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Research Paper

Survival Prediction in High-grade Osteosarcoma Using Radiomics of Diagnostic Computed Tomography

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ABSTRACT

The poor 5-year survival rate in high-grade osteosarcoma (HOS) has not been increased significantly over the past 30 years. This work aimed to develop a radiomics nomogram for survival prediction at the time of diagnosis in HOS. In this retrospective study, an initial cohort of 102 HOS patients, diagnosed from January 2008 to March 2011, was used as the training cohort. Radiomics features were extracted from the pretreatment diagnostic computed tomography images. A radiomics signature was constructed with the lasso algorithm; then, a radiomics score was calculated to reflect survival probability by using the radiomics signature for each patient. A radiomics nomogram was developed by incorporating the radiomics score and clinical factors. A clinical model was constructed by using clinical factors only. The models were validated in an independent cohort comprising 48 patients diagnosed from April 2011 to April 2012. The performance of the nomogram was assessed with respect to its calibration, discrimination, and clinical usefulness. Kaplan–Meier survival analysis was performed.

The radiomics nomogram showed better calibration and classification capacity than the clinical model with AUC 0.86 vs. 0.79 for the training cohort, and 0.84 vs. 0.73 for the validation cohort. Decision curve analysis demonstrated the clinical usefulness of the radiomics nomogram. A significant difference (p-value <.05; log-rank test) was observed between the survival curves of the nomogram-predicted survival and non-survival groups. The radiomics nomogram may assist clinicians in tailoring appropriate therapy.

1. Introduction

Osteosarcoma is the most common primary bone malignancy, with an age-standardized incidence rate of 2.9 per 1 million men and 2.2 per 1 million women [1]. Nearly 90% of cases are classified as high-grade osteosarcoma (HOS) at the time of diagnosis [2]. Although the implementation of neoadjuvant and adjuvant chemotherapies and limb salvage surgeries has gradually increased the survival rate of HOS, the overall survival rate has not increased significantly over the past 30 years [3,4]. The 5-year overall survival rate for HOS ranges from 45% to 75% [5]. Although aggressive treatment plans, including multi-cycle treatments and adjuvant chemotherapies, are beneficial for patients who are likely to exhibit poor survival, not all HOS patients benefit from these treatments [6,7]. If patients with poor survival could be identified preoperatively, personalized treatment plans could be helpful for decision support for these patients. Therefore, there is a critical need to identify patients who are more likely to experience poor survival and thus benefit from additional therapy. Several clinical factors, such as age [8], tumor volume [9], stage [5,10], histologic subtype [11] and pathological fractures [12] have been associated with treatment outcome [13,14]. Nevertheless, a preoperative prognostic model for survival prediction has not yet been constructed. To address this issue, we built a reliable model to predict 5-year survival status at the time of diagnosis in HOS.

Recently, rapid developments in diagnostic imaging have become essential in the context of osteosarcoma decision-making in clinical practice; this especially includes computed tomography (CT) and magnetic resonance imaging (MRI). Notably, CT images can be used to

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determine tumor size, location, and migration status [15]. Radiomics is an emerging field that converts medical images into a high-dimensional mineable feature space via high-throughput quantitative feature extraction [16,17]. Previous radiomics studies have shown that objective and quantitative radiomics features might serve as prognostic imaging biomarkers [18]. In the past 5 years, radiomics has been used in multiple aspects of the clinical assessment of tumors, including detection, diagnosis, curative effect, and prognosis [19–22]. These studies demonstrated the feasibility of developing a nomogram with radiomics features to predict 5-year survival status for patients with HOS.

Hence, this study aimed to develop and validate a survival prediction nomogram that incorporates both a radiomics signature and clinical risk factors at the time of diagnosis for individualized prediction of survival in patients with HOS. In addition, we compared prediction performance between the nomogram and a model built with clinical factors alone. To the best of our knowledge, this is the first study that used radiomics to model survival prediction at the time of diagnosis in HOS, based on CT images.

2. Material and Methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board (IRB) of our institution, which waived the requirement for signed informed consent forms. A total of 150 patients with HOS, diagnosed from January 2008 to April 2012, were enrolled in this study, in accordance with the following inclusion and exclusion criteria. The inclusion criteria were as follows: (a) patients with HOS diagnosed by multidisciplinary teams; (b) an open biopsy or CT-guided core needle biopsy, pathologically evaluated by specialized sarcoma pathologists; (c) a standard CT scan performed at the time of diagnosis; and (d) clinical characteristics available. The exclusion criteria were as follows: (a) patients who underwent chemotherapy treatment before undergoing a CT scan in our institution; (b) patients suffering from other synchronous cancers; (c) incomplete or indeterminate clinical characteristics; and (d) death by a cause other than osteosarcoma. Supplementary Data I shows the patient recruitment pathway.

Treatment options included preoperative neoadjuvant and/or adjuvant chemotherapy and surgery with the aim of achieving a wide excision (either by limb-salvage or amputation surgery). Margins were defined on the basis of Enneking's criteria [23]. Chemotherapeutic regimens included cisplatin, doxorubicin, and high-dose methotrexate. Most patients received neoadjuvant chemotherapy and additional adjuvant chemotherapy after surgery. The total duration of chemotherapy was at least 6–8 months.

The overall patient population was divided into two cohorts on the basis of diagnosis time: training cohort and independent validation cohort. The training cohort was used for construction of the prediction model. This cohort included 102 patients (49 males and 53 females, 8–54 years of age) who were diagnosed between January 2008 and March 2011. The independent validation cohort consisted of 48 patients (25 males and 23 females, 8–47 years of age) who were diagnosed between April 2011 and April 2012; this cohort was used to test the prediction power of the model. Patients who survived ≥5 years after treatment were classified within the survival group, whereas those who died within 5 years of the operation were classified within the non-survival group. The power test was performed to evaluate the reliability of this study by using sample size and 5-year survival rates in both training and independent validation cohorts [24,25].

Baseline clinical data, including age, gender, tumor anatomic site, tumor stage (local/metastatic) [10], and the presence of pathological fracture (no/yes), were obtained from the Electronic Medical Record System (EMRS). All CT images were collected from the Picture Archiving and Communication System (PACS). The tumor stage and presence of pathological fracture at the time of diagnosis were determined by consensus of three experienced radiologists. The follow-up time in our study comprised every 6 weeks in the first and second years after treatment, every 3 months in the third and fourth years, and every 6 months after the fourth year. All data were collected and evaluated in April 2017 with a minimum follow-up of 5 years for all included patients.

2.2. CT Image Acquisition, Region of Interest Segmentation and Radiomics Feature Extraction

CT image acquisition is described in Supplementary Data II. Image resampling and gray level quantization were performed prior to feature extraction. ITK-SNAP software was used for three-dimensional regions of interest (ROI) segmentation [26]. Texture features were extracted by using in-house developed software in MATLAB 2015b (MathWorks, Natick, MA, USA) [27,28]. The feature pool extracted based on the 3-dimension region of interest (ROI) comprised 4 groups: (i) 6 histogram statistics features; (ii) 7 shape features; (iii) 53 texture features; and (iv) 408 wavelet features. Supplementary Data III describes the detailed features and references. The ROI was segmented by 3 orthopedists with 6 years (Orthopedist-1), 4 years (Orthopedist-2), and 4 years (Orthopedist-3) of experience in orthopedic CT interpretation. The patients in the training cohort were segmented separately by Orthopedist-1 and Orthopedist-2. The feature set based on the segmentation of Orthopedist-1 was used for model training. The feature set based on the segmentation of Orthopedist-2 was used to test the reproducibility and stability of each of the features. Patients in the validation cohort were segmented by Orthopedist-3 to test the prediction power of the trained model.

2.3. Feature Selection, Radiomics Signature Building and Validation

Feature selection was performed in 3 steps to select the optimal survival-related features via the training cohort. Firstly, the reproducibility and stability of each feature was determined by calculating the correlation coefficient between feature sets, based on the segmentations of Orthopedist-1 and Orthopedist-2. We only retained stable features with an intra-class correlation coefficient >0.8. Secondly, we used the Spearman rank correlation test to investigate the internal linear correlation between individual features. Redundant features (a linear correlation coefficient >0.95, determined by the Spearman test) were removed [28]. Finally, the least absolute shrinkage and selection operator (LASSO) logistic regression algorithm, which is applicable for high-dimensional data reduction [29], was performed for optimal feature selection. LASSO regression reduced the coefficients for survival-unrelated variables to zero; variables with non-zero coefficients were retained. To select optimal parameters in LASSO regression, we performed 100 iterations of 10-fold cross-validation with binomial deviance minimization criteria from the training cohort [30]. Binomial deviance was used as the loss function in the model training process; the model with the minimum binomial deviance was selected. Then, a radiomics score calculation formula, defined as the radiomics signature, was generated by a linear combination of selected features multiplied by LASSO coefficients. The radiomics signature was a prediction model constructed by using the selected features; the radiomics score was calculated to reflect survival probability by using the radiomics signature for each patient. The performance of the radiomics signature was assessed by its discrimination in both training and validation cohorts, which measured how well the model could distinguish patients in the survival or non-survival groups [31]. Discrimination was demonstrated by a receiver operating characteristic (ROC) curve and the associated area under the ROC curve (AUC); sensitivity and specificity were also calculated.

2.4. Development of the Radiomics Nomogram and Clinical Model

Considering the potential prediction value of the clinical characteristics, a multivariable logistic regression analysis was developed by

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