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Research Paper

Prognostic nomograms for predicting overall and cancer-specific survival of high-grade osteosarcoma patients

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ABSTRACT

Aim: The present study aimed to develop nomograms estimating survival for patients with high-grade osteosarcoma.

Methods: 1990 patients with high-grade osteosarcoma between 1994 and 2013 were retrospectively retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. Data from 12 cancer registries ($n = 1460$) were used to conduct multivariate Cox analysis to identify independent prognostic factors. Nomograms which estimate 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) were constructed. The nomograms were internally validated for calibration and were also externally validated with an independent patient cohort from 1 cancer registry ($n = 530$).

Results: Age, primary site, tumor size, use of surgery, and extent of disease were found to be independently associated with OS and CSS ($p < 0.05$). The nomograms estimating 3- and 5-year OS and CSS were developed based on these prognostic factors. The concordance indices were high in internal validation (0.726 for OS and 0.731 for CSS) and external validation (0.716 for OS and 0.724 for CSS). Internal and external calibration plots demonstrated a good agreement between nomogram prediction and actual observation.

Conclusions: We constructed nomograms that accurately predict OS and CSS of high-grade osteosarcoma patients. The nomograms can be used for counseling patients and establishing risk stratification.

1. Introduction

Among all primary malignant bone tumors, osteosarcoma accounts for 35%, which is the most common form of bone cancer [1,2]. Neoadjuvant chemotherapy followed by surgical removal of the primary tumor has been established as the standard treatment for newly diagnosed osteosarcoma [3]. With the establishment of multidisciplinary treatments, 5-year survival rate of non-metastatic patients is reported to be above 60% [4–7]. However, metastatic osteosarcoma still results in much poorer prognosis [4,5,8–10].

Various prognostic factors influence the survival outcomes of osteosarcoma patients. Tumor site [5,11], tumor size [12], tumor grade [12], patient age [4,13], presence of node involvement [14], and presence of distant metastasis [4,5,9,15] have been identified as independent prognostic factors for patients with osteosarcoma. Moreover, other clinicopathological factors, such as pathologic fracture [16], surgical margins [17,18] have also been reported to be correlated with survival of osteosarcoma patients. Since survival is multifactorial, influenced by many such factors, no single factor can accurately predict survival outcomes for patients with osteosarcoma. Therefore, it would be desirable to establish a statistical prediction model which can integrate all individual prognostic factors to precisely predict the survival of osteosarcoma patients.

Nomogram is a statistical prediction tool that can incorporate all prognostic factors to estimate the survival outcome for individual patient, as has been widely demonstrated in other cancers including lung cancer, prostate cancer, breast cancer, and rectal cancer [19–23]. Since osteosarcoma still cause a substantial number of deaths despite the recent improvement in survival [4,5,8–10], accurate prediction of medium- and long-term survival outcome and identification of subgroups with different levels of risk for patients with high-grade osteosarcoma is highly important. Nomogram serves as a useful tool to potentially address these issues. Ogura et al. have constructed a prognostic nomogram for non-metastatic osteosarcoma patients only [24], however, patients with metastatic osteosarcoma at presentation or patients treated non-surgically were not included in the study, and the

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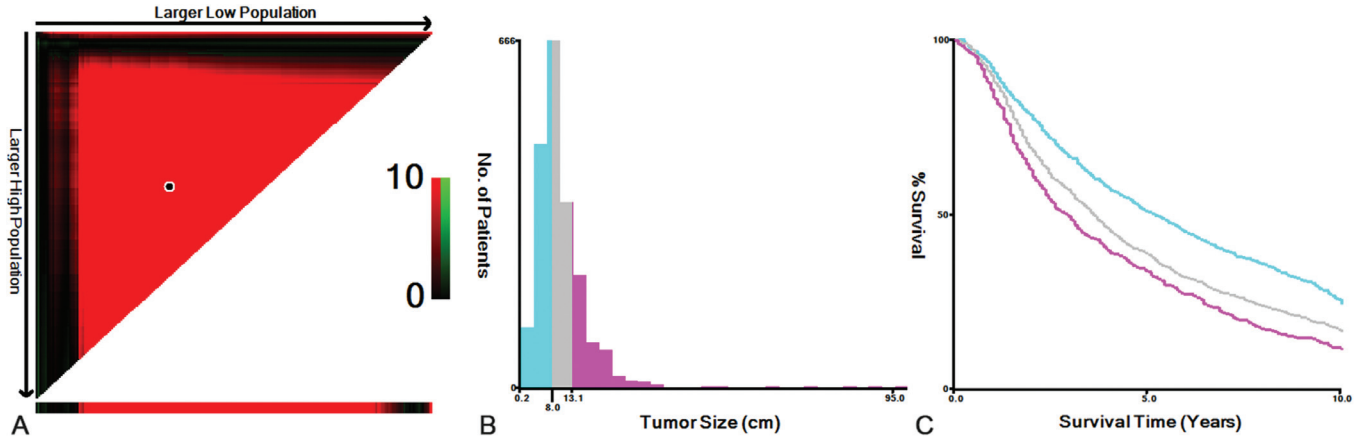

Fig. 1. (A)–(C) The graphs show defining the optimal cutoff values of tumor size via X-tile analysis. (A) The black dot indicates that optimal cutoff values of tumor size have been identified. (B) A histogram and (C) Kaplan–Meier were constructed based on the identified cutoff values. Optimal cutoff values of tumor size were identified as 8.0 cm and 13.1 cm based on overall survival.

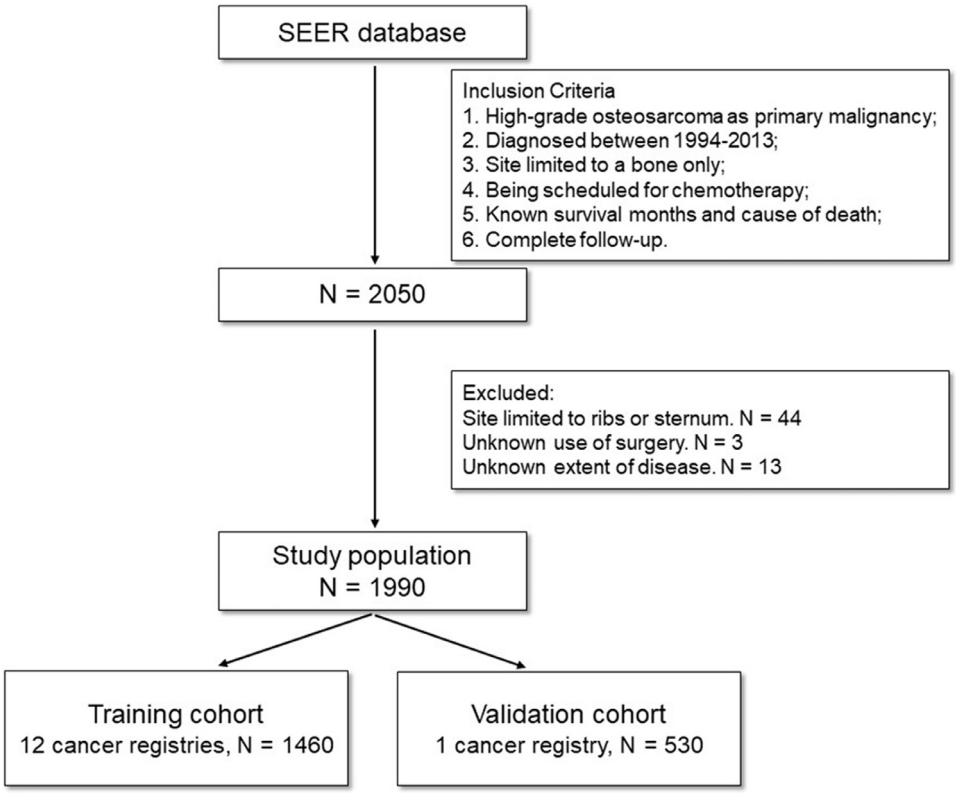

Fig. 2. The flow diagram indicates the process of collecting patients. Based on the inclusion and exclusion criteria, 1990 patients were collected from the SEER database. 1460 patients from 12 cancer registries and 530 patients from 1 cancer registry were assigned into the training and validation cohorts, respectively.

calibration plots did not suggest a good predictive ability (the C-indices were less than 0.70). To our knowledge, nomogram which makes full use of available prognostic factors to predict survival of osteosarcoma patients has not been reported yet.

Established in 1973, the Surveillance, Epidemiology, and End Results (SEER) database collects data from 18 cancer registries and covers 28% of US population [25]. Using the SEER database, we can collect a nationwide, population-based cohort to answer: (1) which clinicopathological characteristics are independently associated with survival of high-grade osteosarcoma patients? (2) Can we precisely predict 3- and 5-year overall and cancer-specific survival of individual osteosarcoma patient?

2. Methods

2.1. Data source and inclusion criteria

All the data were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database comprises 18 population-based cancer registries and represents 28% of US population [25].

The inclusion criteria were as follows: (1) diagnosed with high-grade osteosarcoma as primary malignancy; (2) diagnosed between 1994 and 2013 to ensure a minimal follow-up length of three years; (3) site limited to a bone only; (4) being scheduled for chemotherapy; (5) known survival months and cause of death; (6) complete follow-up. The