

ORIGINAL CONTRIBUTIONS

Esophagus

A Comparison of Endoscopic Treatment and Surgery in Early Esophageal Cancer: An Analysis of Surveillance Epidemiology and End Results Data

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- OBJECTIVES:** Endoscopic therapy for early esophageal cancer is gaining gradual acceptance in the United States. However, little information is available regarding long-term outcome of endoscopic therapy compared to surgical treatment of early esophageal cancer. We aimed to analyze outcomes in terms of cancer-free survival in patients with early esophageal cancer managed with either endoscopic therapy or surgical resection.
- METHODS:** The Surveillance Epidemiology and End Results database of the National Cancer Institute was searched to identify all patients who were diagnosed with stage 0 and stage 1 nonsquamous and squamous cell-type esophageal cancer between 1998 and 2003. Data on demographic features, tumor characteristics, types of treatment received (endoscopic vs surgical resection), and esophageal cancer-specific mortality were analyzed.
- RESULTS:** Data were available for analysis in 742 patients with early esophageal cancer. Only 99 (13.3%) of these underwent endoscopic treatment (group A). The remainder of the patients was managed by surgical resection (group B). In the Cox proportional hazards model, the relative hazard for esophageal cancer-specific mortality in group A was not different from that of group B (relative hazard [RH] 0.89, 95% confidence interval [CI] 0.51–1.56, $P = 0.68$). The significant predictors of survival were age at diagnosis (RH 1.06, 95% CI 1.03–1.08, $P < 0.001$) and absence of exposure to radiation therapy (RH 0.32, 95% CI 0.21–0.48, $P < 0.001$).
- CONCLUSIONS:** Patients with early esophageal cancer managed with endoscopic therapy have equivalent long-term survival compared to those treated with surgical resection. These are the first population-based data that support the effectiveness of endoscopic therapy for managing these patients.

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INTRODUCTION

The incidence of esophageal cancer continues to rise in the United States, and it has been estimated that 14,550 new cases of esophageal cancer were diagnosed in 2006, with 13,770 deaths related to esophageal cancer (1). Of all patients with esophageal cancers, up to one-fifth are diagnosed while the cancer is still localized to the mucosal epithelium (Tis), lamina propria (T1a) or submucosa (T1b), without lymph nodal invasion or distant disease (TisN0M0 [stage 0] or T1N0M0 [stage 1] by TNM staging) (2–4). Although surgical resection has been the standard therapy for early esophageal cancer (defined as Tis/T1N0M0 esophageal cancer), recently, endoscopic therapy with endoscopic resection and/or abla-

tion has gained gradual acceptance (5). Based on promising recent reports of endoscopic therapy for early esophageal cancer, endoscopic therapy for these patients is currently being performed in many centers across the country. However, little information is available regarding comparative efficacy of surgical or endoscopic treatment in terms of long-term cancer-free survival in patients with early esophageal cancer, and optimal management for these patients remains unknown.

In this study, we analyzed the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI) for comparing long-term survival of patients with early esophageal cancer based on types of treatment received.

MATERIALS AND METHODS

SEER Program

The SEER program of the NCI is an authoritative source of information on cancer incidence and survival in the United States (2). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the U.S. population. The SEER registries collect data on all cancer cases within their defined geographic region, primarily from medical records within hospitals, outpatient surgical centers, pathology centers, and free-standing radiology centers. The routine data collection includes detailed information on demographics, diagnosis, and tumor characteristics. The registries maintain active follow-up of all cases. Treatment information is also collected. It is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data.

Study Population

An initial search was performed on the SEER database for first primary esophageal cancer (excluding cardia) in adult patients. All esophageal cancers were identified using the International Classification of Diseases for Oncology (ICD-O)-9 site codes (6). Both nonsquamous cell carcinoma and squamous cell cancers were included in the search. Inclusion criteria included only those patients who were diagnosed with microscopically confirmed esophageal cancers, staged as stage 0 and stage 1 by the modified American Joint Committee on Cancer (AJCC) criterion between January 1, 1998, and December 31, 2003 (at the time of data collection, the SEER data was available up to this date). AJCC recommended TNM staging system as used by the SEER database. The TNM system is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M). A number is added to each letter to indicate the size or extent of the tumor and the extent of spread. For TNM staging of esophageal cancer, Tis represents carcinoma *in situ* and T1 represents tumor invading in to the lamina propria or submucosa. TisN0M0 esophageal cancer is designated as stage 0 and T1N0M0 esophageal cancer as stage 1 (3). Incomplete and missing data and data obtained from autopsy and death certificate were excluded from analysis. Before 1998, detailed data on exact type of operative procedure performed for cancer-directed treatment at the primary site were not systematically recorded. Effective with cases diagnosed from January 1, 1998, and after, there is a summary treatment variable for each patient that classifies cancer-directed treatment of the primary site with designated SEER codes, which enables extraction of information on endoscopic or surgical treatment. The SEER codes are similar to those based on the American College of Surgeons Commission on Cancer's Facility Oncology Registry Data System surgery codes, with supplementary annotations from the previous version of the SEER Program Code Manual (7).

Data Extraction and Statistical Analysis

The study variables were extracted from the SEER database utilizing SEER-Stat software and are summarized in Table 1. The SEER*Stat statistical software (National Cancer Institute, Bethesda, MD) has been developed by the Cancer Statistics Branch of the National Cancer Institute for analysis of cancer registry databases such as SEER (2). All associations were determined using the χ^2 tests of proportions. Significance was determined at the 2-tailed alpha level of less than 0.05. Besides descriptive analysis, multivariate analysis with the Cox proportional hazards model was used to study the independent association of type of treatment received with esophageal cancer-specific mortality, adjusting for potentially confounding factors, including age, race, gender, tumor histology, tumor stage and depth of tumor invasion, and SEER sites (categorized as Northeast, Midwest, South and West). The Cox regression model is a robust, semi-parametric method for modeling time-to-event data in the presence of censored cases to assess the effect of independent predictor variables (covariates) and is used for regression analysis of survival data (8). In the multivariate Cox proportional hazards model, the maximum partial likelihood method was used to estimate the relative hazard (RH) for each variable and the 95% confidence interval (CI) around the estimate. The RH ratio for indicator variables is interpreted as the ratio of the estimated hazard for those with a value of 1 to the estimated hazard for those with a value of 0 (controlling for all other covariates). In a *post hoc* analysis, the minimum sample size required in this Cox proportional hazards model to detect a statistically significant difference in the RH for esophageal cancer-specific mortality in the endoscopic treatment group compared to that in the surgical resection (control) group at a control-to-treatment patients ratio of 6.5, an alpha level of 0.05, and power of 0.8 was estimated to be 542 patients (9). The Kaplan–Meier method was used to determine median survival times and the log-rank test was performed to compare survival between the two groups. All statistical analysis was performed using SPSS software 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

In total, 742 cases of microscopically confirmed stage 0 (131, 17.7%) and stage 1 (611, 82.3%) early esophageal cancer diagnosed between 1998 and 2003 were identified. Overall, 621 (83.7%) were nonsquamous cell-type, with adenocarcinoma being the commonest histological subtype; other less common nonsquamous cell subtypes were signet ring cell carcinoma in 17 patients, papillary and mucinous adenocarcinoma in 7 patients each, and adenosquamous carcinoma in 3 patients. Ninety-nine (13.3%) of these underwent endoscopic therapy (group A), while 643 (86.7%) received surgical therapy (group B). In group A, the majority (65.7%) underwent an endoscopic resection alone; in 14.1% patients, endoscopic resection was combined with thermal ablation or photodynamic therapy (PDT). A subset of 16 patients (16.2%) received PDT

Table 1. Baseline Characteristics of Groups A (Endoscopic Treatment) and B (Surgery)

| Variable | Group A, N = 99 | Group A, Excluding Patients Patients Not Treated by Endoscopic Resection, N = 79 | Group B, N = 643 | P Value* |
|---|-----------------------|--|-----------------------|--------------|
| Mean (SE) age (yr) | 72 (1.1) | 72 (1.1) | 68 (0.6) | < 0.001 |
| Men | 70 (70.7%) | 55 (69.6%) | 538 (83.7%) | 0.002 |
| White race | 96 (97%) | 76 (96%) | 600 (93.3%) | 0.16 |
| Stage 0 | 37 (37%) | 32 (40.5%) | 94 (14.6%) | < 0.001 |
| Histology: nonsquamous | 78 (78.8%) | 62 (78.5%) | 543 (84.4%) | 0.16 |
| Histological grade: Well-differentiated | 8 (8.1%) | 8 (10.1%) | 71 (11%) | 0.37 |
| Tumor size >2 cm in size (information available in 432 [58.2%]) | 7/28 (25%) | 5/28 (17.8%) | 161/404 (40%) | 0.1 |
| Depth of invasion: submucosal | 13 (13.1%) | 10 (12.7%) | 287 (44.6%) | < 0.001 |
| Radiation therapy given | 17 (17.2%) | 17 (21.5%) | 112 (17.4%) | 0.95 |
| Median county-level household income (2000) | \$4,520 (IQR \$1,370) | \$4,511 (IQR \$1,401) | \$4,644 (IQR \$1,157) | 0.42 |
| Median % of <9th grade education | 6.0 (IQR 5) | 6.2 (IQR 5.5) | 6.7 (IQR 6) | 0.06 |
| Median % of families below poverty | 7.1 (IQR 4.9) | 7.1 (IQR 6) | 7.7 (IQR 7.5) | 0.25 |
| SEER site | | | | |
| NE | 22 (22%) | 21 (26.6%) | 101 (16%) | |
| MW | 16 (16%) | 12 (15.2%) | 96 (15%) | |
| S | 12 (12%) | 9 (11.4%) | 84 (13%) | |
| W | 49 (49%) | 37 (46.8%) | 361 (56%) | |
| Mean follow-up in months within the SEER system (SE) [†] | 23.9 (1.8) | 23.7 (1.8) | 25.3 (0.7) | 0.44 |
| Median esophageal cancer-free survival (months)—the Kaplan–Meier estimate [†] | 56 (50–61) | 55 (50–61) | 59 (57–67) | 0.41(LRtest) |

SE, standard error; IQR, inter-quartile range; LR, log rank.

*Compared between group A (all patients) and group B.

[†]Only esophageal cancer-specific cause of death considered.

or thermal ablation only without endoscopic resection, and in another 4 patients, the type of ablative therapy was not specified. The analysis has been presented with and without these 20 patients who were not treated with endoscopic resection. Demographic and cancer-related variables in these patients are compared in Table 1.

The details of the endoscopic therapy performed in group A are shown in Table 2. In the surgical group, more than half (53.4%) of the patients underwent total esophagectomy and partial gastrectomy. (Table 3). The patients in the surgical group were younger and were more likely to be men and had stage 1 disease. Submucosal depth of tumor invasion was seen in 287(44.6%) patients in the surgical group and only in 13 (13.1%) patients in the endoscopic group ($P < 0.001$).

Median cancer-free survival in group A was not significantly different from that in the surgically treated group B (56 and 59 months, respectively, $P = 0.41$) (Fig. 1). In the Cox proportional hazards model, the RH for esophageal cancer-specific mortality in the endoscopic treatment group was not different from that in the surgical resection group (RH 0.89, 95% CI 0.51–1.56, $P = 0.68$). The significant variables asso-

ciated with mortality were higher age at diagnosis (RH 1.06, 95% CI 1.03–1.08, $P < 0.001$) and absence of exposure to radiation therapy (RH 0.32, 95% CI 0.21–0.48, $P < 0.001$) but not tumor stage, with the RH of mortality associated with stage 0 tumor compared to stage 1 tumor being 0.77 (95% CI, 0.43–1.37, $P = 0.37$). Exclusion of the 20 patients in group A who were not treated by endoscopic resection did not change the overall conclusion of the Cox proportional hazards model.

Table 2. Details of Endoscopic Therapy

| Types of Endoscopic Therapy | Number (%) |
|--------------------------------------|------------|
| EMR alone | 65 (65.7) |
| EMR + PDT | 10 (10.1) |
| EMR + thermal ablation (APC + Laser) | 4 (4.0) |
| PDT alone | 11 (11.1) |
| Thermal ablation alone | 5 (5.1) |
| Ablative therapy* | 4 (4.0) |

APC, argon plasma coagulation.

*NOS = not otherwise specified.

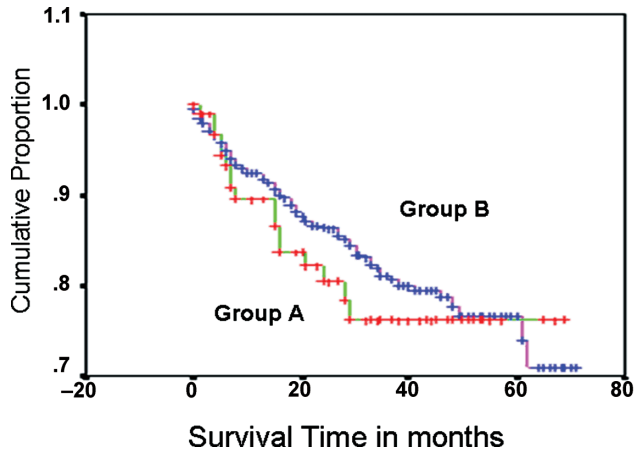


Figure 1. Cancer-free survival by the Kaplan–Meier's estimate in the endoscopic treatment group (group A) versus surgically treated group (group B). There were no difference in survival between the two groups ($P = 0.41$, log-rank test).

DISCUSSION

Early esophageal cancer, particularly esophageal adenocarcinoma, is being detected in the United States with an increasing frequency, which may be at least partially attributed to growing acceptance of endoscopic screening and surveillance for Barrett's esophagus, and also, rapid improvements in endoscopic high-resolution imaging technology. Traditionally, early esophageal cancer has been treated by surgical resection, which, even in the hands of expert surgeons, has significant mortality and postoperative morbidity (10). Also the risk of lymph node metastasis in early esophageal cancer, particularly in the setting of Barrett's adenocarcinoma, is lower than the surgical mortality rate (11). This has led to an increasing interest in endoscopic therapy of early esophageal cancer, which is rapidly becoming an alternative option in some of these patients (5, 12–15). Of all endoscopic therapy, PDT and endoscopic resections are the best-studied nonsurgical approaches. In a recent study, PDT with 5-aminolevulinic acid resulted in long-term remission in 80% of the patients with early mucosal cancer (16). With endoscopic resections, newer reports describe long-term remission rate of more than 90% in patients with early esophageal cancer, although it is recognized that high recurrence rates mandate close endoscopic surveillance and frequent retreatment in these patients (17). Combined modality treatment with EMR and PDT also has been recently shown to be a viable and less morbid alternative to standard esophagectomy in patients presenting

with early Barrett's esophageal adenocarcinoma (18). Similarly, in a recent retrospective study, overall mortality and long-term survival in patients with Barrett's esophagus complicated by high-grade dysplasia was shown to be similar in patients treated with PDT and endoscopic mucosal resection (EMR) or esophagectomy (19).

In the present study, we identified a large number of patients with early esophageal cancer from the SEER database and compared the long-term outcomes in two groups of patients who were treated with either endoscopic therapy or surgical resection. We found no significant difference in the median cancer-free survival in these two groups of patients. Although a number of recent studies have reported excellent outcome with endoscopic therapy for curative treatment of early esophageal cancers (12, 13, 16, 18, 20–22), the role of endoscopic therapy for early esophageal cancer is still a matter of controversy, particularly in the United States, where esophageal resection is currently recommended even for high-grade dysplasia complicating Barrett's esophagus (23). One of the important causes of reluctance in incorporating endoscopic resection in the management of early esophageal cancer has been the relative paucity of long-term follow-up data with this modality of treatment. In our study, the median esophageal cancer-free survival in the group treated with endoscopic therapy was 56 months. Our findings are supported by the recent data reported by Ell *et al.* in which over a mean follow-up period of 36.7 months, excellent outcome was achieved in a cohort of 100 patients with early esophageal adenocarcinoma who were treated by curative endoscopic resection (13). Another criticism of all reports of endoscopic resection of early esophageal cancer is that they are almost always experiences reported from one institution with special interest in endoscopic treatment of early gastrointestinal cancers (15). To a large extent, our study counters this criticism and reports cumulative experiences from multiple institutions across the country.

Chemoradiotherapy has been tried as a nonoperative curative treatment for esophageal, particularly squamous cell-type cancers, but has not gained acceptance for management of early esophageal cancer because of high rates of local recurrence, systemic toxicity and treatment failures, and also, need for prolonged therapy (24). For example, in a case series from Japan of 13 patients with T1 squamous cell cancer who were treated with 50 Gy external beam radiotherapy plus concurrent cisplatin and 5-fluorouracil, grade 3 hematologic toxicity developed in 69% of the patients, and there was one case of grade 3 esophagitis; two patients recurred, and the 3-yr survival rate was 75% (25). In our study, we found that patients with early esophageal cancer are often treated with radiotherapy, and in the multivariate analysis, exposure to radiation therapy was indeed detrimental to the overall survival. We could not study the issue of chemotherapeutic treatment in these patients, given that the SEER database does not routinely collect detailed information regarding chemotherapy.

Table 3. Details of Surgical Therapy

| Types of Surgical Treatment | Number (%) |
|---|------------|
| Partial esophagectomy alone | 118 (18.4) |
| Total esophagectomy | 50 (7.8) |
| Total esophagectomy + partial gastrectomy | 337 (52.4) |
| Esophagectomy + gastrectomy* | 138 (21.5) |

*NOS = not otherwise specified.

There are several limitations of this study. The SEER database reports only consider the most invasive therapy. Therefore, it may be possible that many patients in the surgical resection group may have had an initial attempt endoscopic resection prior to surgery, often done as a staging intervention. However, that is unlikely to alter the findings of our study. Information on comorbidities is not collected in the SEER database, and it is conceivable that patients with higher comorbidity were selected for endoscopic therapy, and thus, our findings of comparable survival in both groups may be biased against endoscopic therapy. It also should be noted that the baseline characteristics of the two groups were not exactly similar, and younger male patients with advanced disease in terms of submucosal invasion may have been selected for surgical intervention. Also, under endoscopic therapy, multiple different and often complementary modalities such as endoscopic mucosal resection, PDT, and thermal ablation were grouped together and this study does not allow evaluation of the efficacy of specific endoscopic therapy. As we considered only the first primary esophageal cancer in this analysis and our primary outcome was esophageal cancer-free survival, so lack of information on incomplete resection and local recurrence should not bias our overall conclusion. It is known that SEER data reflect community practice (26), and given that esophageal resections are frequently done in community hospitals often with a higher mortality rate (27), our study may not be representative of the best surgical practice and the lowest surgical mortality. Also, being a newer intervention, during the study period, endoscopic therapy of early esophageal cancer may have been limited to high-volume centers only. Thus, in absence of provider- and hospital-level data from the SEER database, in our comparison, there may be some heterogeneity and consequent bias against surgical therapy in that we may have compared outcomes from best endoscopic practices to those from surgical practices prevalent in the community.

On the other hand, the SEER database has several recognized advantages, such as population-based case identification with case-finding procedures (including detailed review of medical and pathology records), rigorous data collection procedures, and quality control standards, which ensure a very high accuracy of available data and a patient follow-up rate of greater than 95%. Indeed, the SEER program is considered the standard for quality among cancer registries around the world. In the SEER program, even registered patients who move to a geographic location that is not included in a SEER registry are followed up actively for their mortality status through multiple sources (28, 29). Thus, it can be reasonably assumed that the data on pathology and tumor staging, treatment administered, and follow-up used in the current analysis are fairly accurate, and even with limited data, our conclusions are justified.

In summary, this is the first study that analyzed a large population-based cancer registry and showed equivalent long-term outcome in terms of cancer-free survival in patients undergoing endoscopic therapy or surgical resection for man-

agement of early esophageal cancer. The finding of this study is in agreement with the reported experience from other countries and strongly supports consideration of endoscopic therapy for management of patients with early esophageal cancer. Obviously, management decisions for treatment of early esophageal cancer should be individualized. While younger, otherwise healthy patients with submucosal invasion may benefit from surgery, older patients with limited disease and multiple comorbidities may be more appropriate candidates for endoscopic therapy.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Early esophageal cancer is traditionally treated with surgical resection.
- Significant mortality is associated with surgical resection.
- Endoscopic therapy is gradually gaining acceptance for management of early esophageal cancers.
- Current data on optimal management of early esophageal cancer are scarce.

What Is New Here

- Utilizing the largest population-based cancer registry, we found that there is no significant difference in the median cancer-free survival in patients treated with surgical resection or endoscopic therapy.
- Also, exposure to radiation therapy is detrimental to the overall survival and should not be administered to patients with early esophageal cancer.

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CONFLICT OF INTEREST

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Specific author contributions: Ananya Das: conception and design, acquisition of data, analysis and interpretation of data, and drafting the article and revising it critically for important intellectual content. All other authors contributed in planning, conducting, and drafting the manuscript. All authors approved the final draft submitted.

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