ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2026.2025-11-6

J Oncol Sci

Long-term Outcomes and Prognostic Factors in Chordoma: A 20-year Single-center Experience

Berkay YEŞİLYURT, Efnan ALGIN, Öznur BAL, Selin AKTÜRK ESEN, Doğan UNCU

University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Medical Oncology, Ankara, Türkiye

ABSTRACT

Objective: Chordoma is a rare, locally invasive malignant bone neoplasm originating from notochordal vestiges. However, long-term outcome data remain limited. Radical surgical excision and radiation therapy constitute the primary therapeutic approaches, whereas systemic treatments have demonstrated only marginal efficacy. This investigation sought to examine the clinical attributes, therapeutic approaches, and survival determinants in chordoma cases managed across two decades at a tertiary medical facility in Türkiye.

Material and Methods: A retrospective review was conducted of 18 patients diagnosed with chordoma from 2003 through 2024. Essential data, encompassing demographic, histological, and intervention particulars, were retrieved from the hospital archives. Survival metrics—such as overall survival (OS), progression-free survival (PFS1-3), local recurrence-free survival (LRFS), and metastasis-free survival (MFS)—were estimated using the Kaplan-Meier method. The influence of therapeutic and clinical parameters was evaluated using univariate Cox proportional hazards analyses.

Results: The median participant age stood at 53.5 years, with males constituting 72.2% of the cohort. The median observation duration was 96.2 months. Primary surgery was performed in 15 patients (83.3%), while 80% of patients received supplementary radiotherapy. Median OS (mOS) and PFS1 intervals were 45.3 months and 19.5 months, respectively. Subjects undergoing radiation exhibited significantly longer OS and PFS than non-irradiated counterparts ($p<0.05$). Complete (R0) excision correlated with a substantially extended LRFS (27.7 versus 3.6 months, $p=0.002$). Systemic treatment was associated with a marginal improvement in post-relapse survival ($p=0.064$). Lesion dimensions, patient age, and sex lacked a meaningful association with survival outcomes.

Conclusion: This two-decade institutional survey highlights the pivotal importance of thorough surgical resection and adjuvant radiation therapy in improving prognosis for chordoma patients. Noteworthy survival advantages emerged even with standard photon-based radiotherapy. Timely detection, extensive surgical debulking, and combined-modality strategies remain fundamental to optimizing prognosis in this malignancy. Expanded collaborative research initiatives are essential to further delineate therapeutic protocols and elucidate the utility of systemic agents.

Keywords: Cancer diagnosis and treatments; chemotherapy; medical oncology; oncology

INTRODUCTION

Chordoma represents an uncommon osseous neoplasm arising from vestigial notochordal tissues. The annual occurrence sits around 0.08 per 100,000 individuals, comprising 1-4% of primary bone cancers.[1] These tumors predominantly affect the axial skeleton, most commonly appearing in the skull base (clivus) region (38-39%), followed by the sacral area (34%) and spinal segments (27%).[2] Typically emerging during middle to late adulthood, incidence peaks between the 75-84 year bracket, with a slight male predominance observed at roughly 1.5:1.[2]

Histopathologically classified, these lesions are of notochordal origin, demonstrating slow but locally invasive growth. Although their expansion rate is relatively slow, chordomas exhibit infiltrative behaviour, They often reach large dimensions and compress critical features like

Correspondence: Berkay YEŞİLYURT MD,
University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Medical Oncology, Ankara, Türkiye

E-mail: berkay.byi@gmail.com

ORCID ID: orcid.org/0000-0003-0130-7111

Received: 13.11.2025 **Accepted:** 08.04.2026 **Epub:** 13.04.2026

Cite this article as: Yeşilyurt B, Algın E, Bal Ö, Aktürk Esen S, Uncu D. Long-term outcomes and prognostic factors in chordoma: a 20-year single-center experience. J Oncol Sci. [Epub Ahead of Print]

Available at journalofoncology.org

vascular and neural pathways.[1] Clinical presentations shows regional variability: cranial lesions often manifest as cranial neuropathies or cephalalgia, whereas spinal or sacral masses may produce chronic discomfort, neurological impairment, or mass effect. While metastatic spread does occur, the disease trajectory predominantly hinges on local recurrence and progression.[3,4] Thus, repeated surgeries may be necessary. Prognosis worsens, particularly with multiple recurrences; the literature reports that 5-year overall survival (OS) after the first local recurrence is 50%, but after the second recurrence, it drops below 20%.[4]

Diagnostic confirmation relies upon both radiographic assessment and microscopic evaluation. Pathognomonic vacuolated cells in biopsy specimens, coupled with immunohistochemical brachyury expression, establish conclusive identification.[1] The classic histological pattern predominates, though rarer chondroid and aggressive dedifferentiated variants exist. The exact prognostic significance of these histological variants remains uncertain given their scarcity.

Therapeutic strategies prioritize local intervention due to the tumor's infiltrative nature. Optimal management hinges on achieving maximum feasible surgical excision, with R0 resection representing the treatment standard. Considerable evidence confirms superior local control and survival among patients attaining margin-negative resections.[1] Indeed, large series show that local control and survival are significantly improved in patients who can achieve complete resection.[3,4] However, anatomical constraints often limit radical excision. This is particularly relevant to skull-base, cervical, and sacral lesions, which are frequently large at diagnosis. Salvage procedures often become necessary as recurrence develops, with survival rates dropping precipitously after multiple recurrences, literature indicating five-year survival plunging from 50% after initial recurrence to under 20% following subsequent episodes.[1]

Radiotherapy (RT) is a fundamental component of treatment for cases in which surgical excision remains incomplete or the risk of recurrence is elevated. Although chordomas exhibit notable resistance to traditional photon-based RT, more refined, high-dose fractionated techniques have demonstrated greater efficacy.[5] Particle therapies, notably proton-beam and carbon-ion RT, enhance local tumor control by employing particles with linear energy transfer superior to that of photons. Similarly, innovative RT approaches—such as proton, carbon-ion, or stereotactic high-dose irradiation—have shown promising outcomes in managing residual disease, with select studies reporting results on par with surgical intervention.[6] Typically, RT is advised post-surgery, particularly when surgical margins appear positive; administering elevated doses might then prove advantageous in curbing local relapse.

Systemic treatment options occupy a restricted niche in chordoma management. Conventional chemotherapy is minimally effective, and there is no established protocol. Given the frequent overexpression of platelet-derived growth factor receptors (PDGFR) and epidermal GFR (EGFR) in chordomas, tyrosine kinase inhibitors, such as imatinib, have been evaluated. A phase II trial using imatinib reported disease stabilization in 70% of advanced cases, alongside a median progression-free survival (PFS) of 9 months and OS of 34 months.[7] In a retrospective study, the best response under imatinib was stable disease in 74% of patients, and the median PFS was 10 months.[7] Although partial response or long-term stabilization have been reported in small case series with EGFR inhibitors (erlotinib, gefitinib, etc.) and angiogenesis-targeted agents (sorafenib, pazopanib, etc.), they do not have a standardized level of evidence and cure with systemic treatment alone is rare.[1,8] Presently, an integrated approach—primarily extensive resection combined with RT—dominates chordoma care, while evolving targeted and immunotherapeutic strategies remain confined to investigative settings for refractory disease.

Existing literature is predominantly derived from retrospective, fragmented cohorts with inconsistent follow-up. Consequently, deficiencies persist in robust real-world evidence and extended survival data. Additionally, no comprehensive national dataset exists for chordomas in Türkiye. This investigation seeks to address such omissions by detailing the clinicopathological and oncological trajectories of chordoma patients monitored over two decades at a specialized Turkish institution, thereby refining therapeutic paradigms for these infrequent malignancies.

MATERIAL AND METHODS

Patient Selection

The study was retrospective. Twenty-two patients with histopathologically confirmed chordoma, diagnosed at University of Health Sciences Türkiye, Ankara Bilkent City Hospital between 2003 and 2024, were analyzed using the hospital automation system. Patients with missing or incomplete clinical data in the hospital records were excluded. A total of four patients were excluded for this reason. A total of 18 patients were included in the study. Clinical, pathological, treatment, and survival data were collected from the electronic patient record system. Age, gender, size, resection margin status (R0, R1/R2), primary surgery, whether adjuvant or definitive RT was administered, systemic treatment history, systemic treatments and number of stages received,

surgery in case of recurrence, recurrence RT status, time to development of local recurrence during follow-up, time to distant metastasis, times to progression, date of last follow-up or exitus, tumor location (thoracic-cervical and lumbar-sacral), histological variant features, Ki-67 proliferation index, and EGFR mutation status were recorded. RT was delivered using conventional photon-based techniques. The total dose typically ranged from 60 to 74 Gy, administered in daily fractions of 1.8-2 Gy. RT was delivered postoperatively in most cases, particularly in patients with positive or close surgical margins or as definitive treatment in inoperable cases. Surgical margins were evaluated based on histopathological examination and classified as R0 (microscopically margin-negative) or R1/R2 (microscopically or macroscopically margin-positive). Information on the surgical technique (*en bloc* versus intralesional resection) was not consistently available because the study was retrospective.

Statistical Analysis

For descriptive data analysis, continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR), and categorical variables are presented as numbers and percentages. Follow-up duration was calculated using the Reverse Kaplan-Meier method. Kaplan-Meier methods were used for survival analyses, and differences between groups were assessed using the log-rank test. Patients were monitored with imaging studies (magnetic resonance imaging or computed tomography) at approximately 6- to 12-months intervals, or earlier when clinically indicated. Disease progression was determined based on radiological evidence of local recurrence or distant metastasis, as assessed by the treating physicians. OS (survival), PFS1-3, local recurrence-free survival (LRFS), time from diagnosis to metastasis, survival after first recurrence, survival after metastasis, and metastasis-free survival (MFS) were analyzed as time-to-event outcomes, with surviving patients censored. OS was defined as the time from diagnosis to death from any cause or to last follow-up. PFS1-3 was defined as the time from the initiation of each treatment line to disease progression or death, whichever occurred first. LRFS was defined as the time from surgery to the occurrence of local recurrence. MFS was defined as the time from diagnosis to the development of distant metastasis. The effects of clinical variables (age, sex, tumor size, resection status, RT status, systemic therapy) on survival were analyzed using a univariate Cox proportional hazards model; results are reported as hazard ratio (HR) and 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$. Analyses were performed using SPSS Statistics version 25.1.

Ethics Approval

This study was conducted with the approval of the University of Health Sciences Türkiye, Ankara Bilkent City Hospital Medical Research Scientific and Ethical Evaluation Board and in accordance with the Declaration of Helsinki (approval number: TABED 1-25-1840, date: 05.11.2025).

RESULTS

Descriptive Statistics

Descriptive statistics are presented in Table 1. The majority of the 18 patients were male, and the median age was 53.5 years (Table 1). The median tumor size was 36 mm, the median follow-up time was 96.2 months, and the rate of primary surgery was 83.3%.

Survival Statistics

The median OS (mOS) was 45.3 months (IQR 19.43-93.9), and mPFS1 was 19.5 months (IQR 8.67-66.7). Two-year OS was 72.2%, and five-year OS was 44.4% (Table 2). At the end of follow-up, 7 patients were still alive. During follow-up, 5/18

TABLE 1: Descriptive statistics.

Variable	Value
Number of patients	18
Gender	5 females (27.8%), 13 males (72.2%)
Median age (IQR)	53.5 years of age (IQR: 39.0-66.3)
Median tumor size (IQR)	36 mm (IQR: 25.5-75.5)
Median follow-up time (reverse Kaplan-Meier)	96.2 months (95% CI: 58.8-133.6)
Number of patients undergoing primary surgery	15/18 (83.3%)
Resection margin status	R0: 8/15 (53.3%); R1-R2: 7/15 (46.7%)
Tumor localisation	Lower spine/upper spine 13/5
Adjuvant RT	12/15 (80%)
Systemic treatment	9/18 (50%)

IQR: Interquartile range; R1-R2: Microscopic/macroscopic positive surgical margin; CI: Confidence interval; RT: Radiotherapy.

(27.8%) patients were progression-free at five years after diagnosis. The two-year PFS rate was 50% (9/18).

During follow-up, 83.3% (15/18) of patients experienced recurrence. While the first recurrence in 11 patients was a local recurrence, the first recurrence in 4 patients was a distant metastasis. Additionally, 2 patients developed distant metastases following local recurrence.

The mOS after the first recurrence was approximately 40.1 months, and the mOS after distant metastasis was 20.1 months. The 5-year LRFS was 44.4% (8/18).

According to survival analyses, no significant differences were found in OS or PFS between gender groups or age groups. While female patients appeared to have longer OS and PFS than male patients, this difference was not statistically significant (OS: p=0.420; PFS: p=0.932). Similarly, when comparing the <53.5 and ≥53.5 age groups, no significant difference was found in OS (p=0.800) and PFS (p=0.257).

In contrast, those who received adjuvant or inoperable definitive RT after surgery were associated with significant increases in PFS and OS compared to those who did not receive RT (mPFS 22.4 months vs. 5.97 months, p<0.001; mOS 47.9 months vs. 7.7 months, p=0.042) (Table 3). No significant effect on survival was observed in the classification based on tumor size (<36 mm vs. ≥36 mm). For tumors smaller than 36 mm, the mPFS was 19.5 months; for tumors larger than 36 mm, the mPFS was 10.7 months (log-rank p=0.928). The mOSs were 81.5 and 36.5 months, respectively (log-rank p=0.928). When tumor size was included in the Cox regression model as

TABLE 2: Survival analyses.

Endpoint	Median (months)	IQR/95% CI	2-year ratio (%)	5-year ratio (%)	Notes
OS	45.3	IQR: 19.43-93.9	72.2	44.4	7 patients alive at follow-up
PFS1	19.5	IQR: 8.67-66.7	50.0	-	5/18 patients progression-free at 5 years
PFS2	10.7	IQR: 4.1-21.5	-	-	Calculated in 7 patients
PFS3	14.7	IQR: 7.4-75.5	-	-	Calculated in 3 patients
LRFS	27.2	95% CI: 14.4-40.0	-	44.4	Significantly longer in the group receiving radiotherapy
MFS	8.8	95% CI: 8.1-9.4	-	72.2	Median could not be calculated in the group not receiving radiotherapy
Recurrence rate	-	-	-	83.3 (15/18)	11 local, 4 metastatic first recurrences
Median OS after first recurrence	40.1	-	-	-	
Median OS after metastasis	20.1	-	-	-	

IQR: Interquartile range; CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival; MFS: Metastasis-free survival.

TABLE 3: Comparison of survival outcomes according to treatment modalities in chordoma patients.

Treatment group	Median OS (months)	Median PFS (months)	Median LRFS (months)	Median MFS (months)	Log-rank p	Notes
Radiotherapy (RT)	81.5	22.4	27.2	8.8	<0.001	Significantly longer OS and PFS compared to no RT
No RT	7.7	5.97	Not reached	6.0		
R0 resection	81.5	27.6	27.7	Not reached	0.316	No metastasis observed during follow-up
R1-R2 resection	19.3	8.3	3.6	8.3	0.727	
Systemic therapy	87.9	-	-	25.5	0.064	Trend toward longer post-relapse survival
No systemic therapy	43.2	-	-	12.4		
Primary surgery	-	-	27.2	-		
Non-surgical group	-	-	-	11.4		

R1-R2: Microscopic/macroscopic positive surgical margin; OS: Overall survival; PFS: Progression-free survival; LRFS: local recurrence-free survival; MFS: Metastasis-free survival; RT: Radiotherapy.

a continuous variable, no significant associations were found between tumor size and PFS (p=0.434) or OS (p=0.180).

Comparison between primary operable and inoperable patients was not possible because of the small number of inoperable patients (3/18). Time from diagnosis to metastasis could only be calculated for patients who received RT (median 10.1 months, IQR 6.78-63.98). Analysis for the no-RT group was not possible because there was only one case.

Median LRFS was 27.2 months (95% CI 14.4-40.0) in patients who received RT, while median survival in the no-RT group could not be calculated and was very short. The difference between the groups was statistically significant (log-rank p=0.002).

Among all patients, the median MFS was 8.8 months (95% CI: 8.1-9.4). The median MFS was 38.2 months in those who received RT and 6.0 months in those who did not. The difference between the two groups, although not statistically significant, was within the range of significance(log-rank χ^2=3.0, p=0.083). LRFS was significantly longer in patients who underwent R0 resection than in those who underwent R1-R2 resection (median 27.7 months vs. 3.6 months, p=0.002). None of the eight patients who underwent R0 resection developed metastases during follow-up. While mPFS was 27.6 months after R0 resection, it was 8.3 months after R1-R2 resections (p=0.316). mOS was 81.5 months in the R0 group and 19.3 months in the R1-R2 group (p=0.727).

In analyses stratified by primary surgery status, the median LRFS was 27.2 months in patients who underwent primary surgery and developed local recurrence. The median MFS in non-operated patients was 11.4 months. Two patients progressed to metastasis after local recurrence. One of these patients underwent surgery for recurrence, did not receive RT, and had an RT-free interval between recurrence and metastasis of 0.76 months. The other patient received RT to the recurrent lesion without surgery for the recurrence and had an interval between recurrence and metastasis of 26.76 months.

The median post-relapse survival of the two patients who underwent surgery and RT after local recurrence was 37.17 months, whereas it was 25.5 months for patients who received RT alone. The median LRFS of those whose first progression was local recurrence was 81.5 months (95% CI: 18.2-144.7, log-rank χ^2=0.055, p=0.814).

Among those who did not experience recurrence, the mOS was >100 months. The mOS of patients who developed recurrence was shorter, with a lower median; however, this difference did not reach statistical significance, likely because of the small number of patients (3/18) who did not develop recurrence (χ^2=2.389, p=0.122). Univariate Cox regression analyses for OS revealed no significant associations between resection status (HR=1.266, 95% CI: 0.336-4.777, p=0.728), tumor size (≥36 mm vs. <36 mm) (HR=1.056, 95% CI: 0.321-3.479, p=0.928), and age (<60 vs. ≥60 years) (HR=1.175, 95% CI: 0.336-4.106, p=0.800), but baseline RT status (HR=0.198, 95% CI: 0.035-1.114, p=0.066) and approaching statistical significance (Table 4).

Univariate Cox regression analyses for LRFS revealed no significant effect of tumor size (HR=1.059, 95% CI: 0.302-3.715, p=0.929), but a trend toward a protective effect of younger age (<60 vs. ≥60 years) was observed (HR=0.277, 95% CI: 0.054-1.420, p=0.124). Univariate Cox regression analyses for MFS revealed a protective effect of younger age (<60 vs. ≥60 years), which did not reach statistical significance (HR=0.277, 95% CI: 0.054-1.420, p=0.124), and tumor size was not observed (HR=0.408, 95% CI: 0.025-6.621, p=0.529) (Table 5).

The mean PFS was 8.77 months in thoracic-cervical cases and 22.40 months in lumbar-sacral cases(p=0.137). The mean PFS was 19.47 months in thoracic-cervical cases and 81.46 months in lumbar-sacral cases (p=0.577).

After the first progression, consecutive PFS times could be calculated for a smaller subset of patients. PFS2 was available for 7 patients; the median was 10.7 months (range, 3.8-27.6 months). PFS3 was available for only 3 patients, with

TABLE 4: Univariate Cox regression analysis for prognostic factors affecting survival in chordoma patients.

Variable	HR	95% CI	P-value	Interpretation
Resection status (R0 vs R1-R2)	1.266	0.336 - 4.777	0.728	Not significant
Tumor size (≥36 mm vs <36 mm)	1.056	0.321 - 3.479	0.928	Not significant
Age (<60 vs ≥60 years)	1.175	0.336 - 4.106	0.800	Not significant
Initial RT	0.198	0.035 - 1.114	0.066	Trend toward significance (protective effect)
Younger age (LRFS)	0.277	0.054 - 1.420	0.124	Trend toward better local control
Younger age (MFS)	0.277	0.054 - 1.420	0.124	Trend toward better metastasis-free survival
Tumor size (MFS)	0.408	0.025 - 6.621	0.529	Not significant

HR: Hazard ratio; CI: Confidence interval; RT: Radiotherapy; LRFS: Local recurrence-free survival; MFS: Metastasis-free survival.

TABLE 5: Patterns of recurrence and post-relapse treatments in chordoma patients.	
Recurrence feature	**Value**
Patients without recurrence	3/18 (16.7%)
Patients with recurrence	15/18 (83.3%)
First recurrence type	Local: 11 (73.3%); distant metastasis: 4 (26.7%)
Secondary metastasis after local relapse	2 patients
Salvage surgery + RT after recurrence	1 patient - median OS after relapse: 37.2 months
Salvage RT alone after recurrence	1 patient - median OS after relapse: 25.5 months
Systemic therapy after recurrence	9/18 patients
Median OS after recurrence	25.5 months
RT: Radiotherapy; OS: Overall survival	

a median of 14.7 months (range, 7.4-75.5 months) (Table 6). Median duration of 1st-line therapy: 7.6 months (range, 3.1-15.1). Median duration of 2nd-line therapy: 8.2 months (range, 3.4-14.0). Patients receiving ≥3 lines of therapy (n=3) had numerically longer OS. In most cases, clinical benefit (progressive disease/stable disease) occurred within the first 2 treatment lines. The longest total treatment exposure was in patient 5 (cumulative duration around 40+ months).

Nine (50%) of the 18 chordoma patients included in the study received systemic therapy. Imatinib (n=7) was the most commonly used first-line agent, while 2 patients were treated with internal mammary artery. Three of the 7 patients receiving imatinib were switched to sunitinib, sorafenib, or temozolomide as second-line therapy. In some cases, agents such as dasatinib, erlotinib, carboplatin, and temozolomide were used in third and subsequent lines of therapy. The best responses to first-line therapy were stable disease, partial response, or complete response in 44.4% (4/9) of the patients; progressive disease was observed in 55.6% (5/9). Although a tendency toward longer OS was observed in patients receiving advanced systemic therapies, statistical significance was not reached because of the small number of patients. In the subgroup of patients who developed recurrence, those who received systemic therapy had a longer OS than those who did not, although this difference was not statistically significant (87.9 months vs. 43.2 months, p=0.317). Post-relapse survival was 25.5 months in patients who received systemic therapy and 12.4 months in those who did not (p=0.064). Pathology reports included various histological and molecular findings. One patient had an EGFR mutation and was proficient mismatch repair. Additionally, histological variants were reported in two patients: one a chondroid chordoma and the other a myxoid variant. A limited number of patients in our cohort exhibited different histopathological or molecular features; due to insufficient numbers of patients, their impact on survival could not be assessed.

DISCUSSION

In our series, RT was associated with significantly longer OS and PFS (mOS 81.5 vs. 7.7 months; PFS, p<0.001) compared with surgery alone, underscoring the critical role of adjuvant RT in chordoma treatment. This finding is consistent with reports that high-dose postoperative RT improves local control and survival, particularly in cases of positive surgical margins. Advanced RT modalities such as proton or carbon-ion therapy have achieved tumor control and survival rates comparable to those achieved with surgical resection. These approaches offer an alternative for patients who are not surgical candidates, particularly due to advanced age or high operative risk.[6] Previous studies have demonstrated favourable outcomes wih carbon ion therapy in selected patients.[6] The findings in our series also suggest that the addition of RT has a positive impact on the course of the disease. Notably, although only conventional photon RT was available in our center, its judicious high-dose use still conferred substantial benefit; the future introduction of proton/ion therapy may further improve outcomes. Some patients did not receive RT due to advanced age, comorbidities, or individualized treatment decisions based on clinical judgment.

In our study, patients who underwent *en bloc* R0 resection experienced markedly longer LRFS (median 27.7 vs. 3.6 months) and showed a trend toward improved OS, highlighting the importance of achieving clear margins. Also, none of the eight patients who had an R0 resection developed metastases during follow-up. Larger series have confirmed the value of wide excision. In one analysis of 130 patients, clear surgical margins were an independent predictor of local control (5-year LRFS 47% vs. lower with intralesional resection; p=0.003).[6] That study also identified tumor size as an independent prognostic factor, with larger tumors associated with significantly worse outcomes. In our cohort (mean tumor diameter of ~5 cm), we observed a non-significant trend toward shorter PFS in patients with tumors

TABLE 6: Systemic therapy lines, treatment duration, and best responses in chordoma patients.

Pt. No.	1st-line therapy (duration, mo)	2nd-line (duration)	3rd-line (duration)	4th-line (duration)	5th-line (duration)	≥6th-line (duration)	Other agents	Best response (PR/SD/PD)	Notes
1	Imatinib (4.2 mo)	-	-	-	-	-	-	PD	Progression after short course
2	IMA (3.1 mo)	-	-	-	-	-	-	PD	Primary progression
3	Imatinib (6.4 mo)	-	-	-	-	-	-	SD	Disease stabilization
4	Imatinib (8.5 mo)	Sunitinib (14.0 mo)	Sorafenib (5.0 mo)	Dasatinib (5.4 mo)	Erlotinib (9.3 mo)	-	-	SD	Long OS, multiple lines
5	Imatinib (7.6 mo)	Sunitinib (8.2 mo)	Temozolomide (9.5 mo)	Imatinib rechallenge (3.6 mo)	Dasatinib (5.1 mo)	Erlotinib + carboplatin (6.8 mo)	Temozolomide	SD	Prolonged disease control
6	Imatinib (11.2 mo)	Sunitinib (6.1 mo)	-	-	-	-	-	SD	Stabilization in 2nd line
7	Imatinib (9.8 mo)	Sorafenib (3.4 mo)	-	-	-	-	-	PD	Early progression
8	Imatinib (15.1 mo)	-	-	-	-	-	-	PR	Durable partial response
9	Imatinib (5.6 mo)	-	-	-	-	-	-	SD	Durable stabilization

Pt: Patient; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; OS: Overall survival; Mo: Months.

>36 mm compared to those with tumors 36 mm. This is in line with population-based data showing that greater tumor size at diagnosis confers a poorer prognosis.[9] These findings underscore the value of early intervention.

Tumor location may also influence outcomes, although our sample size was too small to demonstrate a statistically significant effect. Some series suggest that chordomas of the mobile spine have better long-term survival than those of the sacrum or skull base.[10] One single-center study reported approximately 80% 10-year OS in mobile spine chordoma patients versus around 50% in sacral chordomas (a difference that was not statistically significant).[3] For example, while 5- and 10-year mOS values of patients with mobile vertebral chordomas were reported as around 80% in one series, these rates were reported as 78% in 5 years and 48% in 10 years in the same study for sacral chordomas, despite being statistically insignificant.[3] Conversely, another analysis found similar survival between sacral and mobile spine disease, but a higher risk of distant metastasis in sacral tumors.[11,12] These patterns likely reflect the challenges of treating chordomas in certain locations. Tumors in the skull base are adjacent to critical neurological structures, limiting the radiation dose that can be safely delivered.[3,13] In fact, RT doses are limited in skull base chordomas due to their proximity to sensitive brain structures, making local control difficult.[3,14] Sacral tumors often reach large sizes and require extensive resection with considerable morbidity, making complete removal difficult. In our predominantly lumbosacral series, this may explain the pronounced benefit of adjuvant high-dose RT in improving local tumor control and survival.

Patient age did not have a significant impact on outcomes in our cohort (median age 53). This may be due to the relatively small number of older patients in our study. By contrast, larger epidemiological studies have identified older age (especially ≥60 years) at diagnosis as an independent risk factor for worse survival, presumably reflecting factors such as poorer general health and more advanced disease at presentation.[9] It remains important to consider that younger patients are often better candidates for aggressive multimodal therapy, which may lead to better outcomes.

Systemic therapies for chordoma remain controversial adjuncts. In our study, about half of the patients received targeted systemic treatments (mostly tyrosine kinase inhibitors such as imatinib), but we observed no clear survival advantage from these therapies (mOS 88 vs. 43 months with vs. without systemic treatment; p=0.317). Although patients receiving systemic therapy had numerically longer survival, this difference was not statistically significant. Although a trend toward improved survival was observed in patients receiving systemic therapy, the difference did not reach

statistical significance. Therefore, these findings should be interpreted with caution and considered hypothesis-generating. Small series have documented partial responses or prolonged stable disease with various targeted agents (e.g., imatinib, sunitinib, pazopanib, erlotinib), particularly in patients with PDGFR, KIT, or EGFR-positive tumors.[1,7,15] However, without randomized trial data it remains uncertain whether such drugs significantly extend OS, as complete tumor responses are rare and disease control is usually temporary.[7] Novel approaches, including brachyury-targeted vaccines and immune checkpoint inhibitors, have shown promise in isolated refractory cases (with a few partial responses reported).[1] Ongoing research and future clinical trials will be crucial in determining the definitive role of systemic therapies in advanced chordoma.

Study Limitations

This study has several limitations. First, due to its retrospective design, some patients were excluded because of incomplete or missing clinical data, which may have introduced selection bias. In addition, the small sample size limits the statistical power of the analyses and the generalizability of the findings. Treatment-related toxicities were not systematically recorded due to the retrospective design of the study, limiting the ability to assess the safety profile of the treatments.

CONCLUSION

The findings of our study confirm the critical importance of comprehensive surgical resection and RT in the treatment of chordoma. When extensive surgical resection is possible, local recurrence rates decrease and long-term survival increases. When resection is inadequate or patients are at high risk of recurrence, adjuvant high-dose RT significantly contributes to disease control, as emphasized in the literature. Various studies have demonstrated that, thanks to advances in RT technologies, success rates comparable to those achieved with surgery can be achieved even in RT-resistant tumors like chordoma. Our study demonstrates the positive impact of the effective use of existing RT on survival, even in settings where proton or carbon-ion therapy is not routinely available in our country. Furthermore, it reiterates the prognostic importance of factors such as tumor size and patient age, since early diagnosis and intervention may lead to better outcomes in younger and smaller patients. While systemic therapies are not the cornerstone, they may have a role in disease control in selected patients; further studies are needed to confirm their efficacy.

Larger case series are needed in this area, and the results of ongoing clinical trials are awaited. Achieving optimal outcomes in patients with chordoma requires a multidisciplinary approach that integrates surgery and RT, is supplemented by systemic therapies when necessary, and is personalized to each patient. Comparing our experience with data from the literature will contribute to determining optimal treatment strategies for this rare tumor.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Türkiye, Ankara Bilkent City Hospital Medical Research Scientific and Ethical Evaluation Board and in accordance with the Declaration of Helsinki (approval number: TABED 1-25-1840, date: 05.11.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A.E., Concept: D.U., Design: Ö.B., Data Collection or Processing: B.Y., Analysis or Interpretation: B.Y., E.A., Literature Search: B.Y., Writing: B.Y., D.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Meng T, Jin J, Jiang C, et al. Molecular targeted therapy in the treatment of chordoma: a systematic review. Front Oncol. 2019;9:30. [Crossref] [PubMed] [PMC]
2. Das P, Soni P, Jones J, et al. Descriptive epidemiology of chordomas in the United States. J Neurooncol. 2020;148(1):173-178. [Crossref] [PubMed]
3. Zhou Y, Hu B, Wu Z, Cheng H, Dai M, Zhang B. The clinical outcomes for chordomas in the cranial base and spine: a single center experience. Medicine (Baltimore). 2019;98(23):e15980. [Crossref] [PubMed] [PMC]
4. Stacchiotti S, Casali PG, Lo Vullo S, et al. Chordoma of the mobile spine and sacrum: a retrospective analysis of a series of patients surgically treated at two referral centers. Ann Surg Oncol. 2010;17(1):211-219. [Crossref] [PubMed]
5. Guan X, Gao J, Hu J, et al. The preliminary results of proton and carbon ion therapy for chordoma and chondrosarcoma of the skull base and cervical spine. Radiat Oncol. 2019;14(1):206. [Crossref] [PubMed] [PMC]
6. Yolcu YU, Zreik J, Wahood W, et al. Comparison of oncologic outcomes and treatment-related toxicity of carbon ion radiotherapy and en bloc resection for sacral chordoma. JAMA Netw Open. 2022;5(1):e2141927. [Crossref] [PubMed] [PMC]
7. Hindi N, Casali PG, Morosi C, et al. Imatinib in advanced chordoma: a retrospective case series analysis. Eur J Cancer. 2015;51(17):2609-2614. [Crossref] [PubMed]
8. Barber SM, Sadrameli SS, Lee JJ, et al. Chordoma-current understanding and modern treatment paradigms. J Clin Med. 2021;10(5):1054. [Crossref] [PubMed] [PMC]
9. Lee IJ, Lee RJ, Fahim DK. Prognostic factors and survival outcome in patients with chordoma in the United States: a population-based analysis. World Neurosurg. 2017;104:346-355. [Crossref] [PubMed]

10. Chen S, Ulloa R, Soffer J, et al. Chordoma: a comprehensive systematic review of clinical trials. Cancers (Basel). 2023;15(24):5800. [Crossref] [PubMed] [PMC]
11. Zileli M, Karakoç HTE. Outcomes of chordomas of the sacrum and mobile spine: clinical series with average 6-year follow-up. J Craniovertebr Junction Spine. 2021;12(4):412-419. [Crossref] [PubMed] [PMC]
12. Schwab JH, Hornicek FJ. Radiation therapy for primary malignant sacral tumors. In: Ruggieri P, Angelini A, Vanel D, Picci P, editors. Tumors of the sacrum: diagnosis and treatment of benign and malignant tumors. Cham: Springer International Publishing; 2017. p. 365-371. [Crossref]
13. Combs SE, Baumert BG, Bendszus M, et al. ESTRO ACROP guideline for target volume delineation of skull base tumors. Radiother Oncol. 2021;156:80-94. [Crossref] [PubMed]
14. Locquet MA, Brahmi M, Blay JY, Dutour A. Radiotherapy in bone sarcoma: the quest for better treatment option. BMC Cancer. 2023;23:742. [Crossref] [PubMed] [PMC]
15. Le Cesne A, Chevreau C, Perrin C, et al. Regorafenib in patients with relapsed advanced or metastatic chordoma: results of a non-comparative, randomised, double-blind, placebo-controlled, multicentre phase II study. ESMO Open. 2023;8(3):101569. [Crossref] [PubMed] [PMC]