Local and Distant Recurrence in Resected Sacral Chordomas: A Systematic Review and Pooled Cohort Analysis

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Abstract

Study Design: Systematic review.

Objectives: Sacral chordomas are rare, primary tumors of the spine, best treated with en bloc resection. The purpose of this study was to assess the literature for resected sacral chordoma and to quantify the prevalence of, risk factors for, and treatment outcomes of local and distant recurrence therein.

Methods: We searched 5 online databases from January 1980 to May 2016 to find articles that report survival, recurrence outcomes, and/or prognostic factors for the resected sacral chordoma patient population. Characteristics and clinical outcomes of the pooled cohort are reported. Fisher exact tests, unpaired t tests, and one-way analysis of variance were used to investigate patient- and treatment-associated prognostic factors for local and distant recurrence. Survival analyses were performed for time to local recurrence and death. The protocol’s PROSPERO ID is CRD42015024384.

Results: Fifty-seven studies, with 1235 unique sacral chordoma patients, were included in this review. Local and distant recurrence occurred in 42.6% and 22.4% of patients with adequate follow-up, respectively. Kaplan-Meier overall median survival for patients with and without recurrence were 98 and 209 months after surgery, respectively. Wide surgical margin was associated with a lower rate of local recurrence; and wide surgical margin, female sex, and patient age ≥65 years were associated with lower rates of distant recurrence.

Conclusions: While surgical margin remains the most significant prognostic factor for local and distant recurrence, combined surgical approach may be associated with local recurrence. Male sex and age <65 years may be associated with distant recurrence. Patients with risk factors for recurrence should undergo close monitoring to maximize survival.

Keywords
sacral chordoma, recurrent chordoma, systematic review, tumors, lumbosacral, sacrum

Introduction

Chordomas are rare, primary bone tumors of the spine believed to originate from the remnants of the embryological notochord. They most frequently arise at the skull base and the sacrum.¹ These tumors are classically described to be low-grade and malignant. Chordomas have been recently reported to have a 5-year survival rate of 73% to 86% and a 10-year survival rate of 49% to 71%.²

Surgery persists as the mainstay of chordoma management, as the efficacy of radiation therapy alone remains controversial,³ and the slow-growing nature of chordomas confers a high resistance to chemotherapy.⁴ Oncologic staging of chordomas describes most as Enneking Stage 1B, indicating en bloc...
excision with wide margins as the appropriate surgical treatment.\textsuperscript{4, 5} When en bloc excision is not possible due to neural structure involvement or patient fitness, intralesional excision may be appropriate to limit morbidity. Although chordomas have historically proven to be relatively radiation-resistant,\textsuperscript{4, 6} recent promising studies suggest proton beam and carbon ion therapy may contribute to increased local control and improved survival in patients with this disease.\textsuperscript{7-15}

Local recurrence rates following resection of sacral chordoma in large (n \( \geq 50 \)) studies range from 38% to 56%,\textsuperscript{16-21} and distant recurrence rates range from 9% to 33%.\textsuperscript{6, 18-21} In one study with mean follow-up of 8.1 years, local recurrence was associated with a 21-fold increase in risk of tumor-related death and distant recurrence with a 451-fold increase.\textsuperscript{22} However, due to the low incidence of chordomas (fewer than 1/ million/year),\textsuperscript{2} statistically powerful data on prevalence, risk factors, and treatment outcomes for recurrent sacral chordomas are lacking, with the largest studies to date including fewer than 200 patients. The purpose of this study is to systematically review the literature and pool a large number of patient cohorts describing the resected sacral chordoma population to date and to better estimate the prevalence of, risk factors for, and treatment outcomes of local and distant recurrence therein.

\section*{Methods}

\section*{Search Strategy and Selection Criteria}

A systematic review of the literature was performed using PubMed, Embase, CINAHL, Web of Science, and Cochrane, and a review of the bibliographies of relevant articles. The search queries (Supplemental Table S1; available in the online version of the article) were designed to return all articles in English on sacral chordomas that mention surgical treatment published from January 1, 1980, to May 19, 2016. Some patients in these publications had years of presentation back to the 1940s (presentation years listed in Supplemental Table S2). Both individual patient-level data and summary statistics were collected. All patients included in this systematic review underwent surgical treatment for sacral chordoma.

All potentially eligible studies returned by the search strings underwent title and abstract review by 2 authors, and were determined to be eligible or ineligible by consensus, based on inclusion criteria. A third author independently reviewed and verified the decisions. All articles that passed the title and abstract screen underwent full-text review and were subjected to the following exclusion criteria: study size of at least 4 individuals who meet the aforementioned criteria; mean follow-up \( \geq 12 \) months; adequate description of clinical outcome in terms of local control; separate treatment of resected sacral chordoma patients; fully published, peer-reviewed study; and unique patient cohort. Authors of included studies were not contacted for more detailed information on patients.

\section*{Data Analysis}

Two-tailed, Fisher’s exact test \( P \) values were calculated to compare prevalence of recurrence in subgroups of binary prognostic factors. These analyses were not prespecified, as assessment of the availability of data was first needed to determine feasibility of analysis. Time to recurrence \( P \) values for binary prognostic factors were calculated using unpaired, 2-tailed \( t \) tests. GraphPad Software was used (GraphPad QuickCalcs) for these calculations. The \( P \) values comparing prevalence for the 4 surgical margin groups were calculated using a \( \chi^2 \) test. The time to recurrence \( P \) values for surgical margins were calculated using a one-way analysis of variance (ANOVA) test. These calculations were performed in Microsoft Excel (Version 15.24). Relative risk calculations were performed using MedCalc Online.

Cohort-level data was used in the time to recurrence analyses. Mean times to recurrence for each prognostic factor subgroup in each article were used and included in the analyses the appropriate number of times to reflect the number of patients in the subgroup. Patient-level data was used in the survival analyses. All Kaplan-Meier curves were generated using Excel. The Kaplan-Meier log-rank test \( P \) value and the Cox proportional hazards regression were calculated using In-Silico Online. Standard deviations provided with pooled cohort means reflect variation in component study means.

Pearson correlation coefficients for case volume analyses were calculated in Microsoft Excel.

\section*{Definitions}

Margins of a chordoma resection were recorded as follows: wide if the primary study reported the margins to be wide, radical, or greater than 2 cm; marginal if the primary study reported the margins to be marginal, or greater than 0.01 cm and less than 2 cm; intralesional if the primary study reported the margins to be intralesional, positive, inadequate, or Union for International Cancer Control (UICC) category R2;\textsuperscript{23} wide-contaminated if the primary study reported the margins to be wide-contaminated; and negative if the primary study reported the margins to be negative, tumor-free, or UICC category R0, or reported the resection as clean, adequate, gross total, or complete.

\section*{Results}

A literature search was performed using 5 online databases. After exclusion based on the established eligibility criteria, 57 articles were included in the analysis, with a total of 1235 surgical sacral chordoma patients (Figure 1). These studies originated from many different medical departments, with 34 first authors affiliated with orthopedic surgery or oncology, 8 affiliated with general surgery, 6 with neurosurgery, 3 with surgical oncology, and 6 from various other departments including pathology and anesthesiology.
Among the patients for whom gender was known, 62% were male, giving a male-to-female ratio of 1.6:1 (Table 1). The mean age at diagnosis of sacral chordoma was 56.1 ± 5.4 (range 13-85). The primary symptom was pain (87%), followed by palpable mass (50%) and various neurologic symptoms (15% to 30%). The mean follow-up time for the cohort was 72.0 ± 27.5 months.

Approximately 95% of patients underwent biopsy or had had previous sacral surgery before resection at the institution of primary treatment (Table 2). The mean operating time on these sacral chordomas was 9.2 ± 4.5 hours (1.2-26). Mean estimated blood loss was 2991 ± 2841 mL. Fifty-five percent of patients underwent a posterior-only approach to the resection, 45% underwent a combined approach, and one case was anterior only. The mean reported diameter of the sacral chordomas was 10.5 ± 2 cm (2.8-30), and 61% of the tumors extended to S2 or above.

Out of nearly 1000 surgeries, 81% had negative margins (39% wide, 22% marginal, 20% unspecified negative; Table 3). Seventeen percent of cases had a complication that required reoperation; indications for reoperation include operative debridement, repair of intestinal fistula, hardware revision after loss of fixation, and correction of persistent cerebrospinal fluid leak.24-26

Table 1. Characteristics of Patients in Pooled Cohorta.

| Characteristic                                      | % (n) of Patients |
|----------------------------------------------------|------------------|
| Total patients, n                                  | 1235             |
| Sex, n = 1081                                       |                  |
| Male                                               | 62.0% (670)      |
| Female                                             | 38.0% (411)      |
| Ratio (male to female)                             | 1.6              |
| Age, n = 800                                       |                  |
| Mean                                               | 56.1 ± 5.4       |
| Range                                              | 13-85            |
| Previous sacral surgery, n = 601                   | 20.5% (123)      |
| Symptoms at presentation                           |                  |
| Pain, n = 308                                       | 86.7% (267)      |
| Mass/swelling, n = 177                              | 50.3% (89)       |
| Bowel dysfunction, n = 171                          | 27.5% (47)       |
| Bladder dysfunction, n = 180                        | 18.9% (34)       |
| Neuropathic pain, n = 124                           | 16.1% (20)       |
| Neurologic symptoms: unspecified or other, n = 190  | 21.1% (40)       |
| Follow-up, n = 956                                 |                  |
| Mean (months)                                       | 72.0 ± 27.5      |
| Range (years)                                       | 0-34             |

Abbreviation: n, number of patients at risk (in studies reporting characteristic).
aA total of 1235 surgical sacral chordoma patients were included. Among the patients for whom gender was known, 62% were male, giving a male-to-female ratio of 1.6:1. The mean age at diagnosis of sacral chordoma was 56.1 ± 5.4 (range 13-85).

The most common adjuvant medical therapy for these patients was radiation, which was used preoperatively in 16% of reported cases and postoperatively in 37% of cases. In reporting these practices, it is important to note that usage rates of radiotherapy varied widely from center to center. Some articles report use of radiation in all sacral chordoma patients, while others did not augment surgical treatment in any case. Chemotherapy was uncommon across all studies.

Out of 1229 patients with local control follow-up in this study, 43% experienced a local recurrence (Table 4). The mean time to local recurrence was 40 ± 19 (1-228) months after surgery. Metastases were half as prevalent as local recurrence, with only 22% of subjects demonstrating distant recurrence at a mean time after surgery of 60 ± 30 (0-228) months. The most common location for distant recurrence was the lung, accountable for 69% of metastatic lesions with known location. Regarding long-term prognosis, just over a quarter (27%) of all surgically treated sacral chordoma patients died from their chordoma by the end of follow-up. However, nearly another quarter (24%) were continuously disease-free throughout follow-up. An additional 30% had no evidence of remaining chordoma and another 16% were alive with disease at the end of follow-up.

Three factors were found to be significantly associated with local recurrence: history of previous sacral surgery, surgical margin, and adjuvant therapy (Table 5). Patients with a history
of sacral surgery had significantly greater local recurrence compared with patients receiving sacral surgery for the first time (61.3% compared with 38.4%, \( P = .0002 \)). Resection margins were found to be statistically significant in recurrence prognosis as well (\( P < .0001 \)), with patients who received wide, marginal, intralesional, and wide-contaminated margins experiencing local recurrence at rates of 25.6%, 44.4%, 57.0%, and 64.7%, respectively. Patients who received adjuvant therapy had higher rates of local recurrence compared with those who did not receive adjuvant therapy (53.5% vs 42.3%, \( P = .0147 \)). Finally, patients who underwent surgery with combined anterior-posterior approach had a strong trend toward greater local recurrence compared with patients treated by posterior approach only (45.6% vs 35.2%, \( P = .0505 \)).

### Table 2. Tumor and Surgery Characteristics\(^a\).

| Characteristic | % (n) of Patients |
|---------------|------------------|
| Biopsy preoperative, \( n = 458 \) | 94.8% (434) |
| Biopsy type, \( n = 271 \) | |
| Previous surgery | 25.1% (68) |
| Needle\(^b\) | 52.8% (143) |
| Open | 22.1% (60) |
| Enneking staging, \( n = 61 \) | |
| 1B | 96.7% (59) |
| 3A | 1.6% (1) |
| 3B | 1.6% (1) |
| Operating time (hours), \( n = 225 \) | |
| Mean | 9.2 ± 4.5 |
| Range | 1.2-26 |
| Estimated blood loss (mL), \( n = 273 \) | |
| Mean | 2991 ± 2841 |
| Range | 100-28800 |
| Blood transfusion (units), \( n = 60 \) | |
| Mean | 8.7 ± 1.5 |
| Range | 0-35 |
| Approach, \( n = 803 \) | |
| Posterior only | 54.9% (441) |
| Anterior only | 0.1% (1) |
| Combined A/P | 45.0% (361) |
| Proximal extent\(^c\), \( n = 574 \) | |
| L5 | 2.1% (12) |
| S1 | 19.2% (110) |
| S2 | 39.9% (229) |
| S3 | 24.7% (142) |
| S4 | 11.3% (65) |
| SS or below | 2.8% (16) |
| Maximum tumor diameter (cm), \( n = 254 \) | |
| Mean | 10.5 ± 2.0 |
| Range | 2.8-30 |
| Tumor volume (mL), \( n = 261 \) | |
| Mean | 519 ± 146 |
| Range | 4-4532 |

Abbreviations: \( n \), number of patients at risk (in studies reporting characteristic).
\(^a\)Approximately 95% of patients underwent biopsy or had had previous sacral surgery before resection at the institution of primary treatment.
\(^b\)Fine-needle aspiration, computed tomography-guided needle, tru-cut needle, core needle.
\(^c\)Extent of tumor or of resection.

### Table 3. Treatment Details and Complications\(^a\).

| Characteristic | % (n) of Patients |
|---------------|------------------|
| Neoadjuvant therapy, \( n = 179 \) | |
| Radiation | 15.6% (28) |
| Chemotherapy | 2.8% (5) |
| Surgical margin, \( n = 991 \) | |
| Wide\(^b\) | 39.1% (387) |
| Marginal\(^c\) | 21.8% (216) |
| Wide-contaminated | 1.9% (19) |
| Intralesional\(^d\) | 17.2% (170) |
| Negative (not specified)\(^e\) | 20.1% (199) |
| Adjuvant therapy, \( n = 780 \) | |
| Radiation | 37.1% (289) |
| Chemotherapy | 1.8% (14) |
| Complication requiring reoperation, \( n = 335 \) | |
| Radiation | 15.8% (53) |
| Wound complications, \( n = 552 \) | |
| Dehiscence | 19.2% (106) |
| Infection | 17.2% (95) |

Abbreviation: \( n \), number of patients at risk (in studies reporting characteristic).
\(^a\)Out of nearly 1000 surgeries, 81% had negative margins (39% wide, 22% marginal, 20% unspecified negative).
\(^b\)Reported as wide, radical, or >2 cm from tumor.
\(^c\)Reported as marginal or >0.01 cm and <2 cm from tumor.
\(^d\)Reported as intralesional, positive, inadequate, or R2.
\(^e\)Reported as negative, tumor-free, R0, clean, adequate, gross total, or complete.

### Table 4. Disease Control and Outcomes\(^a\).

| Variable | % (n) of Patients |
|----------|------------------|
| Local recurrence event, \( n = 1229 \) | 42.6% (523) |
| Local recurrence, time to (months), \( n = 275 \) | |
| Time to, mean | 40 ± 19 |
| Time to, range | 1-228 |
| Distant recurrence event, \( n = 921 \) | 22.4% (206) |
| Distant recurrence, time to (months), \( n = 75 \) | |
| Time to, mean | 60. ± 30 |
| Time to, range | 0-228 |
| Location of distant recurrence, \( n^b = 127 \) | |
| Lung | 68.5% (87) |
| Liver | 6.3% (8) |
| Spine | 8.7% (11) |
| Elsewhere | 16.5% (21) |
| Oncologic status at end of follow-up, \( n = 776 \) | |
| Continuously disease free | 23.7% (184) |
| No evidence of disease | 29.5% (229) |
| Alive with disease | 15.6% (121) |
| Dead of disease/treatment | 26.7% (207) |
| Dead of other causes | 3.7% (29) |
| Lost to follow-up | 0.8% (6) |

Abbreviation: \( n \), number of patients at risk (in studies reporting characteristic).
\(^a\)Of 1229 patients with local control follow-up in this study, 43% experienced a local recurrence. The mean time to local recurrence was 40 ± 19 (1-228) months after surgery.
\(^b\)Number of metastases (not necessarily patients) with known location.

Combined surgical approach and use of adjuvant therapy were both found to be significantly associated with longer time to local recurrence. Age ≥65 years and presence of neurologic symptoms were also both associated with shorter time to local recurrence.
recurrence, despite having no association with recurrence prevalence.

Four factors were found to be significantly associated with distant recurrence: sex, age, surgical margin, and use of adjuvant therapy. Males had a higher rate of distant recurrence than females (27.8% vs 16.4%, \( P = .0265 \)), and patients <65 years of age had a higher rate of distant recurrence than patients \( \geq 65 \) years of age (25.7% vs 13.8%, \( P = .0304 \)). Wide, marginal, intralesional, and wide-contaminated surgical margins were associated with 16.4%, 40.0%, 52.5%, and 75.0% rates of distant recurrence, respectively (\( P < .0001 \)). Last, the use of adjuvant therapy was associated with a 23.2% rate of distant recurrence, which is significantly higher than the 12.6% rate for patients who did not receive adjuvant therapy (\( P = .0338 \)).

Age and proximal extent of tumor were also both significantly associated with time to distant recurrence. Patients <65 years of age demonstrated a longer mean time to distant recurrence compared with patients \( \geq 65 \) years of age, and higher proximal extent of tumor (above S3) was associated with a longer mean time to distant recurrence than lower proximal extent.

Patients who were treated with a surgery with wide margins had very significantly lower rates of both local and distant recurrence compared with patients with any other surgical margin classification (Table 6). Marginal margins were associated with a lower local recurrence rate than intralesional margins (\( P = .0477 \)), though not a lower distant recurrence rate.

Patient-level data on follow-up, recurrence status, and time to recurrence (as applicable) were available for 349 patients. Of the 349 patients, 169 (48.4%) had a recurrence. Mean time to recurrence was 37 \( \pm \) 36 months (range 2-204), and Kaplan-Meier median was 59 months (Figure 2).

There were 298 individuals for whom time to recurrence (as applicable), total follow-up time, and survival status at the end of the study were known. Of these 298 patients, 127 (42.6%) had a local recurrence. A Kaplan-Meier analysis looking at survival in the local recurrence cohort versus the local control cohort is presented in Figure 3. Median survival in the local recurrence group was 98 months, compared with 209 months in the local control group (\( P = .0005 \)). Survival after surgery at 5, 10, and 15 years for the local control cohort was 88%, 69%, and 61%, respectively, compared with 76%, 37%, and 16% for the local failure cohort. The Cox proportional hazard regression for local recurrence was 2.04 (95% confidence interval = 1.34-3.08).

Table 5. Univariate Analyses for Prognostic Factors for Recurrence.

| Variable                  | Local Recurrence Event % (LR/Total) | \( P \) | Time to LR (Months) | \( P \) | Distant Recurrence Event % (DR/Total) | \( P \) | Time to DR (Months) | \( P \) |
|---------------------------|-------------------------------------|--------|---------------------|--------|----------------------------------------|--------|---------------------|--------|
| Sex                       |                                     |        |                     |        |                                        |        |                     |        |
| Male                      | 47.2% (153/324)                     | .0601  | 37                  | .7441  | 27.8% (54/194)                         | .0265  | 51                  | .7582  |
| Female                    | 38.8% (80/206)                      |        | 38                  |        | 16.4% (19/116)                         |        | 54                  |        |
| Age                       |                                     |        |                     |        |                                        |        |                     |        |
| <65                       | 46.0% (165/359)                     | .6742  | 39                  | .0433  | 25.7% (61/237)                         | .0304  | 55                  | .0457  |
| \( \geq 65 \)             | 43.4% (53/122)                      |        | 30                  |        | 13.8% (11/80)                          |        | 38                  |        |
| Neurologic symptoms\(^b\) |                                     |        |                     |        |                                        |        |                     |        |
| Present                   | 46.7% (28/60)                       | 1.000  | 25                  | .0028  | 16.3% (8/49)                           | .6064  | 47                  |        |
| Absent                    | 45.3% (24/53)                       |        | 38                  |        | 21.3% (10/47)                          |        | 30                  |        |
| Surgical approach         |                                     |        |                     |        |                                        |        |                     |        |
| Combined                  | 45.6% (77/169)                      | .0505  | 49                  | <.0001 | 24.3% (26/107)                         | .0963  | 47                  | .7293  |
| Posterior                 | 35.2% (64/182)                      |        | 26                  |        | 15.2% (19/125)                         |        | 43                  |        |
| Previous surgery          |                                     |        |                     |        |                                        |        |                     |        |
| Yes                       | 60.0% (57/95)                       | .0004  | 50                  | .2964  | 37.0% (10/27)                          | .2244  | 54                  | .8425  |
| No                        | 37.8% (90/238)                      |        | 41                  |        | 24.1% (27/112)                         |        | 52                  |        |
| Surgical margin           |                                     |        |                     |        |                                        |        |                     |        |
| Wide                      | 25.6% (80/313)                      | <.0001 | 47                  | .1034  | 16.4% (23/140)                         | <.0001 | 66                  | .6724  |
| Marginal                  | 44.4% (59/133)                      |        | 37                  |        | 40.0% (24/60)                          |        | 56                  |        |
| Wide-contaminated         | 64.7% (11/17)                       |        | 44                  |        | 75.0% (3/4)                            |        | 39                  |        |
| Intralesional             | 57.0% (73/128)                      |        | 35                  |        | 52.5% (32/61)                          |        | 52                  |        |
| Proximal extent           |                                     |        |                     |        |                                        |        |                     |        |
| Above S3                  | 44.3% (120/271)                     | 1.000  | 42                  | .5819  | 27.0% (38/141)                         | .1984  | 58                  | .0193  |
| S3 or below               | 44.5% (85/191)                      |        | 45                  |        | 18.6% (16/86)                          |        | 35                  |        |
| Adjuvant therapy\(^d\)    |                                     |        |                     |        |                                        |        |                     |        |
| Used                      | 53.5% (115/215)                     | .0147  | 39                  | .0014  | 23.2% (29/125)                         | .0338  | 50                  | .0512  |
| Not used                  | 42.3% (121/286)                     |        | 25                  |        | 12.6% (17/135)                         |        | 31                  |        |

Abbreviations: LR, local recurrence; DR, distant recurrence.
\(^a\)Three factors were found to be significantly associated with local recurrence: history of previous sacral surgery, surgical margin, and adjuvant therapy.
\(^b\)Includes sensory deficit, motor deficit, saddle anesthesia, difficulty walking, neuropathic pain, bowel dysfunction, bladder dysfunction.
\(^c\)Not enough subjects to perform a statistical analysis.
\(^d\)Includes radiation therapy, chemotherapy, cryosurgery.
After data extraction, we performed an overview analysis to investigate the impact of institution caseload on recurrence rate. We used the years over which the databases were queried and the number of patients that met inclusion criteria for this review in order to approximate the number of sacral chordoma resections each institution performed per year. There were 9 single-institution studies that averaged fewer than one resection every 2 years by this metric (“low-volume”), and 6 single-institution studies that averaged more than 3 resections per year (“high-volume”). Two centers meeting the initial criteria for low-volume were excluded for incomplete reporting, leaving 7 studies for this analysis.

Numbers of cases per year varied from 0.22 to 12.8. Of the 39 patients seen at low-volume centers, 24 (61.5%) had a local recurrence (institution recurrence rates ranged from 20% to 75%). Of the 364 patients seen at high-volume centers, 150 (41.2%) had a local recurrence (range 7.7% to 55.2%). This difference was statistically significant ($P = .0173$). Mean known time to recurrence for patients treated at low-volume institutions was 23.0 months, compared with 41.6 months for high-volume institutions ($P < .0001$). Pearson correlation coefficients for caseload versus local recurrence rate and caseload versus time to local recurrence were $-0.175$ and 0.0626, respectively (Supplemental Figure 1).

**Discussion**

Recurrence is often considered the most important prognostic factor for the surgically treated sacral chordoma patient. However, studies comprehensively evaluating recurrence in sacral chordoma are generally small and underpowered. This study was carried out to systematically review the literature and pool patient cohorts to describe the resected sacral chordoma population and to estimate the prevalence of, risk factors for, and treatment outcomes of local and distant recurrence therein.

Tables 1 to 4 serve to characterize the surgical sacral chordoma population and disease course. In Table 1, the mean age at diagnosis of sacral chordoma is reported to be 56, but with a

![Figure 2. Kaplan-Meier curve for the 349 patients for whom specific recurrence data were available. Mean time to recurrence was 37 ± 36 months (range 2-204), and Kaplan-Meier median was 59 months.](image)
low end of the range at 13. Most chordomas present late in life due to characteristically slow growth over years; however, within the current model of embryologic origin, it is not unanticipated that rare pediatric patients could present secondary to the etiology of the disease. In their large epidemiologic study, McMaster et al found that less than 2% of sacral chordoma patients were age 3 to 25 at diagnosis.

In Table 2, the mean estimated blood loss (EBL) across all patients is reported to be \( \sim 3 \) L (range 0.1-28.8 L). Although there are several examples of individual cases with high EBL, there is no single study in this review that reports a mean EBL greater than 9 L; therefore, higher EBLs could be a product of particularly difficult cases (increased tumor size, increased tumor vascularity, invasion of critical structures, etc). The case with the highest EBL in our analysis comes from Ozaki et al, who report an anterior/posterior resection of a 624 mL chordoma lasting 11.3 hours, and extending up to S1. Localio et al note that a higher EBL is associated with staged resections over single-phase surgeries.

The majority of patients underwent a posterior-only or a combined anterior/posterior approach; however, 1 patient in our analysis underwent an anterior-only approach. This patient comes from the study by Chung Rong et al, who do not specify their indication for this surgical plan. The authors write, “As for operative methods, the abdominal/sacral approach was used in 6 cases; and the abdominal approach was chosen in one case.” On analysis, a combined anterior-posterior approach to resection trended strongly toward association with an increased rate of local recurrence compared to a posterior-only approach (relative risk \( RR = 1.30 \), 95% confidence interval = CI 1.00-1.68), which is similar to a previous study by Kayani et al, which also trends in that direction. While some studies traditionally suggest using a combined approach to resect chordomas that extend above S3, some report that a posterior-only approach to all tumors that do not extend above the lumbosacral junction is both feasible and safe.

The debate over the safest and most effective surgical approach to treat spinal chordoma patients is not new and is not unique to sacral chordoma surgery. Surgical planning should take into account surgeon experience and comfort, tumor anatomy, patient surgical history, the patient’s neurologic status, surgical risks, and potential for improving quantity and quality of life.

A history of sacral surgery was also associated with an increased rate of local recurrence compared with no history \( RR = 1.59 \), 95% CI = 1.26-2.00). This finding is consistent with existing literature that reproducibly associates history of sacral surgery with both increased rate of recurrence and decreased survival. Patients in this study with neurologic symptoms experienced, on average, 13 fewer months of local-disease-free survival (95% CI = 5-22 months) than those without neurologic symptoms. In a 2015 study, Varga et al found no association between preoperative motor deficit and local recurrence rates, but found motor deficit to be associated with decreased survival \( P < .01 \). These results suggest that neurologic symptoms might be indicative of more aggressive disease or reflect deeper invasion and a more difficult resection.
Male sex was found to be significantly associated with an increased rate of distant recurrence (RR = 1.70, 95% CI = 1.06-2.71). This is in contrast to existing literature, which finds no association. Male sex was found to be significantly associated with a higher rate of distant recurrence (RR = 1.87, 95% CI = 1.04-3.38), which is also in contrast to existing literature; however, in this study, the mean follow-up time for those under 65 was 6 ± 2.5 years, and for those 65 and over was only 4.5 ± 2.1 years. Thus, the association of young age with higher distant recurrence rates observed by this study can likely be attributed to the confounding impacts of longer survival and follow-up times in a younger population.

In the current study, surgical margin was found to be the most significant predictor of both local (RR for non-wide margins = 2.01, 95% CI = 1.61-2.51) and distant (RR = 2.87, 95% CI = 1.89-4.36) recurrence. These results corroborate conclusions in the existing literature.

Last, this study found adjuvant therapy to be associated with a significantly higher rate of both local (RR = 1.05-1.52) and distant (RR = 1.07-3.18) recurrence. A probable confounding factor in this analysis is a selection bias for the tumors that were treated with adjuvant therapy: tumors with positive resection margins, complex anatomy, large size, protracted clinical course, and aggressive histology were likely more often treated with adjuvant therapy than simple tumors. It is also possible that the damage some forms of adjuvant therapy cause to structures local to the resection site makes adjacent tissue more susceptible to tumor reinvasion. Some previous studies investigating the matter have found no prognostic significance of adjuvant therapy with respect to recurrence. However, in this study, the mean follow-up time for those under 65 was 6 ± 2.5 years, and for those 65 and over was only 4.5 ± 2.1 years. Thus, the association of young age with higher distant recurrence rates observed by this study can likely be attributed to the confounding impacts of longer survival and follow-up times in a younger population.

The current article confirms reports in the literature that local recurrence plays a role in clinical outcomes for these sometimes technically demanding resections. The results from a small analysis in this study show a significantly higher rate of local recurrence in patients treated at institutions that treat fewer than one sacral chordoma patient every 2 years compared with those treated at institutions that treat more than 3 sacral chordomas per year (RR = 1.49, 95% CI = 2.74-24.4). Treatment at a low-volume center was also associated with shorter time to local recurrence (23 months vs 42 months, P < .0001). However, caseload does not appear to be associated with either local recurrence rate or time to local recurrence, as Pearson coefficients of correlation for both were close to 0. These results suggest a threshold effect, such that treatment at an institution

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that performs fewer than one sacral chordoma surgery every 2 years might have a detrimental impact on local recurrence.

Overall, the role of radiation and other adjuvant therapy in the treatment of sacral chordomas remains uncertain. While recent studies investigating proton beam \(^8,13,66\) and carbon ion therapy \(^{13,14}\) suggest a potential future role for these modalities in chordoma management, we advocate for further research to better characterize the subpopulation most likely to benefit from adjuvant treatment. Additionally, although use of chemotherapy is currently limited and largely confined to particular cases of unresectable \(^{19,20}\) or recurrent \(^{50}\) disease, we look forward to the results of continued investigation into novel targeted therapies such as imatinib, which has shown promise in arresting chordoma progression. \(^{67,68}\) In all, sacral chordoma carries with it an uncertain but not necessarily dire prognosis.

As with any systematic review, publication bias raises concern for self-selection of patients and of treatment institutions/level of care. Variability in definitions and types of data reported from study to study represented a constant extraction challenge (further study of this disease would benefit from continued maintenance of an international database, such as that established by AOSpine International \(^{69}\)). Furthermore, all studies included in this review were retrospective, most likely secondary to the extremely low prevalence of sacral chordomas. As such, all studies included in the analysis were at high risk for bias, primarily derived from incomplete outcomes data, absence of a control population, and differential losses to follow up. Regarding statistical analysis, one-way ANOVA and unpaired *t* tests looking at times to recurrence used cohort-level information, slightly artificially decreasing the standard error and associated *P* values for each time-based analysis compared with a data set with patient-level information. Finally, while a multivariate analysis is typically preferred for association studies, low availability of individual-level data, interstudy discrepancy regarding which characteristics were reported, and high collinearity of many of the reported variables made a meaningful and statistically powerful multivariate analysis unfeasible.

Some less commonly reported factors were excluded from analysis in this study and are worth mention. Other characteristics that have been previously associated with increased local or distant recurrence of sacral chordoma include larger tumor size, \(^{16,19,20,69}\) surrounding muscle invasion, \(^{25}\) sacroiliac joint involvement, \(^3\) low CD40 expression, \(^{33}\) and open procedure for biopsy. \(^{51}\) In addition, patient genotype may play a prognostic role in mortality associated with spinal column chordomas. \(^{70}\) For the reader’s consideration, valuable discussions of previously investigated prognostic factors are available from Angelini et al., \(^{16}\) Kayani et al., \(^{19}\) and Varga et al. \(^{60}\) While an important discussion on the management of recurrent chordoma is offered by Ailon et al. \(^{71}\)

**Conclusions**

Despite the consensus in the literature that local control is an essential determinant of long-term survival for patients with sacral chordoma, large studies investigating factors and outcomes for recurrence in sacral chordoma are lacking. Fifty-seven studies consisting of 1235 unique sacral chordoma patients were included in this review. Wide surgical margin was associated with lower rates of local recurrence, and wide surgical margin, female sex, and patient age ≥65 years were associated with lower rates of distant recurrence. Additionally, posterior surgical approach trended strongly toward association with lower rates of local recurrence, and treatment at a very low caseload institution might be associated with a higher rate of local recurrence. To the authors’ knowledge, this is the largest systematic review describing contributing factors, outcome, and prognosis for patients with surgically treated sacral chordoma. Looking forward, there is a need for large, multicenter, randomized investigations into the efficacy of novel adjuvant treatments to be used in conjunction with surgery for management of this disease.

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**Supplemental Material**

The supplemental material is available in the online version of the article.

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