Prognostic Value of Tumor Length for Cause-Specific Death in Resectable Esophageal Cancer

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Background. The current esophageal cancer American Joint Committee on Cancer TNM staging system may not capture the full prognostic implications of the primary tumor. A study is needed to explore the prognostic value of tumor size on esophageal cancer-specific death.

Methods. Patients who underwent surgical resection for non-metastatic esophageal cancer were selected from the Surveillance, Epidemiology and End Results Program database (United States, 1988 to 2014). With the use of statistics methods, maximally selected rank and two hazard models (Cox model and Fine-Gray model), the optimum cutoff point for tumor length in each T classification was estimated and the prognostic value of tumor size on esophageal cancer-specific death was analyzed.

Results. A total of 4,447 patients were identified. The median tumor size was significantly correlated with T classification, with the correlation coefficient of 0.43 ($p < 0.001$). Patients in the T1 to T3 classifications who had larger tumor size showed a larger probability of cancer-specific death. The multivariate Cox model showed that tumor size was significantly associated with an increase in cancer-specific death in T1 (2.15, 95% confidence interval [CI]: 1.72 to 2.69) and T2 (1.31, 95% CI: 1.06 to 1.62) but was marginally significantly associated in T3 (1.12, 95% CI: 1.00 to 1.27) and insignificantly associated in T4 classification ($p > 0.1$). Similar results were found by using the multivariate Fine-Gray model.

Conclusions. We have found that combining T classification with tumor size can increase the precision in identifying the high-risk groups in T1 to T2 classifications. On the basis of esophageal cancer-specific death our study explores the prognostic cutoff point of tumor size by T classification.

(Ann Thorac Surg 2018;■:■–■)
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Esophageal cancer is an aggressive malignancy and a leading cause of cancer-related death worldwide. In Western society, esophageal adenocarcinoma (EAC) has become the dominant histologic type. Despite declines in incidence for the most common cancers, the annual incidence of EAC has increased considerably in the United States. The incidence of EAC will continue to rise over the coming decades [1, 2]. The most recent data from the Surveillance Epidemiology and End Results (SEER) registries in the United States showed that the overall annual incidence of EAC increased ninefold between 1973 and 2011 and 10-fold among white men [3]. Conversely, the incidence of esophageal squamous cell carcinoma (ESCC) declined linearly [2]. Despite all efforts to improve the surveillance, diagnostic procedures, and therapy, the overall survival rates have improved only slightly.

The strongest clinical prognostic factor in patients with esophageal cancer is cancer stage. The most widely used staging system is the American Joint Committee on Cancer (AJCC) system, in which stages of patients depend on the primary tumor (T), regional lymph nodes (N) and distant metastasis (M). The current AJCC-TNM staging system comprises tumor histopathologic type, histologic grade, and tumor location, in addition to T, N, and M classifications. All these factors are tumor-inherent attributes and are used to stage patients' cancer status.

T classification represents invasion depth of tumor, which is not exactly the tumor size. Tumor size, the maximum length of the tumor, may be a supplement to T classification, if it can better reflect the tumor staging for different treatment plans. Improvements on tumor

The Supplemental Figure can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2018.05.018] on http://www.annalsthoracicsurgery.org.

staging will increase the accuracy in selection of patients for curatively intended therapy. Our previous study showed that tumor size was an important prognostic factor for patients undergoing surgical resection of ESCC [4]. However, it was a study with a relatively small sample and therefore had limited precision. The objective of the present study is to explore the effect of tumor size on survival of patients with esophageal cancer resection in different T classifications.

Patients and Methods

Our study was based on the US data from the SEER program database (http://seer.cancer.gov/seerstat/). The SEER program currently collects and publishes information on cancer incidence and survival data from 18 population-based cancer registries covering approximately 28% of the US population. The ASCII text version of 1973 to 2014 data released in November 2016 was downloaded for this study. The SEER data are de-identified and publicly available. Therefore, the study was exempted from institutional review board review.

We identified all cases of first primary esophageal cancer (International Classification of Diseases for Oncology tumor site codes 150 to 155, 158 to 159). Patients diagnosed with EAC (SEER codes 8140 to 8389) or ESCC (SEER codes 8050 to 8089) between 1988 and 2014 were included. Only patients who were definitively treated with esophagectomy and survived more than 3 months after operation were included in the cohort. Other inclusions required microscopic diagnostic confirmation, malignant tumor behavior, age older than 18 years, and active follow-up. Tumor size was measured as the maximum length of the tumor. We excluded those patients whose tumor size was not defined or for whom the value recorded was greater than 25 cm, or tumors with distant metastasis.

Demographic, diagnostic, and survival information were extracted, including sex, age at diagnosis, race, year of diagnosis, primary site, grade, histology, tumor size, and T and N classifications. Pathologic classifying of patients was characterized according to the seventh AJCC-TNM staging system, with the exception of T classification. With respect to T classification, the sixth AJCC-TNM staging system was adopted for lack of

Table 1. Characteristics of Esophageal Cancer Patients Undergoing Resection by T Classification, 1988–2014

Characteristic	T1	T2	T3	T4	Total
All patients	1,219 (27.4)	783 (17.6)	2,127 (47.8)	318 (7.2)	4,447 (100)
Age, years					
<65	660 (54.1)	435 (55.6)	1,230 (57.8)	187 (58.8)	2,512 (56.5)
≥65	559 (45.9)	348 (44.4)	897 (42.2)	131 (41.2)	1,935 (43.5)
Sex					
Male	1,022 (83.8)	631 (80.6)	1,771 (83.3)	259 (81.4)	3,683 (82.8)
Female	197 (16.2)	152 (19.4)	356 (16.7)	59 (18.6)	764 (17.2)
Race					
White	1,102 (90.4)	688 (87.9)	1,900 (89.3)	278 (87.4)	3,968 (89.2)
Others	117 (9.6)	95 (12.1)	227 (10.7)	40 (12.6)	479 (10.8)
Tumor size, mm					
Median (range)	20 (1–135)	35 (1–140)	40 (1–170)	50 (5–150)	37 (1–170)
N stage					
0	996 (81.7)	503 (64.2)	1,027 (48.3)	118 (37.1)	2,644 (59.5)
1–3	223 (18.3)	280 (35.8)	1,100 (51.7)	200 (62.9)	1,803 (40.5)
Grade					
Well differentiated/moderately differentiated	757 (62.1)	443 (56.6)	1,017 (47.8)	142 (44.7)	2,359 (53)
Poorly differentiated/undifferentiated	462 (37.9)	340 (43.4)	1,110 (52.2)	176 (55.3)	2,088 (47)
Histology					
Esophageal adenocarcinoma	977 (80.1)	546 (69.7)	1,560 (73.3)	218 (68.6)	3,301 (74.2)
Esophageal squamous cell carcinoma	242 (19.9)	237 (30.3)	567 (26.7)	100 (31.4)	1,146 (25.8)
Location					
Cervical/upper one-third/middle one-third/thoracic	241 (19.8)	183 (23.4)	394 (18.5)	71 (22.3)	889 (20)
Abdominal/lower one-third	978 (80.2)	600 (76.6)	1,733 (81.5)	247 (77.7)	3,558 (80)
Year of diagnosis					
1988–2006	622 (51.0)	416 (53.1)	995 (46.8)	231 (72.6)	2,264 (50.9)
2007–2014	597 (49.0)	367 (46.9)	1,132 (53.2)	87 (27.4)	2,183 (49.1)

Values are n (%) unless otherwise specified.