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DISEASES OF THE ESOPHAGUS

Original article

Effect of local therapy for the treatment of superficial esophageal cancer in non-operative candidates

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SUMMARY. **Surgical resection is the current standard treatment for patients with early stage cancer of the esophagus. In a subset of these patients, comorbidities prohibit the operative risks of a potentially curative esophagectomy. Such patients may be candidates for local endoscopic treatment. We sought to look at a large cohort of patients with clinically localized esophagus cancer to determine whether high-risk patients survive significantly longer after endoscopic therapy than those who receive no local treatment. T0 or T1, N0 esophageal cancer (EC) patients who did not receive surgery or radiation were identified from the Surveillance, Epidemiology, and End Results cancer registry (1998–2003). The patients were assigned into two groups: local endoscopic therapy (excisional biopsy, photodynamic, local destruction, thermal laser, polypectomy, electrocautery, or cryoablation) versus no endoscopic therapy. Differences in survival were calculated using the Kaplan–Meier method, and a multivariate Cox regression analysis adjusting for potential confounders was used to analyze the effect of local therapy on survival. The study cohort included 166 T0 or T1, N0 EC patients. (75% male; 50% >70 years old). Tumors were adenocarcinoma (60%), squamous cell carcinoma (24%), and other (16%). The 4-year disease-specific survival rate was 84% for patients receiving local therapy compared with 64% for patients receiving no therapy ($P < 0.01$). On multivariate analysis, patients receiving local therapy had a significantly lower hazard of EC-related death ($P = 0.04$). There was no difference in survival curves for deaths secondary to causes other than EC. Local endoscopic therapy significantly prolonged survival in high-risk patients with clinical T0 or T1, N0 EC and is a reasonable alternative for those patients who are not candidates for potentially curative esophagectomy.**

KEY WORDS: **cancer, esophagus, local therapy, prognosis, SEER.**

INTRODUCTION

Esophageal cancer has the fastest increasing incidence of any solid tumor in the United States.[1–7] Although the overall survival rate may be slowly improving from the historical 15% at 5 years, outcome is generally poor, except for those patients who are identified and treated at an early clinical stage.[8–10] In the past 15 years, endoscopic mucosal resection has been offered not only to some otherwise healthy patients with high-grade dysplasia of the esophagus but also as treatment for early carcinoma. In short-term follow-up, endoscopic mucosal resection shows potential to cure patients with intramucosal squamous cell and adenocarcinoma,[11,12] and will likely be incorporated into the treatment algorithm for esophageal cancer.

Esophagectomy still remains the standard modality to cure otherwise fit patients with early stage esophageal cancer, and surgical mortality continues to improve in high-volume centers, with rates now ranging from 1% to 5%.[9,10,13] Nevertheless, for some patients, cardiopulmonary or hepatic morbidities still outweigh the oncologic benefit of an esophagectomy and, thus, they are not offered surgical resection.[14,15] These patients may be treated endoscopically with local excision, thermal or nonthermal laser, or cryoablation.[11,16–22]

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) cancer registry, a nationally representative, population-based cancer

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data source, to assess the relationship between local endoscopic therapy and survival of patients with early stage esophageal cancer. We hypothesized that local therapy for these patients would be associated with improved disease-specific survival.

MATERIALS AND METHODS

Data source and selection of study population

Cases were selected from the SEER registry, a national database that currently covers nearly 26% of the U.S. population and collects information on all incident cancer cases in selected areas of the United States.[23,24] From this database, all cases of primary esophageal tumors that were diagnosed between 1998 and 2003 were identified (tumor site codes 15.0–15.5, 15.8, and 15.9, and International Classification of Diseases–Oncology–second revision morphology codes 8000–8030, 8033, 8041, 8051, 8070–8075, 8120, 8123, 8140–8145, 8210, 8211, 8260, 8460, 8481, 8560, 8800–01, and 8980). From these patients, we then narrowed the focus to cases that were not diagnosed at autopsy or from death certificate data. We limited our analyses to clinical node-negative T0–T1 cancers based on the American Joint Committee on Cancer Tumor, Node, and Metastasis classification by referring to SEER information on the extent of tumor involvement for each case.[25] From this group, we identified all patients who did not receive either surgical resection or radiation treatment, so all remaining patients received either local tumor destruction (SEER surgical codes 10–27) or no intervention (SEER code 00). Therefore, comparisons are made between patients who received either 'local therapy' or 'no therapy.' The final study cohort comprised 166 patients with unresected clinical stage T0–T1, N0 esophageal cancer.

Information about age at diagnosis, sex, race, marital status, tumor histology, tumor location, and cancer therapy was obtained from SEER. Marital status was dichotomized into 'married' or 'not married', the latter category including patients classified as single, separated, divorced, or widowed. Histology subtypes were grouped into categories of adenocarcinoma, squamous cell carcinoma, and other histologic types. Tumors were classified into four groups according to their location: (i) upper esophagus (cervical and upper third of the esophagus tumors; SEER tumor site codes C15.0 and C15.3); (ii) middle esophagus (thoracic and middle third of the esophagus; SEER tumor site codes C15.1 and C15.4); (iii) lower esophagus (abdominal and lower third of the esophagus; SEER tumor site codes C15.2 and C15.5); and (iv) not reported (SEER tumor site codes C15.8 and C15.9). Cases were classified as having received local therapy if the SEER site-specific variable indicated that a procedure had been performed within 4 months of diagnosis.

Statistical analysis

We used the chi-square test to compare the distribution of sex, age category (<60, 60–70, and >70 years), marital status, T status, tumor location, and histology between patients in the 'local therapy' and 'no therapy' group.

The Kaplan–Meier method was used to estimate esophageal cancer-specific survival curves separately for the 'local therapy' and 'no therapy' groups.[26] Differences in survival between groups were examined using the log-rank test. Because the goal of the study was to evaluate the relationship between local therapy and esophageal cancer prognosis, we controlled for competing causes of death by using disease-specific mortality as the primary outcome of the survival analyses. Deaths attributed to causes other than esophageal cancer were censored at the date of death in order to estimate cancer-specific survival. The interval from the date of cancer diagnosis to the date of death provided by SEER was used to determine survival time. The National Center for Health Statistics and state death certificates are the source of cause of death data in SEER. Individuals surviving past December 31, 2003, were classified as censored as this was the latest date of follow-up in SEER.

Inequalities in esophageal cancer survival rates may be due in part to a higher prevalence of comorbid conditions among patients that preclude or significantly increase the risk from local procedures. As SEER does not provide information on the presence or severity of comorbidities among cancer patients, we constructed a survival curve considering only deaths from reasons other than esophageal cancer as an event (non-esophageal cancer survival).[27] This curve allows for comparing the burden of severe comorbid conditions among 'local therapy' and 'no therapy' groups and allows us to indirectly explore whether survival differences among groups may be related to imbalances in the prevalence of coexisting illnesses.

Cox regression models were used to evaluate the association between local therapy and esophageal cancer-specific survival after adjusting for potential confounders such as sex, age, marital status, race/ethnicity, tumor status, histology, and location. All analyses were performed using SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA) statistical package.

RESULTS

A total of 166 eligible patients with primary esophageal cancer who did not receive either surgical resection or radiation therapy were identified from the SEER registry. The median follow-up time for the entire cohort was 17 months (range 1–69

Table 1 Distribution of local procedures

Procedure	No. (%)
Excisional biopsy	19 (40)
Photodynamic	11 (23)
Local destruction (NOS)	6 (13)
Laser therapy	5 (11)
Polypectomy	3 (7)
Electrocautery	2 (4)
Cryoablation	1 (2)
	47 (100)

NOS, not otherwise specified.

months) and esophageal cancer mortality comprised 52% of all deaths. Patients with 'local therapy' and 'no therapy' represented 28% and 72% of the study cohort, respectively. Table 1 shows the distribution of local procedures of which local excision and photodynamic therapy were the most common therapies administered. The baseline patient characteristics are summarized in Table 2. Overall, there were no significant differences, but patients in the local therapy group were more likely to be married ($P = 0.06$).

Survival according to therapeutic group

As shown in Figure 1, esophageal cancer-specific survival was significantly higher for those treated with local therapy than for those with no therapy ($P < 0.01$). The 4-year disease-specific survival rate was 84% (95% confidence interval [CI]: 71–96%) for patients receiving local therapy compared with 64% (95% CI: 54–74%) for patients receiving no therapy. Additionally, the two groups had similar non-esophageal cancer survival ($P = 0.22$), suggesting that there were no differences in the burden of severe comorbidities (Fig. 2).

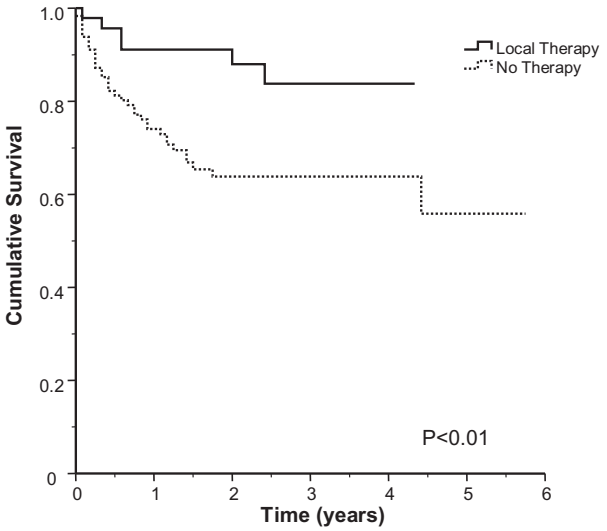

Fig. 1 Esophageal cancer specific survival according to therapy. Disease-specific survival was significantly better for those treated with local therapy ($P < 0.01$).

Table 2 Demographics and tumor characteristics for patients with T0–T1 N0 esophageal cancer

		Therapy		
Characteristic	All Patients ($n = 166$) No. (%)	None ($n = 119$) %	Local ($n = 47$) %	*P*-value
Sex				
Male	119 (72)	70	77	0.45
Female	47 (28)	30	23	
Age (years)				
<60	29 (18)	18	17	0.13
60–70	52 (31)	27	43	
>70	85 (51)	55	40	
Marital status				
Not married	65 (39)	44	28	0.06
Married	101 (61)	56	72	
Race/ethnicity				
White	129 (78)	74	87	0.33
Black	13 (8)	9	5	
Hispanic	12 (7)	9	4	
Other	12 (7)	8	4	
Histology				
Adenocarcinoma	100 (60)	56	72	0.14
Squamous cell carcinoma	40 (24)	27	17	
Other cell type	26 (16)	17	11	
Tumor status				
T0	77 (46)	48	43	0.53
T1	89 (54)	52	57	
Location				
Lower	97 (59)	56	64	0.82
Middle	38 (23)	24	21	
Upper	9 (5)	6	4	
Not reported	22 (13)	14	11	

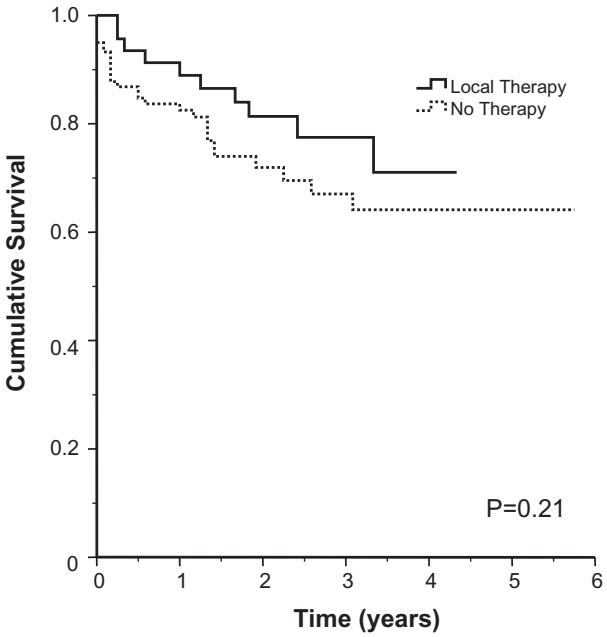

Fig. 2 Death from causes other than esophageal cancer according to therapy. Death from causes other than esophageal cancer was similar among therapeutic groups ($P = 0.21$).

Adjusted survival analysis

We performed Cox regression analysis to evaluate the association between therapy and survival after adjusting for baseline differences in age, sex, marital status, histology, tumor status, and tumor location. As shown in Table 3, this model showed that patients receiving local therapy had a significantly lower hazard of esophageal cancer-related deaths after controlling for these variables ($P = 0.04$). In addition, married patients had a decreased hazard of death ($P = 0.03$). Of interest, histologic subtype did not have a significant association with death, but increased tumor stage had a borderline ($P = 0.06$) increased hazard of death. Further subanalyses revealed that the 4-year disease-specific survival rate was 74% (95% CI: 62–86%) for T0 patients compared with 67% (95% CI: 57–77%) for T1 patients, rates that were not significantly different ($P = 0.10$) on univariate survival analysis.

DISCUSSION

Many reports have indicated that local therapies are a reasonable option for early stage esophageal cancer status in the high-risk patient group, although current guidelines have yet to establish their utility. Using nationally representative data from 166 cases of T0–T1 N0 esophageal carcinoma, we found that the use of any local therapy, as opposed to no therapy, is associated with a significant increase in disease-specific survival.

Table 3 Multivariate analysis of factors predicting survival among patients with T0–T1 node-negative esophageal cancer

Variable	Hazard ratio	95% Confidence interval	*P*-value
Local procedure			
No	Reference	–	
Yes	0.39	0.16–0.96	0.04
Sex			
Male	Reference	–	
Female	1.42	0.66–3.08	0.37
Age (years)			
<60	Reference	–	
60–70	0.59	0.20–1.71	0.33
>70	1.70	0.68–4.23	0.25
Marital status			
Not married	Reference	–	
Married	0.45	0.22–0.92	0.03
Race/ethnicity			
White	Reference	–	
Black	1.14	0.37–3.55	0.82
Hispanic	2.22	0.80–6.19	0.13
Other	0.24	0.03–2.09	0.20
Histology			
Adenocarcinoma	Reference	–	
Squamous cell carcinoma	1.12	0.46–2.73	0.80
Other cell type	0.60	0.19–1.84	0.37
Tumor status			
T0	Reference	–	
T1	1.92	0.96–3.84	0.06
Location			
Lower	Reference	–	
Middle	1.49	0.65–3.44	0.35
Upper	2.76	0.73–10.45	0.14
Not reported	1.36	0.48–3.83	0.57

Since the 1970s, a progressive shift in the predominant esophageal cancer cell type from squamous cell to adenocarcinoma has been observed in the United States and other industrialized countries.[2,7,28] As a consequence, adenocarcinoma currently represents >60% of all esophageal carcinomas in the United States.[2,29,30] In addition, with the subsequent increase in routine surveillance for esophageal cancer, there has been a shift in stage distribution, with a greater incidence of superficial esophageal cancers.[8,31] While esophagectomy remains the standard of care for early stage cancers, there remain a large number of patients for whom surgery is contraindicated because of comorbidities.[19,32,33] For these reasons, information regarding the potential benefits of local therapy is important for both patients and their clinicians.

The most likely explanation for the observed association between local therapy and improved survival is better regional control of the cancer and reduced rates of metastatic spread. The use of local therapies has become more popular in Japan and Europe in the past 20 years and has been shown in multiple single-institution series to have a beneficial effect for superficial esophageal cancer.[11,16,17,21,22] However, no randomized trials have been conducted to date, duration of follow-up beyond 3 years is limited, and these local therapies are not routinely used in the United States. Part of the difficulty in assessing the impact of local therapies is related to the fact that patients who receive local therapies tend to have a greater burden of comorbidities than an operative group, therefore making comparisons unreliable. Before comparing local therapies with the established operative standard of care, it is important as a first step to establish the utility of any local therapy in comparison with no therapy.

The observed lack of any treatment, including radiation, within this nationally representative cohort of esophageal cancer patients is concerning and may be due to multiple factors beyond a simple explanation of severe comorbid illness. The process leading to cancer diagnosis and staging includes several steps that involve the patient, the patient–provider interaction, and the medical system; similar factors may underlie decisions about esophageal cancer treatment. Patients' health beliefs, risk aversion, treatment preferences, and cultural factors, among others, have been shown to influence cancer prevention and health-seeking behaviors.[34–36]

While interpreting the results of our analysis, it is important to consider the strengths and limitations of SEER data. Although we used esophageal specific mortality as the end-point for our analyses, comorbid conditions could affect the outcomes. First, it is possible that some patients whose deaths were a direct consequence of a comorbid condition were misclassified as dying from esophageal cancer. Information about the cause of death in SEER is abstracted from death certificates. Although the death certificate is an important source of data on disease incidence, prevalence, and mortality, inaccuracies in the reported cause of death in this document have been previously observed.[37,38] However, as shown in Figure 2, the burden of severe comorbidities was similar between the 'local therapy' and 'no therapy' groups, thereby minimizing the effect of misclassification.

Additionally, the SEER database does not include detailed clinical information regarding endoscopist training and experience, patient comorbidities, explanations for therapeutic decisions, or specific lesion characteristics such as nodule visibility, dysplasia focality, or length of Barretts present. Similarly, there is no information in SEER regarding chemotherapy use. Although it is possible that some patients in the study may have received chemotherapy, this treatment does not provide local control and would not usually be offered to clinically node-negative, early stage patients. Excluding patients who received radiation therapy also increases the likelihood of excluding chemotherapy patients as radiation therapy and chemotherapy are frequently administered together.

Although we do not have a large enough sample to detect differences between outcomes of individual local therapies, the large sample size of SEER has enabled us to have sufficient power for detecting relatively moderate associations for the group as a whole and permitted the multivariate analyses. Additionally, the SEER registry contains population-based data, so the generalizability of our findings should be relatively good and less subject to the effect of local practice patterns or selection bias than those obtained from smaller single-institution studies conducted in tertiary care centers. The rigorous data extraction and coding procedures allow for the high level of ascertainment (>97% of all cancer cases) and guarantees the quality of cancer data in the SEER registry.[39,40]

In summary, our results indicate that local therapy can improve survival for patients with superficial esophageal cancer who are not candidates for esophagectomy, and these patients should not be designated untreatable simply because of their comorbidities. Potentially beneficial outcomes from results of endoscopic mucosal resection of early stage superficial esophageal cancer may further increase therapeutic options for high operative risk patients with esophageal cancer.

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