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

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Abstract

Objective

Chordomas are rare, slow-growing malignant tumors. Given the paucity of data on it, the treatment strategies are disputed.

Methods

We collected survival and clinical information on patients with chordoma diagnosed between 1975 and 2016 from the Surveillance, Epidemiology, and End Results database and screened them according to inclusion and exclusion criteria. Then, univariate and multivariate Cox regression analyses were used to identify significant prognostic factors, and nomograms was constructed to visualize the results. The concordance index, receiver operating characteristic, calibration and decision curves were used to assess the predictive ability of the nomogram.

Results

A total of 1797 patients were initially enrolled, including 762 (42.4%) cranial and 1035 (57.6%) spinal cord chordoma. A total of 1504 patients, after screening, were further evaluated by statistical analysis. In the cranial group, the surgery (gross total resection (GTR), HR=0.434, 95% CI=0.270-0.699, p=0.001, overall survival (OS); HR=0.455, 95% CI=0.252-0.867, p=0.009, cancer-specific survival (CSS)) and tumor extension (distant metastasis, HR=2.036, 95% CI=1.326-3.125, p=0.001, OS; HR=2.321, 95% CI=1.366-3.943, p=0.002, CSS), the age (HR=2.766, 95% CI=1.635-4.682, p<0.001, OS) were independent prognostic factors for survival. In the spinal cord group, the age (HR=0.339, 95% CI=0.161-0.713, p=0.004), 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), and tumor extension (distant metastasis, HR=2.391, 95% CI=1.734-3.297, p<0.001) were independent prognostic factors for OS; the age (HR=0.335, 95% CI=0.151-0.743, p=0.007), histological type (HR=4.600, 95% CI=2.356-8.983, p=<0.001), GTR (HR=0.284, 95% CI=0.178-0.453, p<0.001) radiation (HR=1.406, 95% CI=1.060-1.866, p=0.018), chemotherapy (HR=2.023, 95% CI=1.222-3.351, p=0.006), and tumor extension (HR=3.381, 95% CI=2.237-5.109, p<0.001) were independent prognostic factors for CSS.

Conclusions

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 should be explored in a further study.

Introduction

Chordomas are rare, slow-growing malignant tumors and are 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 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]. And 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 cord 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 cord chordomas; and developed nomograms for reliable estimation of 3-, 5-, and 10-year survival.

Methods

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

Patient selection

Patient with a diagnosis (from 1975-2016) of cranial and spinal cord 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, 30-59, and 60+years), sex (female, male), tumor location (Supplementary Figure 1A), year of diagnosis (Supplementary Figure 1B), 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 and unknown), adjuvant radiation, adjuvant chemotherapy, and tumor extension (localized, regional and distant)

Patients with a primary tumor location labeled (C41.0, bones of skull and face and associated joints; C41.2, vertebral column; C41.4, pelvie bones, sacrum coccyx and associated joints; C70.0, cerebral menings; C71.0, cerebrum; C71.2, temporal lobe; C71.4, occipital lobe; C71.6, cerebellum; C71.7, brain stem; C71.8, overlapping; 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, categorical data was analyzed using Pearson chi-square or Fisher's examination and student 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 curve (ROC) with the area under the curve value. In addition, decisive curve analysis was used to determine the 3-, 5-, and 10-year survival rates. P<0.05 was considered statistically significant. All data were analyzed using R version. 3.6.3, and extensive packages with "survival", "survminer", "rms", "decisive", 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 cord (n=1035, 57.6%) chordomas. The most histological types were chordoma, NOS (n=1704, 94.8%), others were chondroid chordoma (n=82, 4.6%) and dedifferentiated chordomas (n=11, 0,6%). Distributions of patient demographics and tumor characteristics were 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=526), male (n=357), and 40-59 years old (n=228) 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±17.2mm (range, 1-136mm). 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). (Figure 1A)

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 either 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. (Supplementary Table 1) Patients treated with surgery had a better survival (HR=0.455, 95% CI=0.252-0.867, p=0.009). The receipt of radiation or chemotherapy did not affect survival. (Figure 1B)

Spinal cord group

Of the 1035 cases with chordoma located in spinal cord, 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 20-39 years (HR=0.339, 95% CI=0.161-0.713; p=0.004), spinal cord location (HR=0.288, 95%CI= 0.155-0.553, 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, 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=2.356-8.963; p<0.001) were independent predict factors of OS. (Figure 2A)

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 surgery chemotherapy alone, and 33% (n=288) were treated with surgery plus radiation. (Supplementary Table 2). GTR, as a favorable factor, was associated with best survival among surgery group (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=2.203, 95% CI=1.222-3.351; p=0.006). (Figure 2B)

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. Using the patient data from the SEER database, we constructed a nomogram that indicated survival was associated with many factors. 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 further performed as different follow-up time was a point.

Our result showed that age group (20-39 years) was a favorable factor for both CSS and OS in the patients with spinal cord 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 have better outcome, those in a mix group with chondroid 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.[24,15,11,25,1]

Extent of resection was the most important factor in prediction survival, with only 75.9% (cranial group) and 75.3% (spinal cord group) actuarial 10 year CSS rate for GTR, with 71.8% (cranial group) and 65.1% (spinal cord 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 terms of a high risk commonly seen in the skull base and local invasion of tumor, GTR might be not possible and neurological preservation should be took notice of.

Interestingly, the addition of radiotherapy showed the significantly poor CSS in patients with spinal cord chordoma. Recently, Lee et al and Jawad, using the data from the SEER database, showed similar results that adjuvant radiation was associated with worse survival outcomes.[14,13] These results seemed to contributed to 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 unbelievable finding that surgery with radiation was related to worse survival compared 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] Y et al. described a series of 282 patients with sacral and spinal chordoma, but significantly increased OS was not observed in patients who underwent radiation with a median dose of 58 Gy;[27] while Schuli-Ertner reported that radiation dose more than 60 CGE was a favorable factor for local control;[20] these results suggested high dose radiation could improve survival. In addition, radiation sequence might be a key factor of survival: preoperative radiation+surgery+radiotherapy vs. surgery+radiotherapy.[26,18] Last, patients with poor condition (regional or distant metastasis) were more likely to receive radiation. Maybe that the extension of this tumor counteracted the role the radiation in 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 although 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 cord chordoma. It is important to realize that the rate of radiotherapy receipt was pretty low, in 2.4% of patients with cranial chordoma and in 5.2 of patients with spinal cord 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.

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 morbid surgical approach. Notably, radiotherapy or chemotherapy in addition to surgery did not reduce the hazard risk of cranial chordoma. On the other hand, adjuvant radio- or chemo-therapy imparted a mortality risk increase in patients with spinal cord chordoma. Considered that inherent and retrospective nature of the SEER database, unfortunately, we failed to propose a standard treatment paradigm of these tumors. But a prospective randomized clinical trials to evaluate the role of adjuvant therapies survival could be performed based on our findings.

Declarations

Funding None

Conflict of interest We declare that there is no conflict of interest.

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

Informed consent The informed consents were available for all patients.

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Tables

Table 1. Demographic characteristics of sampled 1797 individuals with cranial and spinal cord chordoma

Variable	Total	Cranial	Spinal cord	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)	
Other	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 & 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*‡
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)	

* Indicates statistical significance
† Chi-square test
‡ Independent t-test

Figures

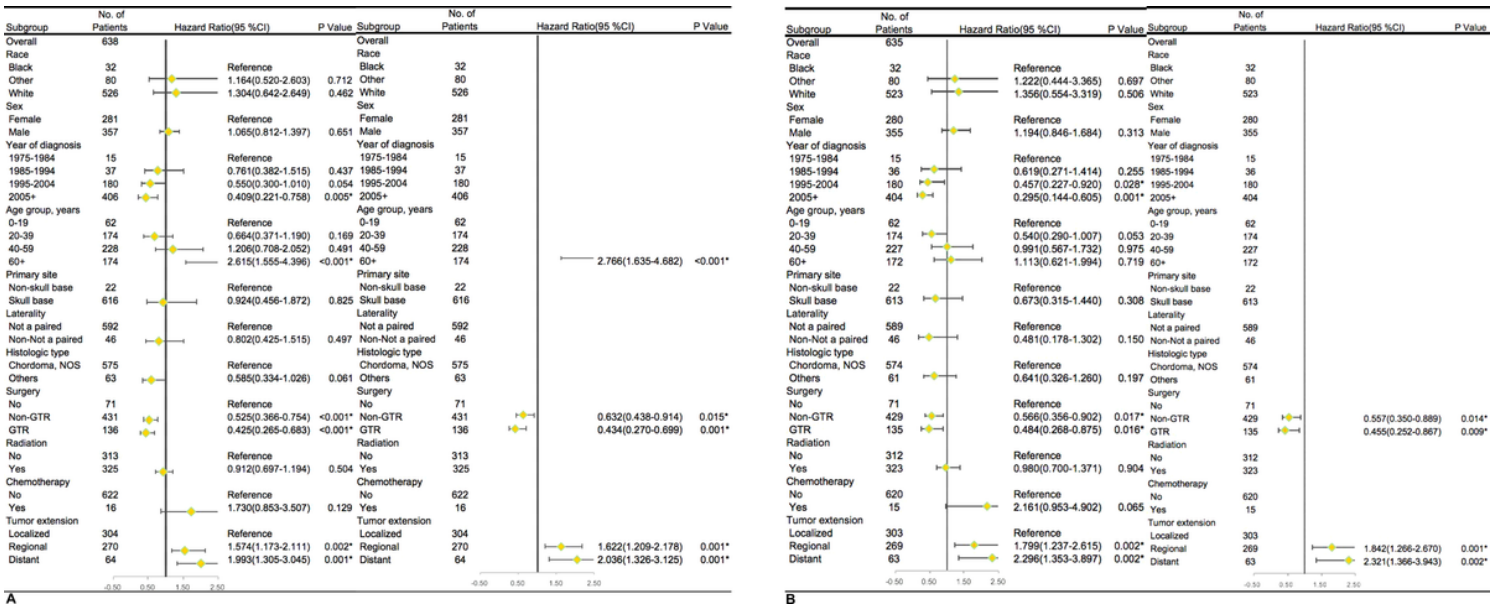

Figure 1

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 (A) and cancer-specific survival (B). *Means P < 0.05.

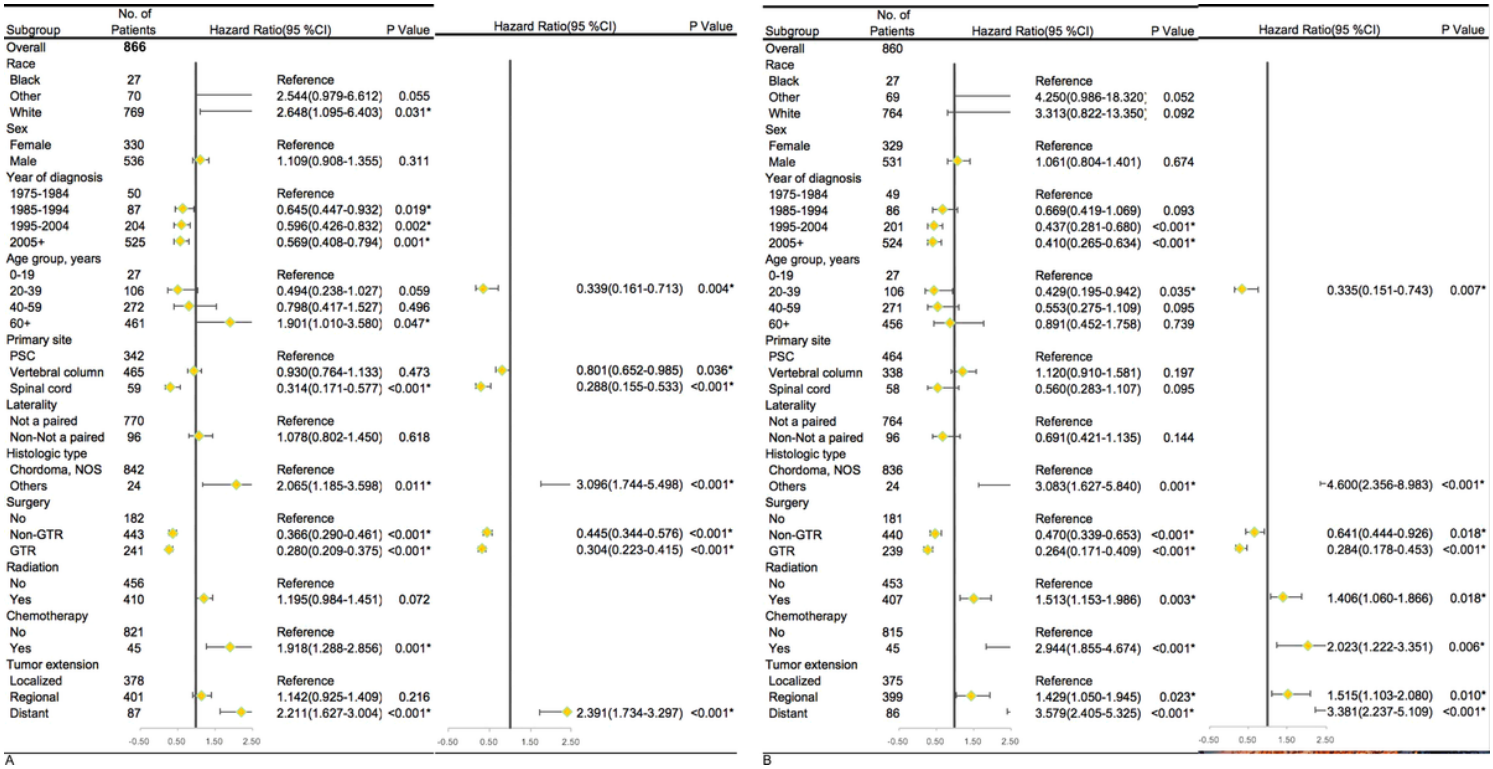

Figure 2

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

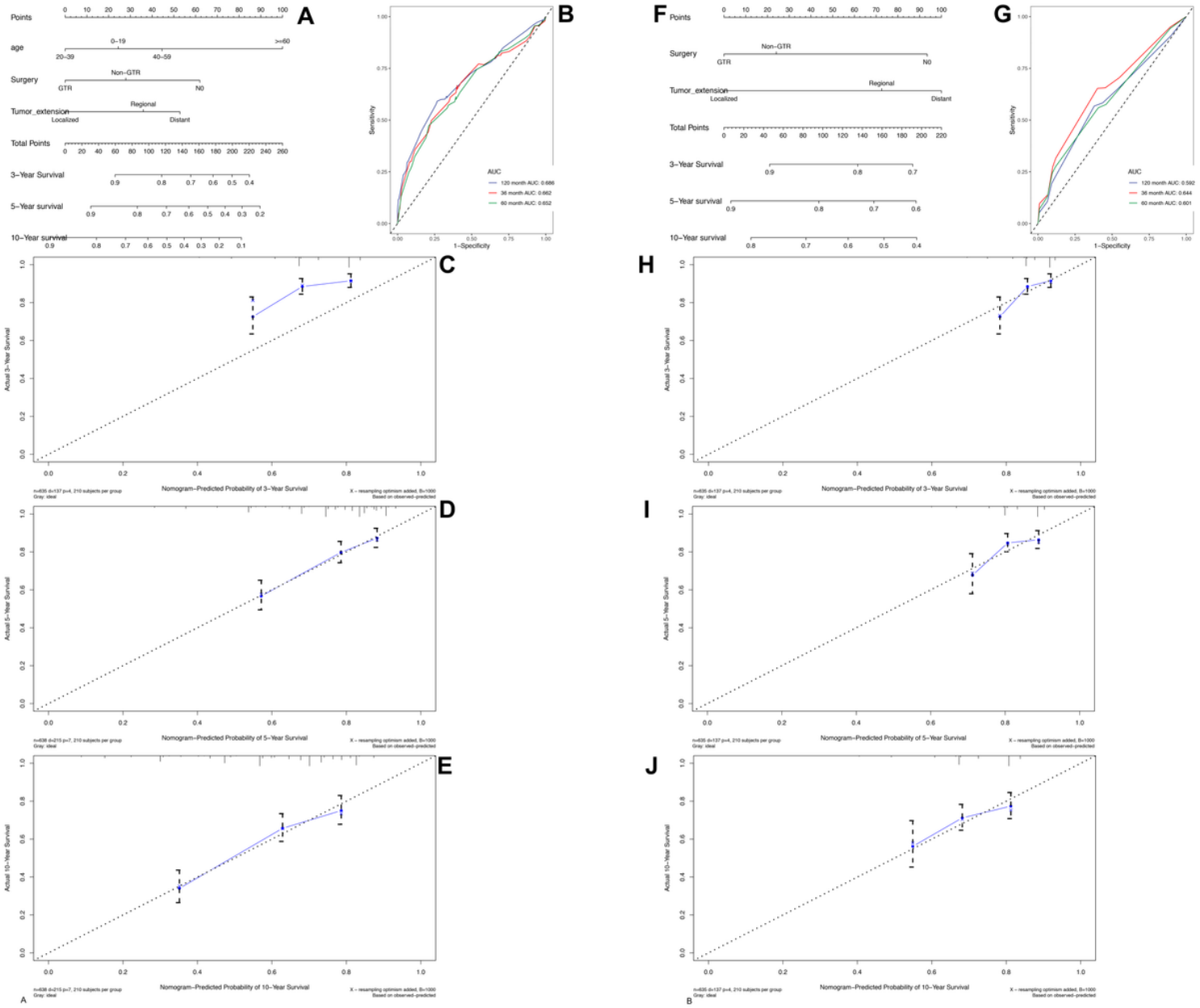

Figure 3

(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.

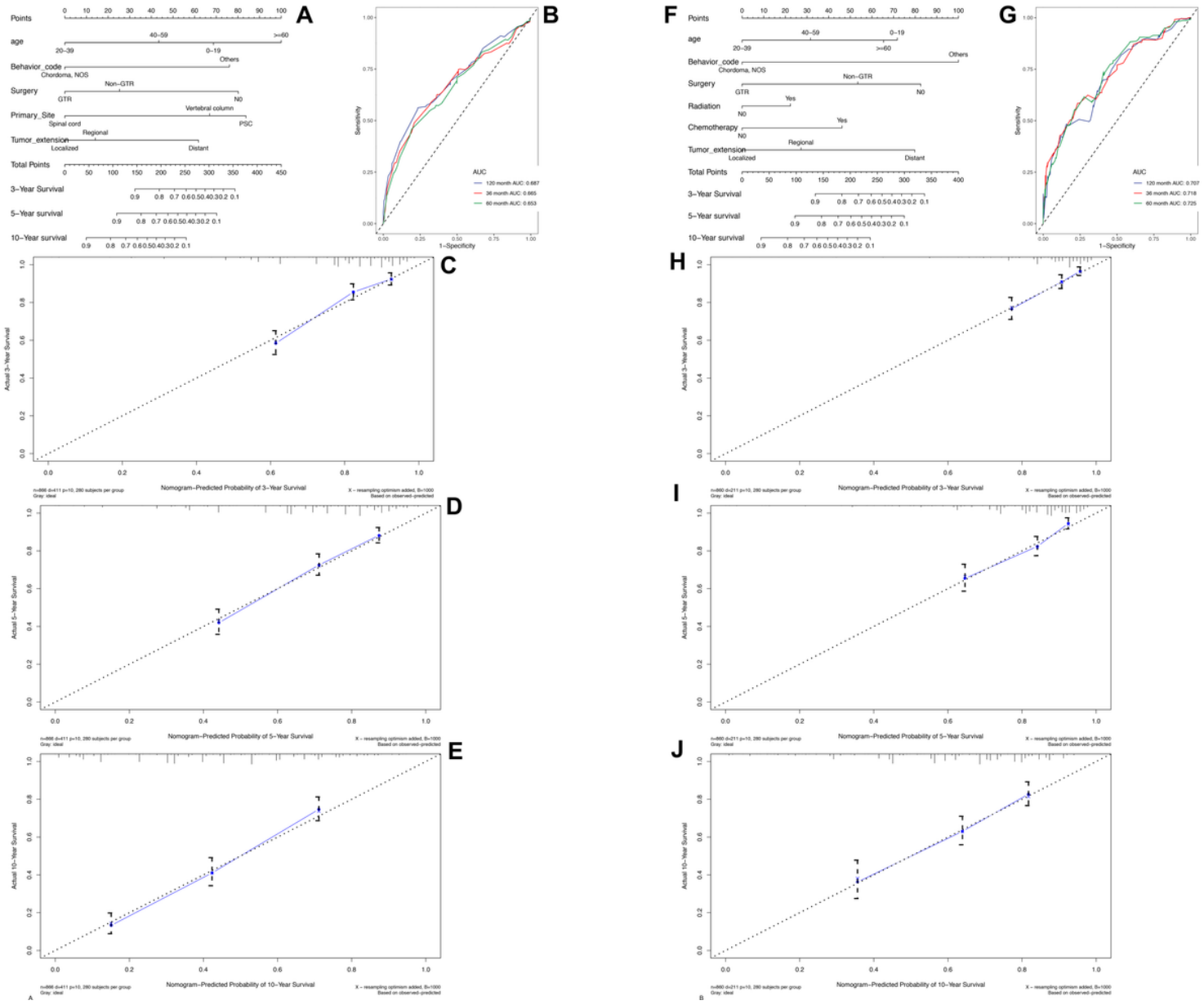

Figure 4

(A) Nomogram used to predict the 3-, 5- and 10-year overall survival rates of patients with spinal cord chordoma. (B) receiver operating characteristic curve of the nomogram for predicting the 3-, 5- and 10-year overall survival rates of patients with spinal cord chordoma. Calibration curve of the nomogram for predicting the 3- (C), 5- (D) and 10-year (E) overall survival rates of patients with spinal cord chordoma. (F) Nomogram used to predict the 3-, 5- and 10-year cancer-specific survival rates of patients with spinal cord 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 cord 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 cord chordoma.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif
- SupplementaryTable1.docx
- SupplementaryTable2.docx