

Spinal column chordoma: prognostic significance of clinical variables and *T (brachyury)* gene SNP rs2305089 for local recurrence and overall survival

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Abstract

Background. Chordomas are rare, locally aggressive bony tumors associated with poor outcomes. Recently, the single nucleotide polymorphism (SNP) rs2305089 in the *T (brachyury)* gene was strongly associated with sporadic chordoma development, but its clinical utility is undetermined.

Methods. In 333 patients with spinal chordomas, we identified prognostic factors for local recurrence-free survival (LRFS) and overall survival and assessed the prognostic significance of the rs2305089 SNP.

Results. The median LRFS was 5.2 years from the time of surgery (95% CI: 3.8–6.0); greater tumor volume ($\geq 100\text{cm}^3$) (hazard ratio [HR] = 1.99, 95% CI: 1.26–3.15, $P = .003$) and Enneking inappropriate resections (HR = 2.35, 95% CI: 1.37–4.03, $P = .002$) were independent predictors of LRFS. The median overall survival was 7.0 years (95% CI: 5.8–8.4), and was associated with older age at surgery (HR = 1.11 per 5-year increase, 95% CI: 1.02–1.21, $P = .012$) and previous surgical resection (HR = 1.73, 95% CI: 1.03–2.89, $P = .038$). One hundred two of 109 patients (93.6%)

with available pathologic specimens harbored the A variant at rs2305089; these patients had significantly improved survival compared with those lacking the variant ($P = .001$), but there was no association between SNP status and LRFS ($P = .876$).

Conclusions. The ability to achieve a wide *en bloc* resection at the time of the primary surgery is a critical preoperative consideration, as subtotal resections likely complicate later management. This is the first time the rs2305089 SNP has been implicated in the prognosis of individuals with chordoma, suggesting that screening all patients may be instructive for risk stratification.

Key words

brachyury | chordoma | rs2305089 | SNP | spine | T gene

Chordomas are rare, locally aggressive bony lesions of the axial skeleton comprising 1% to 4% of all primary bone tumors.¹ From population-based studies with Surveillance, Epidemiology, and End Results (SEER) data, their incidence has been estimated to be 0.8 per 100 000 individuals in the general population and are most often observed in men in their fifth and sixth decades of life.² Despite their indolent course, their locally aggressive nature and large size at diagnosis often complicate management. Wide margin, *en bloc* surgical resection is the evidence-based treatment, but this comes with morbidity challenges due to critical neurological and vascular anatomy. Radiation therapy is now favored as an adjuvant particularly when true oncologic margins are not achievable.^{3,4}

Almost all chordomas demonstrate overexpression of the *T (brachyury)* gene, a transcription factor of the T-box family critical for notochord development. Germline duplications of a region containing only the *T* gene, 6q27, have been found in patients with familial chordoma.^{5,6} Of sporadic chordomas, several single nucleotide polymorphisms (SNPs) have been implicated in chordoma susceptibility, the most prominent of which is rs2305089, where the variant A allele results in a Gly177Asp alteration and has been associated with a sixfold increase in the risk of developing chordoma.^{7,8} The low incidence of chordomas and absence of correlational clinical–histologic data have made identifying other clinical factors with prognostic significance and assessing the value of the rs2305089 SNP difficult. The present study, which included 333 patients from 13 international spine oncology institutions, was conducted with the largest contemporary cohort of patients with chordomas of the spine.⁹ The aims were to (i) identify prognostic factors for local recurrence-free survival (LRFS) and overall survival (OS) of patients with surgically treated spinal chordomas and (ii) assess the prognostic significance of the rs2305089 SNP.

Materials and Methods

Design

Study design was a retrospective review of primarily prospectively collected data with cross-sectional survival. An initial cohort of 333 patients with chordomas treated at 13 centers within Europe, North America, and Australia between December 1985 and January 2013, through the

AOSpine Knowledge ForumTumor (AOSKFT) primary tumor database was reviewed. Patients were included if they were admitted to one of the participating centers and received surgical treatment for their spinal column chordoma. Ethics approval was applied for and received individually at each center prior to accessing patient data. The AOSKFT model and a subset of patients included in this study have been described in previous publications.^{10,11} A secure web-based application (REDCap, Vanderbilt University) was used to gather demographic, clinical, diagnostic, therapeutic, local recurrence, perioperative morbidity, and survival data. For this study, approximately 70% of all data were collected prospectively, with the remaining 30% of data collected through retrospective chart review. Information regarding patient mortality was acquired cross-sectionally. Archived paraffin embedded pathologic specimens were available for 109 patients from 5 of the 13 centers.

Definitions and Staging

The overall neurologic status of patients was classified based on the American Spinal Injury Association (ASIA) impairment scale (AIS) and the Frankel classification system. Patients were all evaluated with CT and MRI of the spine. Tumor volume was estimated using tumor measurements in 3 dimensions in an ellipsoid model.¹² Histologic classification and tumor grading were performed by a musculoskeletal tumor pathologist at each individual center.

For guidance and standardization of treatment, the validated Enneking classification for determination of appropriate surgical margins of musculoskeletal tumors (intralesional, marginal, or wide) was used. A subset of patients when indicated received preoperative embolization and/or adjuvant treatment in the form of preoperative/postoperative chemotherapy and/or radiation therapy. The final surgical margin was based on the pathological assessment, and if wide or marginal margins were achieved, the specimen was classified as Enneking appropriate (EA) resection, while if the specimen was deemed intralesional, the tumor was considered to have undergone Enneking inappropriate (EI) resection.

SNP rs2305089 Genotyping

Chordoma samples were acquired from patients with appropriate consent and institutional approval. DNA

was extracted from formalin-fixed paraffin-embedded (FFPE) slides using the DNA FFPE Tissue Kit (Qiagen, catalog # 56404). Genotyping was performed using Sanger Sequencing of the brachyury gene using the following primers: (forward) 5'-CAGGAAACAGCTATGACCACCGCTA TGAAGTGGGTCT-3' and (reverse) 5'-TAATACGACTCACTAT AGGGCTTTCAGTGCCACCAATCCT-3'.

Statistical Analysis

Descriptive statistics regarding demographics, treatment, recurrence, and mortality were generated. Data are presented as mean±SD, number with (%), or median with interquartile range (IQR). For differences between cohorts, the chi-square test (Pearson's or Fisher's exact) and Student's *t*-tests or Wilcoxon-Mann-Whitney tests were used to establish significance. Kaplan–Meier survival analyses were performed over a 10-year period postoperative and the Mantel–Cox log-rank test was used to assess factors associated with LRFS and OS. Cox proportional hazards regression was used for multivariate analyses. Factors with at least a marginal effect on LRFS and OS ($P \leq .1$) according to univariate analysis were selected for the multivariate analysis. Due to multicollinearity, some variables, although significant at the univariate level, were not finally included in the multivariate models. Data are presented with 95% confidence intervals (CIs). Statistical significance was set at $P < .05$. All statistical analyses were performed using STATA (version 12.0).

Results

Patient Population and Baseline Characteristics

A total of 333 patients with spinal column chordomas treated with surgery were included (Table 1). The majority of patients, 209 (62.8%), were male. Patients had a mean age of 58±14 years at the time of surgery. At the time of presentation, 294 of 318 (92.5%) with available data had pain, 37 of 303 (12.2%) had myelopathy, and 51 of 301 (16.9%) presented with cauda equina syndrome. Most patients did not exhibit significant preoperative neurologic impairment based on their AIS and Frankel scores (Table 1). Sixty-five of 332 patients (19.6%) had previously undergone surgical resection; in 2 of 50 cases (4.0%) wide resection was achieved, 5 (10.0%) marginal resections, and 43 (86.0%) intralesional resections. Upon imaging, tumors were found to be located mostly in the lumbosacral spine, with 78 of 219 patients (35.6%) with lumbar and 63 (28.8%) sacral lesions. Classified as Enneking stage I were 224 of 312 patients (71.8%), and 88 (28.2%) as stage II. Additional tumor parameters are provided in Supplementary Table 1.

One hundred nine patients had pathologic specimens available for study and a comparable mean age at surgery (59±14 y) and gender distribution ($n = 67$, 61.5% male) to the complete study cohort (Supplementary Table 1). Thirty-four (31.2%) had lesions of the mobile spine, while 75 (68.8%) were of the fixed spine. The histologic subtype was known in 36 patients, with 26 (72.2%) with classic chordomas, 3 (8.3%) with chondroid, and 2 (5.6%) with dedifferentiated

Table 1 Demographics, baseline, and chordoma characteristics for the total sample of 333 patients

Variable	
Gender ($n = 333$)	
Male	209 (62.8)
Female	124 (37.2)
Age at surgery, years ($n = 333$)	58 ± 14
Presentation	
Pain ($n = 318$)	294 (92.5)
Myelopathy ($n = 303$)	37 (12.2)
Cauda equina ($n = 301$)	51 (16.9)
Preoperative function	
Frankel classification ($n = 257$)	
A	3 (1.2)
B	1 (0.4)
C	10 (3.9)
D	62 (24.1)
E	181 (70.4)
AIS ($n = 217$)	
A	3 (1.4)
B	1 (0.5)
C	8 (3.7)
D	31 (14.3)
E	174 (80.1)
Previous surgical resection ($n = 332$)	65 (19.6)
Type of previous surgical resection ($n = 50$)	
Intralesional	43 (86.0)
Marginal	5 (10.0)
Wide	2 (4.0)
Chordoma characteristics	
Spinal level ($n = 333$)	
Mobile	166 (49.8)
Fixed	167 (50.2)
Level involved ($n = 219$)	
Cervical	54 (24.7)
Thoracic	24 (11.0)
Lumbar	78 (35.6)
Sacral	63 (28.8)
Number of contiguous levels involved ($n = 330$)	
1	110 (33.3)
2–3	110 (33.3)
≥4	110 (33.3)
Tumor diameter, cm	
Anterior-posterior	5.5 (3.5, 9.5)
Left-right	5.0 (3.3, 8.0)
Superior-inferior	5.0 (3.3, 8.0)
Volume, cm ³ ($n = 265$)	
<100	151 (57.0)

Table 1 Continued

≥100	114 (43.0)
Pathological fracture (<i>n</i> = 320)	36 (11.3)
Diagnostic biopsy (<i>n</i> = 333)	
Open	50 (15.0)
Trocar CT-guided	165 (49.5)
Intraoperative	61 (18.3)
Other	57 (17.1)
Enneking grade (<i>n</i> = 312)	
I	224 (71.8)
II	88 (28.2)

Values are given as number with (%), mean±SD, or as median (p25, p75).

tumors; 102 (93.6%) harbored the A variant at rs2305089, with 66 patients (60.6%) with an AA genotype, 36 (33.0%) GA, and 7 (6.4%) GG. No statistically significant associations were observed between patient SNP status and gender ($P = .426$), ethnicity ($P = 1.000$), age at surgery ($P = .149$), spinal level ($P = .675$), tumor grade ($P = .432$), and chordoma subtype ($P = 1.000$).

Treatment

All patients underwent surgical resection of their chordomas. The treatment data are summarized in **Table 2**. Overall, surgery was classified as EA in 179 out of 300 patients (59.7%) and EI in 121 (40.3%). Several factors were significantly associated with EA resections in a univariate model, including younger age at surgery ($P = .017$), no previous surgical resection ($P < .001$), trocar CT-guided biopsy compared with open and intraoperative biopsy ($P < .001$), lack of neurologic impairment as assessed by the Frankel classification and AIS ($P = .007$), tumors of the fixed spine ($P < .001$), greater number of vertebral levels spanned by the tumor ($P = .029$), nerve root sacrifice ($P < .001$), and lack of adjuvant therapy ($P < .001$) (Supplementary Table 2). The extent of resection was comparable in patients with and without the A variant, with 62 patients (62.6%) harboring the A variant and 3 of 7 (42.9%) without the A variant undergoing EA resections ($P = .426$). Of 326 patients, 117 (35.9%) received adjuvant therapy in the form of radiation therapy or chemotherapy (**Table 2**). Significantly fewer patients harboring the A variant underwent radiation therapy compared with those without [21 (20.6%), 3 (42.9%), respectively; $P = .048$].

Patient Outcomes

Following treatment, 110 of 324 patients (34.0%) experienced local recurrence within 10 years of surgical resection, and 104 of 333 (31.2%) had died (Supplementary Table 3). The median LRFS was 5.2 years from the time of surgery (95% CI: 3.8–6.0) (**Fig. 1A**). In our univariate model, the development of local recurrence was significantly associated with previous surgical resection ($P < .001$),

Table 2 Summary of chordoma treatment for the total sample of 333 patients

Variable	
Preoperative embolization (<i>n</i> = 319)	40 (12.5)
Surgical approach (<i>n</i> = 322)	
Anterior	16 (5.0)
Posterior	169 (52.5)
Combined	137 (42.5)
Fixation (<i>n</i> = 329)	179 (54.4)
Sacrifice of neurologic elements	
Spinal cord (<i>n</i> = 307)	1 (0.3)
Cauda equina (<i>n</i> = 307)	10 (3.3)
Nerve roots (<i>n</i> = 306)	183 (59.8)
Number of levels (<i>n</i> = 7) ^a	3 (2, 4)
Side (<i>n</i> = 129) ^a	
Unilateral	20 (15.5)
Bilateral	109 (84.5)
Level (<i>n</i> = 183) ^{a, b}	
Cervical	12 (6.6)
Thoracic	21 (11.5)
Lumbar	37 (20.2)
Sacral	125 (68.3)
Coccygeal	34 (18.6)
Surgical margins (<i>n</i> = 299)	
Wide or marginal	201 (67.2)
Intralesional	98 (32.8)
Enneking appropriateness (<i>n</i> = 300)	
EA	179 (59.7)
EI	121 (40.3)
Adjuvant therapy (<i>n</i> = 326)	117 (35.9)
Chemotherapy (<i>n</i> = 330)	
Preoperative	10 (3.0)
Postoperative	12 (3.6)
Both	2 (0.6)
None	306 (92.7)
Radiation therapy (<i>n</i> = 326)	
Preoperative	40 (12.3)
Postoperative	65 (19.9)
Both	6 (1.8)
None	215 (66.0)
Type of radiation therapy (<i>n</i> = 97)	
Conventional	41 (42.3)
IMRT	22 (22.7)
Proton beam	26 (26.8)
SRS	8 (8.2)

Values are given as number with (%) or as median (p25, p75).

EA: Enneking appropriate, EI: Enneking inappropriate, IMRT: intensity-modulated radiation therapy, SRS: stereotactic radiosurgery.

^aRepresents the patients with nerve root sacrifice.

^bPercentages given out of 183; patients with tumors spanning multiple levels were counted multiple times.

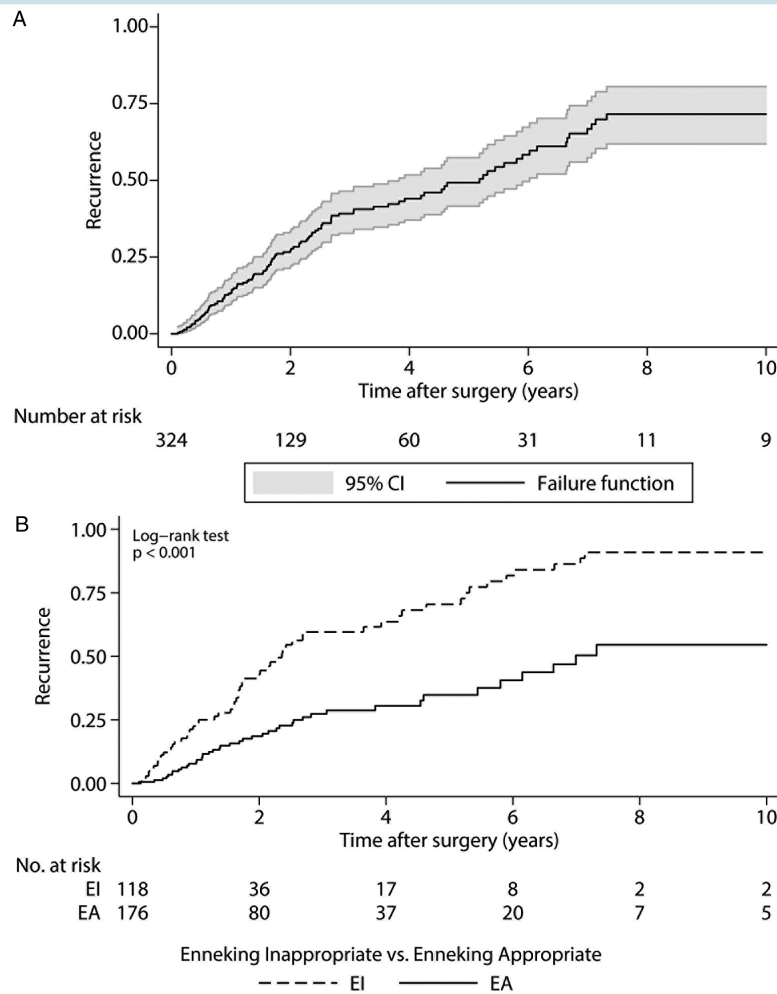


Fig. 1 Kaplan–Meier local recurrence-free survival curves. (A) For 324 patients; (B) 294 patients by Enneking appropriateness. *P* value from log-rank test. Gray shaded regions represent 95% CIs. EA: Enneking appropriate; EI: Enneking inappropriate.

intraoperative biopsy compared with open and trocar CT-guided biopsy ($P < .001$), Frankel classification or AIS grade E at presentation compared with grades A through D ($P = .021$), greater tumor volume ($\geq 100\text{cm}^3$) ($P = .010$), Enneking stage I disease ($P = .045$), sacrifice of nerve roots ($P = .019$), intralesional compared with wide or marginal margins at resection ($P < .001$), EI resection compared with EA (Fig. 1B, $P < .001$), and use of adjuvant therapy ($P = .009$). In the multivariate model, greater tumor volume ($\geq 100\text{cm}^3$) (hazard ratio [HR] = 1.99, 95% CI: 1.26–3.15, $P = .003$) and Enneking appropriateness (EI resection) (HR = 2.35, 95% CI: 1.37–4.03, $P = .002$) were both independent predictors of LRFS (Supplementary Table 4).

The median OS following surgery was 7.0 years (95% CI 5.8–8.4) (Fig. 2). Decreased survival was significantly associated with older age at the time of surgery (≥ 65 y) ($P < .001$), previous surgical resection ($P = .002$), open and intraoperative biopsy compared with trocar CT-guided biopsy ($P = .035$), Frankel classification or AIS grades A through D at presentation compared with grade E ($P < .001$), and use of adjuvant therapy ($P = .036$). Degree of resection and

Enneking appropriateness were not significantly associated with OS ($P = .182$ and $P = .113$, respectively). In our final multivariate model, older age at surgery (HR = 1.11 per 5-y increase, 95% CI: 1.02–1.21, $P = .012$) and previous resection (HR = 1.73, 95% CI: 1.03–2.89, $P = .038$) were associated with decreased survival (Supplementary Table 4).

We repeated the multivariate Cox regression analysis for local recurrence and survival over a 10-year period following surgical resection in the subgroup of 109 patients who had available genotyping data. Regarding local recurrence, adjustment for SNP genotype attenuated somehow the harmful effect of both EI resection and high volume. Nevertheless, there was no evidence for a significant association between local recurrence and SNP genotype. After adjusting for SNP genotype in the multivariate Cox regression model evaluating survival, the association of survival with age at surgery and previous surgical resection, identified in the overall sample size, remained almost unchanged. We revealed significantly higher mortality risk for patients with GA or GG genotype compared with patients with AA (Table 3).

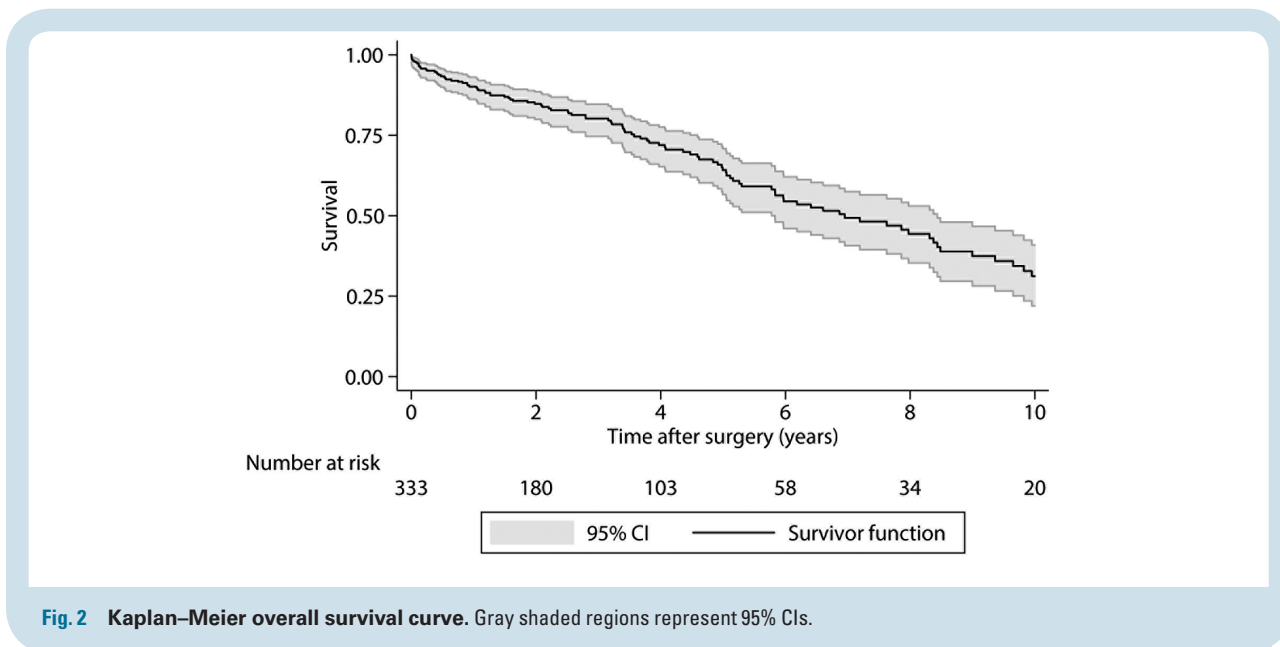


Table 3 Results of the multivariate Cox regression analysis for local recurrence and survival over a 10-year period following surgical resection

Variables	Category	Local Recurrence	
		Hazard Ratio (95% CI)	P value
Age at surgery	5 y more	1.04 (0.90, 1.20)	0.606
Volume (cm ³)	< 100	Ref.	0.193
	≥ 100	1.75 (0.75, 4.05)	
Enneking appropriateness	EA	Ref.	0.118
	EI	2.02 (0.84, 4.86)	
SNP genotype	AA	Ref.	0.735
	GA	0.86 (0.36, 2.07)	
	GG	1.20 (0.26, 5.57)	
Variables	Category	Survival	
		Hazard Ratio (95% CI)	P value
Age at surgery	5 y more	1.17 (1.02, 1.34)	0.024
SNP genotype	AA	Ref.	0.024
	GA	2.80 (1.15, 6.85)	
	GG	6.85 (2.33, 20.17)	
Previous surgical resection	No	Ref.	0.026
	Yes	2.91 (1.14, 7.45)	

EA: Enneking appropriate, EI: Enneking inappropriate.

Of the genotyped patients, 42 of 108 (38.9%) experienced local recurrence within 10 years of surgical resection, and 31 of 109 (28.4%) had died (Supplementary Table 3). Patients harboring the A variant were found to have significantly improved survival, with a median OS of 7.6 years compared with those lacking the variant, at 3.8 years (Fig. 3A, $P = .001$). However, the median LRFS for patients with the A variant was 3.1 years, comparable to 1.8 years in those without (Fig. 3B, $P = .876$).

Discussion

The rarity of chordomas has limited previous studies, as most of the evidence guiding management is single-center level IV or V.⁹ Three hundred thirty-three patients were included in this study from multiple centers, the largest contemporary surgical cohort of chordomas of the mobile spine and sacrum assembled. Overall, the median LRFS was 5.2 years and median OS 7.0 years, comparable to a 2013 study using SEER administrative data up to 2009, where the median OS was 7.7 years.¹³ In our study, greater tumor volume and Enneking appropriateness (EI resection) were both independent predictors of LRFS, and older age and previous surgical resection were independent predictors of OS. In several single-center small studies of chordomas of the mobile spine and sacrum from the 1990s to early 2000s, the degree of surgical resection was the only factor consistently identified as predictive of LRFS and OS.^{14–18} Two studies using registry data by Mukherjee et al and Lee et al included over 400 patients, and metastatic disease, tumor outside of the periosteum and tumor size greater than 5.0cm, use of chemotherapy, and surgical margins were found to be predictive of OS.^{19,20} While adequately powered, these administrative databases lack detailed information regarding patient management and can contain inaccuracies.

Of the more recent studies, that of Stacchiotti and colleagues,²¹ in a series of 138 patients with chordomas of the mobile spine and sacrum, also identified tumor size and surgical margins to be predictive of LRFS in a multivariate model. In contrast to our study, the only factor they found to be an independent predictor of OS was tumor size. Aggressive approaches have been demonstrated in numerous studies to be associated with lower rates of local recurrence and improved disease-free survival.^{9,11,21–23} Violation of the tumor capsule during resection and subtotal resection have both been associated with early local recurrence.^{18,24} However, the ultimate goal of treatment

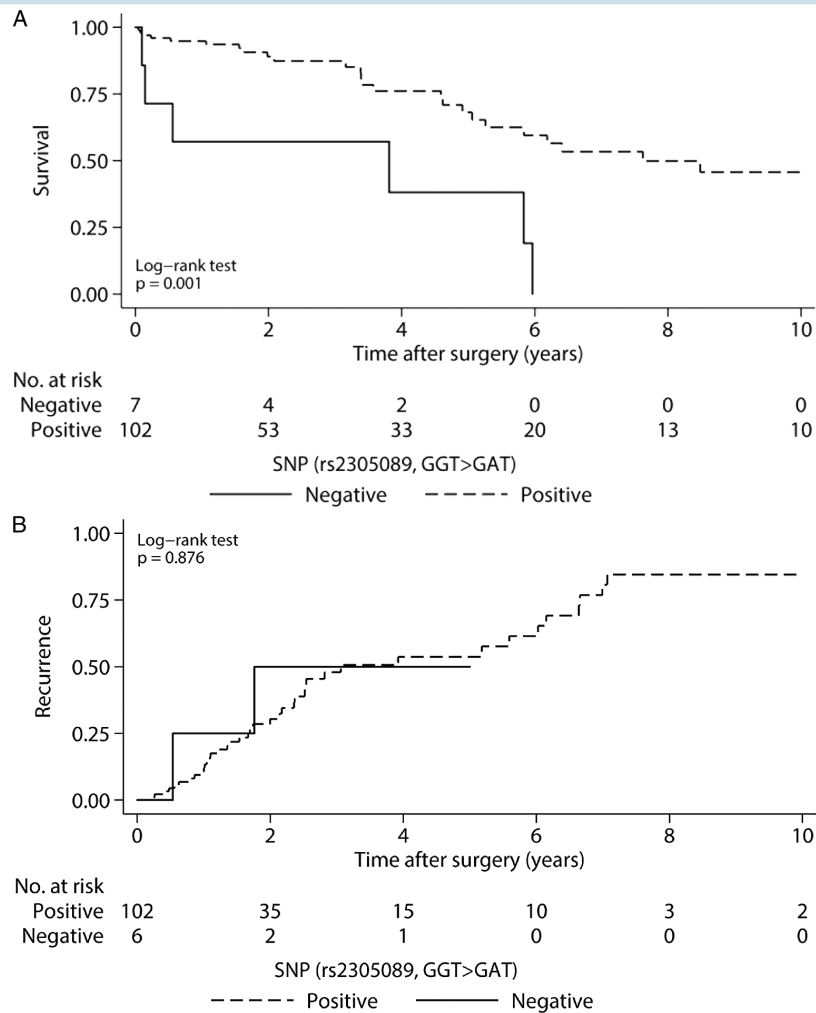


Fig. 3 Kaplan-Meier survival curves for genotyped patients. (A) Overall survival for all 109 genotyped patients by SNP status. (B) Local recurrence-free survival for genotyped patients by SNP status. P values from log-rank tests. Gray shaded regions represent 95% CIs.

is maximal safe aggressive resection and preservation of neurologic function. Previous studies have found that wide *en bloc* resection is achievable in up to 50% of lesions of the sacrum, but at significantly lower rates for spinal and skull base chordomas.^{18,25,26}

Interestingly, in our multivariate analysis of prognostic factors for OS, younger age at surgery and lack of previous surgical resection were the only factors independently associated with improved survival, and Enneking appropriateness was not predictive of survival. The majority of previous studies did not include prior surgery in their analyses of prognostic factors, and of the studies which considered this factor, poorer outcomes were seen in patients who had undergone previous resections. In a study by Boriani and colleagues,¹⁰ 16 of 18 patients (89%) who had undergone prior resections experienced disease recurrence. However, it is important to also recognize the relationship between previous tumor resection and later surgical outcomes. In our cohort, 48 of 50 patients (98.0%) were known to have previous subtotal resections, which likely made achieving an Enneking appropriate resection during reoperation

considerably more difficult. These results suggest that the ability to achieve a wide *en bloc* resection at the time of the primary surgery is a critical preoperative consideration, as intralaminar resections may complicate later treatment options for recurrent disease and ultimately have a negative impact on outcomes. Therefore, consideration should be made to refer these patients to centers that have expertise in the multidisciplinary surgical management of these rare tumors.

The benefit of adjuvant therapy in treating spinal chordomas has still not been definitively demonstrated. Chemotherapy has been used after subtotal resections, but no chemotherapeutic agents are currently approved for chordoma. With respect to radiation therapy, reported rates of local recurrence remain high, with LRFS around 50% to 60% at 5 years.^{3,4} Stacchiotti and colleagues found no significant effect of radiotherapy on OS and LRFS but noted that low doses were used and newer techniques were not employed.²¹ Indeed, most studies of chordoma incorporate patients treated in the 1960s to 1980s, and radiotherapy regimens in these older studies are heterogeneous. Within

our cohort, adjuvant therapy was not a significant predictor of LRFS in the multivariate model, which may be due to the significant association between Enneking appropriateness and adjuvant therapy. However, newer radiotherapy regimens have shown promise in recent clinical trials; in a phase II trial of high dose photo/proton radiotherapy for spinal chordomas and other primary spinal column tumors, high rates of local control were seen at 5 and 8 years posttreatment.^{27,28}

Prior to this study, no biomarkers existed to guide risk stratification. We found that OS was significantly improved in patients with the A variant at rs230508 compared with those without, but this was not accounted for by local recurrence. Relatively little is understood regarding the molecular biology of chordomas compared with other bony malignancies. The *T* (*brachyury*) gene has been implicated in the pathogenesis of the disease, and the A variant at rs2305089, a common SNP found in 47% of individuals of northern and western European ancestry, is associated with sporadic chordoma risk. While brachyury is known to be overexpressed in almost all chordomas, it is also expressed in lung, colorectal, breast, and prostate cancers and is associated with a poor prognosis.^{5,29–31} Upregulation of brachyury results in upregulation of mesenchymal markers, downregulation of epithelial markers, and increased cell migration and invasion; ultimately, it is thought to promote the epithelial-mesenchymal transition. However, the genetic basis of brachyury overexpression appears complex and cannot be completely accounted for by somatic and germline alterations that have currently been identified. High-resolution array comparative genomic hybridization demonstrated the presence of germline duplications of a region of 6q27 containing only the *T* gene in 4 out of 7 multiplex families.⁶ Subsequently, somatic copy number gains, including minor allelic gain in 4.5% and amplification in 7% of 181 chordoma cases were identified, but studies have not revealed any mutations of the coding exons or promoter regions of the *T* gene.³²

Pillay et al found that in copy number–neutral chordoma cases, the relative expression of *T* and its downstream targets was significantly higher in chordomas with the AA genotype compared with the GA genotype, and suggested that the rs2305089 SNP could alter the binding capacity of brachyury.⁷ However, these findings and the association of brachyury with cell migration and invasion appear incongruous with our results that patients with the A variant have a significantly improved prognosis compared with those without. It is possible that the SNP may simultaneously increase brachyury expression and increase chordoma vulnerability to innate antitumor mechanisms or certain treatment modalities. Alternatively, chordomas in patients without the SNP may rely on alternate mechanisms to upregulate brachyury or other pathways, which could result in a more aggressive phenotype. The ultimate impact of the rs2305089 SNP on brachyury is unknown and requires further investigation utilizing high quality, prospectively gathered samples; however, screening all patients for the SNP may still be instructive for risk stratification. A limitation to this study is that only DNA derived from archived FFPE samples was studied, limiting our ability to query for T-gene duplications, which could potentially impact overall survival.

Despite the use of large-scale population-based multicenter data, the current study remains limited by the rarity of chordomas and variability between institutions. The limited number of patients in our cohort without the A variant prevented us from exploring possible interactions among SNP status, adjuvant therapy, and other prognostic factors and their impact on OS. Further studies are needed to fully elucidate the significance of rs2305089 SNP status. Nevertheless, this study remains the largest contemporary series of spinal chordomas and is the first time the rs2305089 SNP has been implicated in the prognosis of individuals with chordoma.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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Conflict of interest statement. No conflicts of interest to disclose.

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