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Survival of Patients with Superficial Esophageal Adenocarcinoma Following Endoscopic Treatment vs Surgery

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Abstract

Background & Aims—Endoscopic therapy can improve long-term outcomes of patients with superficial esophageal adenocarcinoma (EAC), producing fewer complications than esophagectomy. However, there have been few population-based studies to compare long-term outcomes of patients that received these treatments. We used a large national cancer database to evaluate the outcomes of patients with superficial EAC who underwent endoscopic therapy or surgery.

Methods—We used the Surveillance Epidemiology and End Results database to identify 1618 patients with Tis or T1 N0M0 EAC, from 1998 through 2009. Patients were grouped based on whether they received endoscopic therapy (n=306) or surgery (n=1312). Multivariate logistic regression was performed to identify factors associated with endoscopic therapy. We collected survival data through the end of 2009; overall survival and esophageal cancer-specific survival were compared after controlling for relevant covariates.

Results—The use of endoscopy therapy increased progressively, from 3% in 1998 to 29% in 2009. Factors associated with use of endoscopic therapy included age greater than 65 y, diagnosis in 2006–2009 vs 1998–2001, and the absence of submucosal invasion. Overall survival after 5 y was higher in the surgery group than in the endoscopic therapy group (70% vs 58%, respectively). After adjusting for patient and tumor factors, patients treated by endoscopy had similar overall survival times (hazard ratio [HR]=1.21; 95% confidence interval [CI], 0.92–1.58) and esophageal cancer-specific survival times (HR=0.74; 95% CI, 0.49–1.11).

Conclusion—In a population-based analysis, the use of endoscopic therapy for superficial EAC tended to increase from 1998 through 2009. Long-term survival of patients with EAC did not appear to differ between those that received endoscopic therapy and those treated with surgery.

Keywords

endoscopic therapy; esophageal cancer; database analysis; retrospective study

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Background

Esophageal cancer is a highly fatal malignancy associated with a 5-year overall survival of approximately 19%. In the United States, it is estimated that approximately 17,460 new cases of esophageal cancer were diagnosed in 2012, accompanied by an estimated 15,070 cancer deaths[1]. Adenocarcinoma is the most common form of esophageal cancer in Western countries. The incidence of esophageal adenocarcinoma (EAC) continues to increase, with the annual increase of 1.5% between 1998 and 2008[2].

The rising of EAC along with the increased use of endoscopic surveillance in patients with Barrett's esophagus has contributed to an increased proportion of patients with early stage adenocarcinoma [3]. For early EAC, esophagectomy was once considered the mainstay of treatment, but it is associated with a mortality of 6–10% and with significant morbidity in 43–56%[4,5]. Over the past decade, endoscopic therapy (ET), such as endoscopic resection and ablative therapies, has become an effective treatment option for early stage EAC. However, it is unknown whether this treatment modality has been widely adopted in the general community.

Despite the lack of evidence from randomized trials, there are a few studies that suggest ET and surgery are equally effective in treating patients with high-grade dysplasia (HGD) and intramucosal carcinoma[6–8]. The overall 5-year survival rate exceeded 80% in patients treated endoscopically and appeared to be similar to those treated with surgery[6,7]. Although ET is associated with a higher rate of cancer recurrence (6–12% in ET group vs 0–2% in surgery group), most can be managed successfully using close follow-up and repeat endoscopic treatment [6–8]. The limitation of these studies is that they were conducted in highly specialized centers; thus, the results may not be generalizable to other community-based practice settings. Moreover, they included a relatively small sample size, which may be underpowered to determine small differences in long-term outcomes between the two groups. To date, the population-based data on long-term outcomes of patients with EAC following ET and surgery is limited.

In this study, we analyze the Surveillance Epidemiology and End Results (SEER) database to evaluate outcomes of esophageal cancer-specific survival and overall survival of patients with early EAC treated by ET or surgery. Our secondary aims were to evaluate the trends in the management of early EAC over the past decade and to determine the factors that may influence the use of ET in these patients.

Method

Study population and data source

We used the SEER 18 database to examine trends and long term outcomes in the endoscopic and surgical treatment of EAC from 1998 through 2009. SEER is a national database that comprises 28% of the United States population. [9] We extracted the relevant demographic data, cancer-specific information, type of treatment, and survival status during follow-up through December 31, 2009. We included: (1) cases of primary esophageal cancer (C15.0–C15.9) with a microscopically confirmed diagnosis, (2) adenocarcinoma histology based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), (3) stage 0 (TisN0M0) and stage 1 (T1N0M0) cancer, and (4) received treatment with either ET or surgical resection. We excluded patients with cancer diagnosed solely on autopsy or death certificate.

The depth of tumor invasion was defined as Tis (HGD), T1a (invades lamina propria or muscularis mucosae) and T1b (invades submucosa). SEER Surgery codes for primary cancer were based on the American College of Surgeons Commission on Cancer's Facility Oncology Registry Data System [10]. Tumor size was categorized into: smaller than 1.5 cm and larger than 1.5 cm. Anatomic location of tumor in the esophagus was based on ICD-O-3 and grouped into upper, middle, lower esophagus.

Statistical analysis

The study population was divided into two groups based on treatment: patients who were treated solely endoscopically and those who underwent surgical resection. In SEER, only the most invasive treatment performed as the first course of cancer-directed therapy was captured. Differences between the groups' categorical clinical characteristics were tested by using χ^2 tests. Independent *t* tests were conducted for continuous clinical variable differences between the groups. A logistic regression model was performed to study the factors associated with receiving ET. Survival time was calculated from the date of diagnosis to the date of death or the date of the last follow-up. Overall survival, esophageal cancer-specific survival, and other causes of death were determined from SEER cause of death data. We calculated Kaplan-Meier estimates for overall and esophageal cancer-specific survival, stratified by treatment and compared with the log-rank tests. We used Cox proportional hazards model to examine association between treatment options and survival, after controlling for potentially confoundings. For the main analysis, we compared the long-term outcomes of patients with Tis and T1 tumor between the two groups. We then performed an *a priori* defined subgroup analysis of patients with (1) Tis and T1a stage and (2) T1b stage.

Factors included in the multivariable analysis were age, race, gender, year of diagnosis, tumor stage, tumor location (lower esophagus vs other sites), treatment groups, radiation, and SEER region (Northeast, Midwest, South, and West, as defined by the U.S. Census Bureau). Because a significant number of patients did not have information on tumor grade and size, we included all relevant patient demographics and tumor variables except tumor grade and size in the multivariable analysis. However, analyses including these two variables in the Cox proportional hazards model did not change the overall conclusion on the association between the treatment modalities and overall survival or esophageal cancer specific survival (data not shown). Because a small proportion of patients were also given radiation therapy, we performed a sensitivity analysis to assess the robustness of our findings by repeating our analyses after excluding patients who received radiotherapy. Significance level for all tests was two-sided at 5%. All data were analyzed using SPSS Statistics software (version 16; IBM Corporation, USA) and JMP software (version 9.0; SAS Institute Inc., NC).

Results

During the period between January 1998 and December 2009, a total of 1,618 patients with early stage EAC, who fulfilled the inclusion and exclusion criteria, were identified from the SEER database. This included 1,312 (81%) treated surgically and 306 (19%) treated with ET. There was a progressive increase in the proportion of ET from 3% in 1998 to 29% in 2009; whereas, the proportion of surgical treatment steadily declined from 96% in 1998 to 71% in 2009 (Figure 1).

Patient characteristics in both groups are shown in Table 1. ET was used more frequently in older patients and tumors with no submucosal invasion. Surgery was used more likely in male patients, in tumors larger than 1.5 cm, and in moderately or poorly differentiated cancers. Most patients in ET group (85%) had endoscopic resection with or without other

techniques as complementary therapy. Details of treatment in both groups were shown in Supplement table S1. In ET group, 39 patients (12%) had T1b cancer and were significantly older than patients with T1b cancer in surgery group; mean age: 71 years (SD 11) versus 63 years (SD 9), $p < 0.001$. The proportion of patients diagnosed in each year period was similar to the whole cohort of ET group (12.8% in 1998–2001, 25.6% in 2002–2005 and 61.5% in 2006–2009).

In logistic regression analysis, the odds ratio (OR) for ET in patients with EAC diagnosed between 2006 and 2009 compared with those diagnosed in 1998 through 2001 was 2.79 (95%CI 1.78–4.37). Other significant predictors of receiving ET included older age (OR 3.74, 95%CI 2.74–5.10), female gender (OR 1.66, 95%CI 1.10–2.51), the absence of submucosal invasion (OR 4.21, 95%CI 2.85–6.21) and radiation therapy (OR: 0.56, 95%CI 0.34–0.92) (Table 2).

During a median follow-up time of 36 months (interquartile range: 14 – 66 months), 365 (27.8%) patients in the surgery group and 90 (29.4%) patients in the ET group died. Esophageal cancer was identified as the cause of death for 31 patients (10.2%) treated with ET and 209 patients (16%) treated with surgical resection. In unadjusted analyses, patients treated with surgery had better overall survival: 5-year overall survival rate of 70% in the surgery group versus 58% in the ET group ($p=0.003$); although, 5-year cancer-specific survival was similar between the two groups: 82% in the ET group versus 78% in the surgery group ($p=0.26$) (Table 3 and Supplement Figure s1).

We observed no difference in overall survival (Hazard ratio [HR] 1.21, 95%CI 0.92–1.58) and esophageal cancer-specific survival (HR 0.74, 95%CI 0.49–1.11) between treatment groups in a multivariate Cox proportional hazards model that was adjusted for age, gender, race, depth of tumor invasion, year of diagnosis, site of cancer, SEER sites, and radiation therapy. The significant variables associated with decreased overall survival were older age at diagnosis (HR 1.05, 95%CI 1.04 – 1.06) and radiation therapy (HR 2.17, 95%CI 1.70 – 2.77). Similarly, factors associated with decreased esophageal cancer-specific survival were older age at diagnosis (HR 1.04, 95%CI 1.03–1.05) and radiation therapy (HR 2.85, 95%CI 2.13–3.84). Submucosal invasion was significantly associated with poor outcomes. The HR of overall survival and cancer-specific survival associated with T1b tumor compared to Tis/T1a tumor was 1.37 (95% CI 1.12–1.69) and 1.65 (95% CI 1.28–2.16), respectively. In subgroup analyses stratified by tumor stage, overall survival and esophageal cancer-specific survival of patients with Tis/T1a and T1b tumor were not significantly different between the two groups (Table 4) (Supplement table s2).

Of 1,618 patients in both cohorts, 246 (15%) patients received radiation therapy. These patients, were more likely to have submucosal invasion (48% vs 37%, $p = 0.008$), poorly differentiated tumor (46% vs 31%, $p < 0.001$), larger tumor size (percent of tumor size > 1.5 cm : 46% vs 31%, $p < 0.001$), and were more likely to undergo esophagectomy (88% vs 80%, $p = 0.003$) compared to those did not receive radiation. In Cox proportional hazards model excluding patients who had exposure to radiation treatment, receiving ET compared with undergoing esophagectomy was still not an independent predictor of overall or esophageal cancer specific survival (data not shown).

Discussion

To date, the population-based data about the use and effectiveness of ET for early stage EAC is very limited. One report using the SEER database [11] compared the outcomes of 742 patients with early esophageal cancer diagnosed between 1998 through 2003 and found comparable esophageal cancer specific survival patients treated with endoscopic methods

and surgery. However, this study is limited by inhomogeneous histologic types; the study included patients with both squamous cell cancer and adenocarcinoma; overall survival was not reported; separate analysis for mucosal and submucosal tumors was not performed and this study used SEER data from an earlier time period which may not reflect more recent practice patterns in the treatment of early EAC.

In this study we used the population-based SEER database to identify a large cohort of patients with early stage EAC. We found an increase in trends of endoscopic therapy from 1998 to 2009, while surgical resection rates decreased during this study period. Patients treated endoscopically were at a presumably higher risk for surgery, as reflected in our study that older patients were more likely to have ET, which could partly explain lower unadjusted overall survival in ET group. Nonetheless, after adjusting for clinical factors, ET was associated with equivalent overall and esophageal cancer-specific survival. This finding was also true for the subgroups of tumor stage Tis/T1a and T1b after adjusted multivariable regression analyses.

Based on the available evidence, ET was incorporated into 2012 National Comprehensive Cancer Network guidelines for esophageal cancer. For a medically fit patient with localized disease, ET is the primary treatment for Tis tumors and is the preferred option for T1a cancer. Esophagectomy is the primary treatment for T1b tumor[12]. ET is recommended for medically unfit patients with Tis and superficial T1a or T1b cancer. Accordingly, our findings are in line with the reports from tertiary centers[6–8] and in agreement with national guidelines that recommend ET as the treatment option for patients with Tis and T1a EAC. In our study, 12% of patients in ET group had T1b cancer in which surgery should be the standard of care. The reason is unknown. Given that fact that these patients were significantly older than those who underwent surgery, it is possible that they were not a surgical candidate. Although long-term outcomes of patients with T1b cancer were not different between the two treatment modalities, the number of T1b cancer in ET group was small (n=39) and thus it should be interpreted with caution. Since the risk of lymph node metastases in patients with submucosal esophageal adenocarcinoma is high, up to 20% [13], ET was considered unsuitable in patients who were candidates for surgery.

Most patients in ET group received endoscopic resection. As radiofrequency ablation (RFA) has emerged in recent years as an effective treatment for HGD[14], it is obvious that the majority of ET in our study occurred prior to the RFA era. The long term outcomes of patients received ET may be different when this technology becomes widely used in general practice.

Interestingly, we found that a small proportion of patients with superficial EAC were treated with radiation. In multivariable analysis, radiation therapy was associated with poorer outcomes. This finding was similar to the previous SEER study by Das et al [11]. The reason for this finding is unclear, but our observation that patients with more unfavorable tumor characteristics were selected to radiation treatment might negatively bias the outcome of patients in this subgroup. Exclusion of patients who received radiation therapy did not change the overall conclusion of multivariable analysis.

The increased utilization of ET relative to surgery over the last decade reflects the increasing acceptance of ET as a viable alternative and availability with dissemination of ET techniques from select academic centers to the general community. As the recent national guidelines recommend ET as a primary treatment in certain patients with early stage EAC[12], we expect that the utilization of ET in the United States will continue to increase in the future. It has been shown that a number of patients with superficial esophageal cancer did not receive any treatment, including ET and radiation[15]. The reason is unknown, but

could be related to medical comorbidities contraindicated to esophagectomy[16]. For these patients, ET is a far more appealing option and should be considered for patients who are not candidates for surgery.

There are a number of limitations in our study. The SEER database does not collect several important prognostic factors, such as coexisting medical illnesses, provider information (hospital volume, experiences of endoscopists and surgeons), treatment-related complications, details on surgical procedure (open surgery or minimally invasive techniques), the use of chemotherapy and disease recurrence. Therefore, we were unable to adjust for these factors in our survival analysis. Since this is a non-randomized study, our results could be influenced by selection bias and confounders. Also, the baseline characteristics of the 2 groups were not similar. The patients who received ET were more likely to have a lower stage of disease and might appear to have equivalent oncologic outcomes to those underwent surgery. We attempted to minimize some of this bias by adjusting the hazard ratio for the effect of ET on survival and used both overall and cancer-specific survival as the main outcomes of interests.

Despite these limitations, we recognize a number of strengths of our study. Our data are derived from a population-based cohort. The results of our study may be more generalizable to the US population than data from tertiary cancer centers. We had a large sample size with a relatively long period of follow-up, which allowed us to conduct survival analysis and enough power to detect differences between the two groups. Although the SEER Program does not provide data on disease recurrence, it provides cause of death to calculate cancer specific survival, which is temporally correlated with cancer recurrence.

In summary, using a large population-based cancer dataset, we found that the overall and cancer-specific survival is equivalent in patients with early stage EAC treated endoscopically or surgically after adjusted for clinical factors. The results of our study are in agreement with the reports from tertiary centers and support the use of ET for these patients. Although the utilization of ET compared to surgery is increasing, the overall utilization rate is still low. As this emerging technique has become an accepted standard of care in cases who meet the clinical criteria, patients with early stage EAC should be provided information about its existence, effectiveness, risk of recurrence, and the need for post-treatment surveillance in order to make decision on their treatment modality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EAC	Esophageal Adenocarcinoma
ET	Endoscopic therapy
HGD	High-grade dysplasia
HR	Hazard ratios

SEER Surveillance Epidemiology and End Results
RFA radiofrequency ablation.

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Figure 1.
Trends in treatment of early stage esophageal cancer from 1998 to 2009

Table 1

Patient and tumor characteristics (n=1,618)

	Endoscopic treatment (n=306)	Surgery (n=1,312)	p value
Age, mean (SD)	70.5 ± 10	63 ± 9.6	< 0.001
Male	247 (80%)	1168 (89%)	< 0.001
Race: White	297 (98%)	1259 (96%)	0.1
Year of diagnosis			< 0.001
1998–2001	37 (12%)	279 (21%)	
2002–2005	86 (28%)	488 (37%)	
2006–2009	183 (60%)	545 (42%)	
Site of cancer			0.002
Upper esophagus	7 (2%)	26 (2%)	
Mid esophagus	37 (13%)	80 (6%)	
Lower esophagus	233 (76%)	1078 (82%)	
Overlapping sites	2 (0.7%)	27 (2%)	
Unspecified	27 (9%)	101 (8%)	
Stage			< 0.001
Tis	55 (18%)	110 (8.4%)	
T1a	174 (57%)	561 (43%)	
T1b	39 (12%)	523 (40%)	
T1, NOS	38 (12%)	118 (9%)	
Histological grade:			< 0.001
Well-differentiated	41 (13%)	160 (12%)	
Moderately-differentiated	69 (23%)	495 (38%)	
Poorly-differentiated	41 (13%)	313 (24%)	
Undifferentiated	1 (0.3%)	27 (2%)	
Unknown	154 (50%)	317 (24%)	
Region			0.045
West	165 (54%)	627 (48%)	
South	40 (13%)	258 (20%)	
Northeast	38 (12%)	149 (11%)	
Midwest	63 (20%)	278 (21%)	
Tumor size: > 1.5 cm	42 (41%)	461 (56%)	0.008
[available in 933 cases (58%)]			
Marital status : Married	207 (71%)	936 (73%)	0.55
Radiation therapy given	30 (10%)	216 (16%)	0.003
Median family income (in tens) 2000	5536 ± 1211	5516 ± 1302	0.07

NOS: Not otherwise specified; SD: standard deviation

Table 2

Factors predicting the use of endoscopic therapy in multivariable analysis

Variables	Odds ratio (95%CI)	p value
Age at diagnosis, y (< 65 vs ≥ 65 [*] vs)	3.74 (2.74–5.10)	<0.001
Gender (female vs male [*])	1.66 (1.10–2.51)	0.02
Marital status (married vs unmarried [*])	1.14 (0.81–1.60)	0.44
Race (white vs nonwhite [*])	2.72 (0.90–8.22)	0.08
SEER region (vs Midwest [*])		
Northeast	0.96 (0.55–1.68)	0.89
West	1.07 (0.74–1.56)	0.71
South	0.68 (0.41–1.13)	0.14
Depth of invasion (vs T1b [*])		
Tis and T1a	4.21 (2.85–6.21)	<0.001
T1, unspecified	5.32 (2.93–9.64)	<0.001
Year of diagnosis (vs 1998–2001 [*])		
2002–2005	1.42 (0.88–2.29)	0.15
2006–2009	2.79 (1.78–4.37)	<0.001
Lower esophagus (vs other sites [*])	0.66 (0.43–1.00)	0.05
Radiation given (vs not given [*])	0.56 (0.34–0.92)	0.02

* Reference category for logistic regression model.

CI, Confidence interval.

Table 3

Long-term outcomes of patients with early stage esophageal adenocarcinoma in the two groups.

	All patients	Endoscopic treatment	Surgery	p value
Estimated 5-year overall survival				
Tis and all T1 tumor	68%	58%	70%	0.003
Tis and T1a tumor	74%	60%	76%	0.002
T1b tumor	63%	66%	64%	0.26
Estimated 5-year esophageal cancer survival				
Tis and all T1 tumor	77%	81%	77%	0.26
Tis and T1a tumor	84%	83%	84%	0.64
T1b tumor	72%	89%	71%	0.31
Cause of death*				
Death from any cause	455	90 (29%)	365 (28%)	
Death from esophageal cancer	240	31 (10%)	209 (16%)	
Other causes				
Non-esophageal malignancy	42	6 (2%)	36 (3%)	
Cardiovascular disease	69	24 (8%)	45 (3%)	
Other non-malignant diseases	97	27 (9%)	70 (5%)	
Unknown	7	2 (0.6%)	5 (0.4%)	

* Endoscopic treatment group (n=306) and surgery group (n=1,312). Median follow-up time was 36 months (interquartile range: 14 – 66 months).

All p value represents the comparison endoscopic treatment vs surgery by log-rank test.

Table 4

Overall survival and esophageal cancer specific survival in multivariable analyses

	Overall survival		Esophageal cancer-specific survival	
	Hazard ratio (95%CI)	p value	Hazard ratio (95%CI)	p value
Endoscopic therapy vs surgery (reference)				
Tis and T1 stage [*]	1.21 (0.92–1.58)	0.16	0.74 (0.49–1.11)	0.14
Tis and T1a stage ^{**}	1.29 (0.93–1.81)	0.13	0.69 (0.40–1.19)	0.18
T1b stage ^{**}	0.97 (0.53–1.77)	0.93	0.46 (0.16–1.28)	0.14

CI, Confidence interval.

^{*} adjusted for age, gender, race, depth of tumor invasion, year of diagnosis, site of cancer, SEER sties and radiation therapy^{**} adjusted for age, gender, race, year of diagnosis, site of cancer, SEER sties and radiation therapy