Translational Oncology
www.transonc.com

Volume 11 Number 5 October 2018 pp. 1097–1103 1097

Development and Validation of a Nomogram for Predicting Overall Survival in Pancreatic NeuroendocrineTumors[1,2]

Dong-liu Miao[*,3], Wei Song[*,3], Jun Qian[†], Zhi-gang Zhu[*], Qiong Wu[*], Chang-guang Lv[*] and Lei Chen[*]

[*]Department of Intervention and Vascular Surgery, Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou Cancer Medical Center, Suzhou, Jiangsu, 215001, China; [†]Department of Oncology, Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou Cancer Medical Center, Suzhou, Jiangsu, 215001, China

Abstract

BACKGROUND: The objective of current study was to develop and validate a nomogram to predict overall survival in pancreatic neuroendocrine tumors (PNETs). *METHODS:* The Surveillance, Epidemiology, and End Results (SEER) database was queried for patients with PNETs between 2004 and 2015. Patients were randomly separated into the training set and the validation set. Cox regression model was used in training set to obtain independent prognostic factors to develop a nomogram for predicting overall survival (OS). The discrimination and calibration plots were used to evaluate the predictive accuracy of the nomogram. *RESULTS:* A total of 3142 patients with PNETs were collected from the SEER database. Sex, age, marital status, primary site, TNM stage, tumor grade, and therapy were associated with OS in the multivariate models. A nomogram was constructed based on these variables. The nomogram for predicting OS displayed better discrimination power than the Tumor-Node-Metastasis (TNM) stage systems 7th edition in the training set and validation set. The calibration curve indicated that the nomogram was able to accurately predict 3- and 5-year OS. *CONCLUSIONS:* The nomogram which could predict 3- and 5-year OS were established in this study. Our nomogram showed a good performance, suggesting that it could be served as an effective tool for prognostic evaluation of patients with PNETs.

Translational Oncology (2018) 11, 1097–1103

Introduction

Pancreatic neuroendocrine neoplasms (PNETs) comprises a heterogeneous collective of malignant tumors arising from the islets of Langerhans and accounting for approximately 1% to 3% of all pancreatic neoplasms [1,2]. Although PNETs is a relatively rare malignancy, its incidence and mortality have been increasing over the last decades, due to the improved medical technology of detection. The annual incidence of all PNETs in the United States is 8/1000,000 [3]. They are broadly categorized as functioning and non-functioning PNETs. The majority (60%) of PNETs are non-functional and are more aggressive compared with the functional PNETs. Although they are generally considered to be indolent, PNETs are highly heterogenous neoplasms and some subgroups can be highly malignant [4,5]. As the majority of PNETs do not secrete hormones that cause clinical symptoms, patients are predominantly diagnosed with disseminated disease for whom curation is not possible [1,6]. Due to this heterogeneous nature of PNETs, identifying reliable prognostic features have been a challenge.

Address all correspondence to: Lei Chen, Department of Intervention and Vascular Surgery, Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou Cancer Medical Center, No.16, Baita West Road, Suzhou, Jiansu, 215001, China. E-mail: chenleidennis@163.com

[1] Conflicts of Interest: The authors declare no conflicts of interest.
[2] Sources of Funding: The present study was funded by the Special projects for diagnosis and treatment of clinical special diseases in Suzhou (no. LCZX201713).
[3] Authors contributed equally to this work.
Received 28 May 2018; Revised 28 June 2018; Accepted 28 June 2018

1936-5233
https://doi.org/10.1016/j.tranon.2018.06.012

Currently, the American Joint Commission on Cancer (AJCC) TNM stage systems 8th edition [7], which is widely used for prognostic evaluation of PNETs, only takes tumor size and histological metastasis into account. However, many other important variables such as age, gender, race, tumor size, tumor site, and tumor differentiation can also influence the survival of individual patients. In addition, the TNM 8th edition is still deficiently formulated for the prognostic prediction. In this sense, the traditional TNM staging system still needs further validation and improvement. Therefore, there is an urgent need to develop a staging system which is technically feasible and clinically easy-accessible to stratify the prognosis of patients with PNETs.

Nomogram, as a simple statistical predictive tool, has been widely used in clinical practice to predict prognosis [8–10]. Construction of a nomogram not only considers the prognostic weight of each factor when calculating the probability of an outcome, but also combines multiple independent factors to draw the best conclusion. Compared to the AJCC TNM staging system, nomograms can more accurately estimate survival for individual patients by integrating important prognostic variables [11,12]. However, to our knowledge, a nomogram for patients with PNETs on the basis of population-based data has not been reported. Therefore, the current study sought to develop and validate a nomogram for predicting OS based on population-based data from the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods

Patients

The SEER program of the US National Cancer Institute provides data on cancer incidence and survival in the United States and covers approximately 30% of the US population across several geographic regions [13]. For this research, data about patients with a diagnosis of PNETs were extracted from the SEER Program (2004–2015), using the SEER*Stat software version 8.3.5. The study cohort consisted of patients with the following International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology codes: 8150, 8151, 8152, 8153, 8155, 8156, 8157, 8240, 8241, 8242, 8243, 8246 and 8249; and the ICD-O-3 site codes: C25.0-C25.9. Patients were excluded if the number of months survived was unknown, if they had more than 1 primary cancer and the PNETs was not the first, or if they had incomplete clinicopathological information (TNM stage and therapy). In addition, patients registered at the time of autopsy or death certificate only were excluded. To establish and validate the nomogram, all patients were randomly allocated to a training set and a validation set. Institutional review board approval was not required in the current study because SEER research data is publicly available and we received permission from SEER to access the research data (accession number: 10165-Nov 2017).

Variables

Demographic and clinical variables were extracted from the SEER database, including age, sex, race, marital status, primary site, tumor size, functional status, histological differentiation, T, N, and M stage, TNM stage, follow-up information and cause of death. Age and tumor size as continuous variables, were transformed into categorical variable on the basis of recognized cutoff values. The primary endpoint was OS. OS was defined as the time from diagnosis of PNETs to death or last follow-up, with no restriction on the cause of death.

Statistical Analyses

Construction of the Nomogram. Categorical data were shown as frequencies and proportions and compared with chi-square test and Fisher's exact test. Survival curves were generated using the Kaplan–Meier method and the log-rank test was used to compare the difference between the groups. Univariate and multivariate Cox regression analyses were performed to identify independent prognostic variables for predicting OS. A nomogram was formulated based on the results of the multivariate analyses.

Validation of the Nomogram. The nomogram was validated by measuring discrimination and calibration curves both internally (training set) and externally (validation set). Discrimination between observed and predicted outcome was assessed using the concordance Index (C-index) [14]. A higher C-index indicates a better ability to separate patients with different survival outcomes. Comparison between the nomogram and the AJCC TNM staging system 7th edition was performed with the rcorrp.cens package in Hmisc in R and were evaluated by the C-index. The calibration curves were used to compare the predicted probability with the cohort observed in the study. All statistical analyses were conducted using SPSS software (SPSS Inc., Chicago, USA, version 23) and the R software version 3.13 (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). A P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 3142 eligible patients with PNETs diagnosed between 2004 and 2015 were included in the study. Of those, 1555 patients were in the training set and 1587 were in the validation set. In the whole study set, the median age was 60 years (11–94 years). Among the eligible patients, 1721(54.8) were male and 1421 (45.2) were female. The majority of patients in both sets were married (62.2%) and white (76.6%). The most common tumor site was the pancreatic tail (34.3%), followed by pancreatic head (30.6%) and other sites. As to tumor size, ≥ 4 cm (36.1%) was the most common, followed by 2–4 cm (33.1%) and < 2 cm (29.3%). Well differentiation (53.7%) was most common tumor grade. In both sets, most patients received surgery, and had T1 stage (36.4%).

The median follow-up time was 20 months (range: 0–71 months) in both sets. By the end of follow up, 307 (19.7%) patients in the training set had died, including 268 (17.2%) who died from PNETs and 590 (2.5%) who died from other causes. The demographic features and clinicopathological characteristics are summarized in Table 1.

Nomogram Construction

Data on the patients' sex, age, race, marital status, primary site, tumor size, functional status, TNM stage, tumor grade, and therapy were collected in the training set. In the univariate analysis, sex, age, marital status, primary site, tumor size, functional status, tumor grade, TNM stage, and therapy were significantly associated with OS, while race was not significantly related to OS ($P > .05$) (Table 2).