EBioMedicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

A New Metastatic Lymph Node Classification-based Survival Predicting Model in Patients With Small Bowel Adenocarcinoma: A Derivation and Validation Study

Shan Wu [1], Jin-Nan Chen [1], Qing-Wei Zhang [1], Chao-Tao Tang [1], Xin-Tian Zhang, Ming-Yu Tang, Xiao-Bo Li *, Zhi-Zheng Ge *

Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, Shanghai, China

ARTICLE INFO

Article history:
Received 11 March 2018
Received in revised form 23 April 2018
Accepted 17 May 2018
Available online xxxx

Keywords:
Small bowel carcinoma
Metastatic lymph node
Survival predicting model
TNM staging

ABSTRACT

Background: Current methods of lymph node (LN) staging are controversial in predicting the survival of SBA. We aimed to develop an alternative LN-classification-based nomogram to individualize SBA prognosis.
Methods: Based on the data from the Surveillance, Epidemiology, and End Results (SEER) database of patients diagnosed with SBA between 2004 and 2014, we identified the cut-off points for the number of LNs examined and the number found to be metastatic using the K-adaptive partitioning (KAPS) algorithm. Using metastatic LNs, a nomogram predicting the survival of SBA was derived, internally and externally validated, and measured by calibration curve, C-index, and decision curve analysis (DCA), and compared to the 8th TNM stage.
Results: A total of 1516 patients were included. The cut-off of 17 was the optimal examined LN number. For metastatic LN numbers, the cut-off points were 0, 2, and 8. The C-index for the nomogram was higher than the 8th TNM staging (internal: 0.734; 95% CI, 0.693 to 0.775 vs. 0.677; 95% CI, 0.652 to 0.702, $P < 0.001$; external: 0.715; 95% CI, 0.674 to 0.756 vs. 0.648; 95% CI, 0.602 to 0.693, $P < 0.001$). Also, the nomogram showed good calibration in internal and external validation and larger net benefit than TNM staging.
Conclusion: We modified current N staging into a 4-level staging system based on the number of metastatic LNs: N0, no LN metastasis; N1, 1–2 metastatic LNs; N2, 3–8 metastatic LNs, and N3, >8 metastatic LNs and set the least examined LN number to 17. A nomogram based on this staging showed great clinical usability than TNM staging for predicting the survival of SBA patients.

1. Introduction

Small bowel tumors are one of the major causes of obscure gastrointestinal bleeding [9]. Small bowel adenocarcinomas (SBA) are the third most common histology of small bowel tumors [23]. Advancements in enteroscopy, capsule endoscopy, and cross-sectional imaging techniques [22] have allowed patients to be diagnosed earlier and more accurately. Although SBA is rare in the gastrointestinal tract, it has a poorer stage-stratified, cancer-specific survival than colon cancer [11,19,26]. The current American Joint Committee on Cancer TNM staging system (TNM staging) of SBAs and the number of examined lymph nodes (LNs) remain controversial in predicting survival [18,20]. Meanwhile, other independent factors, such as age, grade, and tumor size, could also affect the survival significantly [3].

The effect as assessed by the number of LNs was not found to have a linear relationship to survival, and the cut-off points were essential. Traditional statistical methods can only divide cases into groups using artificial cut-off points to evaluate the difference in survival. The K-adaptive partitioning (KAPS) algorithm [8] is a useful tool for obtaining heterogeneous subgroups by survival and finding the best cut-off points by evaluating potential multi-splits.

For this reasons, we aimed to determine the optimal number of examined LNs and alternative staging of metastatic LN number through

Abbreviation: SBA, Small bowel adenocarcinoma; LN, lymph nodes; SEER, Surveillance, Epidemiology and End Results; KAPS, K-adaptive partitioning; DCA, decision curve analysis; CSS, cause-specific survival; HR, hazard ratio; C-index, concordance index; tdROC, time-dependent receiver operating characteristic; KM-weight, censoring weighting estimators; OS, overall survival; AUC, Area under curve; AJCC, American Joint Committee on Cancer.

* Corresponding authors.
E-mail addresses: lxb_1969@163.com, (X.-B. Li), zhizhengge@aliyun.com (Z.-Z. Ge).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.ebiom.2018.05.022

the population-based Surveillance, Epidemiology, and End Results (SEER) database by the KAPS algorithm. We here developed and validated a nomogram based on this LN staging for predicting survival for SBA patients.

2. Methods

2.1. Study Design and Data Collection

This study was based on data from the SEER 18 database which includes incidence and survival data from multiple population-based cancer registries [13]. We initially analyzed 6440 patients over 18 years old who were diagnosed SBA between 2004 and 2014. To explore the pathogenesis and influencing factors for survival of SBA, we excluded patients with distant metastatic tumors and those who survived <3 months. Since we used the pathology of lymph node as the gold standard, we excluded patients who had not undergone surgery or for whom no detailed pathology was available, and those with unknown lymph node examination or an unknown number of metastatic lymph nodes. For further comparison of the feasibility of nomogram with the 8th TNM staging (Amin) [1], we excluded patients with unknown grade of tumor, with unknown T stage, with unknown N stage, and with unknown M stage. We also excluded patients without known prognostic characteristics, including race, tumor size and location. We then collected the clinicopathologic variables from the SEER 18 database, including age, gender, race, and location of tumor, TNM staging (8th TNM staging, shown in Appendix 1), grade of tumor, histologic grade, number of lymph nodes examined, number of positive lymph nodes, tumor size, and months survived.

2.2. Outcomes

The main outcome was to evaluate the effect of lymph nodes in SBA patients, including the optimal number of lymph nodes examined and alternative staging of metastatic lymph nodes with cause-specific survival (CSS) because SBA was the main endpoint. We further constructed a survival prediction model based on this metastatic lymph nodes staging for SBA patients and validated it by comparing it to TNM staging.

2.3. Statistical Analysis

Lymph nodes were evaluated in all of the participants. To establish the optimal number of examined lymph nodes, we use the modified KAPS algorithm described by Eo et al. [8] to categorize all cases into two groups to find the optimal set of cut-off points. We also used this algorithm to evaluate multi-group split points of metastatic lymph nodes and selected the optimal number of subgroups. Survival was compared between the subgroups using Kaplan-Meier survival curves and Cox regression analysis. A univariate and multivariate Cox regression model was used to calculate the hazard ratio (HR) and the adjusted HR of the alternative examined lymph nodes and metastatic lymph nodes for survival of SBA after adjusting for age, T stage, M stage, grade, histology, and tumor size.

We used the univariate and multivariate logistic regression model to calculate odds ratios (OR) of factors influencing further LN harvesting. In construction of the survival predicting model, we divided participants into two groups. The internal cohort included patients diagnosed with SBA between 2004 and 2010, while the external validation cohort consisted of participants diagnosed between 2011 and 2014. The model was selected and constructed using the internal cohort by

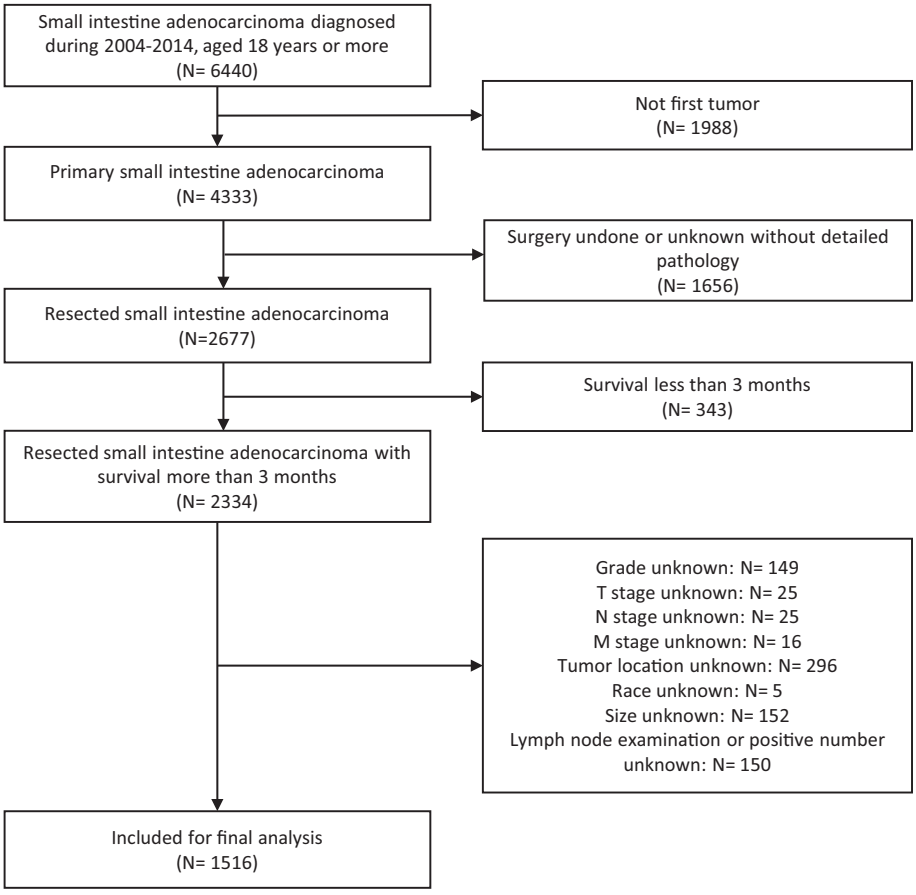

Fig. 1. Flowchart of patient selection for this study.

Please cite this article as: Wu S, et al, A New Metastatic Lymph Node Classification-based Survival Predicting Model in Patients With Small Bowel Adenocarcinoma: A Derivation..., EBioMedicine (2017), https://doi.org/10.1016/j.ebiom.2018.05.022