European Journal of Surgical Oncology xxx (2018) 1–6

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Predicting prognosis in resected esophageal squamous cell carcinoma using a clinical nomogram and recursive partitioning analysis

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ARTICLE INFO

Article history:
Accepted 8 April 2018
Available online xxx

Keywords:
Esophageal squamous cell carcinoma
Prognosis
Nomogram
Recursive partitioning analysis

ABSTRACT

Background: Development demand of precise medicine in resectable esophageal squamous cell carcinoma (ESCC) require to recognize patients at high risk treated by surgery alone. Thus, our aim was to construct a clinical nomogram and recursive partitioning analysis (RPA) to predict long-term survival in ESCC treated by surgery alone.

Methods: Based on the patients with ESCC who treated by three-incisional esophagectomy and two-field lymphadenectomy alone, we identified and integrated significant prognostic factors for survival to build a nomogram. The nomogram was calibrated for overall survival (OS) and the predictive accuracy and discriminative ability was measured by concordance index (c-index) and Akaike information criterion (AIC). Based on the nomogram, the RPA was performed for risk stratification.

Results: A total of 747 patients were included for analysis. Five independent prognostic factors were identified and entered into the nomogram. The calibration curves for probability of 1-, 3-, and 5-year OS showed optimal agreement between nomogram prediction and actual observation. The AIC value of the nomogram was lower than that of the 7th edition staging system, whereas the c-index of the nomogram was higher than that of the 7th edition staging system. The risk groups stratified by RPA allowed significant distinction between survival curves within respective TNM categories.

Conclusion: The RPA based on a clinical nomogram appears to be suitable for risk stratification in OS for resected ESCC. This practical system may help clinicians in decision making and design of clinical studies.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide [1]. In the past decades, although great improvement has been achieved in multimodality treatment such as targeted therapy, adjuvant treatment, as well as preoperative treatment in various solid tumor, there has been little progress and no clear consensus in esophageal squamous cell carcinoma (ESCC) [2–10].

Recently, clinical nomograms have developed with intuitive graphs to quantify risk by incorporating important factors for oncologic prognosis. Several authors have reported that nomograms are more accurate in prediction of prognosis than the traditional staging systems in various human cancer [11–14]. We believe that, building such models in patients with ESCC treated by surgery alone would help to identify the cohort with high risk, which would further promote precise multimodality treatment. Therefore, the purpose of this investigation is to report a risk stratification system based on a clinical nomogram risk calculator for the prediction of long-term survival in resected ESCC without pre-/postoperative multimodality treatment.

Methods

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center. Patients diagnosed with ESCC who underwent three-incisional esophagectomy and two-field lymphadenectomy at the thoracic surgery department of

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https://doi.org/10.1016/j.ejso.2018.04.011
0748-7983/

Sun Yat-sen University Cancer Center from January 2000 to December 2012 were screened for study recruitment. Inclusion criteria included: (1) received three-incisional esophagectomy and two-field lymphadenectomy; (2) pathologic T status of T1, T2, T3, or T4a; (3) without visceral metastasis; (4) microscopically complete resection (R0). Patients received neoadjuvant or adjuvant anti-cancer therapy were excluded.

Surgical procedure applied in this study included three-incisional esophagectomy and two-field lymphadenectomy. The details of these common surgical procedures were described in prior studies [15]. Pathologic staging was reassessed based on the 7th AJCC staging system [16]. The median time from the date of surgery to the last censoring was 48.5 months.

Statistical analysis to define risk factors was performed using the SPSS 22.0 software package (SPSS, inc., Chicago, IL). Overall survival (OS) was defined from the date of surgery to the date of death or final follow-up. Censored cases were defined as patients who were lost during the follow-up or still alive in the end. The survival rate was calculated using the Kaplan-Meier method, and the differences between curves were assessed by the log-rank test. Univariate Cox regressions were constructed to identify prognostic factors. Predictors assessed in this investigation included: age, gender, body mass index (BMI), pathologic T status, pathologic N status, cell differentiation, tumor location, amount of resected nodes. Factors with $P < 0.1$ in univariate survival analysis would be introduced into multivariate analysis. Multivariate analysis was performed by the Cox proportional hazard model using the forward procedure based on likelihood ratio for variable selection.

A nomogram was formulated on the basis of the results of the multivariable analysis and an internal validation was performed by bootstrap with 1000 resamples. Performance of each prognostic system was described by The Akaike information criterion (AIC) and concordance index (c-index) [17,18]. A smaller AIC value indicated a more goodness-of-fit while larger c-index value indicated more accurate predictions. A recursive partitioning analysis (RPA) method was adopt to establish a new risk grouping method based on the nomogram predicted scores. Nomogram and RPA were performed by rms package and rpart package in R 3.3.2 (http://www.r-project.org) [11,19]. Statistical significance was reached when $P < 0.05$, all hypotheses were two-sided. Details of nomogram and RPA analysis is presented as an appendix.

Results

Patient characteristics and prognostic analysis

A total of 747 patients were enrolled in this study. Patients' characteristics were described in Table 1. The median age of diagnosis was 59 years (ranging from 34 to 79 years). The median amount of resected nodes was 25 (ranging from 3 to 105). Based on the 7th staging system, the 5-year OS rate for stage IA, IB, IIA, IIB, IIIA, IIIB, and IIIC was 87.6%, 82.4%, 69.7%, 63.1%, 46.6%, 23.3%, and 20.0%, respectively ($P < 0.001$ by log-rank test).

To determine factors independently prognostic of patient survival, we analyzed OS using a Cox proportional hazards model. As shown in Table 2, all parameters found to be potentially significant in univariate analysis were included in a multivariate analysis. We found that gender ($P = 0.009$), age ($P = 0.020$), amount of resected nodes ($P < 0.001$), pT status ($P < 0.001$), and pN status ($P < 0.001$) were independent prognostic factors.

Clinical nomogram for OS

A nomogram that incorporated aforementioned significant prognostic factors was established (Fig. 1A). The nomogram illustrated pT status, amount of resected nodes, and pN status as sharing the largest contribution to prognosis. Age and gender showed a moderate impact on the survival. Each subtype within these variable was assign a score on the point scale (Supplementary Table 1). By adding up the score we could obtain the nomogram score of each patient (median, 171.4, range, 72.3–262.4). The calibration plots presented an excellent agreement between the nomogram prediction and actual observation for 1-, 3-, and 5-year OS (Fig. 1B).

Table 1
Patients' characteristics.

Characteristics	Case No. (%)
Gender	
Male	556 (74.4)
Female	191 (25.6)
Age (year)	59.5 ± 8.8
Body mass index (kg/m^2)	22.0 ± 3.1
Amount of resected nodes	27.5 ± 15.6
Tumor Location	
Upper	106 (14.2)
Middle	432 (57.8)
Lower	209 (28.0)
pT status	
T1	78 (10.4)
T2	160 (21.4)
T3	482 (64.5)
T4a	27 (3.6)
pN status	
N0	401 (53.7)
N1	220 (29.5)
N2	103 (13.8)
N3	23 (3.1)
Cell differentiation	
Well	164 (22.0)
Moderate	410 (54.9)
Poor	173 (23.2)
7th staging system	
IA	8 (1.1)
IB	81 (10.8)
IIA	132 (17.7)
IIB	216 (28.9)
IIIA	192 (25.7)
IIIB	80 (10.7)
IIIC	38 (5.1)

The performance of the nomogram and 7th system were then quantified based on the likelihood ratio chi-square, AIC, and c-index. As shown in Table 3, the AIC value for the nomogram system was smaller than the 7th edition (3616.565 *vs.* 3663.243), indicating that the nomogram version yields a better prognostic stratification; the c-index value was larger for the nomogram version (0.708; 95%CI, 0.680–0.737) than for the 7th version (0.672; 95%CI, 0.640–0.703), indicating that it is more informative regarding patient outcome ($P = 0.006$).

Risk stratification based on nomogram score

These results proved the predictive efficacy in long-term survival of our established nomogram system. Thus, we perform RPA for the dichotomous OS according to the nomogram score, partitioned the patient population into four risk strata defined as follows: low risk (nomogram score, <120) (n = 61, 8.2%), relative low risk (nomogram score, ≥120&<171) (n = 307, 41.1%), relative high risk (nomogram score, ≥171&<210) (n = 269, 36.0%), and high risk (nomogram score, ≥210) (n = 110, 14.7%) (Fig. 2A). The risk stratification system presented fairly well operating characteristics for prediction of long-term survival (Supplementary Table 2); in the entire cohort, 5-year OS of patients with low risk, relative low risk,

Please cite this article in press as: Zheng Y, et al., Predicting prognosis in resected esophageal squamous cell carcinoma using a clinical nomogram and recursive partitioning analysis, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2018.04.011