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The clinical outcomes for chordomas in the cranial base and spine

A single center experience

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Abstract

Owing to the special growth pattern of chordomas and the limited treatment options currently available, the treatment of chordoma still remains difficult. In this study, we hope to further clarify the relationship between surgical treatment and radiotherapy of chordoma and disease progression.

All patients with a primary histopathological diagnosis of clival or spinal chordomas recorded in our institution between 1976 and 2017 were examined.

A total of 60 patients (location: skull base/clival, n=24; vertebral column, n=5; sacrum, n=31) had a mean follow-up time of 7.7 years (range 12 months–35 years). Compared with patients who received subtotal resection (n=5, 5-year and 10-year survival=61% and 39%, respectively), the annual survival rate of patients who received total resection (n=55, 5-year and 10-year survival=67%, respectively) was significantly higher. The overall 10-year survival rate (58%) of patients treated with surgery alone was significantly different from those treated with a combination of surgery and radiation (73%). The long-term prognosis of sacral chordoma was the worst (10-year survival rate=48%).

The best treatment strategy for improved long-term survival in chordoma was a combination of surgical resection and radiation therapy. Adjuvant radiotherapy for chordoma significantly improves disease-free survival, although the long-term survival benefit remains to be determined. A worse prognosis and poor long-term survival are seen in sacral chordomas.

Abbreviations: CDK4 = cell cycle dependent kinase 4, c-MET = methionine, CN VI = cranial nerve VI, Gy = absorbed dose of radiation, iNOS = inducible nitric oxide synthase, mTOR = mammalian target of rapamycin, pAKT = phosphorylated protein kinase, PDGFR-a = platelet-derived growth factor receptor-a, RFA = radiofrequency ablation, VEGFR-2 = vascular endothelial growth factor receptor-2.

Keywords: chordomas, radiation therapy, surgical resection

1. Introduction

Chordomas are rare primary bone tumors that originate from residual elements of the embryonic notochord. They are a type of inert but recurring bone tumor. Although they can metastasize, we have found that the long-term clinical outcome of patients does not depend on this, but rather depends on whether there is local recurrence. Therefore, our patients often require repeated surgery and even radiation therapy. Because of the poor long-term prognosis, especially when the recurrence of reoperation is more likely to cause more serious complications, most chordomas are treated as early as possible with comprehensive resection and postoperative radiation therapy.[1–4] Because we often need to consider important tissue next to the tumor in postoperative radiotherapy, especially when the target is close to the brain stem, optic chiasm, and important brain nerves and tissues, we often consider dose reduction to avoid severe side effects; this can also lead to recurrence.[5] Therefore, thorough tumor resection and effective decompression of the surrounding tissue are crucial for patients with chordomas, especially those with skull base chordomas.[3,6]

With the recent increase in the detection rate of chordomas, as well as a lack of consensus regarding treatment strategies, we conducted a retrospective study of our experience to assess clinical outcomes in chordoma patients. We evaluated the relationship between the degree of surgical resection, adjuvant radiation therapy, and clinical outcomes such as disease survival and disease progression.

2. Materials and methods

We identified 60 patients with a histopathological diagnosis of chordoma through a retrospective review of the database at the

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The datasets during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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The authors declare that they have no competing interests.

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First Affiliated Hospital of Nanchang University, from January 1976 to June 2017. All patients underwent clinical and radiographic evaluation by the neurosurgery/orthopedic department. The Human Subjects Office Institutional Review Board of the First Affiliated Hospital of Nanchang University approved this retrospective research.

2.1. Radiation therapy

Patients were treated using radiation therapy, ranging from 2 Gy once daily to 54 Gy. The mean target volume was 85 cm^3 (0.048–2000 cm^3).

Progression-free and disease survival intervals were calculated using the Kaplan–Meier method. Statistical associations were assessed using the log-rank Mantel-Cox analysis with GraphPad Prism, version 7.0 for Windows.

3. Results

This study included a total of 60 patients with chordoma (39 men and 21 women). According to the anatomy of the lesion, they were classified into the following groups: skull base/clivus: n = 24, sacrum: n = 31, lumbar spine: n = 3, cervical spine: n = 1, and thoracic spine: n = 1 (Table 1). Figure 3 shows the imaging and histopathological data of related typical cases, as shown by arrows.

3.1. Clival chordomas

There were 24 patients (n = 24, 40%) with clival chordomas, which included 14 male and 10 female patients (Table 2). The average age of onset is 37 years old (range: 5–62 years). Presenting symptoms included neurological deficits in 24 patients (100%), including multiple (>1) cranial nerve palsies in 5 patients, visual disturbance in 10 patients, and CN VI palsy in 2 patients. Thirteen (n = 13, 54%) patients presented with headaches because of local tumor growth. The mean time from symptom onset to clinical treatment was 8 months (range: 3 days–12 months). All patients underwent complete resection of lesions that were validated in follow-up imaging examination. Eleven patients encountered tumor recurrence in situ (confirmed radiographically) at a mean interval of 36 months (range: 1–96 months) after the first total resection (Table 2). Of these, 1 patient underwent radiotherapy and 1 patient died 1 month after surgery with hydrocephalus and pulmonary infection. Four patients (74%) underwent repeat surgery. Six patients received conservative treatment, followed by continuous clinical follow-up and imaging examination. One patient (n = 1; 24.4%) was identified as having a second recurrence. Auxiliary radiation therapy was recommended and performed in 16 patients after initial surgery (Table 3). Only 1 patient underwent radiation therapy after tumor recurrence (n = 1, 9%; Table 3). No patients were lost to clinical follow-up in the postoperative period. The 24 patients had a mean follow up period of 5.9 years (range: 1–19 years). Sixteen patients were alive and 8 patients had died by the final follow-up. Cumulative 5-year and 10-year survival rates for these patients were 69% and 60%, respectively (Table 2 and Fig. 1).

3.2. Sacral and vertebral chordomas

Five patients' (2 men, 3 women) lesions were located within the mobile spine and 31 patients' tumor grew into the sacrum. The

Table 1

The information about the individual therapy for each patient.

No.	Gender	Location	Age	Surgical	Radiotherapy
1	M	Sacrum	53	T	1
2	F	Sacrum	38	T	0
3	F	Sacrum	59	T	1
4	F	Sacrum	24	T	0
5	M	Sacrum	71	T	1
6	M	Sacrum	47	T	0
7	M	Sacrum	60	T	0
8	M	Sacrum	24	T	1
9	M	Sacrum	17	T	0
10	M	Sacrum	46	T	1
11	F	Sacrum	66	T	1
12	M	Sacrum	41	S	1
13	F	Sacrum	38	T	1
14	M	Sacrum	62	T	1
15	M	Sacrum	75	T	1
16	M	Sacrum	57	T	0
17	M	Sacrum	34	T	1
18	M	Sacrum	54	T	1
19	M	Sacrum	39	T	1
20	M	Sacrum	61	T	1
21	M	Sacrum	74	T	0
22	M	Sacrum	50	T	0
23	M	Sacrum	69	T	0
24	F	Sacrum	45	T	1
25	F	Sacrum	51	T	0
26	M	Sacrum	59	T	0
27	M	Sacrum	53	T	0
28	M	Sacrum	50	T	0
29	M	Sacrum	54	T	1
30	M	Sacrum	70	T	0
31	F	Sacrum	55	T	0
32	M	Clival	36	T	0
33	F	Clival	55	T	0
34	M	Clival	43	T	1
35	F	Clival	36	T	0
36	M	Clival	56	T	1
37	M	Clival	26	T	1
38	F	Clival	30	T	1
39	M	Clival	62	T	1
40	F	Clival	63	T	0
41	F	Clival	35	T	1
42	F	Clival	55	T	1
43	M	Clival	47	T	1
44	M	Clival	46	T	0
45	F	Clival	60	T	1
46	M	Clival	44	T	1
47	F	Clival	40	T	1
48	M	Clival	25	T	1
49	M	Clival	19	T	1
50	M	Clival	37	T	0
51	F	Clival	23	T	1
52	M	Clival	16	T	0
53	M	Clival	5	T	0
54	M	Clival	17	T	1
55	F	Clival	18	T	1
56	F	Mobile Spine	33	T	1
57	F	Mobile Spine	21	T	0
58	M	Mobile Spine	67	T	1
59	F	Mobile Spine	60	T	0
60	M	Mobile Spine	72	T	0

0: Did not receive radiotherapy.
1: receive radiotherapy.
T: Total resection.
S: Subtotal resection.

Table 2

Summary of clinical presentation and course classified by primary site.

	Clivus, n = 24	Vertebral, n = 5	Sacral, n = 31
Age mean (range), yr	37	51	51
Sex: Male	14	2	23
Female	10	3	8
Interval to symptom presentation: mean (range), mo	8	9	25
Predominant presenting symptom	Pain = 12 Neurological deficit = 24	Pain = 4 Neurological deficit = 2	Pain = 26 Neurological deficit = 11
Interval to disease recurrence: Mean (range), mo	36 (1–96)	5	43 (8–120)
Number of recurrences: Mean (range)	11	1	12
5-yr progression-free survival (%)	53	80	62
5-yr survival (%)	69	80	78
10-yr survival (%)	60	80	48

Table 3

Summary of clinical outcomes in chordomas.

	5 yr disease free survival (%)	5 yr survival (%)	10 yr survival (%)	*P*-value
Surgical resection outcomes				
Total resection, n = 55	67	67	67	.11
Subtotal resection, n = 5	48	61	39	
Radiation therapy outcomes				
Surgical resection only, n = 26	31	58	46	<.001
Surgical resection and radiation therapy, n = 34	56	73	58	

number of male patients with sacral chordoma was higher than the number of female patients (male: n = 23, 74%; female: n = 8, 26%). The mean age of onset for vertebral chordoma patients was 51 years (range: 21–72 years). Patients with sacral chordoma had the same mean age at presentation of 51 years (range: 17–75 years; Table 2). The main symptom of spinal and sacral chordoma was local pain, as noted in 4 patients (80%) with spinal chordomas and all patients (n = 23, 74%) with sacral chordomas. Only 1 spinal chordoma patient was found to have an in-situ mass that was increasing gradually in size. Neurological deficits were found in 4 patients within the spinal chordoma group, including lower limb numbness or weakness in 3 patients and urine retention in 1 patient. There were no patients with bladder incontinence or cranial nerve palsy. Five patients with sacral chordoma presented with urinary/fecal incontinence, and 1 patient had saddle anesthesia. The mean duration of the chief complaint for spinal chordoma patients (9.0 months, range: 4 days–82 months) was shorter than that for sacral chordoma patients (25 months, range: 1–84 months). Subtotal resection was conducted in 1 patient (n = 1/31, 3%) with sacral chordoma and no patients (n = 0) with vertebral chordoma in the primary surgery. Total mass resection was performed in 5 patients (n = 5/5, 100%) with spinal chordoma and 30 patients (97%) with sacral chordoma. Tumor recurrence was checked in 1 patient (n = 1/5, 20%) with spinal chordoma 5 months after primary surgery. Tumor recurrence was found in 12 patients with sacral chordoma (n = 12/31, 39%) at a mean interval of 43 months (range: 8–120 months) after the initial resection. Adjuvant radiotherapy following initial surgery was performed in 2 patients (40%) with spinal chordoma. One patient with lumbar and thoracic chordoma, was treated with adjuvant radiation at an outside facility. Two of the 31 patients (6.5%) with sacral chordoma received radiotherapy after recurrence. The only patient with recurrent spinal chordoma did not undergo radiation therapy after recurrence (Table 2). The mean dose of radiotherapy was 54 Gy (49–60 Gy). Patients with spinal chordoma had better survival rates than patients with clival- or sacral-based chordomas with 5- and 10-year survival rates of 80% each (statistically nonsignificant; *P*-value > .01) (Table 2 and Fig. 1). The 5- and 10-year survival rates for patients with sacral chordoma was 78% and 48%, respectively (statistically nonsignificant; *P*-value > .01). Similar 5- and 10-year survival rates of 69% and 60%, respectively, were found in patients with clival chordomas (statistically nonsignificant; *P*-value > .01) (Fig. 1).

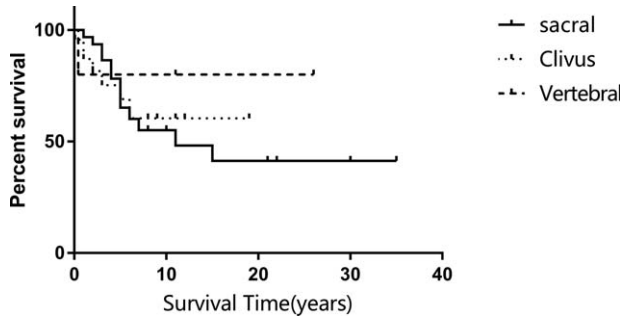

Figure 1. Survival curve of patients with different sites of chordoma.

3.3. Treatment summary – surgical resection and radiation therapy

The cumulative 5- and 10-year survival rates were higher (67% for both) in patients (n = 55) who underwent gross total resection

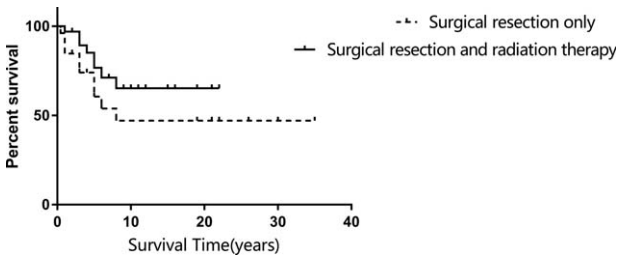

Figure 2. Survival curve of patients treated with surgery alone and surgery combined with radiotherapy.

after their primary treatment, compared to those who had undergone subtotal mass resection (n = 5, 61% and 39%, respectively, *P*-value > .01). Clinical outcomes were grouped by the location of the tumor, extent of surgical resection and use of adjuvant therapy. In patients with chordoma, the patients with gross total resection in the initial surgery had higher 5- and 10-year survival rates (n = 55, 67% for both) than patients who underwent subtotal resection (n = 5, 61% and 39%, respectively, Table 3). Surgical resection combined with radiation therapy significantly improved the survival and progression-free rates of patients with chordoma (Fig. 2).

4. Discussion

As with all retrospective studies, our conclusions and related data mining are limited by the retrospective nature of the data collection.

As previously reported, clival chordomas tend to have an onset at an earlier age (mean age = 40 years).[7,8] In clival chordomas, the most common complication was a cranial nerve deficit, especially cranial nerve VI palsy.[4] This may explain the relatively shorter interval between onset and presentation (mean = 8 months). The purpose of surgical resection of chordoma is to remove lesions in order to optimize the response to postoperative radiotherapy.[4,7,3,9] The 5- (69%) and 10-year (60%) survival rates within this subgroup of our study population are consistent with previous reports.[4]

Back pain was the most common complaint in patients with chordomas within the spine, similar to previous reports.[2,10,11] This subgroup had the best clinical prognosis, as reflected by the survival rates (5-year survival: 80% and 10-year survival: 80%) (Fig. 1).

The mean age at onset for sacral chordoma was the same as that for vertebral chordoma (mean = 51 years), younger than previous reports (70-years old).[14] Due to the slow hidden growth pattern, pain was often the only clinical manifestation in the patient, and the chief complaint took a long time to develop. One patient died within 12 months of the initial resection. In the other 30 patients, 16 patients received

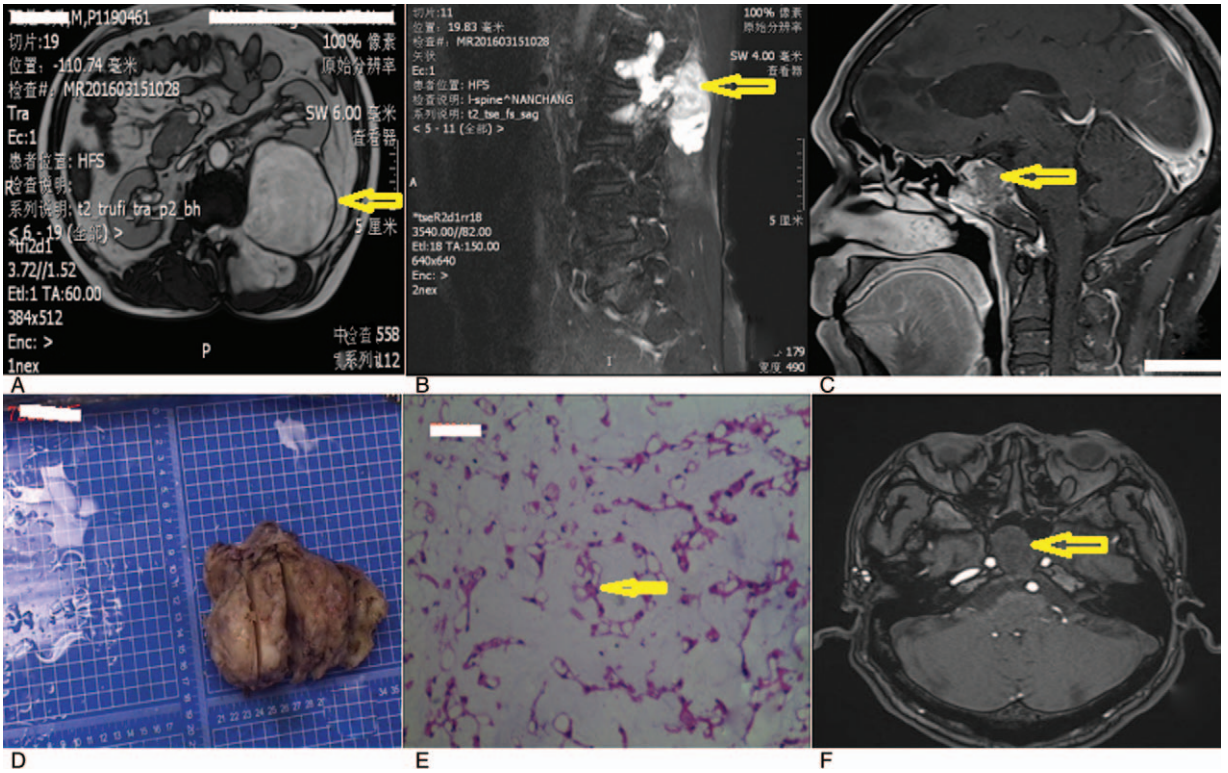

Figure 3. (A and B) Axial MRI shows a large inhomogeneous mass causing compression of the left kidney. Sagittal MRI shows that the vertebral laminae of L2 was eroded and the left L2 intervertebral foramen was enlarged. D and E show the mass removed from lesions during the operation. Histological sections of the mass display tumor tissue in a myxoid background and cords and lobules of vacuolated physaliphorous cells with abundant cytoplasm and a large amount of mucus. The nucleus was round or oval-shaped without definite mitosis (original magnification, ×100). (C and F) MRI shows that the solid occupying lesions are seen in the saddle-bottom slope area. The enhanced scan shows uneven and moderate enhancement, with increased pituitary pressure (arrowheads). MRI = magnetic resonance imaging.

radiation therapy. The overall survival within this subgroup was not poor for all measures; it had the highest mean survival rate at 5 years relative to patients with clival and/or spinal chordomas. Fifteen (48%) of our patients with sacral chordomas were still alive at the 10-year follow-up. Within this subgroup, the 5-year survival was 78%, which is higher than previous reports (Fig. 1).[12–14]

Local recurrence is considered to be the most important prognostic factor for long-term disease survival after primary resection.[19] Ten-year survival rates (67%) after total resection were considerably higher than in patients with a subtotal resection (39%), consistent with previous reports. This highlights that complete removal of tumors where feasible is very positive for long-term prognosis.[9,12,19]

Consistent with previous findings, the exposed surgical margin is also a prognostic factor for chordomas.[15] However, sometimes the complete exposure of the tumor is very difficult. Thus, we introduce another technique. When conventional treatment methods such as surgery, radiotherapy, and chemotherapy are difficult to perform, such as in the treatment of solid brain tumors, radiofrequency ablation (RFA) is still safe and feasible.[16] Neeman et al[17] revealed that RFA could reduce the volume of the tumor after the first percutaneous RFA treatment for chordomas. Magnetic resonance-guided RFA through multiplanar observation allows safe entry into the tumor directly.[18]

Adjuvant radiation therapy has been adopted for patients with chordoma by some clinics.[13,20,21] Although some patients received radiation therapy, their clinical outcomes were not significantly improved.[11,22,23] However, in our study, the combination of radiation therapy after resection of lesions for the initial surgery did significantly improve 5- and 10-year disease survival. Because of the need to protect tissues around the tumor, the dose of conventional radiotherapy can usually only reach 50 to 60 Gy.[24] At present, our institution has not conducted high-dose radiation therapy; however, there are reports of high-dose radiation therapy in the related literature. Like proton beam radiation therapy, it is possible to provide high-dose segmented radiotherapy within the target tumor volume while having minimal radiation exposure of the surrounding key structures, making it an attractive option for the treatment of skull base slope chordomas.[6] At present, radiation therapy based on proton beams is not widely performed, making it an unlikely option for most patients.

Since the Chordoma Foundation (www.chordomafoundation.org) was founded in 2007, we have been working hard to improve our understanding of this type of tumor. However, chordomas still present a great challenge to clinicians.[25] Factors associated with a potentially worse prognosis for patients with chordoma include pAKT,[26] Raf-1,[27] Survivin,[28] iNOS,[29,30] VEGFR-2,[30] and mTOR,[26] as well as overexpression of PDGFR-a,[31] brachyury,[32] CDK4,[27] c-MET,[31] and p53.[27] In addition, epigenetic dysregulation with miR111 or miR-1237-3p downregulation,[33] or overexpression of miR-140-3p[34] or miR-155[35] may also be associated with poor prognosis. Because the annual incidence does not exceed 1 in a million,[36,37] chordoma-related research is a very challenging field, and unfortunately, the number of samples in most studies is limited. Furthermore, spinal chordoma cases are even rarer.[27] Therefore, in order to be able to conduct effective molecular medical research on chordoma, we must cherish every sample, and at the same time we must strive for multi-center cooperation to maximize the limited resources.

According to our statistical data regarding chordoma and the related literature, we propose the following suggestions for the treatment of chordoma.

(1) The age of onset of chordoma of the slope is relatively young and the long-term survival is better. Therefore, it is recommended to remove the lesion as early as possible, and to protect the peripheral nerves from the lesion as much as possible to reduce nerve injury. Our patients receiving radiotherapy after surgery are relatively few in number, and the long-term efficacy is not significantly different from that previously reported. Therefore, radiation therapy requires more evidence to demonstrate it.
(2) In our case, the spine chordoma easily invaded the dural sac, and invaded the dorsal aspect of the lamina to compress surrounding tissues and organs, such as the kidneys. In particular, the early clinical symptoms of chordoma in the lumbosacral region are mainly lower back pain or painless masses, which can easily be confused with lumbar disc herniation and schwannomas. Therefore, vigilance is needed, and the diagnostic rate can be improved through early imaging examinations. During surgery, all lesions should be removed as much as possible to relieve the pressure on the surrounding tissues and organs.
(3) The current long-term efficacy of the cases we treat is still not satisfactory. We hope that in the future there will be more effective treatments beyond surgery, radiotherapy, and other means. In this regard, we believe that in the future, molecular medicine-based tumor-targeted therapy is an important development direction for the treatment of chordoma.

5. Conclusion

The best treatment is combined surgical resection with radiation therapy to improve long-term survival. Adjuvant radiotherapy for chordoma significantly improves disease-free survival, although the long-term survival benefit remains to be determined. Patients with a sacral chordoma have a worse prognosis and poorer long-term survival.

Author contributions

ZYB conceived and conducted the experiments and prepared the manuscript. HBL contributed to sort and analyze the data. Houyun Gu, WZW, CHX, Shengtao Zhang helped to perform the analysis with constructive discussions. ZB and DM contributed to the conception of the study and approved the final manuscript. All authors read and approved the final manuscript.

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