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ORIGINAL ARTICLE

Survival and treatment of cranial and spinal chordomas: a population-based study

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Abstract

Chordomas are rare, slow-growing malignant tumors. Given the paucity of data of the disease, the treatment strategies are disputed. We collected clinical and survival information of patients with chordoma diagnosed between 1975 and 2016 from the Surveillance, Epidemiology, and End Results database. A total of 1797 patients were initially enrolled, including 762 (42.4%) cranial and 1035 (57.6%) spinal chordoma. A total of 1504 patients were further evaluated after screening. In the cranial group, the surgery (gross total resection (GTR): $p=0.001$ for overall survival (OS); $p=0.009$ for cancer-specific survival (CSS)), tumor extension (distant metastasis: $p=0.001$ for OS; $p=0.002$ for CSS), and the age ($p<0.001$ for OS) were independent prognostic factors for survival. In the spinal group, the age ($p=0.004$), location ($p<0.001$), GTR ($p<0.001$), and tumor extension (distant metastasis, $p<0.001$) were independent prognostic factors for OS; the age ($p=0.007$), histological type ($p<0.001$), GTR ($p<0.001$), radiation ($p=0.018$), chemotherapy ($p=0.006$), and tumor extension ($p<0.001$) were independent prognostic factors for CSS. In this large cohort, a significant association was noted between extent of resection and outcome. Even though adjuvant radiation or chemotherapy did not benefit patients with chordoma, the effect on prognosis can be explored in a further study based on our findings.

Keywords Cranial · Spinal · Chordoma · Treatment

Introduction

Chordomas are rare, slow-growing malignant tumors and commonly seen between 60 and 70 years, accounting for 1–4% of all primary malignant bone tumors; they typically arise from the embryonic cells of the primitive notochord [7]. In the year of 1857, chordoma was first described by Virchow [19], the dedifferentiated chordoma was first described by Debernardi in 1913 [23], and then Heffelfinger and colleagues firstly reported chondroid chordoma in 1973 [10]. Surgery has been well established in the initial treatment of chordomas [28], but surgery alone may be insufficient and impossible for long-term local control [29]. Treatment regime varies among patients, with controversial or no accepted criteria [8]. Besides treatment, it is necessary to combine variables such as age, sex, and tumor characteristic to further predict the long-term outcome of patients.

However, limited studies constructed a detailed prediction model used to perform individualized survival estimation for patients with cranial and spinal chordomas. Therefore, we aimed to evaluate the clinical behavior, the extent of resection, and adjuvant radiation as well as chemotherapy, as they related to survival in cranial and spinal chordomas, and developed nomograms for reliable estimation of 3-, 5-, and 10-year survival.

Gui-Jun Zhang and Yu-Shi Cui contributed equally to this work.

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Material and methods

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute includes 9.7 million patients with cancer and accounted for approximately one third of the US population.

Patient selection

Patient were diagnosed (from 1975 to 2016) of cranial (Fig. 1A, B and C) and spinal chordomas as defined by the International Classification of Disease for Oncology Third Edition (ICD-O-3) histology codes: 9370/3 (chordoma, not specific (NOS)), 9371/3 (chondroid chordoma), and 9372/3 (dedifferentiated chordoma).

Analyzed patient demographics included age group (0–19, 20–39, 40–59, and 60 + years), sex (female, male), tumor location (Fig. 2A), year of diagnosis (Fig. 2B), marital status (divorced, married, separated, single, unmarried or domestic, partner, and widowed as well as unknown), laterality (bilateral, left, right, not a paired site, only one site, and paired site), tumor size, surgery (no, non-GTR, GTR, surgery (NOS), and unknown), adjuvant radiation, adjuvant chemotherapy, and stage (localized, regional, distant, and unknown).

Patients with a primary tumor location labeled (C41.0, bones of skull and face and associated joints; C41.2, vertebral column; C41.4, pelvic bones, sacrum coccyx and associated joints; C70.0, cerebral meninges; C71.0, cerebrum; C71.2, temporal lobe; C71.4, occipital lobe; C71.6, cerebellum; C71.7, brain stem; C71.8, overlapping lesion of brain and CNS; C71,9, brain; C72.0, spinal cord; C72.5, cranial nerve; C72.8, overlapping lesion of brain; C75.1, pituitary gland; C75.3, pineal gland) were included.

Overall survival (OS) was measured from the date of random assignment to the date of death (all reasons); cancer-specific survival (CSS) was measured from the date of random assignment to the date of death (only related cancers).

Statistical analysis

Patients were excluded from univariate and multivariate analysis if survival time was 0 (n = 41), unknown surgery information (n = 26), and unavailable tumor extension information (n = 242). The missing data regarding tumor size was more than 20% of sample size, so we did not explore the association between size and survival in this study.

When appropriate, data was analyzed using Pearson chi-square or Fisher's examination and Student's t test. Survival analysis was conducted using the Cox proportional hazards model. The nomograms were established to estimate 3-, 5- and 10-year CSS and OS rates. To verify the prediction accuracy, we calculated concordance index (C-index), and time-independent receiver operating characteristic (ROC) curve with the area under the curve value. $P < 0.05$ was considered statistically significant. All data were analyzed using R version. 3.6.3, and extensive packages with "survival," "survminer," "rms," and "foreign" were used.

Results

A total of 1797 patients were identified in SEER database between 1975 and 2016 with a diagnosis of cranial (n = 762, 42.4%) and spinal (n = 1035, 57.6%) chordomas. The most histological types were chordomas, NOS (n = 1704, 94.8%); others were chondroid chordomas (n = 82, 4.6%) and dedifferentiated chordomas (n = 11, 0.6%). Distributions

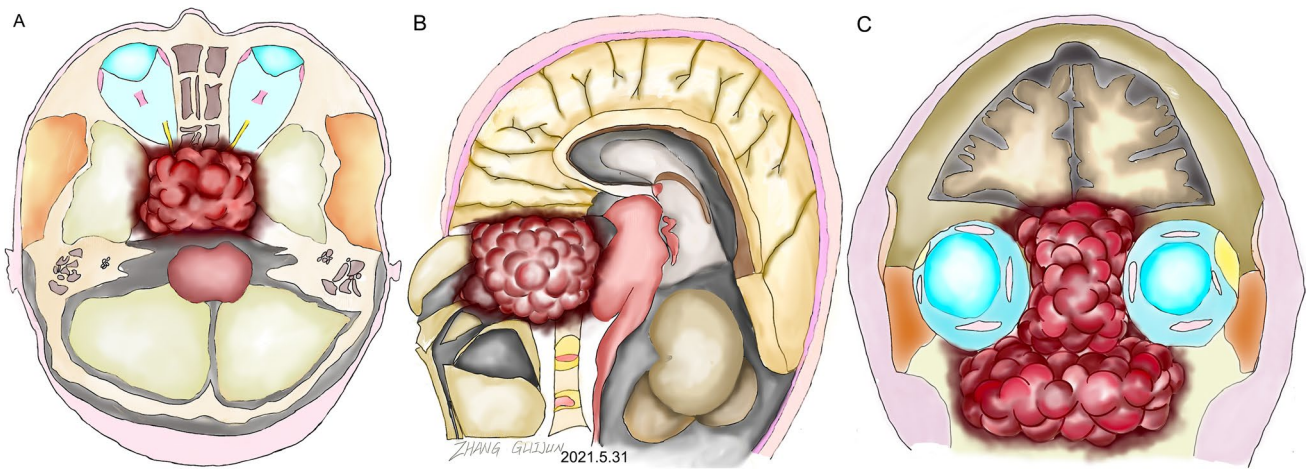

Fig. 1 Description of the cranial chordoma: axial, sagittal, and coronal

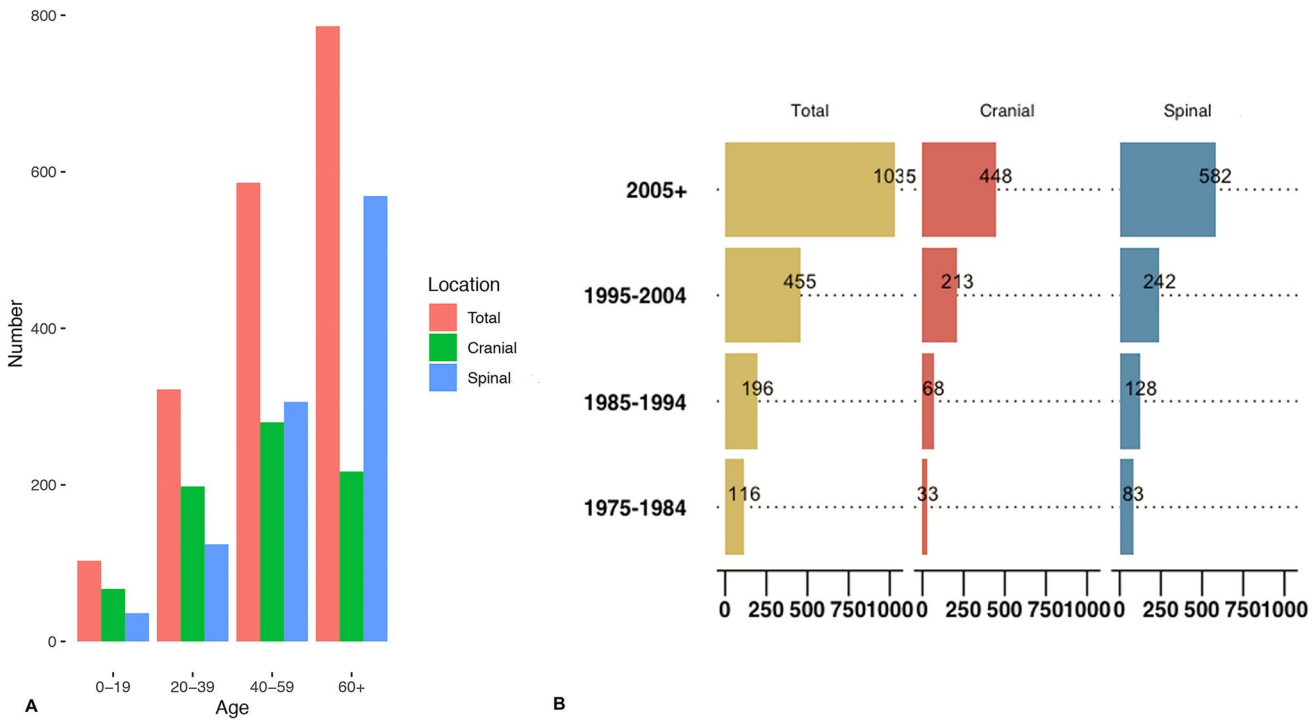

Fig. 2 **A** Distribution of cranial and spinal chordomas by age. **B** Distribution of cranial and spinal chordomas by year

of patient demographics and tumor characteristics are described among each behavior group in Table 1.

Cranial group

Forty-two percent (n = 762) of the patients were diagnosed with the cranial chordoma, and the majority of them were white (n = 627, 82.3%), male (n = 407, 53.4%), and 40–59 years old (n = 306, 40.2%) at diagnosis. Six hundred and ninety-five (91.2%) were chordoma NOS, 65 (8.5%) were chondroid chordoma, and 2 (0.3%) were dedifferentiated chordoma. The mean of tumor size was 35.2 ± 17.2 mm (range, 1–136 mm). Three hundred and fifteen (41.3%) cases happened to localized extension, 275 (36.1%) happened to regional extension, and 67 (8.8%) happened to distant metastasis. Univariate analysis revealed that age more than 60 years old was related to a poor OS (HR = 2.615; 95% CI 1.555–4.396; p < 0.001), correspondingly, this did reach a significance in multivariate analysis (HR = 2.766; 95% CI 1.635–4.682, p < 0.001, OS) (Fig. 3A) (Table 1).

Treatment for CSS

Of the patients included in this study, GTR was achieved in 21.3% (n = 135) of patients, while 67.6% (n = 429) of patients had a non-GTR and 11.2% (n = 71) of patients declined surgery. Two hundred and sixty-one (41.1%) underwent surgery alone, 25 (3.9%) underwent radiotherapy alone, 3 (0.5%) underwent chemotherapy alone, and 291 (45.8%) underwent surgery with radiation (Table 2). Patients treated with GTR had a better survival (HR = 0.455; 95% CI 0.252–0.867, p = 0.009; multivariate analysis). The receipt of radiation or chemotherapy did not affect survival (Fig. 3B).

The nomogram for chordoma in cranial location for OS comprised 3 prognostic factors — age, surgery, and tumor extension (Fig. 4A) — and for CSS comprised 2 prognostic factors: surgery and tumor extension (Fig. 4F). The C-index was 0.683 and 0.621 for OS and CSS, respectively. Time-dependent ROC analysis showed that the risk assess model had good predictive performance for the predictive ability both OS and CSS (Fig. 4B and G). The predicted calibration curves were close to the standard curves for 3-, 5-, and 10-year survival for both OS and CSS (Fig. 4C–E and H–J).

Spinal group

Of the 1035 cases with chordoma located in spinal location, 642 (62.0%) were male and 393 (38.0%) were female, with a mean age of 59.6 ± 18.1 years (range, 0–98 years). On both univariate and multivariate analysis for OS: age group between 20 and 39 years (HR = 0.339; 95% CI 0.161–0.713; p = 0.004), spinal cord location (HR = 0.288, 95% CI 0.155–0.533, p < 0.001), GTR (HR = 0.304; 95% CI 0.223–0.415; p < 0.001) were significantly favorable factors for better OS; other histological types including chondroid chordoma and dedifferentiated chordoma (HR = 3.096;

Table 1 Demographic characteristics of sampled 1797 individuals with cranial and spinal chordomas

Variable	Total	Cranial	Spinal	P value
	n (%)	n (%)	n (%)	
	1797	762 (42.4)	1035 (57.6)	
Sex				< 0.001*†
Male	1049 (58.4)	407 (53.4)	642 (62.0)	
Female	748 (41.6)	355 (46.6)	393 (38.0)	
Race				< 0.001*†
White	1542 (85.8)	627 (82.3)	915 (88.4)	
Black	67 (3.7)	38 (5.0)	29 (2.8)	
Others	175 (9.7)	94 (12.3)	81 (7.8)	
Unknown	13 (0.7)	3 (0.4)	10 (1.0)	
Age, years				< 0.001*‡
Range	0–98	0–92	0–98	
Mean	54.5 ± 19.6	47.6 ± 19.5	59.6 ± 18.1	
Median	57	49	62	
Marital status				< 0.001*†
Divorced	116 (6.5)	51 (6.7)	65 (6.3)	
Married	1031 (57.4)	417 (54.7)	614 (59.3)	
Separated	25 (1.4)	14 (1.8)	11 (1.1)	
Single	401 (22.9)	211 (27.7)	190 (18.4)	
Unknown	81 (4.5)	28 (3.7)	53 (5.1)	
Unmarried or domestic partner	4 (0.2)	2 (0.3)	2 (0.2)	
Widowed	139 (0.3)	39 (5.1)	100 (9.7)	
Location				NA
BSF	579 (7.7)	579 (76.0)	-	
Cerebral meninges	2 (0.1)	2 (0.3)	-	
Cerebrum	2 (0.1)	2 (0.3)	-	
Temporal lobe	8 (0.4)	8 (1.0)	-	
Occipital lobe	5 (0.3)	5 (0.7)	-	
Cerebellum, NOS	14 (0.8)	14 (1.8)	-	
Brain stem	20 (1.1)	20 (2.6)	-	
Overlapping lesion of brain	2 (0.1)	2 (0.3)	-	
Brain, NOS	78 (4.3)	78 (10.2)	-	
Cranial nerve, NOS	2 (0.1)	2 (0.3)	-	
Overlapping lesion of brain and CNS	1 (0.1)	1 (0.1)	-	
Pituitary	47 (2.6)	47 (6.2)	-	
Pineal gland	2 (0.1)	2 (0.3)	-	
Vertebral column	400 (22.3)	-	400 (38.6)	
PSC	531 (29.5)	-	531 (51.3)	
Spinal cord	104 (5.8)	-	104 (10.0)	
Histological type				< 0.001*†
Chordoma, NOS	1704 (94.8)	695 (91.2)	1009 (97.5)	
Chondroid chordoma	82 (4.6)	65 (8.5)	17 (1.6)	
Dedifferentiated chordoma	11 (0.6)	2 (0.3)	9 (0.9)	
Laterality				< 0.001*†
Bilateral	6 (0.3)	2 (0.3)	4 (0.4)	
Left	53 (2.9)	23 (3.0)	30 (2.9)	
Right	48 (2.7)	21 (2.8)	27 (2.6)	
Not a paired site	1632 (90.8)	709 (93.0)	923 (89.2)	
Only one side	5 (0.3)	1 (0.1)	4 (0.4)	
Paired site	53(1.6)	6 (0.8)	47 (4.5)	
Tumor size, mm				< 0.001*‡

Table 1 (continued)

Variable	Total	Cranial	Spinal	P value
Range	1–610	1–136	5–610	
Mean	57.0 ± 44.4	35.2 ± 17.2	75.0 ± 51.4	
Median	45	32	64	
Unknown	991 (55.1)	397 (52.1)	594 (57.4)	
Surgery				< 0.001*†
No	351 (19.5)	103 (13.5)	248 (24.0)	
Non-GTR	663 (36.9)	368 (48.3)	295 (28.5)	
GTR	394 (21.9)	143 (18.8)	251 (24.3)	
Surgery, NOS	363 (20.2)	139 (18.2)	224 (21.6)	
Unknown	26 (1.4)	9 (1.2)	17 (1.6)	
Radiation				0.424†
Yes	834 (46.4)	362 (47.5)	472 (45.6)	
No	963 (53.6)	400 (52.5)	563 (54.4)	
Chemotherapy				0.001*†
Yes	74 (4.1)	18 (2.4)	56 (5.4)	
None/Unknown	1723 (95.9)	744 (97.6)	979 (94.6)	
Stage				0.297†
Localized	704 (39.2)	315 (41.3)	389 (37.6)	
Regional	692 (38.5)	275 (36.1)	417 (40.3)	
Distant	159 (8.8)	67 (8.8)	92 (8.9)	
Unknown	242 (13.5)	105 (13.8)	137 (13.2)	

BSF bones of skull and face and associated joint; *GTR* gross total resection; *NOS* not specific; *PSC* pelvic bones, sacrum, coccyx, and associated joints

* Indicates statistical significance

†

Chi-square test or Fisher's examination

‡ Independent t test

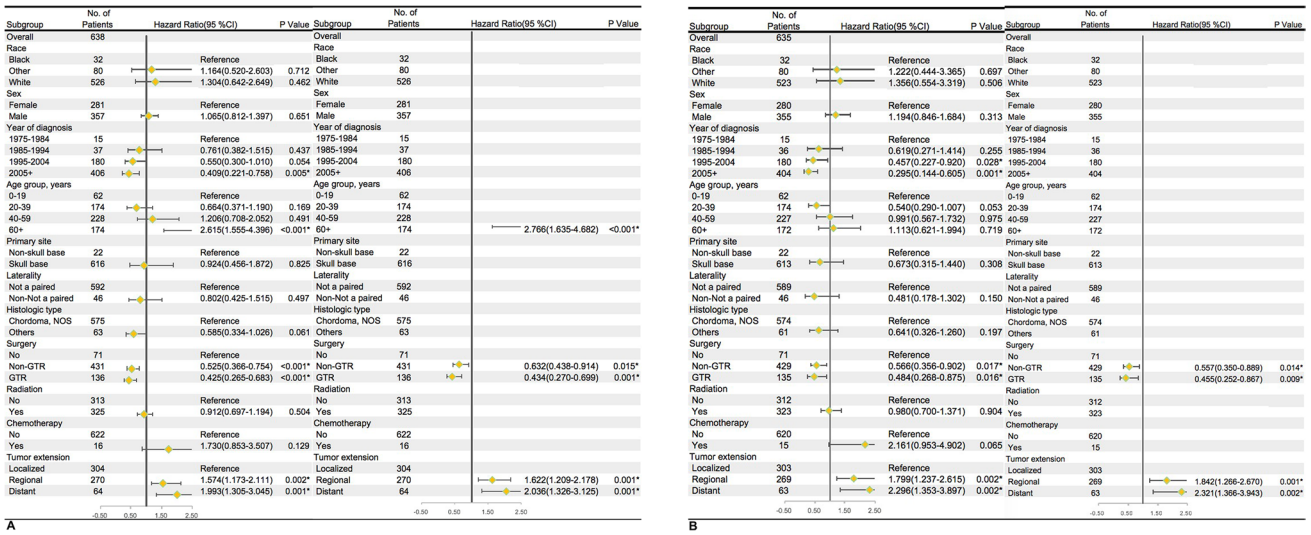

Fig. 3 The forest map of Cox regression analysis in the cranial group. Univariate Cox regression and multivariate Cox regression analyses estimating the risk factors for overall survival (all cause death) (**A**) and cancer-specific survival (**B**). *Means $P < 0.05$

Table 2 Clinical data of treatment strategies (cancer-specific survival) in patients with cranial chordoma

Variable	Surgery alone	RT alone	Surgery + RT	p value
No. of patients, (%)	261	25	291	
Female,	115 (44.1)	16 (64.0)	124 (42.6)	0.118†
Age, yrs	45.8 ± 17.9	64.7 ± 17.0	45.5 ± 19.3	< 0.001‡*
Extension				0.127†
Localized	119 (45.6)	8 (32.0)	150 (51.5)	
Regional	116 (44.4)	12 (48.0)	119 (40.9)	
Distant	26 (10.0)	5 (20.0)	22 (7.6)	
Death, n (%)	59 (22.6)	11 (44.0)	53 (18.2)	0.008†*

RT radiation

† Chi-square test

‡ One-way ANOVA

* $p < 0.05$

95% CI 1.744–5.498; $p < 0.001$) and distant metastasis (HR = 2.211; 95% CI 1.627–3.004; $p < 0.001$) were adverse factors for worse OS. On multivariate analysis for CSS, age group (HR = 0.335, 95% CI 0.151–0.743; $p = 0.007$), tumor extension (HR = 3.381; 95% CI 2.237–5.109; $p < 0.001$), and histological type (HR = 4.600; 95% CI 2.356–8.983; $p < 0.001$) were independent predict factors of CSS (Fig. 5A).

Treatment for CSS

Non-GTR was achieved in 51.2% of cases (n = 440), GTR was achieved in 27.8% of cases (n = 239), and 21.0% of cases (n = 181) declined surgery. Forty-three percent of tumors (n = 368) were treated with surgery alone, 11.0% (n = 93) were treated with radiation alone, 1% (n = 10) were treated with chemotherapy alone, and 33% (n = 288) were treated with surgery plus radiation (Table 3). GTR, as a favorable factor, was associated with best survival among surgery groups (no surgery, non-GTR, and GTR) (HR = 0.284; 95% CI 0.178–0.453; $p < 0.001$).

Surprisingly, patients who received surgery and radiotherapy showed a worse survival compared with those who received surgery alone (HR = 1.406, 95% CI 1.060–1.866; $p = 0.018$); plus, patients who received surgery and chemotherapy showed a decreased survival compared with those who received surgery alone (HR = 2.023; 95% CI 1.222–3.351; $p = 0.006$) (Fig. 5B).

The nomogram for chordoma in spinal location for OS comprised 5 prognostic factors — age, behavior code, primary site, surgery, and tumor extension (Fig. 6A) — and for CSS comprised 6 prognostic factors: age, behavior code, surgery, tumor extension, radiation, and chemotherapy (Fig. 6F). The C-index was 0.724 for OS and 0.714 for CSS, respectively. Time-dependent ROC analysis showed that the risk assess model had good predictive performance for the predictive ability both 3-, 5-, and 10-year OS and CSS (Fig. 6B and G). And the predicted calibration curves were close to the standard curves for survival for both OS and CSS (Fig. 6C–E and H–J).

Discussion

Chordomas, with locally aggressive behavior and poor prognosis, are thought to arise from embryo notochordal remnants of the neuraxis, predominantly in the skull base, vertebral column, and sacrococcygeal area [12, 21]. No wonder that clinical management of chordoma is usually challenging for its locally invasive growth pattern. Despite the location-specific prognostic factors among chordomas, the previous literature grouped cranial and spinal location together for survival analysis, making the differences in subsets unclear. Compared to that study, we sought to conduct comprehensive prognostic evaluations focusing on the chordomas in cranial and spinal location separately and developed nomograms for reliable estimation of 3-, 5-, and 10-year survival using the patient data from the SEER database [14]. The C-index and the graphical calibration method suggested that nomogram exhibited a good predictive ability. Univariate analysis revealed that year of diagnosis was a predictor of survival, but further multivariate analysis was not performed as different follow-up time was a point.

Our result showed that age group (20–39 years) was a favorable factor for both increased CSS and OS in the patients with spinal tumor. Younger age, with a tendency to aggressive clinical behavior, has been described as an adverse factor for poor survival, which is consistent with our finding, on multivariate analysis, that patients under 20 had a worse survival [5, 21].

The histological variants are classified into 3 groups: classical (conventional), chondroid, and dedifferentiated [9]. While patients diagnosed with chordoma, NOS had better outcome, those in a mix group with chondroid chordoma,

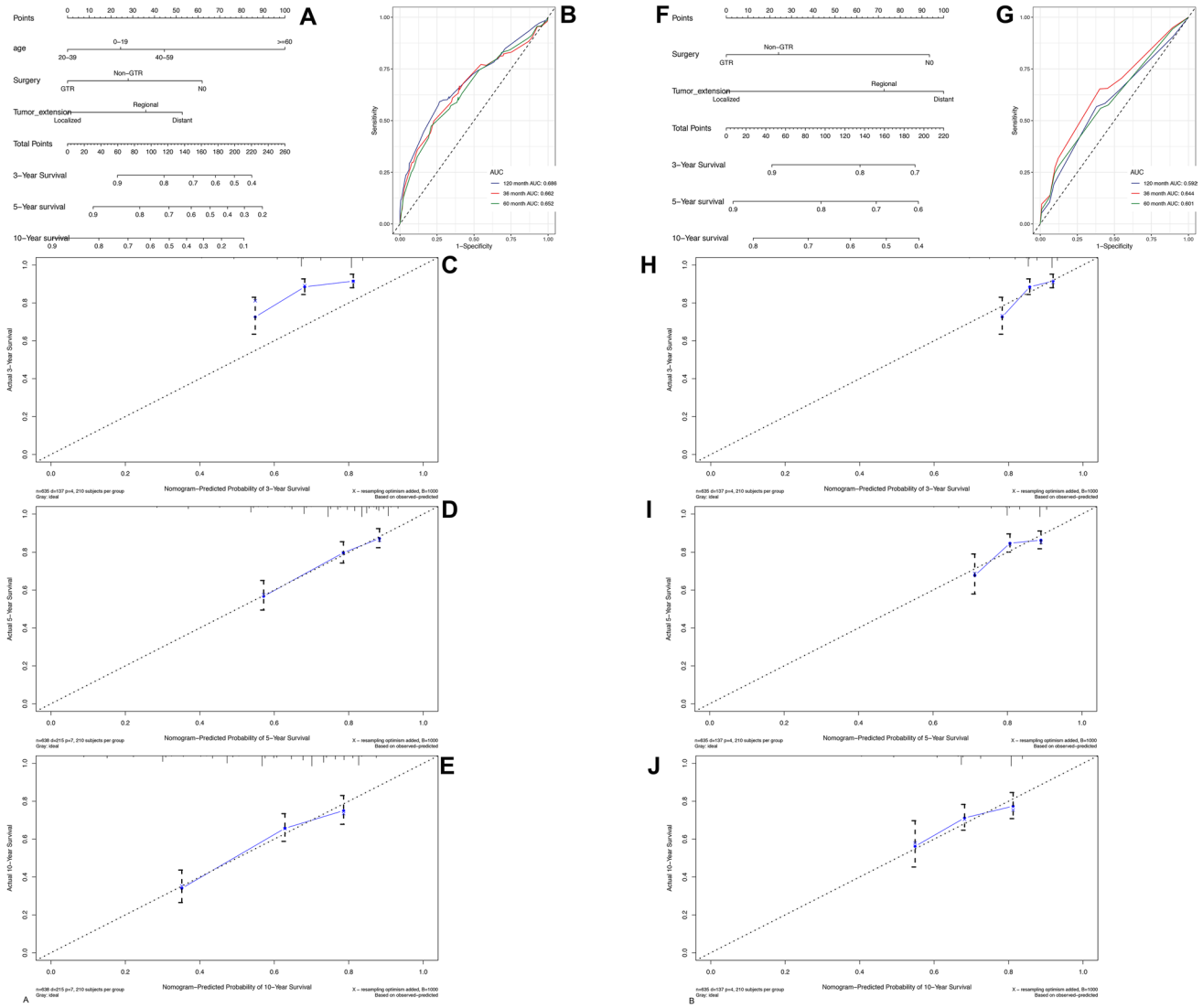

Fig. 4 **A** Nomogram used to predict the 3-, 5-, and 10-year overall survival rates of patients with cranial chordoma. **B** Receiver operating characteristic curve of the nomogram for predicting the 3-, 5-, and 10-year overall survival rates of patients with cranial chordoma. Calibration curve of the nomogram for predicting the 3- (**C**), 5- (**D**), and 10-year (**E**). Overall survival rates of patients with cranial chordoma. **F** Nomogram used to predict the 3-, 5-, and 10-year cancer-specific survival rates of patients with cranial chordoma. **G** Receiver operating characteristic curve of the nomogram for predicting the 3-, 5-, and 10-year cancer-specific survival rates of patients with cranial chordoma. Calibration curve of the nomogram for predicting the 3- (**H**), 5- (**I**), and 10-year (**J**) cancer-specific survival rates of patients with cranial chordoma

and dedifferentiated chordoma had a poor survival in our study.

This current study demonstrated that surgery played an important role in the treatment of patients of chordomas. Also, this outcome added support to previous literature suggesting a better survival related to aggressive treatment [1, 11, 15, 24, 25].

Extent of resection was the most important factor in prediction survival, with only 75.9% (cranial group) and 75.3% (spinal group) actuarial 10-year CSS rate for GTR, with 71.8% (cranial group) and 65.1% (spinal group) actuarial 10-year CSS rate for non-GTR. One retrospective study, with 31 pediatric chordomas, showed 90% survival in 10 patients with GTR, compared with only 29% OS rate at 10 years after subtotal resection [17], but in cases of high risk commonly seen in the skull base and tumors with local invasion, GTR might be less possible and neurological preservation should be noticed.

Interestingly, the addition of radiotherapy showed the significantly poor CSS in patients with spinal chordoma. Recently, Lee et al. and Jawad, using the data from the SEER database, showed similar results that adjuvant radiation was

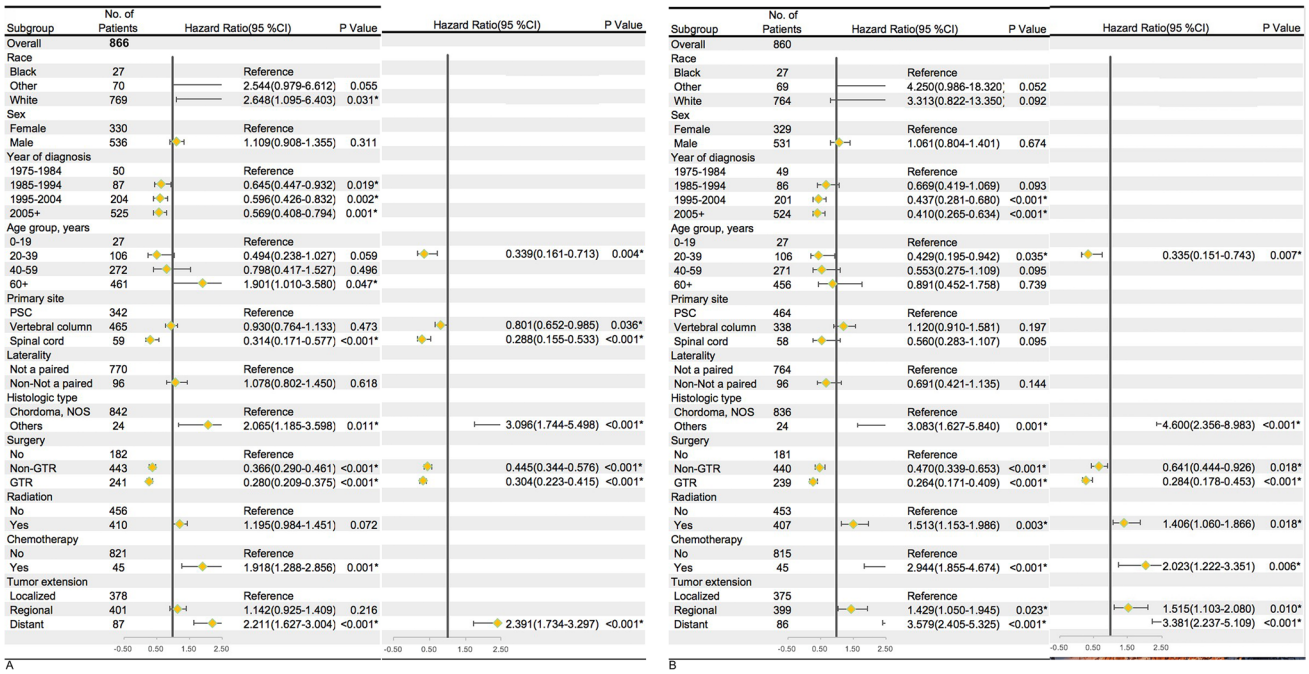

Fig. 5 The forest map of Cox regression analysis in the spinal group. Univariate Cox regression and multivariate Cox regression analyses estimating the risk factors for overall survival (all cause death) (**A**) and cancer-specific survival (**B**). *Means $P < 0.05$

Table 3 Clinical data of treatment strategies (cancer-specific survival) in patients with spinal chordoma

Variable	Surgery alone	RT alone	Surgery + Radiotherapy	p value
No. of patients, (%)	368	93	288	
Female,	139 (37.8)	39 (41.9)	107 (37.2)	0.703†
Age, yrs	57.8 ± 16.8	70.3 ± 14.3	55.7 ± 17.3	< 0.001*‡
Extension				0.112†
Localized	173 (47.0)	39 (41.9)	113 (39.2)	
Regional	168 (45.7)	39 (41.9)	155 (53.8)	
Distant	27 (7.3)	15 (16.1)	20 (7.0)	
Death, n (%)	71 (19.3)	28 (30.1)	76 (26.4)	0.027†

CT chemotherapy, *RT* radiation

† Chi-square test

‡ One-way ANOVA

* $p < 0.05$

associated with worse survival outcomes [13, 14]. These results seemed to verify the relation between the use of radiotherapy and disappointing survival. Indeed, radiotherapy alone, in a large number of people, led to a poor prognosis, to some degree, which caused an interesting finding that patients who received surgery with radiation had a worse survival compared with those with surgery alone. Moreover, there was no identified treatment dose or objective quality assessment in this retrospective study. Radiotherapy was traditionally recommended in the form of hypofractionated proton beam or photo beam with at least 74 Gy for patients with chordoma [2]. In a series of 282 patients with sacral and spinal chordoma, Yagiz et al. did not observe increased OS in patients receiving radiation with a median dose of 58 Gy [27]; while Schuli-Ertner reported that radiation dose more than 60 Gy was a favorable factor for improved local control [20]; these results suggested higher dose radiation could potentially improve survival. In addition, radiation sequence might be a key factor of survival: preoperative radiation + surgery + radiotherapy vs. surgery + radiotherapy [18, 26]. Furthermore, patients with poor condition (regional or distant metastasis) were more likely to receive radiation. The extension of tumor might counteract the effect of radiation on survival.

In particular, there was a paucity of studies regarding the association between chemotherapy and survival. The routine use of chemotherapy in addition to surgery is controversial because some pervious report advocated that chemotherapy could increase survival [16], others suspected this finding [4, 22].

In this current study, no difference in survival was observed between surgery alone and surgery with chemotherapy for cranial chordoma; to our surprise, patients with surgery and chemotherapy had a worse survival compared with those with surgery alone for spinal chordoma.

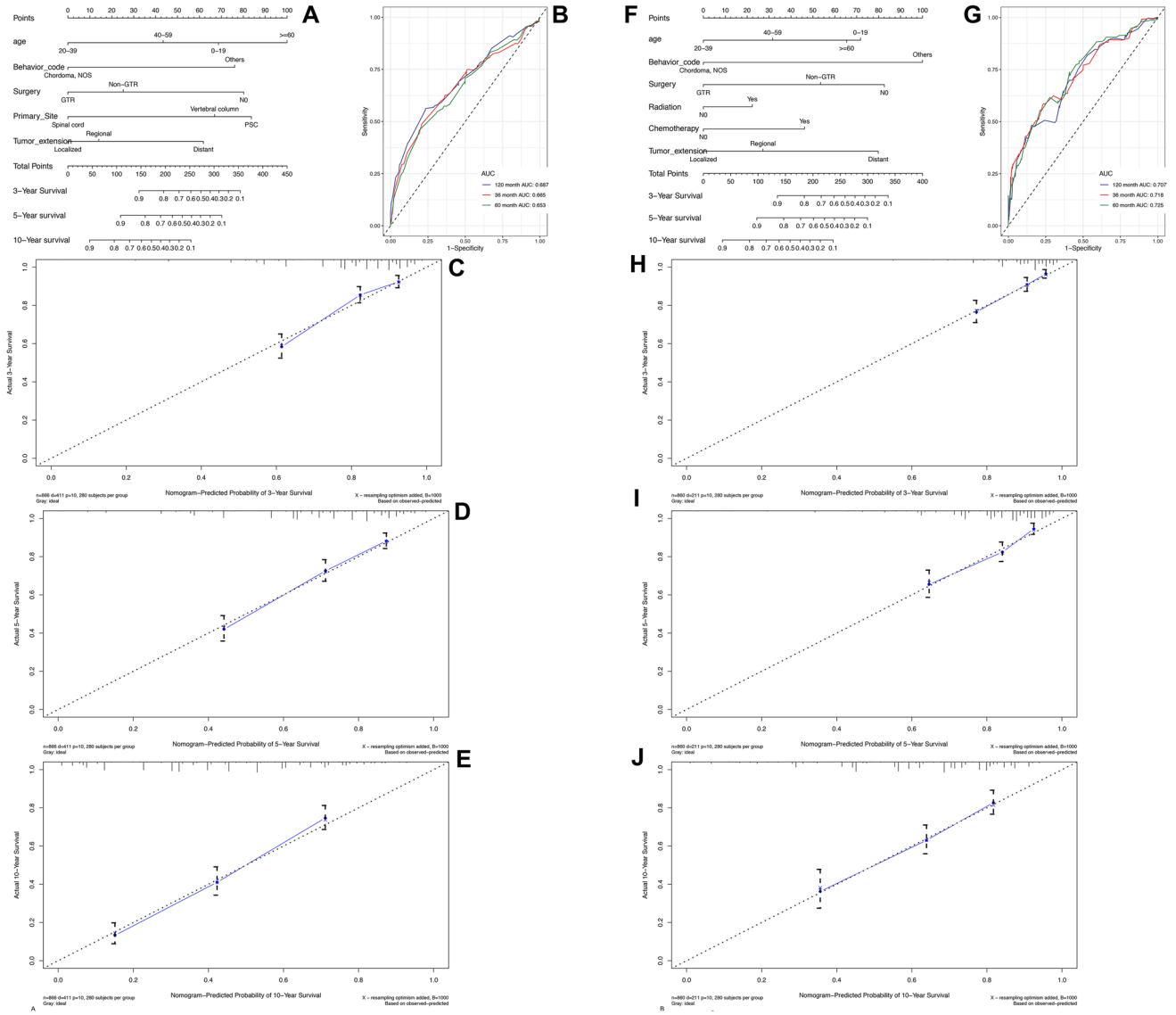

Fig. 6 **A** Nomogram used to predict the 3-, 5-, and 10-year overall survival rates of patients with spinal chordoma. **B** Receiver operating characteristic curve of the nomogram for predicting the 3-, 5-, and 10-year overall survival rates of patients with spinal chordoma. Calibration curve of the nomogram for predicting the 3- (**C**), 5- (**D**), and 10-year (**E**) overall survival rates of patients with spinal chordoma. **F** Nomogram used to predict the 3-, 5-, and 10-year cancer-specific survival rates of patients with spinal chordoma. **G** Receiver operating characteristic curve of the nomogram for predicting the 3-, 5-, and 10-year cancer-specific survival rates of patients with spinal chordoma. Calibration curve of the nomogram for predicting the 3- (**H**), 5- (**I**), and 10-year (**J**) cancer-specific survival rates of patients with spinal chordoma

Meanwhile, it is important to realize that the rate of chemotherapy receipt was pretty low, in 2.4% of patients with cranial chordoma and in 5.4% of patients with spinal chordoma, respectively.

Considering its malignancy [3, 6], with local recurrence and distant metastasis, it is imperative to need evidence from a randomized trial supporting the addition of chemotherapy.

Limitations

Some limitations should be underlined as follows: the SEER database had its inherent limitations; clinical information was limited since SEER did not provide information on pre-postoperative Karnofsky Performance Status, clinical symptoms, neurological function, and recurrence

status. Radiologic information was not obtained so that the extent of resection was not justified, and surgical status of many patients was undetailed. And there was no clear information about spinal location of cervical, thoracic, or lumbar chordomas from the SEER database, so we could not provide survival in different locations. Moreover, the doses of radiation were missing, and it was important that high dose might be a potential favorable factor for survival. In addition, further validations are imperative, although nomogram models were constructed according to the large cohort.

Conclusion

Poor prognosis is mainly due to regional or distant progression. Initial aggressive treatment is necessary for patients with chordoma, and we have better to make an attempt to achieve GTR with minimally invasive surgical approach. Notably, radiotherapy or chemotherapy in addition to surgery did not reduce the hazard risk of cranial chordoma. On the other hand, in patients with spinal chordoma, adjuvant radio- or chemotherapy increased mortality risk. Given the retrospective nature of the SEER database, we failed to propose a standard treatment paradigm of these tumors. But a prospective randomized clinical trial was recommended to evaluate the role of adjuvant therapies in survival based on our findings.

Author contribution Conception and experimental design: all authors.
Acquisition of data: all authors.
Analysis and interpretation of data: all authors.
Drafting the article: Gui-Jun Zhang and Yu-Shi Cui.
Statistical analysis: Gui-Jun Zhang and Yu-Shi Cui.
Approved the final version of the manuscript on behalf of all authors: Huan Li.

Code availability R software.

Declarations

Ethics approval This study was approved by the Institutional Review Board.

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