster than any other malignancy in the United States, with adenocarcinoma being

more common than squamous cell carcinoma in the United States.¹ Barrett's esophagus (BE) is a strong risk factor for the development of esophageal adenocarcinoma. Overall survival after the diagnosis of EAC remains poor (<20% at 5 years).² Esophagectomy has been the mainstay of treatment for EAC with the addition of chemoradiotherapy (predominantly preoperatively), adding a modest survival benefit in some studies.³

Although esophagectomy remains the conventional treatment for EAC, it is associated with significant mortality and morbidity, with estimates of mortality varying from 1% to 2% at high-volume centers to 5% to 10% at lower-volume centers,⁴ and morbidity rates varying from 30% to 50%.⁵ Lymph node metastases in EAC have been correlated with the depth of tumor invasion in studies: with mucosally confined EAC being associated with a low (0%–2%) rate of metastatic lymphadenopathy.⁶ This low rate of metastases has provided a rationale for the endoscopic treatment of mucosal (T1a) adenocarcinoma for curative intent using only endoscopic mucosal resection (EMR) alone or in combination with other mucosal ablation techniques such as photodynamic therapy (PDT). Initial studies reporting results on outcomes after endoscopic therapy for mucosal EAC appear promising.^{6–11}

However, currently available studies of outcomes after endoscopic therapy have been limited by small numbers, relatively short duration of follow-up evaluation, use of outcomes such as short-term rates of remission, and the absence of an appropriate comparison group such as patients treated with esophagectomy.¹² Although the ideal design would be a randomized controlled trial to compare outcomes between these 2 treatment modalities, this would be difficult to achieve given the small number of cases of mucosal EAC, which would make recruitment

Abbreviations used in this paper: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ENDO, endoscopically treated group; HGD, high-grade dysplasia; IQR, interquartile range; PDT, photodynamic therapy; SURG, surgically treated group.

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times prohibitively long, the large sample size that would be needed to compare overall or cancer-related mortality between the 2 groups, and the difficulty in randomizing patients to these 2 radically different treatment approaches. In addition, recurrence of neoplasia after initial remission remains poorly defined in terms of time course and possible clinical and biologic predictors.

We aimed to compare overall and cancer-free survival of 2 cohorts of patients with early EAC: those treated endoscopically and those treated with conventional esophagectomy over the previous decade. In addition, we also aimed to define the rates and clinical predictors of recurrent EAC after initial remission in the cohort of patients treated endoscopically.

Methods

Study Design

This was a retrospective cohort study. Patients were either referred for endoscopic treatment of mucosal EAC to the Barrett's Esophagus Unit by physicians or were under surveillance for high-grade dysplasia (HGD) in the BE Unit. All patients seen in the BE Unit for endoscopic therapy had received consultation either with thoracic surgeons at the Mayo Clinic or at their local hospitals. Patients referred for esophagectomy usually were referred directly by their physicians or were elected to undergo surgery after initial evaluation at the BE Unit.

Endoscopically Treated Cohort

Data from a prospectively maintained database were obtained on consecutive patients with BE and mucosal EAC who were treated endoscopically between 1998 and 2007 at the BE Unit at the Mayo Clinic (Rochester, MN). Patients with evidence of submucosally invasive carcinoma on pretreatment histopathology (typically from EMR specimens on initial evaluation) were excluded ($n = 30$). All patients underwent 4-quadrant biopsies for every centimeter of the visible BE segment. Baseline assessments also included endoscopic ultrasound and EMR for any mucosal abnormalities. Computerized tomography scans of the chest and upper abdomen were obtained in all patients as well as positron emission tomography scans to exclude distant metastatic disease (this was performed since 2003). PDT was delayed a minimum of 4 weeks if an EMR was performed to allow healing of the EMR site(s).

EMR. EMR was performed as previously described.¹³ The initial technique was a variceal ligation method in which a Bard Six-Shooter (Bard Interventional Products, Billerica, MA) and suction were used to retract the lesion of interest and had a band placed over it to create a pseudopolyp, which then was resected. Beginning in April 2000, EMR was performed using a commercially available EMR cap (EMR-001; Olympus America Inc, Center Valley, PA). Lesions were lifted using submucosal

injection with 4 to 10 mL of 1:200,000 strength saline epinephrine solution. Mucosal resection was performed by suctioning the lesion into the cap after positioning of a crescent snare. The snare then was closed with application of cautery current (energy setting of 16 W blend 2 using a Meditron unit [Meditron Devices Inc, Hackensack, NJ]) removing the tissue. Since 2004, EMR also was performed using the Duette multiband mucosectomy device (Cook Ireland, Limerick, Ireland), using previously described techniques.¹⁴ Submucosal injection was used in the same manner as described earlier, as well as the same energy settings with resection being performed using a hexagonal snare, which is part of the kit. Patients with smaller lesions likely to be removed by a single resection typically underwent EMR using the Olympus EMR cap, whereas those with larger lesions underwent EMR using the Duette device (which allows multiple resections in a single intubation) in an effort to obtain clean margins.

Ablative therapy. PDT was administered as previously described¹⁵ after the achievement of histologic remission (defined as the absence of carcinoma on histology from 2 consecutive surveillance endoscopies). In brief, porfimer sodium (Photofrin; Axcan Pharma, Mont-Saint-Hilaire, Quebec, Canada) at a dose of 2 mg/kg, was administered intravenously 48 hours before photoradiation. Photoradiation was performed using a bare cylindrical diffusing fiber. The cylindrical diffusing fibers were either 2.5- or 5.0-cm long fibers (Fibers Direct, Andover, MA). The cylindrical diffusing fiber was passed through the accessory channel of the endoscope and placed in the center of the esophageal lumen. The light was delivered from a laser (Lambda Plus; Coherent, Palo Alto, CA; or Diomed; Diomed Inc, Andover, MA) producing 630 nm of light with an adjusted power output of 400 mW/cm fiber, delivering a total energy of 200 J/cm fiber energy to the mucosa. PDT was performed more frequently after resection of carcinoma and achieving remission during the initial phase of the study (1998–2003). Patients who had mucosal carcinoma diagnosed on mucosal biopsy specimens alone without visible lesions also were more likely to receive PDT. During the latter phase of the study this was performed selectively given the lack of consensus on whether ablation after initial remission definitively reduces the risk of metachronous neoplasia.

Pathology assessment. A pathology assessment was performed according to the protocol in our BE Unit as previously published.¹³ Patients had their diagnosis of mucosal EAC confirmed by at least 2 experienced gastrointestinal pathologists and all cases were reviewed by a single study pathologist (T.T.W.) with expertise in BE-associated neoplasia using previously described standard criteria for the classification and diagnosis of BE, dysplasia in BE, and adenocarcinoma.^{16,17} Intramucosal adenocarcinoma was diagnosed once there was invasion through the basement membrane into lamina propria or into muscularis mucosae. The former often is characterized by sin-

gle cells or clusters of cells within the lamina propria. Invasive adenocarcinoma was defined as tumor that invaded through the muscularis mucosae into the submucosa (if duplicated muscularis mucosae was appreciated,¹⁸ invasion through both layers of the muscularis mucosae into the submucosa was required). Surgical pathology of all esophagectomy specimens was reviewed by gastrointestinal pathologists as well.

Follow-up evaluation. All patients were placed on twice-a-day proton pump inhibitor (PPI) therapy after PDT and/or EMR at the standard dose of the proton pump inhibitor. Patients were educated carefully regarding PDT, EMR, and their possible immediate and delayed complications, especially risk of bleeding, perforation, photosensitivity, and stricture formation by the physicians, nurse practitioner, and clinical coordinators. Follow-up evaluation included endoscopic surveillance with biopsies and EMR if indicated, performed every 3 months for 2 years, then every 6 months for 1 to 2 years, and annually thereafter. Recurrence was defined as the presence of adenocarcinoma detected on either biopsy or EMR specimens after complete remission (defined as the absence of carcinoma in biopsy and/or EMR specimens from 2 successive surveillance endoscopies). Data on photosensitivity, bleeding, and stricture formation was collected prospectively.

Surgically Treated Cohort

Patients were identified by a retrospective review of all patients in the Mayo Clinic pathology database who underwent esophagectomy for esophageal carcinoma at the Mayo Clinic between 1998 and 2007. Thirty-eight patients underwent preoperative endoscopic ultrasound for staging. Patients with mucosally confined (as per prior classification described earlier) adenocarcinoma were included in this study. All patients underwent esophagectomy performed by experienced thoracic surgeons using either the transthoracic or the transhiatal route. All except 2 patients underwent surgery at the Mayo Clinic (Rochester, MN): these 2 patients underwent esophagectomy at other large-volume surgical centers after initial evaluation at the Mayo Clinic. Only overall survival and cancer-free survival data were included in the analysis for these 2 patients. Data extracted by chart review on the remaining 44 patients included postoperative course, days to discharge, complications, and follow-up data. Follow-up evaluation in the surgically treated (SURG) cohort was at intervals defined by the practice of the individual thoracic surgeons.

Survival Data

Survival (vital status and death date) information for both groups was assessed by using an institutionally approved internet research and location service (www.accurint.com). Cause of death was obtained from either the medical records, the prospective BE Unit database, as

well as from review of death certificates if data were not available from the first 2 sources. In addition, patients who had not been seen for more than 12 months were contacted via telephone using an institutional review board-approved telephone script to obtain information on care received elsewhere and evaluation for esophageal carcinoma recurrence.

Statistical Analysis

Data management and statistical analysis were performed using JMP software (version 6.0; SAS Institute Inc., Cary, NC). Baseline continuous data were compared using the 2-sample *t* test or the Wilcoxon rank-sum test depending on the data normality. Baseline categorical data were compared using the chi-squared test (or the Fisher exact test when necessary because of small sample size). Overall survival was defined as the time between the date of diagnosis of EAC and death from any cause for patients who died (for the endoscopically treated [ENDO] group), or the time between esophagectomy and the last date of follow-up evaluation (for the SURG group). Cancer-free survival was defined as the time between the date of remission and last cancer-free follow-up evaluation or death. Overall survival and cancer-free survival were analyzed with the Kaplan-Meier product limit method. The log-rank statistic was used to compare overall and cancer-free survival between patients treated with endoscopic therapy and esophagectomy. Baseline variables (age, sex, length of BE segment, age-adjusted Charlson comorbidity index score,¹⁹ and propensity score) were analyzed as factors affecting overall survival using Cox proportional hazards modeling. (The propensity score is the predicted probability of being in the PDT group based on age, sex, length of BE, and the age-adjusted Charlson comorbidity index.) The propensity score was obtained using logistic regression.²⁰ Estimates of hazard rates and 95% confidence intervals were determined.

Results

A total of 132 patients underwent endoscopic therapy (ENDO group) and 46 patients underwent esophagectomy (SURG group) for mucosal EAC between 1998 and 2007 at the Mayo Clinic (Rochester, MN) and were included in this study. The baseline characteristics of these patients are summarized in Table 1. As is evident from Table 1, patients treated endoscopically were older and had more medical comorbidities than those treated surgically. In addition, patients in the SURG group also had a longer BE segment than those treated endoscopically. Thirty patients in the ENDO group were detected during surveillance for HGD and the remaining 102 were referred with a diagnosis of esophageal adenocarcinoma for consideration of endoscopic therapy.

Figure 1 summarizes the treatment of patients in the ENDO group. The median size of the lesions treated endoscopically was 1 cm (interquartile range [IQR], 0.9–

Table 1. Comparison of Baseline Characteristics in the Two Treatment Groups

Variables	ENDO group (N = 132)	SURG group (N = 46)	P value
Mean age, y (SEM)	71.2 (0.96)	67.7 (1.4)	.006*
Male sex, n (%)	111 (84)	43 (94)	.15†
Mean BE length, cm (SEM)	5.5 (0.36)	7.3 (0.77)	.03*
Cardiac disease, %	38	26	.21†
Pulmonary disease, %	17	6	.06†
Diabetes mellitus, %	20	14	.40†
Prior malignancy, %	24	16	.30†
Median age-adjusted Charlson Comorbidity Index, (IQR)	4 (0–5)	0 (0–4)	<.001‡

NOTE. Cardiac diseases include coronary artery disease, valvular heart disease, and congestive heart failure; pulmonary diseases include chronic obstructive pulmonary disease and restrictive lung diseases; previous malignancy (in remission) includes lung cancer, breast cancer, prostate cancer, colon cancer, and skin cancer.

SEM, standard error of the mean.

*Obtained using the Student *t* test.

†Obtained using the chi-square test.

‡Obtained using the Wilcoxon test.

1.6 cm). Fifty-nine percent of EMRs were performed using the Olympus EMR cap, 21% using the Duette multiband device, and the remaining 20% by using the single-banding device followed by snare resection. All patients who had PDT received only 1 PDT treatment except 2 patients who had 2 sessions. The median number of treatment sessions (EMR and/or PDT) needed to achieve remission was 1 (IQR, 1–2), with a maximum of 5 treatment sessions needed in 1 patient. The median time to remission from the index endoscopy was 3.3 months (IQR, 2–5 mo). Remission was achieved successfully in 124 patients (94%) using EMR and/or PDT. Pathology on surveillance endoscopies after documentation of remission as defined previously (no evidence of carcinoma on 2 successive surveillance endoscopies) was as follows: no BE, 10 (8%); nondysplastic BE, 55 (45%); low-grade dysplasia, 18 (15%); and HGD, 41 (33%) patients. There was no statistically significant difference in the rate of achieving remission between the EMR group and the EMR + PDT groups. Eight patients elected to undergo esophagectomy before remission could be achieved because EAC was detected on a surveillance endoscopy after the index treatment session. Histology from esophagectomy specimens in these patients revealed residual mucosal adenocarcinoma (T1a) in 5 patients without metastatic lymphadenopathy and no evidence of residual carcinoma in the remaining 3 patients.

Endoscopic treatment generally was well tolerated with an overall complication rate of 13% (18 of 132). Eight patients developed strictures, all of whom had received PDT. All were treated successfully using endoscopic dilation with a median of 2 dilations needed to treat strictures. Five patients developed clinically significant bleeding needing

hospitalization and/or transfusions or endoscopic therapy. The remaining 5 patients developed mild photosensitivity, which was treated with conservative measures. Endoscopic therapy was completed successfully in all patients in an outpatient setting with no procedure-related mortality.

Twenty-nine patients had surgery performed via the transthoracic approach and the remaining patients had surgery via the transhiatal approach. Of the 46 patients who underwent esophagectomy (SURG group), 4 had evidence of metastatic lymphadenopathy (8.6%) and 1 patient received postoperative chemoradiation therapy. One patient died from postoperative complications (yielding a postoperative mortality rate of 4%). Three patients were re-admitted within 90 days of surgery for medical and surgical issues. The median length of hospitalization was 8 days (IQR, 7–13 days; range, 5–57 days). Seventeen (34%) patients developed postoperative complications such as anastomotic leaks, anastomotic strictures, cardiopulmonary complications, and feeding jejunostomy leaks.

Follow-up evaluation was 244 person-years in the SURG group and 464.6 person-years in the ENDO group (Table 2). The cumulative mortality was 17% (23 of 132) in the ENDO group and 20% (9 of 46) in the SURG group ($P = .75$). Causes of death in both groups are listed in Table 2. One patient in the ENDO group died with recurrent intramucosal carcinoma: this patient recurred despite EMR and 2 PDT treatments. He was a poor surgical candidate who elected to undergo palliative che-

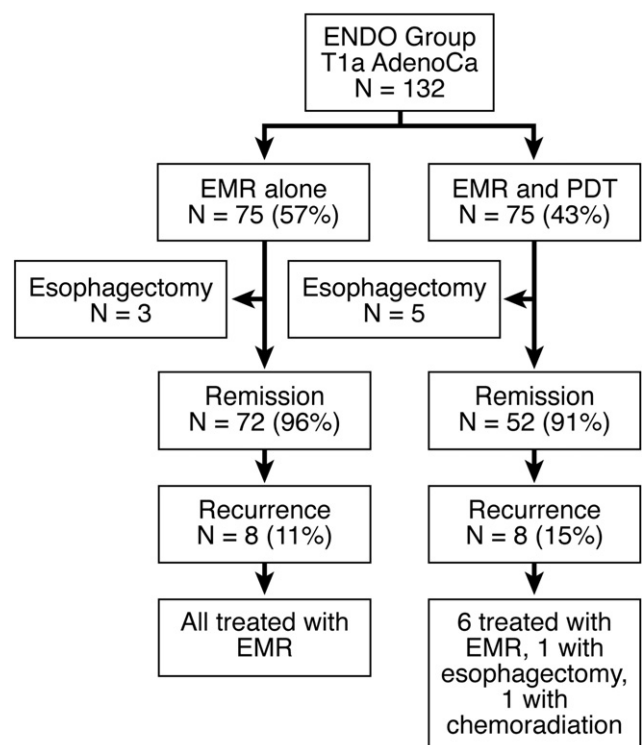
**Figure 1.** Flowsheet of patients treated with endoscopic therapy.

Table 2. Comparison of Outcomes (Overall Mortality, Recurrent Carcinoma) in the Two Groups

	ENDO group (N = 132)	SURG group (N = 46)
Follow-up period, person-years	464.4	243.8
Total number of deaths	23	9
Overall mortality, incidence rate	4.9/100 person-years	3.7/100 person-years
Causes of death (N)	Pneumonia (5) Congestive heart failure/myocardial infarction (4) Metastatic lung cancer (3) Metastatic esophageal carcinoma (1) Parkinson's disease (1) Alzheimer's dementia (2) Chronic obstructive pulmonary disease (2) Metastatic prostate cancer (1) Lymphoma (1) CVA (3)	Postoperative complications (1) Metastatic esophageal carcinoma (1) Metastatic lung cancer (2) Pulmonary fibrosis (1) Congestive heart failure/myocardial infarction (4)
Number of recurrent cancers	16	1
Recurrent carcinoma, incidence rate	5.5/100 person-years	0.56/100 person-years

moradiation therapy. One patient in the SURG group died with metastatic esophageal carcinoma, which appeared as multiple cutaneous nodules (which were aspirated and showed metastatic carcinoma) 6 months after esophagectomy. There was no evidence of metastatic lymphadenopathy in the surgical resection specimen in this patient. Overall survival was comparable between the 2 groups (Figure 2). Overall survival at 5 years was 83% in the ENDO group and 95% in the SURG group. The incidence rate ratio for overall mortality was 1.32 (ENDO group vs SURG group). Cancer-free survival in the 2 groups is shown in Figure 3 and was 80% at 5 years in the ENDO group and 97% in the SURG group. By using Cox proportional hazards modeling, overall survival was comparable between the 2 groups after adjusting for age, sex, length of BE segment, Charlson comorbidity score, and the propensity score, whereas cancer-free survival was superior in the SURG group (Table 3).

Sixteen patients (12%) in the ENDO group had recurrent carcinoma detected during follow-up evaluation compared with 1 patient in the SURG group. The inci-

dence ratios for recurrent carcinoma are shown in Table 2, with an incidence rate ratio of 9.8 (ENDO group vs SURG group). The median time to recurrence in the ENDO group was 19 months (IQR, 10–30 mo). All recurrences were intramucosal carcinomas, appearing as small nodular lesions, and all except 1 was managed by EMR (1 patient opted for esophagectomy, which revealed a residual microscopic focus of intramucosal carcinoma without metastatic lymphadenopathy). All except 1 patient had recurrence of HGD before detection of intramucosal carcinoma.

Factors predictive of recurrent carcinoma were explored using Cox proportional hazards modeling. The results are shown in Table 3. Only univariate analysis was performed given the limited number of patients with recurrence (15). The presence of residual dysplastic BE was a significant factor predicting recurrent carcinoma on univariate analysis. The presence of any residual BE (without dysplasia), increasing length of the BE segment at baseline, and presence of an incident carcinoma (carcinoma detected after 6 months of surveillance for HGD

Figure 2. Overall survival in the ENDO and SURG groups (Kaplan–Meier curves). Black line: ENDO group; gray line: SURG group. Log-rank test, *P* = .15.

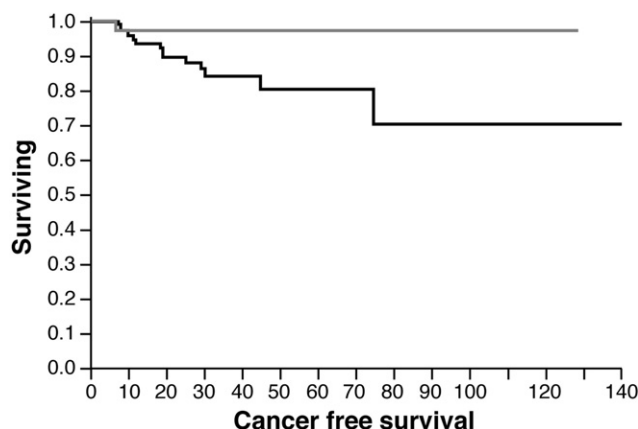


Figure 3. Cancer-free survival in the ENDO and SURG groups (Kaplan–Meier curves). Black line: ENDO group; gray line: SURG group. Log-rank test, *P* = .01.

Table 3. Overall and Cancer-Free Survival in the ENDO and SURG Groups

Variable	Hazard ratio (95% confidence interval)	P value
Overall patient survival adjusting for treatment modality and propensity score	1.54 (0.64–3.75)	.33
Cancer-free survival adjusting for treatment modality and propensity score	2.64 (1.70–4.08)	<.001

NOTE. The propensity score is the predicted probability of being in the ENDO group derived from a logistic model comprising age, sex, length of BE segment, and Charlson comorbidity index.

in BE) approached statistical significance as predictors of an increased risk of cancer recurrence. Of particular interest, additional ablative therapy with PDT did not lead to a reduced risk of recurrence on univariate analysis.

Discussion

Early stage EAC (T1 stage disease confined to the mucosa or submucosa) comprises approximately 20% of all cases of EAC diagnosed in the United States.^{21,22} Endoscopic therapy of mucosal EAC has been proposed as an alternative to surgical resection given the low risk of metastatic lymphadenopathy in these patients.⁶ In this large cohort study we studied outcomes after the endoscopic and surgical treatment of mucosal (T1a) EAC and found that overall survival and cumulative mortality rates were comparable between the 2 cohorts. This was despite patients in the ENDO group being older and having greater comorbidity than those in the SURG group. Patients treated endoscopically did have a recurrence rate of 12%, but this could be re-treated endoscopically (in all patients except one who opted for esophagectomy) with no influence on overall survival. This recurrence rate did give esophagectomy an advantage as far as cancer-free survival was concerned but it is important to note that all of these recurrent cancers including the one managed with esophagectomy could be managed endoscopically. Given these results, endoscopic management appears to be a viable alternative to esophagectomy for patients with mucosal (T1a) esophageal adenocarcinoma.

Esophagectomy has been the standard of care for patients with esophageal adenocarcinoma. It is associated with not insignificant mortality (2%–10%, dependent on hospital volume⁴ and patient comorbidities) and substantial morbidity (30%–40%).⁵ The average length of hospital stay after esophagectomy was 20 days in a recent large report of esophagectomies conducted for esophageal carcinoma in more than 800 patients from the surveillance epidemiology and end results (SEER) database.⁵ Although recent studies from higher-volume centers have reported results of patients undergoing esophagectomy for HGD/early esophageal cancer with no mortality, mor-

bidity rates continue to approximate 30%.²³ Minimally invasive esophagectomy has been reported from a few specialized centers.^{24–27} Reduced hospital stay, mortality, and morbidity have been reported. However, surgical mortality rates ranging from 0% to 8% and morbidity rates of 30% to 40% continue to be reported that are not different from traditional open techniques. In addition, the learning curve of this procedure is steep, limiting generalizability. Vagal-sparing esophagectomy is a technique wherein the vagus nerve is spared by removing the esophagus without regional lymphadenectomy, leaving the vagal innervation of the distal stomach intact: a technique thought to be ideal for patients with HGD and intramucosal adenocarcinoma who have a low risk of metastatic lymphadenopathy.²⁸ However, in a study comparing the outcomes of this technique with the Ivor Lewis technique and the transhiatal technique, a 30-day mortality of 2% and an overall morbidity rate of 30% were reported. Hence, it appears that even newer and less-invasive techniques of esophagectomy continue to have significant rates of morbidity and not insignificant mortality rates.

Survival of patients with esophageal adenocarcinoma in general continues to be poor (<20% at 5 years).^{2,3} Patients with mucosal EAC, however, appear to have better outcomes with both endoscopic and surgical series describing 5-year survival rates exceeding 80%.^{6,12,28,29} Factors predictive of survival after esophagectomy include absence of metastatic lymphadenopathy,⁶ tumor histology, achieving clear margins (R0 resection), response to chemoradiotherapy, and stage of the tumor.³ En bloc resection with lymphadenectomy has been suggested to improve survival compared with transhiatal resection. Survival and outcomes after endoscopic therapy have been reported primarily from Europe,^{9,29–31} with smaller case series (with relatively short-term follow-up evaluation) from the United States.^{7,10} A recent study compared the outcomes of patients with early EAC treated endoscopically and surgically using data from the SEER database and found that cancer-free survival was comparable between the 2 groups. Age and absence of exposure to radiation therapy were the only predictors of cancer-free survival.²¹ Although an important study, this was limited by the inclusion of submucosal cancers, histologic heterogeneity (inclusion of squamous carcinomas and adenocarcinomas), relatively small number of patients with mucosal adenocarcinoma who underwent endoscopic therapy (65), absence of follow-up information in terms of endoscopic surveillance, and a possible bias against surgical outcomes given that these vary significantly with hospital and surgeon volumes. In addition, overall survival data were not presented. Our study, although confined to a single institution, has intrinsic advantages including expert endoscopists and surgeons treating both cohorts, perhaps limiting bias in terms of expertise, review of histology by expert pathologists, pre-

senting both overall and cancer-free survival, and having information on causes of death and data on recurrences and their management. Our results are comparable with another single-center study of endoscopic therapy of mucosal EAC, in which the 5-year survival rate was 84%.¹² This study did not have a surgical control group but instead found survival of study subjects to be comparable with an age- and sex-matched population. This study also reported that no patient died from EAC.

Recurrence of neoplasia is an important consideration in patients treated with endoscopic therapy. Prior studies have reported rates from 11%³² to 21%¹² in adenocarcinomas treated endoscopically, with higher rates in the latter study perhaps owing to the inclusion of HGD and carcinoma in the definition of recurrence. Rates of 25% have been reported in squamous esophageal carcinoma treated endoscopically.³³ Most of the recurrences are mucosally confined and amenable to endoscopic therapy as reported in the earlier-described studies and in our study as well. This most likely was owing to the close and rigorous follow-up algorithms being followed by centers with expertise in this area and underscores the importance of meticulous endoscopic evaluation after remission has been achieved. Risk factors for recurrence have been explored and have included long-segment BE, piecemeal resection, and ablation of the residual BE segment after remission has been achieved.^{12,33} Univariate analysis of factors influencing recurrence in our study was limited by the small number of recurrent cancers (introducing the possibility of type 2 error), but does suggest (Table 4) that patients with residual dysplastic BE, patients with longer BE segments, and those with incident carcinomas (detected on HGD surveillance) might be more likely to recur. We did not see a difference in the rate of recurrence between those treated with EMR alone and those treated with EMR followed by PDT (Figure 1 and Table 3). As mentioned in the Results section, a proportion of patients had residual HGD after achieving remission. This cohort of patients was part of a control group followed

up with surveillance endoscopy (with biopsies and EMR if indicated) for another study. Circumferential BE EMR has been proposed as a method of resecting the entire BE segments in patients with neoplasia arising in BE to remove the entire at-risk epithelium. A recent study of 24 patients followed up for 28 months reported good results with only 1 patient showing recurrence.⁷ A drawback of this technique is the substantial rate of stricture formation after multiple consecutive EMRs (10%–20%) as well as the risk of bleeding and perforation.

In this article we have compared the results of endoscopic therapy for the treatment of mucosal carcinoma with those of patients treated surgically. Endoscopic therapy consisted of EMR and/or PDT. PDT was administered in 43% in the endoscopic therapy group. Although the use of PDT may decline with the advent of newer and better tolerated ablative modalities (such as radiofrequency ablation), this report supports an important principle: that the overall survival of patients with mucosal carcinoma treated endoscopically (using EMR with or without an additional ablation technique) can be comparable with those treated surgically. Even with the advent and widespread use of radiofrequency ablation, we believe EMR (which was used almost universally in the ENDO cohort of this study) will remain a cornerstone for the staging and therapy of most patients with early esophageal cancer. A few preliminary reports of the utility of radiofrequency ablation with EMR in the treatment of early esophageal carcinoma have appeared in the literature^{34,35}; however, results from larger cohorts using techniques such as PDT, which have been used in the treatment of esophageal neoplasia over the past decade, such as reported in this article, we believe, lay the foundation for the wider application of newer techniques such as radiofrequency ablation in the treatment of esophageal neoplasia in BE.

The results of this study could remain susceptible to biases because assignment to the ENDO and SURG groups was not randomized. Patients in the ENDO group were either poor surgical candidates, or did not wish to undergo surgery, and were referred by their local physicians or were self-referred for endoscopic therapy, as opposed to those who underwent esophagectomy who were referred primarily by local physicians. In addition to some of the differences between the cohorts as mentioned earlier (longer BE segment length, higher comorbidity scores, and a higher rate of metastatic lymphadenopathy in the SURG group than previously reported), it is possible that this cohort of patients was intrinsically different from the SURG cohort with biases that are unknown. To alleviate some of this, we used overall survival as an objective end point and used robust statistical techniques such as adjustment for comorbidities and propensity score (which accounts for the chance of being assigned to either treatment group). This primary outcome also was assessed in the same manner in both

Table 4. Results of Cox Proportional Univariate Analysis of Factors Predictive of Recurrent Carcinoma After Initial Remission in the ENDO Group

Variable	Hazard ratio (95% confidence interval)	P value
Age, y	1.0 (0.96–1.04)	.99
Male sex	1.10 (0.30–3.96)	.89
Length of BE segment	1.08 (0.97–1.21)	.15
Incident carcinoma	2.59 (0.87–7.74)	.09
Number of treatments needed to achieve remission	1.24 (0.58–2.7)	.58
Size of primary lesion	1.55 (0.46–5.2)	.48
PDT	1.34 (0.86–2.09)	.31
Presence of any residual BE after remission achieved	4.24 (0.96–18.80)	.06
Presence of residual dysplastic BE after remission achieved	3.7 (1.25–10.9)	.02

cohorts. Assessment of other outcomes, particularly in the SURG group, was retrospective with a possibility of underestimation. Although this was a large single-center US study, it is possible that the current sample size was inadequate to detect smaller differences in overall survival between the 2 groups.

In summary, endoscopic therapy with EMR and/or ablative therapy appears to be a reasonable alternative to esophagectomy in patients with mucosal esophageal adenocarcinoma. Overall survival appears to be comparable with low recurrence rates. Recurrent carcinoma is endoscopically treatable in most patients without influence on overall survival.

References

- Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142–146.
- Surveillance Epidemiology and End Results. <http://seer.cancer.gov>. Accessed April 2009.
- Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol* 2007;25:3719–3725.
- Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
- Chang AC, Ji H, Birkmeyer NJ, et al. Outcomes after transhiatal and transthoracic esophagectomy for cancer. *Ann Thorac Surg* 2008;85:424–429.
- Stein HJ, Feith M, Bruecher BL, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 2005;242:566–575.
- Larghi A, Lightdale CJ, Ross AS, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. *Endoscopy* 2007;39:1086–1091.
- Overholt BF, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. *Gastrointest Endosc* 2003;58:183–188.
- Pech O, May A, Gossner L, et al. Curative endoscopic therapy in patients with early esophageal squamous-cell carcinoma or high-grade intraepithelial neoplasia. *Endoscopy* 2007;39:30–35.
- Schembre DB, Huang JL, Lin OS, et al. Treatment of Barrett's esophagus with early neoplasia: a comparison of endoscopic therapy and esophagectomy. *Gastrointest Endosc* 2008;67:595–601.
- Pacifico RJ, Wang KK, Wongkeesong LM, et al. Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2003;1:252–257.
- Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 2008;57:1200–1206.
- Prasad GA, Buttar NS, Wongkeesong LM, et al. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. *Am J Gastroenterol* 2007;102:2380–2386.
- Peters FP, Kara MA, Curvers WL, et al. Multiband mucosectomy for endoscopic resection of Barrett's esophagus: feasibility study with matched historical controls. *Eur J Gastroenterol Hepatol* 2007;19:311–315.
- Prasad GA, Wang KK, Buttar NS, et al. Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2007;132:1226–1233.
- Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol* 2001;32:368–378.
- Montgomery E, Goldblum JR, Greenson JK, et al. Dysplasia as a predictive marker for invasive carcinoma in Barrett esophagus: a follow-up study based on 138 cases from a diagnostic variability study. *Hum Pathol* 2001;32:379–388.
- Lewis JT, Wang KK, Abraham SC. Muscularis mucosae duplication and the musculo-fibrous anomaly in endoscopic mucosal resections for Barrett esophagus: implications for staging of adenocarcinoma. *Am J Surg Pathol* 2008;32:566–571.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
- D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–2281.
- Das A, Singh V, Fleischer DE, et al. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. *Am J Gastroenterol* 2008;103:1340–1345.
- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241–2252.
- Chang LC, Oelschlager BK, Quiroga E, et al. Long-term outcome of esophagectomy for high-grade dysplasia or cancer found during surveillance for Barrett's esophagus. *J Gastrointest Surg* 2006;10:341–346.
- Bizekis C, Kent MS, Luketich JD, et al. Initial experience with minimally invasive Ivor Lewis esophagectomy. *Ann Thorac Surg* 2006;82:402–407.
- Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003;238:486–495.
- Luketich JD, Landreneau RJ. Minimally invasive resection and mechanical cervical esophago-gastric anastomotic techniques in the management of esophageal cancer. *J Gastrointest Surg* 2004;8:927–929.
- Luketich JD, Schauer PR, Christie NA, et al. Minimally invasive esophagectomy. *Ann Thorac Surg* 2000;70:906–912.
- Peyre CG, DeMeester SR, Rizzetto C, et al. Vagal-sparing esophagectomy: the ideal operation for intramucosal adenocarcinoma and Barrett with high-grade dysplasia. *Ann Surg* 2007;246:665–674.
- Pech O, Gossner L, May A, et al. Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest Endosc* 2005;62:24–30.
- Chang CC, Fang CL, Lou HY, et al. Metachronous esophageal cancer and colon cancer treated by endoscopic mucosal resection. *J Formos Med Assoc* 2007;106:S5–S9.
- May A, Gossner L, Pech O, et al. Intraepithelial high-grade neoplasia and early adenocarcinoma in short-segment Barrett's esophagus (SSBE): curative treatment using local endoscopic treatment techniques. *Endoscopy* 2002;34:604–610.
- Eil C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007;65:3–10.
- Esaki M, Matsumoto T, Hirakawa K, et al. Risk factors for local recurrence of superficial esophageal cancer after treatment by endoscopic mucosal resection. *Endoscopy* 2007;39:41–45.

34. Pouw RE, Gondrie JJ, Sondermeijer CM, et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. *J Gastrointest Surg* 2008;12:1627–1637.
35. Seewald S, Ang TL, Groth S, et al. Detection and endoscopic therapy of early esophageal adenocarcinoma. *Curr Opin Gastroenterol* 2008;24:521–529.

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Conflicts of interest

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