

# The clinical outcome of recurrent sacral chordoma with further surgical treatment

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## Abstract

Case series.

To analyze the clinical results and related factors of further surgical treatment for recurrent sacral chordomas.

Chordomas are rare primary malignant tumors with a high recurrence rate. The treatment of recurrent tumors is difficult and controversial. Contamination by previous operations and disturbed local anatomical structures may increase the risk of reoperation. Most previous studies have focused on the primary tumor; there are very few reports on the clinical diagnosis, treatment, and prognosis of recurrent sacral chordomas.

Thirty-four patients with recurrent sacral chordomas from 1979 to 2014 were included in this study. The patients comprised 25 men and 9 women with an average age of 50.7 (24–75) years. The average time until recurrence was 19.4 (4–51) months postoperatively, and 85.3% of the recurrent tumors were located in bone. The patients had an average of 1.2 (1–3) recurrences before further operations were performed in our hospital. The mean maximum tumor diameter was 8.1 (4.6–12.0) cm. Thirty-one patients underwent further tumor resection in our hospital. The postoperative recurrence, metastasis, and survival results were followed and analyzed.

The mean follow-up after surgical treatment of recurrence was 49.6 (12–144) months. Nine patients (37.5%) developed recurrence again after an average of 26.7 months. The 3-year and 5-year recurrence-free survival rate was 69.4% and 63.1%, respectively. Multivariate analysis showed that the tumor level within the sacrum ( $P = .001$ ) and the surgical margin ( $P = .001$ ) were significant recurrence-related factors. Four patients (16.7%) developed lung metastasis. Eighteen patients were alive at last follow-up. The 5-year and 10-year survival rate after surgical treatment of recurrence was 67.3% and 53.9%, respectively.

Most recurrent tumors are located in bone, and a safe osteotomy margin is important. The surgical margin is the only controllable factor of further tumor recurrence. Some patients with recurrence achieve long survival and obtain a clinical benefit from repeated operations if complete resection is achieved.

**Abbreviations:** CT = computed tomography, EGFR = epidermal growth factor receptor, MRI = magnetic resonance imaging, OS = overall survival, RFS = recurrence free survival, RT = radiation therapy.

**Keywords:** chordoma, outcome, recurrence, sacrum, surgery

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## 1. Introduction

Chordomas are rare primary malignant tumors arising from embryonic notochordal remnants.<sup>[1]</sup> They account for approximately 17.5% of axial primary malignant bone tumors.<sup>[1,2]</sup> Although chordomas may arise at any location in the spine,<sup>[3,4]</sup> most are located in the sacrum. Many patients present with large tumors because of delayed diagnosis and treatment. Surgical resection of the tumor is the most effective treatment for sacral chordoma. However, surgical treatment of sacral chordomas is challenging due to the complex structures and huge blood loss. The postoperative recurrence rate of sacral chordomas is high.<sup>[5–15]</sup>

Because of the high recurrence rate of sacral chordomas, postoperative follow-up and related examinations are necessary and important for timely detection of tumor relapse. The treatment of recurrent tumors is even more difficult. Contamination by previous operations and disturbed local anatomical structures may increase the risk of reoperation. Most previous studies have focused on the primary tumor. Few reports have described the clinical diagnosis, treatment, and prognosis of recurrent sacral chordomas.<sup>[16]</sup> In the present study, we analyzed the clinical results and related factors after further surgical treatment for recurrent sacral chordomas. The clinical characteristics of the recurrent tumors and outcomes during postoperative follow-up were also assessed.

Characteristics	Value	Cases
Age	Mean 50.7 (24–75) years	
Gender	Male	25
	Female	9
Recurrence time	Mean 19.4 (4–51) months	
Tumor level	S2–5	7
	S3–5	23
	S4–5	4
Tumor maximum size	Mean 8.1 (4.6–12.0) cm	
Tumor transverse size	Mean 7.6 (4.5–11.0) cm	

**2. Materials and methods**

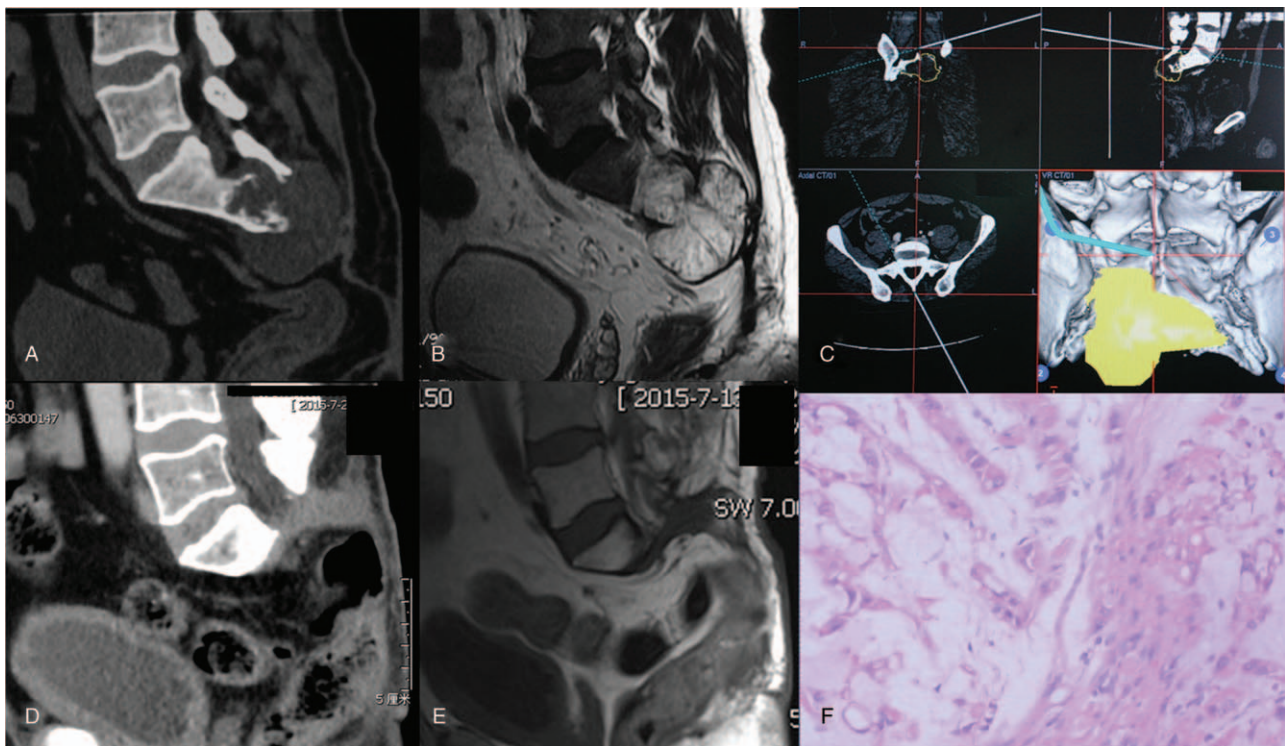
**2.1. Clinical characteristics**

All cases in the present study were identified from the database of our department. Thirty-four patients with complete clinical, radiological, and pathological data were included in this study from 1979 to 2014 (Table 1). The institutional review board of Beijing Ji Shui Tan Hospital approved this study. All patients provided written informed consent for the use of their data in this study. All patients had undergone initial surgical treatment in local hospitals. Postoperative follow-up revealed local recurrences, and the patients received further management in our hospital (Fig. 1). The diagnosis of chordoma in all patients was confirmed by the pathologist in our hospital (Fig. 2). Radiological examinations included plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) of the primary

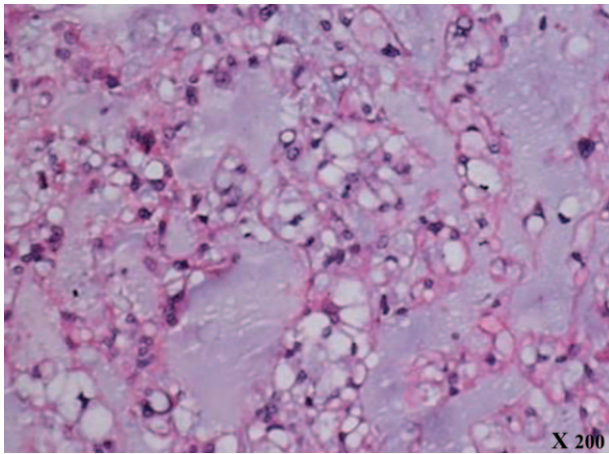
tumor sites and whole-body bone scanning. The maximum tumor diameter and maximum transverse diameter in the axial plane were measured by CT or MRI. The recurrence site was the sacrum (osteotomy site) in 29 (85.3%) patients and the gluteus maximus (soft tissue) in 5 patients. The average time until recurrence was 19.4 months (median, 17.5; range, 4–51 months) postoperatively. The average number of recurrences was 1.2 (range, 1–3) before the patients came to our hospital.

**2.2. Surgical treatment**

After confirmation of tumor recurrence and performance of preoperative examinations, 31 patients underwent tumor resection in our hospital. The surgical approach was either a combined approach (posterior and anterior) or a single posterior approach. The anterior retroperitoneal approach was applied to reveal the iliac vascular and lumbosacral nerve root. The anterior approach allowed for ligation of the internal iliac artery to reduce bleeding. The combined approach was seldom used with the application of preoperative embolization. The posterior approach allowed for exposure of the dorsal sacrum and iliac wing, facilitating complete tumor resection. The average operation time was 246.7 (90–415) minutes, and the average intraoperative blood loss was 2760.0 (800–6000) mL. The postoperative tumor specimens were soaked in formalin and then cut along the maximum diameter of the tumor for cross and sagittal sections, thus allowing for evaluation of the surgical margin. According to the Enneking surgical staging system for musculoskeletal tumors, the surgical margin showed intralesional resection in 15 cases, marginal resection in 11 cases, and wide resection in 5 cases.



**Figure 1.** A 43 years old male patient with recurrent sacral chordoma received further tumor resection in our hospital. The sacral CT (A) and MRI (B) showed local recurrence of tumor which involved the second sacral vertebrae after initial surgery. Then the patient received computer navigation assisted tumor resection through the first sacral vertebrae in our hospital (C). The sacral CT (D) and MRI (E) showed no tumor recurrence 90 months postoperative. The postoperative pathological examination (F HE staining 100 ×) confirmed the diagnosis of chordoma. CT=computed tomography, MRI=magnetic resonance imaging.



**Figure 2.** The HE staining (X 200) of tumor specimen showed funicular or cluster structure atypia vacuolated tumor cells in background of mucus. Droplet like tumor cells showed mild atypia.

**2.3. Postoperative follow-up**

During the first 2 years postoperatively, all patients were followed every 3 months. A physical examination; plain radiography of the chest, sacrum, and lower lumbar spine; and ultrasonography of the primary surgical site were also performed at each follow-up. Lumbosacral CT and whole-body bone scanning were performed every 6 months. The patients were followed once a year after the third year postoperatively.

**2.4. Statistical analysis**

The data were analyzed by SPSS software, version 19.0 (IBM Corp., Armonk, NY). The Kaplan–Meier method was applied for overall survival (OS) and recurrence-free survival (RFS) analysis.

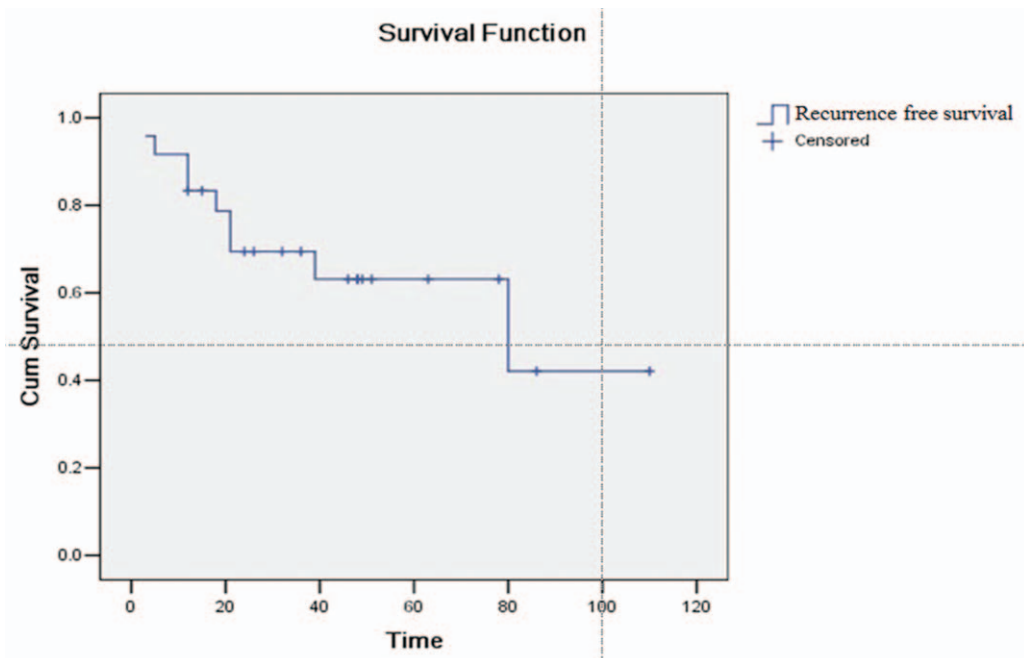
Multiple Cox regression was applied for risk factor analysis. The log-rank test was applied to compare survival in different groups. Continuous variables were compared with the *t* test, and categorical variables were compared by the chi-square test or Fisher exact probability method. Pearson correlation test was applied for parametric factors, and Spearman correlation test was applied for nonparametric factors. A *P* value of <.05 was considered statistically significant.

**3. Results**

**3.1. Recurrence**

The postoperative follow-up was longer than 12 months in 24 patients. Therefore, the recurrence, metastasis, and survival results were analyzed in these 24 patients. The mean postoperative follow-up (in our hospital) was 49.6 months (median, 41 months; range, 12–144 months). Nine patients (37.5%) developed recurrence after an average of 26.7 months (median, 16.5 months; range, 3–80 months). Four recurrences (44.4%) were found in the first 2 years, and 5 recurrences (55.6%) were found in the first 5 years (Fig. 3). The Kaplan–Meier analysis showed that the 3-year and 5-year RFS was 69.4% and 63.1%, respectively. The median RFS time was 69.7±10.1 months (Fig. 3).

The multivariate analysis showed that the tumor level within the sacrum (*P*=.001) and the surgical margin (*P*=.001) were significant risk factors for local recurrence (Tables 2 and 3). Age (*P*=.447), gender (*P*=.524), tumor size (*P*=.666), operation time (*P*=.368), and intraoperative blood loss (*P*=.296) were not significant factors. Therefore, the tumor level within the sacrum and the surgical margin were further analyzed (Table 3). The recurrence rate was significantly higher in patients with the tumor level above than below S3 [3/5 (60.0%) and 6/19 (31.6%), respectively; *P*=.004] (Fig. 4). The recurrence rate was not significantly different among patients with intralesional resection



**Figure 3.** Recurrence free survival curve showed the 3-year and 5-year recurrence free survival rate was 69.4% and 63.1%, respectively.

**Table 2**  
Multivariate analysis of recurrence related factors.

Factors	Recurrence rate	P value	HR (95% CI).
Age		.447	0.812 (0.725–0.921)
Gender	Male	7/16 (43.8%)	.524
	Female	2/8 (25%)	0.625 (0.403–0.835)
Tumor size		.666	0.702 (0.583–0.862)
Tumor level	Above S3	3/5 (60%)	.001
	Below S3	6/19 (31.6%)	0.497 (0.374–0.712)
Operative time		.368	0.712 (0.598–0.833)
Blood loss		.296	0.693 (0.513–0.791)
Surgical margin	Intralesional	7/13 (53.8%)	.001
	Marginal	2/9 (22.2%)	0.347 (0.135–0.527)
	Wide	0/2 (0%)	0.113 (0.052–0.232)

**Table 3**  
Clinical characteristics of patients in recurrence and non-recurrence group.

Factors		Recurrence group	Non-recurrence group	P value
Age	Mean	53.3	50.9	.680
Gender	Male	7	9	.191
	Female	2	6	
Maximum tumor size	Mean (cm)	7.9	8.2	.786
Tumor level	Above S3	3	2	.004
	Below S3	6	13	
Operative time	Mean (mins)	289	233	.662
Blood loss	Mean (ml)	3550	2450	.483
Surgical margin	Intralesional	7	6	.021
	Marginal	2	7	
	Wide	0	2	

(7/13, 53.8%), marginal resection (2/9, 22.2%), and wide resection (0/2, 0.0%) ( $P=.021$ ) (Fig. 5).

**3.2. Metastasis**

Four patients (16.7%) developed metastasis. One patient underwent lung metastasis resection and 1 received radiotherapy. The other 2 patients did not receive treatment and died of lung metastasis. Although the chi-square test showed that the metastasis rate in patients with and without recurrence was 33.3% and 6.7%, respectively ( $P=.001$ ), the multivariate analysis showed that metastasis was not a significant risk factor (Tables 4 and 5).

**3.3. Survival**

At the last follow-up, 18 patients were alive and 6 (25%) had died. Two patients died of lung metastasis. Two patients died of cachexia and consumption due to repeated tumor relapse, and they were finally unable to tolerate an operation. One patient died

in the perioperative period. One patient died of another disease unrelated to chordoma. Kaplan–Meier survival analysis showed that the 5-year and 10-year survival rate was 67.3% and 53.9%, respectively (Fig. 6).

The multivariate analysis results showed that age ( $P=.337$ ), gender ( $P=.083$ ), tumor level ( $P=.251$ ), tumor size ( $P=.177$ ), recurrence ( $P=.884$ ), and metastasis ( $P=.641$ ) were not significant risk factors for survival. The chi-square test showed that the survival rate in patients with and without recurrence was 66.7% (6/9) and 80.0% (12/15), respectively ( $P=.221$ ), and the survival rate in patients with and without metastasis was 50.0% (2/4) and 80.0% (16/20), respectively ( $P=.001$ ). Kaplan–Meier analysis showed that the 5-year OS in patients with and without recurrence was 90.9% and 57.1%, respectively ( $P=.207$ ) (Fig. 7), and the 5-year OS in patients with and without metastasis was 75.0% and 81.6%, respectively ( $P=.797$ ) (Fig. 8).

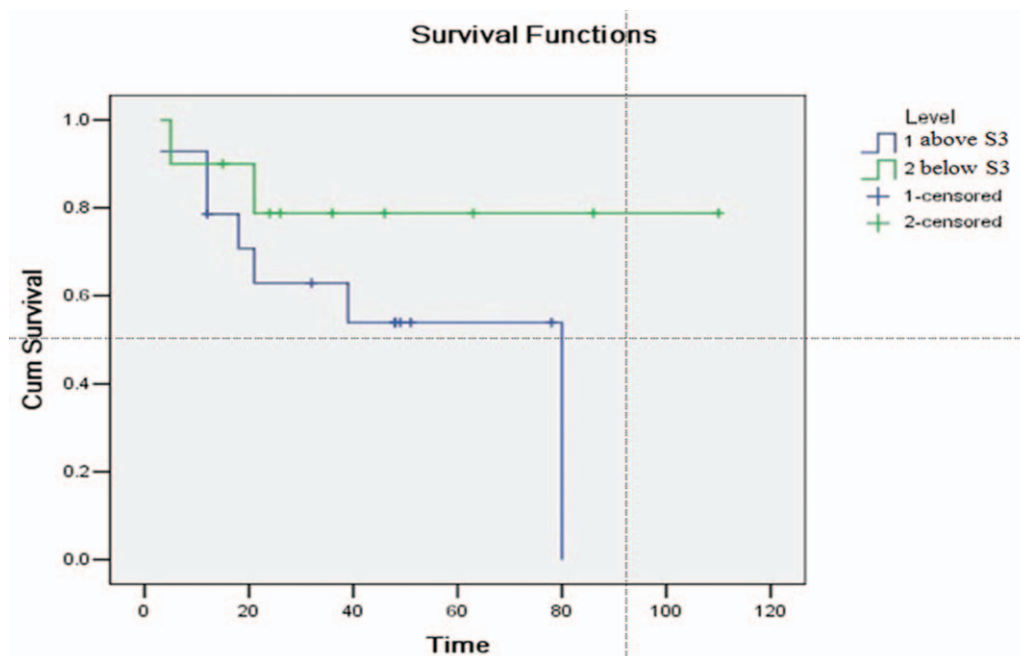


Figure 4. Recurrence free survival curve in different tumor levels (1 for group above S3 and 2 for group below S3,  $P < .001$ ).

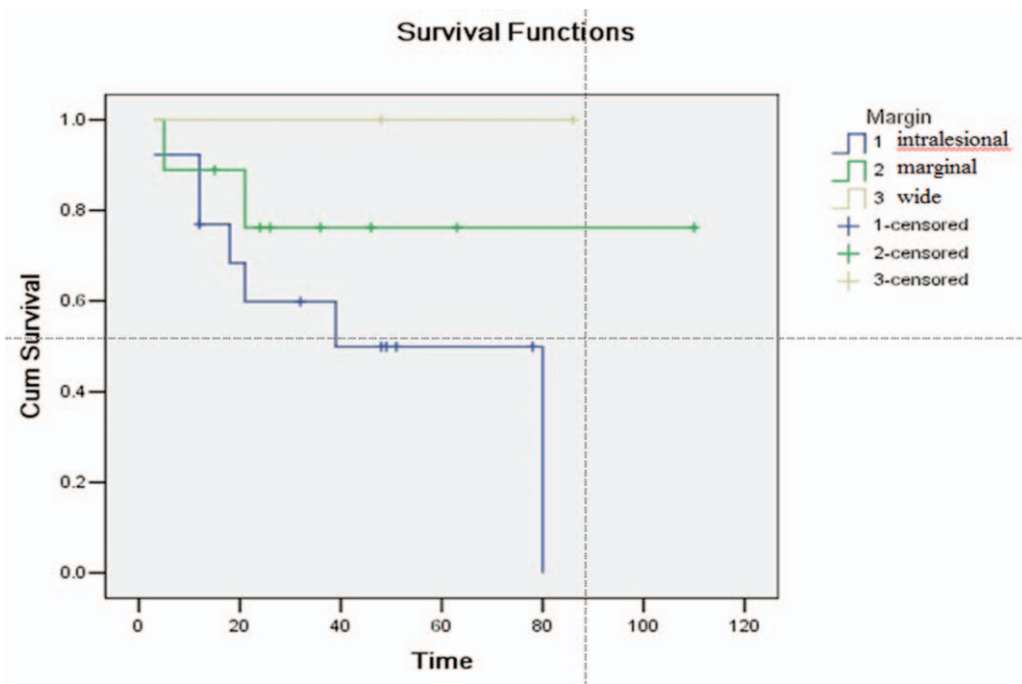


Figure 5. Recurrence free survival curve in different surgical margins (1 for intralesional resection, 2 for marginal resection and 3 for wide resection,  $P < .001$ ).

4. Discussion

Surgical treatment of sacral chordoma is difficult, and postoperative recurrence is common. However, the outcome after further surgical treatment of recurrent chordoma is not clear. Therefore, we performed the present study to investigate the treatment and prognosis of recurrent sacral chordoma. The clinical characteristics and outcomes of recurrent tumors with postoperative follow-up were analyzed.

In the present study, the mean time interval between the last operation at local hospitals and the development of postoperative recurrence was relatively short (19.4 months). The mean time from the further operation in our hospital to the development of postoperative recurrence was 26.7 months. A previous study showed that most postoperative recurrences occurred within 3 years postoperatively.<sup>[16]</sup> The reason for the quick postoperative recurrence in our study may have been due to the unsafe surgical margin of the last operation or even the presence of residual tumor tissue. The average maximum tumor diameter was 8.1 cm,

which is similar to that of primary sacral chordoma.<sup>[2,16]</sup> This suggests that the symptoms of postoperative recurrence were not significant in the early stage. The patients complained of no special discomfort from the time at which the tumor recurred until it grew to a large size. Delayed diagnosis and treatment may also occur in patients with recurrent sacral chordoma. Therefore, regular postoperative follow-up is very important.

The recurrence site was the sacrum (osteotomy site) in 29 patients and the gluteus maximus (soft tissue) in 5 patients in our study. Therefore, most of the local recurrences were associated with bone. Previous reports<sup>[7,17,18]</sup> have also shown most recurrences were located around the sacrum and other sites including the gluteus maximus and ischioanal fossa. Xie et al<sup>[16]</sup> assessed 30 patients with recurrent sacral chordomas and found that most recurrent tumors were located in sacrum (20 patients)

Table 4  
Multivariate analysis of metastasis related factors.

Factors	Metastasis rate	P value	HR (95% CI)
Age		.914	0.902 (0.812–0.991)
Gender	Male	3/16 (18.8%)	.657
	Female	1/8 (25%)	0.732 (0.603–0.896)
Tumor size		.900	0.867 (0.735–0.917)
Tumor level	Above S3	0/5 (0%)	.396
	Below S3	4/19 (21.1%)	0.317 (0.204–0.423)
Surgical margin	Intralesional	2/13 (15.4%)	.567
	Marginal	1/9 (11.1%)	0.345 (0.232–0.465)
	Wide	1/2 (50%)	0.221 (0.183–0.313)
Recurrence	Yes	3/9 (33.3%)	.702
	No	1/15 (6.7%)	0.235 (0.113–0.395)

Table 5  
Clinical characteristics of patients in metastatic and non-metastatic group.

Factors		Metastatic group	Non-metastatic group	P value
Age	Mean	54.8	51.2	.648
Gender	Male	3	13	.713
	Female	1	7	
Maximum tumor size	Mean (cm)	7.6	8.2	.632
Tumor level	Above S3	0	5	.281
	Below S3	4	15	
Operative time	Mean (mins)	278	258	.822
Blood loss	Mean (mL)	2100	3180	.480
Surgical margin	Intralesional	2	11	.642
	Marginal	1	8	
	Wide	1	1	
Recurrence	Yes	3	1	.001
	No	6	15	

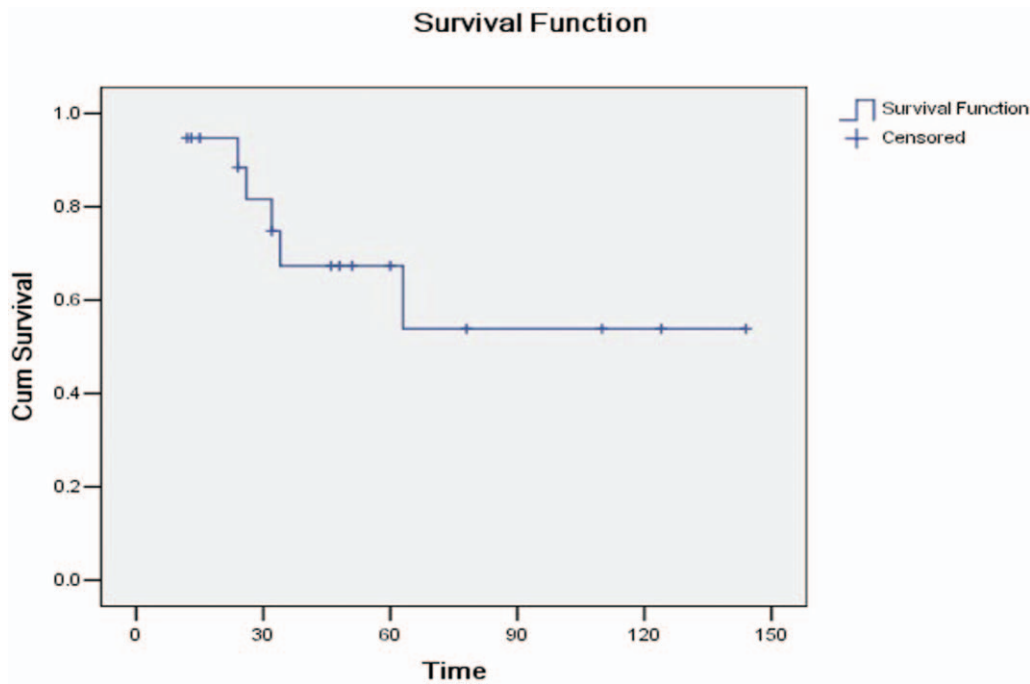


Figure 6. Overall survival curve showed the 5-year and 10-year survival rate was 67.3% and 53.9%, respectively.

and that some were located in the gluteus maximus (6 patients). Recurrence in other sites was rare. Combining the findings of the present study and previous reports, most recurrences were located in the sacrum (osteotomy site). Thus, a clear osteotomy line and safe margin in bone are very important for local control.

Nine patients (37.5%) developed further recurrence at an average of 26.7 months postoperatively in the present study. Most of the recurrences occurred in first 5 years postoperatively.

The median RFS time was 69.7 months in our study. The recurrence rates after primary surgical treatment were quite variable (30%–75%) in previous reports.<sup>[5–13,15–28]</sup> Xie et al<sup>[16]</sup> reported that 9 patients with recurrence underwent further tumor resection and that 3 patients developed recurrence again. The recurrence rate in their report is similar to that in the present study. Although some patients still developed local recurrence after repeated surgical treatment, most did not develop

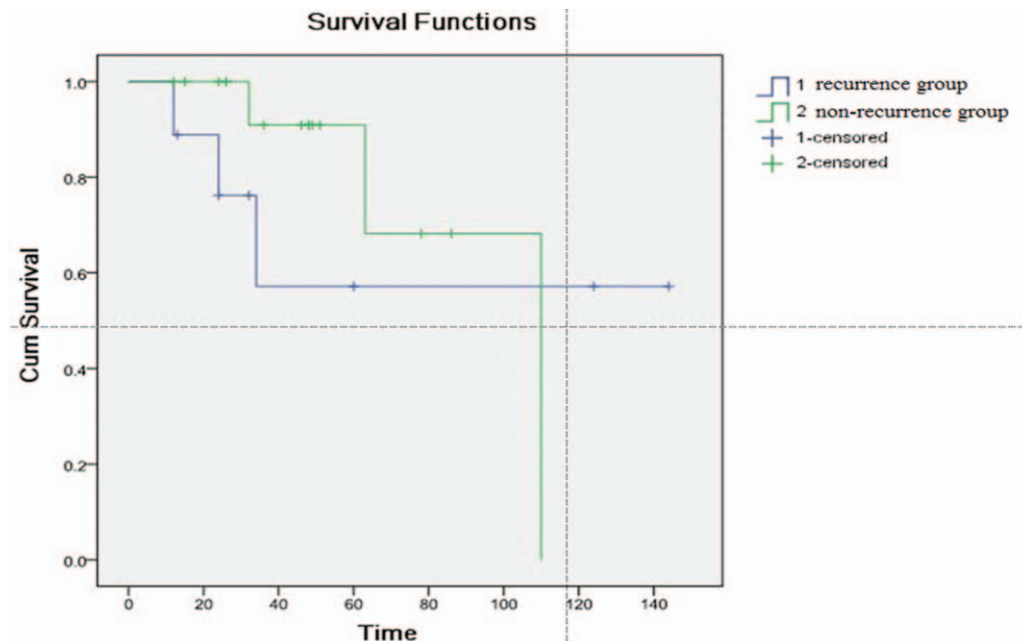


Figure 7. Survival curve in recurrence group (1) and non-recurrence group (2) ( $P = .207$ ).

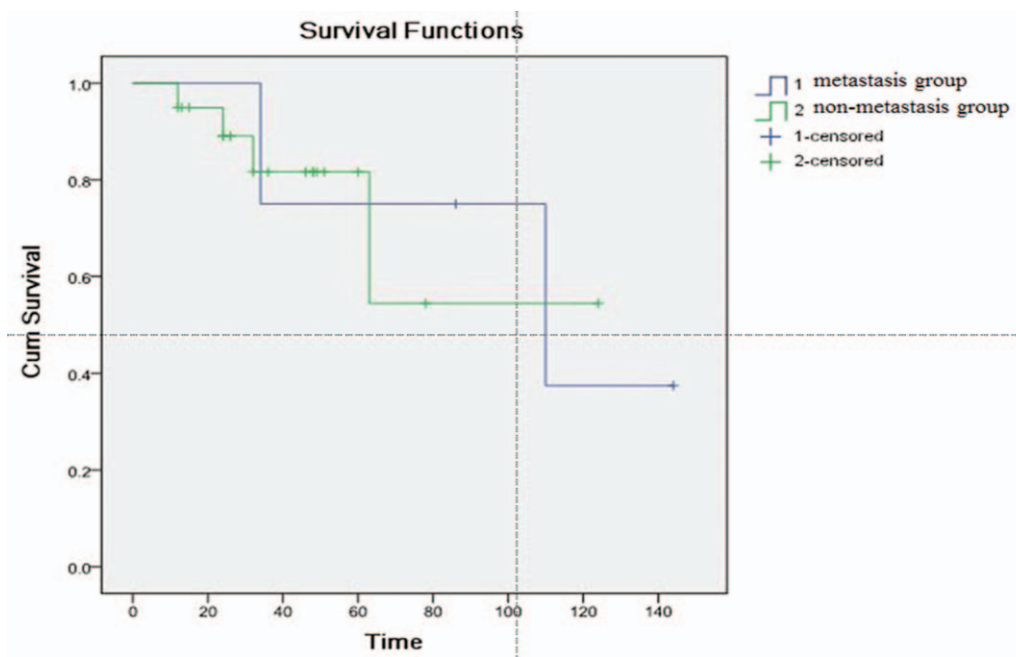


Figure 8. Survival curve in metastasis group (1) and non-metastasis group (2) ( $P = .797$ ).

recurrence again and remained alive without tumors. Therefore, local recurrence can also be managed by further operations in most patients. Many patients can obtain clinical benefits from further operations.

This study showed that the tumor level within the sacrum and the surgical margin were significant risk factors for local relapse. This result regarding local control is similar to that obtained by the analyses of primary sacral chordomas in previous reports.<sup>[8,9,13,20-23]</sup> Thus, the surgical margin is the only controllable factor in the treatment of recurrent sacral chordomas. Complete resection of the recurrent tumor is the most important aim of further operations. The present study suggests that accurate preoperative evaluation and careful intraoperative management should be performed to obtain a safe surgical margin.

The metastasis rate was 16.7%, and all of the metastases were located in the lung in our study. Although the metastasis rate was higher in patients with than without recurrence (33.3% vs 6.7%, respectively), the multivariate analysis did not show the same result, and no significant factors were found. This negative result may be associated with the small number of patients with metastases.

At the last follow-up, 18 patients were alive and 6 (25%) had died. Two patients died of lung metastasis, and 2 patients died of cachexia and consumption due to repeated tumor relapse. This result suggests that patients with recurrence should undergo an operation if the tumor can be completely resected. The Kaplan-Meier survival analysis showed that the 5-year and 10-year survival rate was 67.3% and 53.9%, respectively. This survival rate of patients with recurrent sacral chordoma is lower than that of patients with primary tumors in previous reports. Radaelli et al<sup>[19]</sup> reported that among 99 patients with primary sacral chordoma, the 5-year and 10-year survival rate was 92% and 63%, respectively. Ruggieri et al<sup>[20]</sup> reported that among 56 patients with primary sacral chordoma, the 5-year and 10-year survival rate was 97% and 71%, respectively. Xie et al<sup>[16]</sup> reported that among 54 patients with primary sacral chordoma, the 5-year and 10-year survival rate was 82% and 57%,

respectively. Finally, Baratti et al<sup>[7]</sup> reported that among 28 patients, the 5-year and 10-year survival rate was 87.8% and 48.9%, respectively. In the present study, although the survival rate was lower in patients with than without metastasis (50% vs 80%, respectively) the multivariate analysis did not show a similar result. This negative result may be related to the small sample size. Previous reports of primary chordoma showed that metastasis was associated with a poor prognosis.<sup>[11,15,21]</sup>

Radiation therapy (RT) is applied in combination with surgery to improve local control of sacral chordomas.<sup>[29-31]</sup> RT may have a certain role in the treatment of recurrent sacral chordoma. After application of a combination of high-energy proton-beam and photon-beam RT, the local control rates were higher in patients with primary chordomas than in those with recurrent tumors.<sup>[32]</sup> A prospective trial showed that high-dose photon/proton RT resulted in 5- and 8-year local control rates of 94% and 85% for primary tumors and 81% and 74% for recurrent tumors, respectively.<sup>[33]</sup>

Systemic therapy may also be effective in the control of recurrent chordoma. The epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (mTOR) have been implicated in the pathogenesis of chordomas, and this has led to the development of targeted therapies.<sup>[34,35]</sup> In a phase II study of 56 patients with advanced chordoma, 70% of patients had stable disease after treatment with imatinib (tyrosine kinase inhibitor).<sup>[36]</sup> Another phase II study of patients with recurrent and metastatic chordoma showed that lapatinib (EGFR inhibitor) induced a partial response in 33% of patients and that 39% of patients had stable disease.<sup>[37]</sup>

This study had some limitations. First, it was a nonrandomized retrospective study. Second, only patients who received surgical treatment were followed and analyzed. Patients who could not undergo an operation for any reason were not included in this study, which may have resulted in selection bias. Third, our results showed that local recurrence and metastasis have no significant impact on OS. These statistical results were biased due

to the limited sample size of this study and the fact that only 6 patients had died at the last follow-up. Fourth, we only explored independent factors and validated the results in the same group. As a next step, a new study is needed to verify the relationship between the risk factors found in this study and the prognosis.

In conclusion, this study was performed to investigate a relatively large series of recurrent sacral chordomas and the clinical outcomes of this rare bone tumor. Regular and careful follow-up is necessary to detect recurrence. Most recurrent tumors are located in the sacrum, not the soft tissue; thus, a safe osteotomy margin is important. The surgical margin is still the only controllable factor of further tumor recurrence. Most patients can survive for a long period of time and still obtain a clinical benefit from repeated operations if complete resection is achieved.

### Author contributions

**Conceptualization:** Yongkun Yang, Hairong Xu, Xiaohui Niu.

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**Supervision:** Hairong Xu.

**Writing – original draft:** Yongkun Yang.

**Writing – review & editing:** Xiaohui Niu.

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