Factors for Overall Survival in Patients with Skull Base Chordoma: A Retrospective Analysis of 225 Patients

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BACKGROUND: **Although a controversial and complex issue, the prognostic factors of skull base chordomas are worth exploring.**

METHODS: **Prognostic factors associated with overall survival (OS) were retrospectively estimated in an individual cohort of skull base chordomas prospectively maintained for 10 years by a Kaplan-Meier method and univariate Cox proportional hazards model. Multivariate analysis by Cox regression analysis was performed to identify the independent prognostic factors. A nomogram was then formulated by R software based on the results.**

RESULTS: **A total of 180 primary patients and 45 recurrent cases were included, with a mean follow-up period of 43.7 months (range, 4–127 months). The OS of the primary group at 5 years and 7 years was 84% and 78%, and the mean OS was 103.8 months, which was significantly longer than the recurrent group, in which the mean postrecurrent OS was 68.4 months. In the primary group, preoperative Karnofsky Performance Status (KPS) score ($P = 0.004$) and a decline of perioperative KPS score ($P = 0.015$) were identified as independent predictors of OS. A nomogram was contracted to predict 5-year, and 7-year OS, which was well calibrated and had good discriminative ability (adjusted Harrell C statistic, 0.74). In the recurrent group, visual deficit was verified as an independent risk factor associated with postrecurrent OS ($P = 0.014$).**

CONCLUSIONS: **Both pathologic and perioperative KPS score evaluations are significant in OS prediction of both primary and recurrent cases. The nomogram for primary lesions, consisting of preoperative functional status and its perioperative changes, appears useful for risk stratification of long-term survival.**

INTRODUCTION

Chordoma is a rare bone cancer with an annual incidence of 0.1 in every 100,000 individuals; it is aggressive, locally invasive, and has a poor prognosis.[1,2] It was believed to arise from the remnants of notochord, with an almost equal distribution in the skull base (32%), mobile spine (32.8%), and sacrum (29.2%).[1] Skull base chordomas, which need more comprehensive consideration of preservation of neurologic function, are usually more complicated than lesions in other locations, in terms of treatment strategies, which usually consist of maximum but safe resection and postoperative external-beam radiation therapy.

Since a study by Eriksson et al.[3] in 1981, some clinical studies have focused on the prognostic factors of skull base chordoma. Several attempts have been made to correlate clinical and histologic features, such as age, gender, and pathologic subtype, with prognosis.[4-12] Some studies examined the correlations between their treatment choices, including extent of resection, timing and options of postoperative radiotherapy, and prognosis.[4,6,8,13-17]

However, these studies did not reach any consensus on prognostic factors of overall survival (OS). For example, Forsyth et al.[4] found that patients younger than 40 years survived longer than the older patients, and Samii et al.[7] found that the outcome was better

Key words
- Chordoma
- Overall survival
- Prognostic factor
- Skull base
- Surgery

Abbreviations and Acronyms
CI: Confidence interval
KPS: Karnofsky Performance Status
OS: Overall survival
PFS: Progression-free survival
pr-OS: Postrecurrent overall survival

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in patients older than 40 years. In a more recent systematic review by Jian et al.,[9] there was no difference in OS between 2 groups when a cutoff point was set as 40 years old. A similar controversy also existed for gender. The long-term outcomes were better for male patients in some studies,[7] whereas, on the contrary, men had a higher risk of progressive disease and death in other studies.[10] A retrospective study by the authors identified an association of chondroid chordoma and prolonged survival,[8] which could not be verified by subsequent studies.[9,12,14] Even gross total resection, which was associated consistently with better outcomes in most series,[4,6,8,13] failed to show its prognostic value in a study by Choy et al.[14]

For the last decade, we have treated more than 250 patients with skull base chordoma, whose information was collected in a prospectively maintained database. For primary lesions, our treatment philosophy included maximally safe surgery, gross total resection whenever possible, and a consultation of oncologic radiotherapy, commonly Gamma Knife (Elekta, Stockholm, Sweden), 3 months postoperatively. Whether adjuvant radiation therapy is performed depends on the radiologist's specialized evaluation. For recurrent tumors, the treatment choices, including tumor re-resection, palliative surgery, such as ventriculoperitoneal shunt, radiation therapy, and a wait-and-see policy, were decided on in a comprehensive consideration of patients' physical status, their willingness, and the opinions of the consulting neurosurgeons and radiologists. In this study, the prognostic factors for OS in these patients were retrospectively evaluated by dividing them in to primary and recurrent groups. With relatively consistent treatment strategies and classification standards, the analysis results from this cohort may provide some helpful information for current controversies.

METHODS

Patients

With permission from the institutional review board of Beijing Tiantan Hospital, Capital Medical University, records of patients who underwent surgery in the Skull Base Center of Beijing Tiantan Hospital from February 2005 to December 2014 were retrieved from a prospectively maintained database. Patients without any forms of tumor resections, those with unclear pathologic results, and those who were lost to follow-up were excluded from this study.

Baseline information retrieved comprised age, sex, diameters, duration of initial symptoms, treatment history, surgical approaches, operation time, blood lost, surgical complications, inpatient stays, and perioperative Karnofsky Performance Status (KPS) scores, which were initially measured at the first and last day of inpatient care as an evaluation indicator of the functional status.

All patients were recommended to be followed up on an outpatient basis at a 3-month interval for the first follow-up evaluation, then at a 6-month interval for the second time, and annually for life thereafter. The information, including the last update of follow-up, which was performed via telephone interviews in April 2015, was collected by 3 trained researchers (K.T., J.M., K.W.).

Assay Methods

Tumor volume was approximatively calculated by the cubature formula: $V = (D1 \times D2 \times D3)\pi/6$, in which D1, D2, and D3 represent the longest diameter measurement in 3 dimensions (sagittal, coronal, and axial), respectively. The evaluations of tumor location and extent of bone invasion were independently conducted by 2 researchers (L.W., K.T.), according to the classification criteria described in our previous studies. Whether the skull base dura had been broken through by the tumor was identified according to the description in the operation report.

Regarding the clinical information, initial symptoms were classified as headache and neck pain, diplopia, visual deficits (including hypopsia and hemianopia) cavernous sinus symptoms (comprising proptosis, ophthalmoplegia, ptosis, or trigeminal sensory loss), and others.

Surgeries were performed through anterior midline approaches, including microscopic and endoscopic endonasal approaches, or lateral open approaches. A uniform residual tumor classification was used on the basis of postoperative magnetic resonance images within 1 week: marginal resection was defined as greater than 90% excision, and intralesional resection was defined when less than 90% was resected.[18]

Adjuvant radiotherapy was defined as receiving any form of the following radiation therapies within 6 months postoperatively: proton or photon-beam radiation, Gamma Knife, intensity-modulated radiation therapy, and CyberKnife (Accuray, Sunnyvale, California, USA). The information for radiation therapy, such as treatment protocols, doses, and timing, was obtained from the medical records in the follow-up system and telephone interviews.

The resected chordomas were diagnosed as conventional, chondroid, or dedifferentiated subtypes according to their histologic appearance and immunohistochemical staining, including S-100, CK8/18, EMA, vimentin, brachyury, and Ki-67, by 2 isolated pathologists.[19,20]

According to reports[4,21-24] and our findings,[25] a rapid-growth subgroup was distinguished from conventional chordoma when it met one of the following criteria: 1) necrosis and hemorrhage were present; 2) $\geq$3 mitotic figures were counted in 10 high-power fields; and 3) Ki-67 $\geq$6% was identified when available. The results were double checked by 1 pathologist (J.D.), who independently reviewed all slides.

The enrolled patients were classified into the primary group, whose lesions were newly diagnosed, and the recurrent group, who had a history of surgery with or without radiotherapy. This study focused on factors that influence patients' OS. The end point of the primary group was OS, defined as the time from the start of follow-up to the date of death, whatever the cause. The end point of the recurrent group was postrecurrent OS (pr-OS), which was defined as the period from the beginning of enrolled follow-up to the date of death, no matter the cause. Patients with no events were censored at the date of their last follow-up.

Statistical Analysis

Patient characteristics (demographic, clinicopathologic, surgical, and outcomes) are described either by mean (median, range) for quantitative data or by counts and percentages for qualitative data. We compared these baseline characteristics between 2 groups using the Pearson χ^2 test for categorical variables and the Wilcoxon Mann-Whitney test for continuous variables.

For survival analysis, a Kaplan-Meier method was used and Cox proportional hazards models (univariate and multivariate) were

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