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A novel multivariate scoring system for determining the prognosis of lymph node-negative esophageal squamous cell carcinoma following surgical therapy: An observational study

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Abstract

Background: Identifying patients with esophageal squamous cell carcinoma (ESCC) with negative prognostic factors, which have an extremely low survival rate, has been problematic.

Methods: We retrospectively collected clinical data for 648 patients with lymph node-negative ESCC who were treated at the Sun Yat-Sen University Cancer Center from 1990 to 2005. Survival difference was compared using Kaplan–Meier analysis and multivariate Cox regression analysis.

Results: We identified advancing age, smoking history, alcohol consumption history, decreased forced expiratory volume in 1 s (FEV1), surgical procedure, tumor location, number of resected lymph nodes, poor tumor differentiation, and surgical stage as independent prognostic risk factors. Furthermore, based on the results of multivariate analysis, we constructed a novel scoring system that included the factors of age, smoking history, alcohol consumption history, number of resected lymph nodes, tumor differentiation, and surgical stage. Risk score (RS) was computed with the scoring system, and patients were divided into Class A (RS: 0–5) and Class B (RS: 6–10). $P < 0.001$ indicated statistical significance. A significant difference ($p < 0.001$) demonstrated that Class B was strongly related to a low survival rate and poor prognosis.

Conclusion: We developed a new simple flexible scoring system of high prognostic significance, which has the potential to guide postoperative therapeutic strategies and follow-up frequency and to provide better prognostic information for patients and their families.

Keywords: Esophageal cancer; Scoring system; Prognosis; Esophageal surgery

Introduction

Esophageal cancer is the 6th most common cause of cancer-related mortality worldwide.[1,2] Almost half the total reported cases have occurred in China, which also has the highest mortality rate.[3–5] Surgical resection remains the mainstay of treatment for patients with localized esophageal cancer.[6,7] However, 5-year survival remains unsatisfactorily low. Studies have shown that the 5-year survival rate following resection rarely exceeds 30%,[8] and it is <10% in patients with locally advanced disease (stages IIB and III).[9,10] Despite a recent increase in the 5-year survival rate to approximately 40% because of advances in early diagnosis and improved surgical techniques,[11,12] the survival rate after esophagectomy continues to be unsatisfactory.

Identifying such patients before surgery is problematic because such a high-risk population may also receive

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chemotherapy and chemoradiotherapy. Several factors have been investigated to help refine prognosis, and some have been found to be effective, such as positive lymph node metastasis,[13] histopathological results,[14] smoking history,[15,16] and alcohol consumption history.[17] However, these previous studies were limited to single factors; therefore, these findings have been considered inconclusive.

In this study, we constructed a novel multivariate scoring system, which included age, smoking history, alcohol consumption history, and surgical stage as components, to determine the prognosis of lymph node-negative esophageal squamous cell carcinoma (ESCC) following surgical therapy. We aimed to determine whether this scoring system can independently and significantly predict survival in patients with lymph node-negative ESCC and assist in prospective prognostic evaluation.

Patients

With ethics committee approval, we conducted a large-scale retrospective study of the esophageal cancer database of the Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China. We included 648 patients who underwent esophagectomy between 1990 and 2005 for lymph node-negative ESCC. Patients who received neoadjuvant radiotherapy or chemotherapy were excluded, whereas those who received postoperative radiotherapy and/or chemotherapy were included. Patients received postoperative treatment according to the NCCN guidelines for esophageal carcinoma. Postoperative mortality cases were excluded.

All clinicopathological data and post-operative survival information were systematically extracted by trained physicians using a standardized abstraction form. Medical records were reviewed carefully, including the hospital registry and the records of return visits that each postoperative patient was required to attend regularly at the outpatient department every 3 months in the first 2 years after surgery, every 6 months in the 3rd year, and once a year in the following years. Patients discontinuing the return visits were contacted by the research coordinator through telephone; for those who could not be contacted by phone we asked for help from the village committee and the local police office. The end date was acquired through the patient's contact person in the medical records.

Patients with a smoking history were designated as smokers, and the smoking index was defined as the product of the number of cigarettes, pipe tobacco, or cigars consumed per day and the number of smoking years. According to this definition of smoking index, a patient with a smoking index of >500 was considered as a heavy smoker, while a patient with a smoking index of <500 was considered a light smoker. Drinkers were patients who consumed >100 g/day of alcohol for >1 year; those who did not satisfy this criterion were designated as nondrinkers. Patients who indicated but failed to quantify alcohol consumption were excluded from analyses.

Histological tumor differentiation was judged postoperatively by a pathologist. Tumors were staged after surgery by size, lymph node metastasis, and distant metastasis (TNM) according to the 6th edition of the American Joint Committee on Cancer (AJCC) TNM classification.[18]

Methods

Statistical analyses were performed using SPSS Statistics version 16.0 (IBM SPSS, Inc., Chicago, IL, USA). Descriptive statistics (e.g., frequency, mean, and standard deviation) were obtained for demographic, epidemiological, and clinical characteristics. Receiver operating characteristic curves were constructed to select cutoff values for continuous variables, including age, smoking index, and perioperative blood loss, and variables with the best sensitivity and specificity values were selected. Kaplan–Meier analyses were used to calculate 3- and 5-year survival rates and to compare the survival difference. Survival curves were generated and the logrank test was used to determine the statistical significance of differences between survival curves. Two-sided p-values of <0.05 were considered statistically significant. Cox proportional hazards regression models were used to derive hazard ratios (HRs) and 95% confidence intervals (CIs), with adjustment for known or suspected prognostic factors and exclusion of confounding factors that may affect survival. Cases were censored at death or the follow-up end point.

Results

We identified 648 eligible patients [459 (70.8%) males; median age, 57 years]. The distribution of selected demographic characteristics, surgical conditions, and clinical pathologies is presented in Table 1. Of the 648 eligible patients, 227 (35.0%) were categorized as heavy smokers, and 127(19.6%) had an alcohol assumption history. Further, 534 (82.4%) patients could not attain a normal FEV1 (3.18 L for men and 2.35 L for women[19]; median, 2.24 L), partly because of age and smoking history.

With regard to surgical therapy and tumor biological characteristics, 459 (70.8%) tumors were located in the middle thorax. In 322 (49.7%) patients, the muscular layer had been infiltrated, whereas in 208 (32%), the adventitial layer had been infiltrated. In 350 (54.0%) patients, fewer than 8 lymph nodes were resected. All patients had early stage disease [stage IA in 51 (7.9%) patients, IB in 310 (47.8%) patients, and IIA in 287 (44.3%) patients]. Traditional left thoracotomy was performed during surgery in 501 (77.3%) patients; 129 (19.9%) underwent the McKeown approach and 18 (2.8%) underwent the Ivor Lewis approach. All patients had negative lower esophagectomy margins, whereas 2 (0.3%) patients had positive upper margins. Vascular invasion occurred in 2 (0.3%) patients. 18 patients received