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Clinical Study

Clinical features and prognostic factors of pediatric spine giant cell tumors: report of 31 clinical cases in a single center

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ABSTRACT

BACKGROUND CONTEXT: Giant cell tumors (GCTs) of the bone are benign but locally aggressive. Pediatric spine giant-cell tumors (PSGCTs) have been infrequently reported in the literature because of the rarity of the disease.

PURPOSE: The purpose of this study was to define the overall occurrence rate of PSGCTs among all spinal GCTs in our center and investigate the clinical features and prognostic factors of this rare disease.

STUDY DESIGN: A retrospective review.

PATIENT SAMPLE: Thirty-one PSGCT patients, screened from 226 patients with spine GCTs who received treatment in our center between 1998 to 2017.

OUTCOME MEASURES: The clinical symptoms, neurologic status, radiologic manifestations, treatment, outcome, and complications were recorded and analyzed.

METHODS: The postoperative recurrence-free survival (RFS) rate was estimated by the Kaplan-Meier method. Factors with p values ≤.1 were subjected to multivariate analysis for RFS by proportional hazard analysis, among which p values ≤.05 were considered statistically significant.

RESULTS: A total of 31 (31 of 226, 13.7%) PSGCTs patients (9 male and 22 female) were included in the study, with a mean age of 15.9 years and a mean follow-up period of 85.1 (median 84.0; range 12−221) months. The majority of patients (80.6 %) were 14−18 years of age. Recurrence was detected in 12 (38.7%) of the 31 patients. Univariate and multivariate analyses suggested that Jaffe grade II−III was an adverse prognostic factor for RFS, while total spondylectomy and bisphosphonate treatment were positive prognostic factors.

CONCLUSIONS: Total en bloc spondylectomy (TES) is associated with excellent prognosis for PSGCTs, and total piecemeal spondylectomy is a viable alternative if total en bloc spondylectomy is unfeasible. Long-term bisphosphonate administration could significantly reduce the recurrence risk of PSGCTs. Denosumab treatment is recommended, especially for advanced PSGCTs. Jaffe grade II−III is an adverse prognostic factor for recurrence.

Keywords: Bisphosphonate; Denosumab; Giant cell tumor; Jaffe grade; Pediatric; Recurrence; Spine; Total en bloc Spondylectomy (TES); Total piecemeal spondylectomy (TPS)

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Introduction

Giant cell tumors (GCTs) of bone are among the most common benign bone tumors, accounting for 22% of benign bone tumors and 4%–7% of all primary bone tumors [1,2]. Typical GCTs usually present as metaphyseal lytic lesions of the long bones in adults between 20 and 40 years of age [1–4]. Pediatric GCTs are exceptionally rare, with an incidence between 0.5% and 10.6% in the western world [1,3,4]. A multicenter retrospective study in China [5] showed that the incidence of GCTs around the knee was 6.9% in patients younger than 20 years, but there is no information about the occurrence rate of pediatric spine GCTs (PSGCTs). According to Alyaa et al. study [6], the spine ranks as the third common bone site (21%) of pediatric GCTs after the tibia (25%) and the femur (22%). According to our previous report [7], the occurrence rate of PSGCTs in all pediatric spine tumors was 6.8% (13 of 190).

Although there are some individual reports about pediatric GCTs [1,3,4,6,8,9], they mainly focused on the prognostic study of GCTs of the extremities and few addressed the clinical features or survival prognosis of PSGCTs. Although surgery is established as a viable and beneficial treatment option for GCTs, controversies about the relative merits of total resection for PSGCTs exist and treatment recommendations are mainly based on some sporadic case reports [10–14]. Some studies [1,3,4] reported that the recurrence rate of GCTs in children was lower than that in adults (8%–20% vs. 20%–38%), while others [6,9] showed no significant difference between children and adults. The overall recurrence rate for spinal GCTs ranges from 22.4% to 41.7% [2,15,16], but there is no recurrence information about PSGCTs. In addition, bisphosphonate, which has been documented as an adjuvant therapy to reduce the local recurrence rate of GCTs in adults after surgery, has not been studied in PSGCTs. There is therefore a need for a systematic analysis to identify the clinical features and prognostic factors associated with the recurrence of PSGCTs.

The purpose of this study was to define the overall occurrence rate of PSGCTs among all spinal GCTs admitted to a large tertiary orthopedic center in Eastern China and investigate the prognostic factors through a survival analysis of a series of 31 consecutive cases by focusing specifically on the postoperative recurrence rate.

Materials and methods

Patients

This study identified 226 patients who were diagnosed with spinal GCTs and treated surgically at our center between 1998 and 2017, from whom patients younger than 18 years were retrospectively included and their clinical and pathologic data were retrieved from the database of our hospital. This research was approved by the ethics committee of the hospital, and written informed consent was obtained from patients or their legal guardians.

Fine-needle aspirate biopsies were usually recommended and the needle pathway was selected according to the expected treatment. The diagnosis of GCTs was confirmed by two pathologists of musculoskeletal oncology in all patients. The preoperative neurologic status was classified according to the Frankel score [17]. The quality of life was assessed with the Karnofsky Performance Status score in all patients [18]. The pathologic features were evaluated by Jaffe grading system [19]. Tumor extension was described according to the Weinstein–Boriani–Biagini (WBB) system and Campanacci grading systems based on computed tomography and magnetic resonance imaging [20,21]. An individualized surgical strategy was decided for each patient according to WBB system. The one-stage anteroposterior approach was usually employed for cervical lesions because of the complex structures (including the vertebral arteries, spinal cord, and cervical nerve roots), and posterior approach was usually employed for thoracic and/or lumbar and/or sacral lesions, except for large lesions that necessitated an anteroposterior approach. To maintain spinal stability and balance, selection of the reconstruction method depended on the individualized surgical procedure. Occipitocervical fusion by bone graft in combination with occipitocervical internal fixation was used for the lesions at the upper cervical spine. The vertebral body was replaced by a titanium mesh filled with morcellized autograft or allograft bone. A pedicle screw system was placed where the treated segment was determined to be unstable as assessed by the Spinal Instability Neoplastic Score [22]. All surgeries were conducted with the help of traditional fluoroscopically assisted techniques. Intraoperative neurophysiologic monitoring (IOM) was usually utilized for patients with severe spinal cord compression (usually Frankel score A–C).

This study tried to identify the overall occurrence rate and clinical features of PSGCTs and explore the prognostic factors by focusing on Recurrence Free Survival (RFS) after the initial surgery. The recurrence status was confirmed on the basis of clinical manifestations and imaging findings during the outpatient follow-up period or pathologic evaluation of the second surgery. The postoperative surveillance schedule included a visit every 3 months for 2 years and then annually thereafter. Local X-ray radiography of the surgical segment and the adjacent vertebrae was performed at every visit, and chest X-ray radiography was performed yearly. At the 3-month follow-up visit after surgery, the neurologic function was re-evaluated. The follow-up period was defined as the interval from the date of surgery to death, or until September 2018 for patients alive.

Statistical methods

Quantitative data are described by mean, median (range), and qualitative data are described as counts and percentages.

The univariate and multivariate analyses of various clinical factors were performed to identify independent variables that could predict recurrence. The patient factors were age, gender, duration of symptoms, and preoperative Frankel score. The tumor factors were location, number of involved segments, aneurysmal bone cyst (ABC), pathologic features, and Campanacci grading systems. The treatment factors were preoperative selective artery embolism (PAE), surgical approach, resection mode, intraoperative chemotherapy (IC), intraoperative blood loss, bisphosphonate treatment, and adjuvant radiotherapy. Data were analyzed using SPSS version 21.0. (SPSS Inc. Chicago, IL, USA). The postoperative RFS rate was estimated by the Kaplan-Meier method, and differences were analyzed by the log-rank test. Factors with p values of ≤.1 were subjected to multivariate analysis for RFS by proportional hazard analysis. p Values ≤.05 were considered statistically significant.

Results

From the 226 patients with spinal GCTs, 31 cases of PSGCTs were identified, with an incidence of 13.7% (31 of 226). They comprised nine males (29%) and 22 females (71%), with a mean age of 15.9 (median 16; range 9−18) years (Table 1). Of these patients, 25 (80.6 %) patients were between 14 and 18 years. The lesions were detected in the cervical spine (N=11), thoracic spine (N=10), lumbar spine (N=4), and the sacrum (N=6). Tumors with one segmental involvement occurred in 20 cases, while the other 11 cases had multisegmental involvement. Localized pain in the spine was the most consistent complaint, with a mean duration of 4.19 (median 3; range 1−18) months. Neurological symptoms, varying from simple and slight radicular pain to paraplegia, occurred in 21 patients (67.7 %), and spinal deformities including scoliosis, torticollis, and kyphosis were found in seven patients (22.6%). Secondary ABC was detected in seven patients. According to the WBB system, associated anterior and posterior involvement was most common (30 of 31), and anterior-only involvement was found in one patient. Extraosseous paravertebral (layer A) or epidural space (layer D) invasion was detected in 27 and 28 cases, respectively.

The Karnofsky Performance Status score was elevated to 80−90 and all patients was able to walk independently with the Frankel score being D-E 3 months after surgery. The mean follow-up period was 85.1 (median 84.0, range 12 −221) months. Recurrence was detected in 12 patients (38.7 %) after the initial surgery and two patients died of the disease. The mean time from surgery to recurrence was 9.9 (median 8.5; range 1−30) months. Of these patients, 11 (91.6 %) developed recurrence within 24 months.

Univariate analysis of prognostic factors for recurrence

Postoperative recurrence is not uncommon in PSGCT patients, and the overall recurrence rate in our series was 38.7 %. The results of univariate analysis of the clinical factors are shown in Table 2. In this study, the recurrence rate in patients of 14−18 years was significantly higher than that in other age group (p=.048). The Recurrence rate was significantly different between patients with Jaffe grade I and II−III (p=.019).

Fine-needle aspirate biopsies were conducted in 27 (87.1%) patients in this series whereby 25 patients were diagnosed accurately. Open surgical biopsy and frozen section analysis at open surgical resection were done in 2 and 4 patients, respectively. Subtotal spondylectomy (SS) was applied in 13 patients, Total Piecemeal Spondylectomy (TPS) in 14 patients (Fig. 1), and Total En bloc Spondylectomy (TES) in four cases, with the number of recurrence cases being 9, 3 and 0, respectively. The recurrence rate was obviously different between total and subtotal spondylectomy modes (p=.001). The postoperative RFS rate in TES was 100% vs. 78.6% in TPS (p=.43), and 78.6% in TPS vs. 30.8% in SS (p=.067) (Supplement Table 1). Cisplatin and methotrexate were used as IC to soak the surgery field after tumor resection in our center [2]. The mean intraoperative blood loss was 2,251.6 (median 2,100; range 500−5,500) mL. There was no significant difference in recurrence between patients receiving IC treatment or not (p=.802), or between intraoperative blood loss >2,000 mL and≤2,000 mL (p=.568). PAE was used in 17 patients to reduce intraoperative blood loss, but no significant difference in recurrence was observed (p=.300).

Since 2007, a single intravenous dose of bisphosphonate before surgery and one dose every month after surgery for 2 years have been used as a routine for the treatment of spine GCTs in our center. Sixteen patients received bisphosphonate treatment in our series, which significantly lowered the recurrence rate in these patients (p=.034). Adjuvant radiotherapy (30−45 Gy) was administered postoperatively in 11 patients, but no significant difference in recurrence was observed (p=.415). There was no significant difference in other factors of gender, duration of symptoms, ABC, location, preoperative Frankel score, Campanacci grade, and surgical approach.

Multivariate analysis of prognostic factors for recurrence

Potential prognostic factors of age, number of segmental involvement, Jaffe pathology grade, resection mode, and bisphosphonate treatment extracted by univariate analysis were submitted to the multivariate Cox regression model for analysis of RFS.

The risk of recurrence was significantly increased in patients with Jaffe grade II−III (p=.033, the hazard ratio [HR] 4.085 (95 % confidence interval [CI] 1.121−14.889) (Fig. 2A). Total spondylectomy by either TES or TPS was significantly associated with better overall RFS (p=.042, HR 4.578, 95% CI 1.053−19.898) (Fig. 2B). The bisphosphonate treatment could significantly decrease the risk of recurrence. The HR for bisphosphonate treatment was 0.127 (p=.007, 95% CI 0.031−0.606) (Fig. 2C).

Table 1
Patients' demographic details of PSGCTs

No.	Age /Gender	location	Jaffe	Deformity	SOD	PAE	Campanacci grade	WBB	ABC	Pre-/Post KPS	Pre-/Post-FS	IC	surgical approach	surgical modes	bleeding	Bis	RT	Recurrent	F-U time	Last status
1	16/M	C4	I	Kyphosis	1	No	III	2-11/A-D	No	70/90	D/E	yes	P+A	piecemeal	2200	Yes	Yes	No	125	NED
2	11/M	L3	I	No	6	Yes	II	4-12/B-D	Yes	80/90	E/E	yes	P	piecemeal	1100	No	Yes	No	123	NED
3	18/F	C1-2	II	No	3	No	I	3-9/B-D	No	80/90	E/E	no	P+A	enblock	2000	Yes	No	No	120	NED
4	15/F	T10	II	No	2	No	III	1-9/A-D	Yes	80/90	E/E	no	P	subtotal	4000	Yes	Yes	Yes(2)	112	NED
5	14/M	T6-7	I	No	1	Yes	II	1-6/A-D	Yes	30/70	B/D	yes	P	enblock	2500	Yes	No	No	78	DOD
6	18/F	C7	I	No	13	No	III	4-12/A-D	Yes	70/90	D/E	yes	P+A	piecemeal	2200	Yes	Yes	No	98	NED
7	16/F	T6	II	Kyphosis	1	Yes	III	3-12/A-D	No	70/90	D/E	no	P	piecemeal	2800	No	No	Yes(18)	92	NED
8	16/F	S1-2	I	No	1	Yes	I	3-10/B-D	No	70/90	D/E	yes	P	subtotal	4500	Yes	No	Yes(8)	89	AWD
9	13/F	C2	I	Torticollis	6	No	III	4-12/A-C	Yes	80/90	E/E	yes	P+A	piecemeal	500	No	No	No	84	NED
10	13/F	L1	I	Kyphosis	8	Yes	III	3-10/A-D	No	60/90	D/E	yes	P	piecemeal	2500	No	No	No	72	NED
11	18/F	C4	I	No	18	No	III	4-12/A-D	No	70/90	E/E	yes	P+A	piecemeal	2500	Yes	No	No	59	NED
12	18/F	T7	II	Kyphosis	3	Yes	III	3-9/A-D	No	30/70	B/D	yes	P	enblock	1200	Yes	No	No	51	NED
13	9/M	S2-3	III	No	1	Yes	III	1-12/A-D	Yes	80/80	E/D	yes	P	subtotal	1500	Yes	No	No	48	NED
14	17/M	T9-11	II	No	1	Yes	III	2-11/A-D	No	30/70	B/D	No	P+A	subtotal	6000	No	No	Yes(2)	48	NED
15	16/F	T8	II	Kyphosis	1	Yes	III	4-9/A-D	No	20/60	B/D	No	P	piecemeal	1000	No	No	Yes(9)	43	AWD
16	18/F	C2	II	No	1	No	III	3-10/A-C	No	50/80	C/D	yes	P+A	piecemeal	1800	No	No	Yes(18)	39	NED
17	14/M	S2	I	No	1	Yes	III	4-9/A-D	No	70/90	D/E	yes	P	piecemeal	4000	Yes	No	No	37	NED
18	18/F	L2	I	No	1	Yes	III	3-9/A-D	No	70/90	D/E	yes	P	enblock	1200	Yes	No	No	31	NED
19	16/F	S1-3	II	No	3	Yes	III	1-12/A-D	No	70/90	D/E	Yes	P	subtotal	3000	Yes	Yes	No	24	NED
20	15/F	T1-2	III	No	1	Yes	III	2-10/A-D	No	30/70	B/D	yes	P	subtotal	2500	No	Yes	Yes(1)	12	DOD
21	15/F	C3	I	No	10	No	III	5-9/A-D	No	90/90	E/E	No	A	subtotal	1000	Yes	Yes	No	26	NED
22	15/F	S1-2	I	No	3	Yes	III	1-12/A-D	No	90/90	E/E	yes	P	subtotal	2000	No	No	Yes(6)	113	NED
23	16/F	L4	I	Scoliosis	3	No	II	4-11/A-D	No	70/90	D/E	no	P	piecemeal	2000	No	YES	No	187	NED
24	18/M	T4-5	I	No	5	No	II	1-9/B-D	Yes	30/80	B/D	Yes	P	piecemeal	2200	Yes	No	No	71	NED
25	18/M	S2-3	I	No	4	Yes	III	3-10/A-D	No	70/90	D/E	Yes	P+A	subtotal	3200	No	Yes	Yes(30)	137	AWD
26	16/F	C5	II	No	2	No	II	4-12/A-D	No	50/80	C/E	yes	P+A	subtotal	600	Yes	No	Yes(5)	16	NED
27	16/F	C2	I	No	3	No	III	2-10/A-C	No	70/90	D/E	no	P+A	piecemeal	1600	No	No	No	102	NED
28	17/F	T7	II	No	6	Yes	II	2-11/A-D	No	80/90	E/E	yes	P	subtotal	2100	No	No	Yes(9)	94	NED
29	18/M	C5	I	No	8	No	III	3-11/A-D	No	80/90	E/E	no	P	subtotal	1800	No	No	Yes(11)	136	NED
30	18/F	C6	I	No	6	No	III	3-10/A-D	No	80/90	D/E	no	P+A	piecemeal	1900	No	Yes	No	151	NED
31	17/F	T10	II	No	7	Yes	III	2-10/A-D	No	60/80	C/E	no	P	subtotal	2400	No	Yes	No	221	NED

PSGCT, pediatric spine giant cell tumor; M, male; F, female; C, cervical; T, thoracic; L, lumbar; S, sacrum; SOD: Duration of Symptoms; PAE, percutaneous artery embolization; ABC, aneurysmal bone cyst; FS, Frankel Score; IC, intraoperative chemothrpapy; P, posterior; A, anterior; Bis, bisphosphonate; RT, radiotherapy; F-U, follow-up; NED, no evidence of disease; AWD, alive with disease.

Table 2
Patient characteristics and log-rank analysis of prognostic factors affecting recurrence of PSGCTs

Factors	No.	RFS %	P
Age,≤13/14–18	6/25	100/52	0.048*
Gender,F/M	22/9	59.1/66.7	0.619
Duration of symptoms,≤3/>3	19/12	52.6/75.0	0.156
Location cervical/thoracic/lumbar/sacrum	11/10/4/6	72.7/40.0/100/50.0	0.136
No. of involved segment, mono/multisegment	20/11	70.0/45.5	0.091*
Preoperative Frankel score, A–C/D–E	9/22	44.4/68.2	0.151
ABC, yes/no	7/24	85.7/54.2	0.18
Jaffe grade, I/II-III	18/13	77.8/38.5	0.019*
Cam grade, I-II/III	8/23	62.5/60.9	0.939
Preoperative selective arterial embolism, yes/no	17/14	52.9/71.4	0.300
Surgical approach, posterior/anterior/combined	19/1/11	57.9/100/63.6	0.728
Resection mode, SS/TS	13/18	30.8/83.3	0.001*
Resection mode, SS/TPS/TES	13/14/4	30.8/78.6/100	0.003*
Intraoperative blood loss, ≤2,000/>2,000	12/19	66.7/57.9	0.568
IC, yes/no	21/10	61.9/60.0	0.802
Bisphosphonate treatment, yes/no	16/15	81.3/40.0	0.034*
Adjuvant radiotherapy, yes/no	11/20	72.7/55.0	0.415

PSGCT, pediatric spine giant cell tumor; M, male; F, female; ABC, aneurysmal bone cyst; SS, subtotal spondylectomy; TS, total spondylectomy; TES, Total en bloc spondylectomy; TPS, total piecemeal spondylecyomy; ABC, aneurysmal bone cyst; IC, intraoperative chemothrpapy;
* p Value less than 0.1.

The above results showed that Jaffe grade II–III, total spondylectomy, and bisphosphonate treatment were independent prognostic factors for PSGCTs. Details are listed in Table 3. The Kaplan-Meier curves of RFS for Jaffe grading system, surgical modes, and bisphosphonate treatment are shown in Fig. 2.

Complications

Pleural damage occurred in 2 patients (Case 7 and 14). Pleurocentesis and drainage were conducted to alleviate the postoperative pleural effusion. Two patients with sacral lesions suffered from wound infection, for which debridement was performed. No instrumentation failure occurred in the follow-up period.

Treatment for recurred lesions

The treatment modalities and outcomes for the 12 recurrent patients are listed in Table 4. Of them, nine patients received one revised surgery and two patients received two revised surgeries. Two patients rejected the revised surgery and were administered with denosumab for 2 and 3 years, and no progression of the disease was found during the

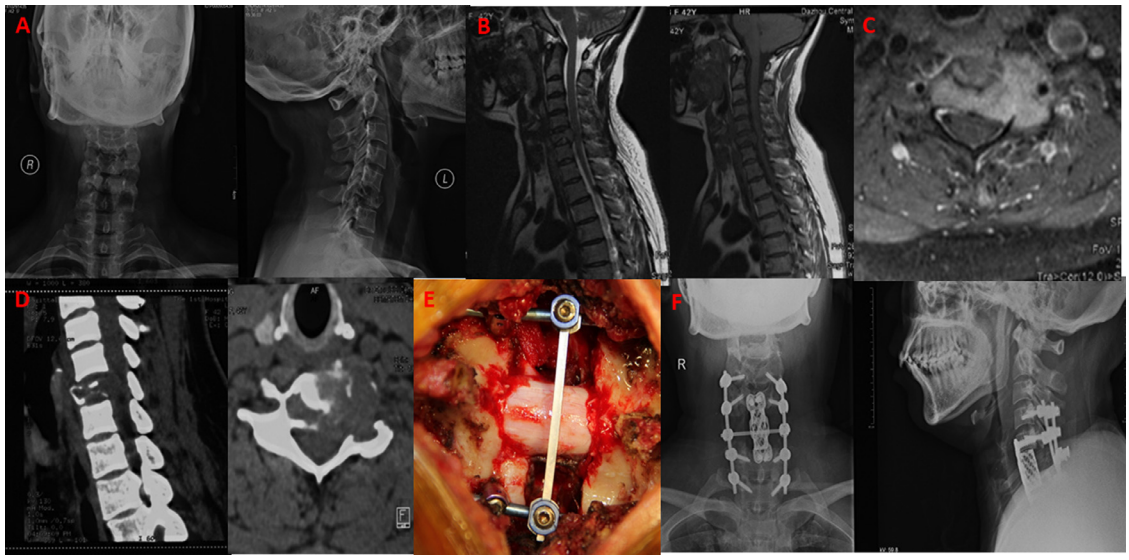

Fig. 1. A 18-year-old girl (case 30) (**A**) X-ray showed the compression fracture of C6 before surgery; (**B**) Preoperative sagittal MRI scan (T2 and T1) showed an osteolytic lesion in vertebral body of C6; (**C**) Preoperative transverse section of the lesion (MRI scan) showed the WBB classification: 3-9/A-D. (**D**) Preoperative CT scans showed the osteolytic fracture; (**E**) Intraoperative picture showed the total spondylectomy and instrumentation; (**F**) Postoperative X-ray showed decompression and instrumentation.

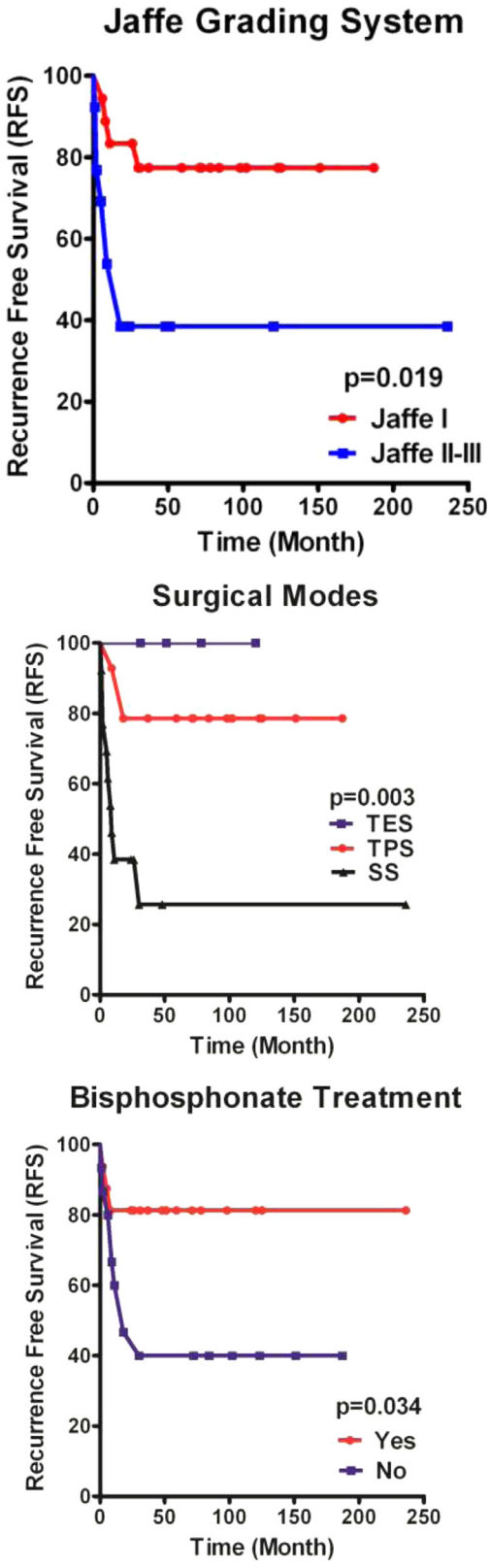

Fig. 2. Kaplan-Meier curves of RFS for Jaffe grading system (**A**) surgical modes (**B**), and bisphosphonate treatment (**C**). TES, Total en bloc spondylectomy; TPS, Total piecemeal spondylectomy; SS, Subtotal spondylectomy.

Table 3
Multivariate analysis of the prognostic factors affecting RFS of PSGCTs

Factors	B	HR (95%CI)	p
Age,≤14/14−18	\	\	0.967
No. of involved segment, mono/multisegment	2.824	0.665−11.99	0.159
Jaffe grade, I/II-III	5.252	1.214−22.73	0.026*
Resection mode, subtotal/total	4.578	1.053−19.898	0.042*
Bisphosphonate treatment, yes/no	0.137	0.031−0.606	0.009*

* p Value less than 0.05.

follow-up period. For the revised surgery, total spondylectomy was applied eight times and subtotal spondylectomy was carried out five times.

Discussion

Primary osseous spinal column tumors are uncommon in children and young adults, accounting for about 1% of all spine and spinal cord tumors combined [23,24]. Although the occurrence of pediatric GCTs has been well documented [1,3,4,6,9], PSGCTs are rare pathological lesions with no case series reported in the literature. The previously reported incidence of pediatric GCTs varies between 0.5% and 10.6% [1,3,9]. However, the present study showed a higher occurrence rate of 13.7% of PSGCTs from 226 patients with spinal GCTs in our center. In this study, we analyzed the clinical data of 31 cases of PSGCTs and performed statistical analyses to investigate the prognostic factors affecting RFS. The overall recurrence rate was 38.7 %, which was similar to the previous reports [2,6,9]. The results suggested that Jaffe grade II−III, total spondylectomy, and bisphosphonate treatment were independent prognostic factors for PSGCTs. The results of the present study may help understand the clinical features, the risk of recurrence and factors affecting the survival prognosis of PSGCTs.

In our patients, 25 (80.6 %) patients were at the age of 14−18 years, which is in accordance with previous reports [13,14] that most cases aged between 14 and 18 years for pediatric populations. In addition, the results of log-rank analysis showed that the age of 14−18 years was associated with a higher recurrence rate than age ≤13 year olds, which is contrary to the previous conclusion that patient age was not correlated with RFS [6]. Although there are disputes on the female predilection for GCTs [1,2,25], interestingly, numerous reports have shown a clearly larger female predominance (60%−82%) in pediatric groups [1,4,6,9], which may be because females reach skeletal maturity 2 years earlier than males [14]. The female distribution in our study is 71.0%, which is within the reported range of 60%−82%. In our series, PSGCTs were most likely to infringe upon the cervical spine, which is different from previous studies reporting that the sacrum or thoracic segments were

Table 4
Patients' details of recurrent PSGCTs

No.	Age/Gender	times	site	time to LR	CAM	Jaffe	FS	Surgery	bis	RT	Denosimy	FS latest	F-U time	Last status
1	15/F	1	T10		III	II	D	TS	Yes	Yes	No	E	112	NED
		2	T10-11	2	III	II	D	TS	Yes	No	No			
2	16/F	1	T6		III	II	D	TS	No	No	No	E	92	NED
		2	T5-7	18	III	II	C	TS	Yes	No	No			
3	16/F	1	S1-2		I	I	D	SS	Yes	No	No	E	89	AWD
		2	S1-2/Lung	8	III	II	C	TS	Yes	Yes	No			
4	17/M	1	T9-11		III	I	B	SS	No	No	No	D	48	NED
		2	T9-11	2	III	I	C	TS	No	No	Yes(3 years)			
5	16/F	1	T8		III	II	B	TS	No	No	No	D	43	AWD
		2	T8	9	III	/	D	No	No	No	Yes(2 years)			
6	18/F	1	C2		III	II	C	TS	No	No	No	E	39	NED
		2	C2	18	III	II	D	TS	Yes	No	No			
7	15/F	1	T1-2		III	III	B	SS	No	No	No	D	12	DOD
		2	T1-3	1	III	III	C	SS	/	/	/			
8	15/F	1	S1-2		III	I	D	SS	No	No	No	E	113	NED
		2	S1-3	6	III	I	D	SS	No	No	No			
		3	S1-3	2	III	I	D	SS	Yes	No	No			
9	18/M	1	S2-3		III	I	D	SS	No	Yes	No	E	137	AWD
		2	S1-3	30	III	I	D	SS	Yes	No	No			
10	16/F	1	C5		II	II	C	SS	Yes	No	No	E	16	NED
		2	C5	5	III	II	D	TS	Yes	No	No			
11	17/F	1	T7		II	II	D	SS	No	No	No	E	94	NED
		2	T7	9	III	II	D	SS	No	No	No			
		3	T6-7	1	III	II	D	TS	No	Yes	No			
12	18M	1	C5		III	I	D	SS	No	No	No	E	136	NED
		2	C5	11	III	I	D	TS	Yes	No	No			

PSGCT, pediatric spine giant cell tumor; M, male; F, female; C, cervical; T, thoracic; L, lumbar; S, sacrum; LR, local recurrence; SS, subtotal spondylectomy; TS, total spondylectomy; Bis, bisphosphonate; RT, radiotherapy; FS, Frankel Score; F-U, follow-up; NED, no evidence of disease; AWD, alive with disease.

more frequently affected sites [2,10]. The most frequent clinical feature of PSGCTs is localized pain, which is common in almost all spine tumors. The incidence of spinal deformities including scoliosis, torticollis, and kyphosis in our series was 22.6%, which is similar to 25% reported in the previous literature [24].

Histopathologically, PSGCTs can be classified by Jaffe grade system into three categories: conventional GCTs (grade I) with no appreciable stromal cell atypia, mitoses and abnormalities; aggressive GCTs (grade II) with stromal cells showing only slight or more marked atypia, which is not enough to justify a diagnosis of malignancy; malignant GCTs (grade III) with obvious features of malignancy [19,26]. Sanerkin et al. [19] and Xu et al. [2] considered that this grading system was unable to predict the clinical behavior and prognosis of GCTs. In the study of aggressive GCTs [15], Jaffe grade III was significantly associated with lower RFS. In our analysis, a significant difference was found between Jaffe grade I and Jaffe grade II−III.

Intraoperative neurophysiologic monitoring allows for continuous, real-time monitoring of spinal cord function, and therefore is frequently used to assess the function of neurologic pathways during pediatric orthopedic spinal surgery [27]. In our series, IOM was utilized for patients with severe spinal cord compression (usually Frankel score A−C), and no patients suffered from neurological deterioration. PAE is a useful way to decrease overall blood loss and provide greater intraoperative visualization of the surgical field [28]. However, embolization of cervical tumors can be technically challenging because of the complex arterial anatomy and the higher risk of neurologic complications [29]. As a result, we did the embolization in patients with lesions under T4 level. In this series, PAE was conducted for 17 lesions with clear tumor-feeding arteries, which were identified by angiographic appearance. Although there is no difference of the RFS rate between patients receiving PAE and those not, it is still an important method to improve the safety of surgery [30].

The possible surgical procedures for PSGCTs, including subtotal spondylectomy (SS), TPS, and TES, were weighted in every pediatric case against the procedure-related morbidity risk [2,13,20]. In previous study about pediatric GCTs, the recommended treatment varies from intralesional curettage to wide compartmental excision depending on the histology, size of the tumor, soft-tissue involvement, and location [11]. Most authors [1−3,9,15] reported that tumor recurrence was commonly associated with inadequate excision, but other reports [6] showed no significant difference between wide resection and intralesional treatment. As PSGCT has high possibility of recurrence and malignant transformation, we propose that total spondylectomy should be considered first. According to

WBB classification, TES was possible for type 3, 4, and 5 lesions and is relatively indicated for type 1, 2, and 6 lesions [31]. However, it is impossible to apply TES in all PSGCT patients, especially for Campanacci grade III lesions because of anatomical complexity and possible complications [32]. Furthermore, for lesions in the upper cervical and lower lumbar spine, some important anatomical structures often preclude TES for lesions in these segments [31]. Although TPS is associated with a possibility of tumor cell contamination in the surgical field, it is adopted sometimes to remove the lesion to the most extent [2]. Our experience suggests that total spondylectomy including TES and TPS could significantly decrease the recurrence rate of PSGCTs. TES was performed in four patients in our series with no recurrence. TPS was performed in 14 patients and only three of them developed local recurrence. The results of log-rank analysis indicated the higher RFS rate of TPS when compared with SS (p=.067). Therefore, for the PSGCTs, TES is associated with excellent prognosis, and TPS is a viable alternative if TES is unfeasible. The choice was made individually for each patient mainly according to the WBB classification, the experience of the surgeon and the neurologic status of the patient.

Unlike adults, skeletal development is immature in children, which is a factor that must be taken into account in surgery. The incidence of postlaminectomy deformity without instrumentation in children has been reported to be 25%–46% [33] which is mainly attributed to loss of the posterior supporting structures. As a result, reconstruction after PSGCT resection can help buildup greater stability [34] and improve the outcome in some series [35]. Pedicle screw fixation is the standard method for pediatric spine instrumentation owing to long-term maintenance of correction and a low revision rate [36]. In total spondylectomy, a titanium mesh cage with a morcellized autograft or allograft was utilized as the anterior strut [37]. For posterior screw-rod fixation, two-above and two-below segmental fixation is recommended in cases where one vertebra is resected (Fig. 1F), while in cases where two vertebrae need to be removed, three-above and three-below segmental fixation is recommended [31].

Compared with the traditional fluoroscopically assisted techniques, computer-aided surgical navigation system is a typical mutually exclusive surgical platform to provide precise and accurate resection in spine surgery, especially in pediatric patients in whom the anatomy is often disproportionally smaller and prone to change [38]. Although all surgeries and instrumentations were conducted with the help of traditional fluoroscopically assisted techniques with no instrumentation failure during the follow-up period in this retrospective case series, the computer-aided surgical navigation system is still a good choice for surgery of PSGCTs.

Clinically, sacral GCTs have no specific symptoms in the early stage and tend to be quite large at the time of diagnosis, which make diagnosis and treatment extremely difficult. Multiple recent studies have reported that sacrectomy and reconstruction using a posterior-only approach are feasible and safe for patients with malignant sacral tumors [39]. In our center, posterior-only approach has been widely used for sacral tumors, and 5 of 6 pediatric patients received posterior-only approach with no severe complications.

Radiation has been used as a means of local control, primarily in adult patients with unresectable GCTs without significant morbidity [14,40]. With the advent of computed tomography- and magnetic resonance imaging-based simulation and 3D treatment planning in the recent decade, intensity-modulated RT has become the mainstream of clinical practice, including in pediatric neuro-oncology [41]. However, in pediatric GCTs, radiation therapy as a means of local control is generally not recommended unless other modes are impossible or have failed [14], mainly because of an increased risk of malignant transformation of 10% at 10 years and postradiation sarcoma [10]. In addition, statistical results showed no significant function of radiotherapy in prolonging RFS in our study.

Intravenous bisphosphonate has been widely used for the treatment of osteoporosis in children for many years, demonstrating a favorable side-effect profile and improvement in bone mineral density [42]. However, there are rare data about the use of bisphosphonate for pediatric GCTs in the literature [24] and the effect of bisphosphonate in preventing the recurrence of PSGCTs has not been defined. According to this study, bisphosphonate administration is the biggest determinant of RFS of PSGCTs (p=.007), and bisphosphonate in combination with surgical treatment should be able to provide an excellent prognosis. Although no patient in our series experienced clinically significant adverse events, the possible association between long-term use of bisphosphonate and severe complications should not be ignored [42].

In 2013, Denosumab, a monoclonal antibody that activates the receptor activator of nuclear factor kappa-B ligand (RANKL), was approved by Food and Drug Administration to treat GCTs in adults and skeletally mature adolescents and denosumab has dramatically altered treatment of GCT in the past 5 years [14,43,44]. The criterion of skeletally mature adolescents usually means age >12 years and weight >45 kg [14]. A study (N=282) was recently published and confirmed the high efficacy of denosumab in bone GCT [43]. However, long-term treatment may be needed for long-term local tumor control, during which significant adverse effects need to be monitored meticulously [44]. In our center, denosumab has been used for the treatment of GCTs since 2015 to reduce the tumor size knowing that it can inhibit osteoclastogenesis. In this study, two patients who suffered from lesion recurrence received the treatment of Denosumab for 2 years and 3 years respectively, during which no disease progression was observed, suggesting that denosumab may be a viable drug for the treatment of advanced PSGCTs. However, the economic status and cost-benefit effect should be justified

in using denosumab or bisphosphonate, especially in economically poor and resource-poor settings.

Limitations

Firstly, this was a retrospective study, although it is to our knowledge the largest series to date of PSGCT. Secondly, as our orthopedic oncology center is more skilled in spine tumors, all patients included in this study are spine GCTs which may be one of the reasons for higher occurrence incidence of PSGCT. Thirdly, the total number of subjects (31) is small, and this limits the power of statistical analysis and tests, especially the multivariate models. These findings may need to be confirmed by larger populations from multiple centers in future study.

Conclusions

Spinal GCTs, although predominantly a disease of adults, can also occur in pediatric populations. TES is associated with excellent prognosis for PSGCTs, and TPS is a viable alternative in cases where TES is unfeasible. Long-term bisphosphonate administration can significantly reduce the recurrence risk of PSGCTs and should be an effective postoperative adjuvant therapy. Denosumab treatment is recommended especially for advanced PSGCTs. Jaffe grade II–III is an adverse prognostic factor for recurrence.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.02.011.

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