



Symptomatic aneurysmal bone cysts of the spine: clinical features, surgical outcomes, and prognostic factors

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Abstract

Purpose The aim of the study was to report the long-term outcomes and analyze the potential prognostic factors that may contribute to symptomatic patients with aneurysmal bone cyst (ABC) of the spine undergoing surgical treatments.

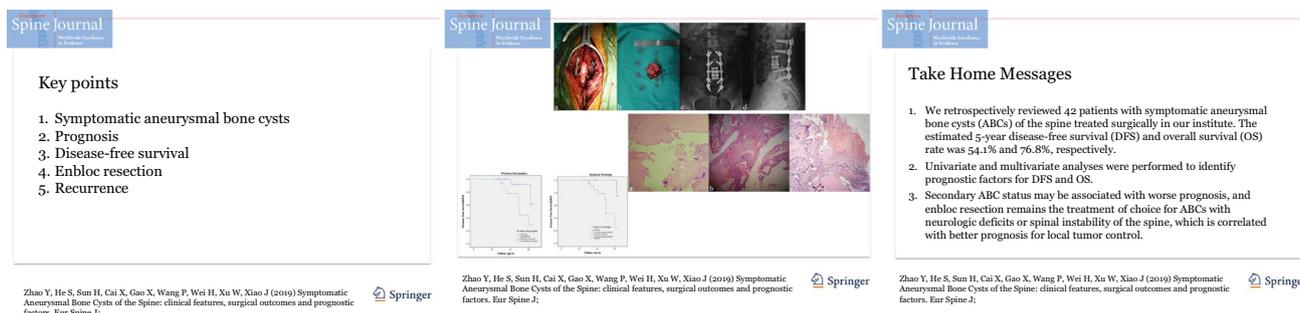
Methods A retrospective analysis of consecutive patients with ABCs of the spine was performed. The clinical features were reviewed, and the disease-free survival (DFS) and overall survival (OS) rates were estimated using the Kaplan–Meier method. Factors with p values ≤ 0.05 were subjected to multivariate analysis by Cox proportional hazards model to identify the independent prognostic contributors. p values < 0.05 were considered statistically significant.

Results A total of 42 patients with ABCs of the spine were included in the study. All patients received surgical treatments. The mean follow-up period was 41.3 months (median 39.5, range 24–64). Local recurrence was detected in eight patients after surgery in our center, whereas death occurred in three patients. The estimated 5-year DFS and OS rate was 54.1% and 76.8%, respectively. The statistical analyses indicated that both en bloc resection and primary/secondary tumor status were independent prognostic factors for DFS.

Conclusions Secondary ABC status may be associated with worse prognosis, and en bloc resection remains the treatment of choice for ABCs with neurologic deficits or spinal instability of the spine, which is correlated with better prognosis for local tumor control.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.



Yuechao Zhao, Shaohui He and Haitao Sun have contributed equally to this work.

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Extended author information available on the last page of the article

Keywords Aneurysmal bone cyst · En bloc · Prognosis · Disease-free survival · Recurrence

Introduction

Aneurysmal bone cyst (ABC) is a benign, pseudotumoral hyperemic–hemorrhagic osseous lesion of unknown etiology, which was firstly described by Jaffe and Lichtenstein in 1942 [1]. It is classified as primary lesion with no present underlying disease and secondary status from some osseous neoplasms like giant cell tumor, osteoblastoma, chondroblastoma, telangiectatic osteosarcoma [2–4]. Primary ABCs are rare with the metaphyseal region of long bone more frequently involved, accounting for approximately 1% of primary bone tumors [3]. However, ABCs arising from the mobile spine are less common and constitute 10–30% of all cases [1, 3–6]. Generally, ABCs of the spine may become symptomatic during any age with a peak incidence in the first two decades [1, 4, 7]. There is a slight predilection for female patients, and ABCs occur at any level of spine with a predilection for lumbar spine [8, 9]. The most common complaint is night pain, occurring localized to the lesion [10]. Meanwhile, pathologic fracture and neurologic involvement may also be the presenting symptoms [4, 11, 12]. The combination of direct radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) is helpful in diagnosis. Fluid–fluid levels seen on both CT and MRI as well as an expansile osteolytic cavity in direct radiographs are pathognomonic in many cases. However, it is indistinguishable from osteoblastoma or giant cell tumor when the lesions are located in the vertebral body [4, 10, 13]. Management of ABC of the spine is controversial due to the various surgical interventions, including intralesional curettage and bone grafting, radiotherapy, selective arterial embolization, and en bloc resection [1, 4, 7, 9, 10]. Surgical treatment still remains the first choice in the cases with spine instability or symptomatic cord compression or pathologic fractures [1, 4, 7, 14]. However, little information has been reported regarding surgical outcomes on symptomatic ABCs of the spine. Detailed data about postoperative disease-free survival (DFS) and overall survival (OS) were not reported yet. Therefore, the objective of our study is to report the clinical characteristics, present long-term outcomes, and identify the prognostic factors for patients with symptomatic ABCs of the spine undergoing surgery in a single center.

Patients and methods

Inclusion and exclusion

The inclusion criteria of our study were: (1) aneurysmal bone cysts of the spine; (2) surgical intervention; (3) clear follow-up records. And the exclusion criteria were: (1) aneurysmal bone cysts of other locations (limbs, pelvis, skull); (2) non-surgical treatment (only radiotherapy or selective arterial embolization); (3) lost to follow-up and blurred records. The study was approved by the hospital ethics committee, and written informed consents were obtained from all patients or their legal guardians. The diagnosis of all the patients was histologically confirmed by a pathologic specialist with training in musculoskeletal oncology. Pretreatment plasma D-dimer level (D-D) was measured within 1 week before surgery as part of routine examination. According to manufacturer's recommendation, plasma D-D level of 0.5 mg/mL was used as cutoff for normal versus high D-D values. Medical records of all the patients were retrospectively retrieved from our center database. Preoperative and postoperative status was evaluated including the Frankel grading system and the Spinal Instability Neoplastic Score (SINS) [15, 16]. Aneurysmal bone cysts were classified according to the Enneking staging systems and the Weinstein–Boriani–Biagini systems [17, 18].

Surgical strategy

Our principle of surgical treatments was based on the presence of neurologic dysfunction, pathologic fractures or intolerable local pain, and the tumor locations as well as previous treatments. The typical radiologic images are illustrated in Fig. 1. The surgical strategy was decided and performed by the same surgical team. Selective arterial embolization (SAE) was performed to minimize intraoperative blood loss while cervical ABCs were excluded for SAE because of the risk of spinal cord ischemia or ectopic embolization. For all 42 cases, either of the two surgical strategies (complete curettage and en bloc marginal excision) was applied based on the extension and location of the tumor according to Weinstein–Boriani–Biagini system: intralesional curettage in 30 patients and en bloc resection in 12 patients. It is preferable to operate en bloc resection when tumors residing only within the anterior portion of the vertebral column (sectors 4–9) or tumors with extension within the anterior elements (sectors 1–3 and/or 10–12) and restricting within layers A–C without extension into the canal and spinal dura.

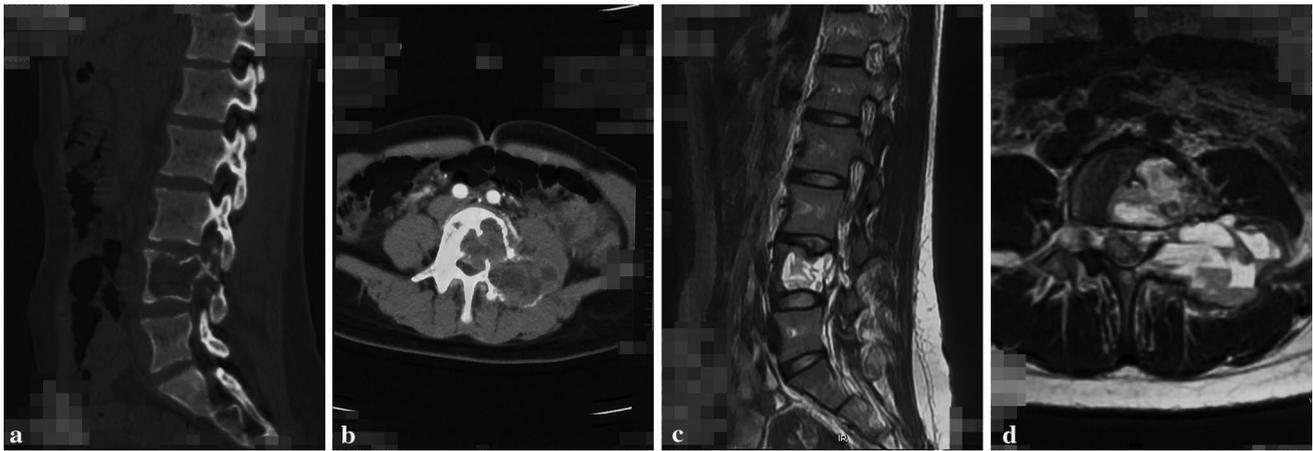


Fig. 1 The computed tomography (CT) and magnetic resonance imaging (MRI) of typical primary ABC. **a, b** Preoperative CT showed obvious osteolytic destruction in L4 level with epidural com-

pression and paravertebral invasion. **c, d** Preoperative MRI indicated high signal intensity of the lobulated lesion on T2-weighted images

Patients' willingness and symptoms like local immobilized pain could get consideration as well [17, 18]. An extracapsular excision through a posterior or combined with anterior approach was performed to remove the whole tumor lesion as well as the surrounding tissue as much as possible.

Postoperative follow-up

Our study specifically focused on the disease-free survival (DFS) and death status after surgery in our center. DFS was defined as the interval from the date of surgery to local recurrence and/or metastasis of ABC as demonstrated by laboratory testing, radiologic testing, or new progressive symptoms like pathologic fracture and/or neurologic defects like paresthesia or sphincter dysfunction, or death, whichever occurred first. Overall survival (OS) was related to the death caused by this disease. Time of death and death status were obtained through telephone interviews and office visits. Radiologic and physical examination was performed at a 3-month interval in the first year, then a 6-month interval for the next year, and annually for life thereafter.

Statistical analysis

Qualitative data were represented as counts and percentages, whereas quantitative data were represented as mean (median, range). The DFS and OS rates were estimated by the Kaplan–Meier method, and the log-rank test was applied in univariate analysis to figure out independent variables. Continuous variables were categorized on the basis of the knowledge in clinical and statistical experience, and factors with p value of 0.05 or lower were subjected to multivariate analysis by Cox proportional hazards analysis. p values < 0.05 were considered statistically significant. All

statistical calculations were performed by SPSS version 19.0. (SPSS, Inc., Chicago, IL, USA).

Results

Demographic features

Forty-seven patients with symptomatic ABCs of the spine were surgically treated and followed up from April 2011 to August 2018 in the Spinal Tumor Center of Changzheng Hospital. Five patients were lost to follow-up. The flowchart of the included 42 eligible patients is shown in Fig. 2. Of the forty-two patients admitted in our hospital, the vertebral body was involved and the neurologic involvement was found in all these cases, while 17 (40.5%) suffered from the pathologic fractures. Nine

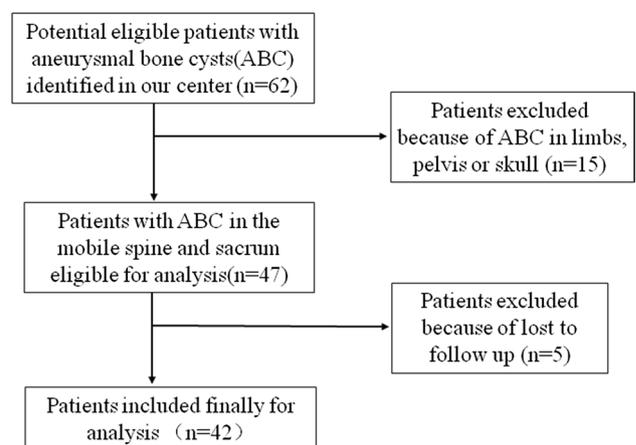


Fig. 2 The flow chart of the enrollment strategy of eligible patients

patients were referred for local recurrence after the initial treatments from other institutions.

The patients in our study comprised 17 men and 25 women, with a mean age of 26.0 years old (median 21, range 6–64). The most leading two preoperative symptoms were segmental pain (88.1%) and sensory weakness of extremity (40.4%). Other symptoms included motor deficits (16.7%) and sphincter disturbances (9.6%). The duration of the preoperative symptom was 0.3 to 24 months, with an average of about 5.6 months. The mean preoperative Visual Analogue Scale (VAS) was 5.3 (median 5, range 1–10). Preoperative status of neurologic function indicated 7 (16.7%) patients with Frankel grade A–C and 35 (83.3%) with grade D. Thirty-two (76.2%) patients were evaluated on SINS of 7–12 and 10 (23.9%) of 13–18. The distribution of the tumors was cervical spine 15 (35.7%), thoracic spine 2 (4.8%), lumbar spine 20 (47.7%), and sacral spine 5 (12.0%). All patients had a lytic, expansive lesion of posterior elements of the spine with their tumors extended into vertebral body separately. Spinal canal stenosis was present in 13 cases and paravertebral soft tissues involvement in 14 patients. Of all these patients, 33 (%) were admitted for the initial lesions (primary 19 cases and secondary 14 cases), whereas the remaining 9 were recurrent cases after the initial surgical treatment in other institutions. In our institute, the twenty secondary series were composed of giant cell tumor in 11 cases, fibroma 4 cases, osteoblastoma 3 cases, and chondroblastoma 2 cases. Figure 3 depicts primary ABC and two typical secondary ABC histologic types (giant cell tumor and osteoblastoma). Preoperative and postoperative Frankel status of all the patients is shown in Table 1.

Table 1 Preoperative/postoperative Frankel status of 42 patients

Preoperative status	Postoperative status
Frankel A 1 case	Frankel B 1 case
Frankel B 2 cases	Frankel B 1 case Frankel C 1 case
Frankel C 4 cases	Frankel C 1 case Frankel D 2 cases Frankel E 1 case
Frankel D 35 cases	Frankel D 8 cases Frankel E 27 case

Surgical findings and other postoperative treatments

Twenty-five patients underwent SAE of the tumor no longer than 24 h before the operation. Thirty patients underwent intralesional curettage. Based on the extent and location of the lesion, single posterior approach was adopted in thirty patients while combined anterior and posterior approaches were performed in remaining twelve patients.

Twelve patients underwent en bloc resection. As shown in Fig. 4, en bloc resection was conducted, and the fourth lumbar vertebral body and appendix were removed. The postoperative X-rays showed the fourth lumbar spine was removed and replaced by artificial vertebral body, with solid internal fixation. And seven with positive or uncertain tumor margin underwent local postoperative conventional radiotherapy 4–6 weeks postoperatively with total dosage of 30 to 50 Gy (unknown dose in three patients). In addition, denosumab was administrated in two patients (GCT with ABC) while twenty-three followed the bisphosphonate therapy in case of recurrence.

The mean follow-up period was 41.3 months (median 39.5, range 24–64). Recurrence was detected in 8 patients

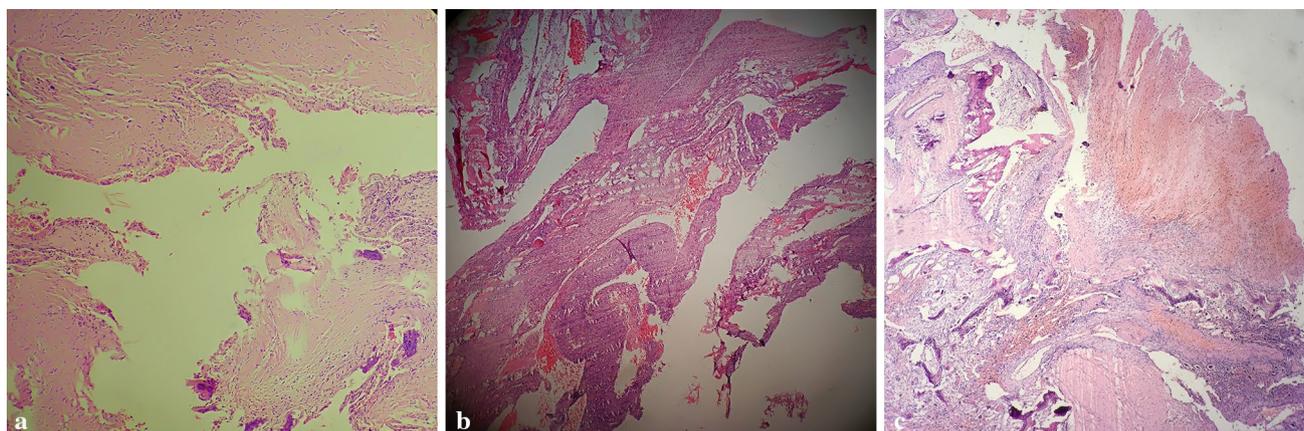


Fig. 3 Three different typical postoperative histological types. **a** Primary ABC. **b** ABC secondary to giant cell tumor. **c** ABC secondary to osteoblastoma

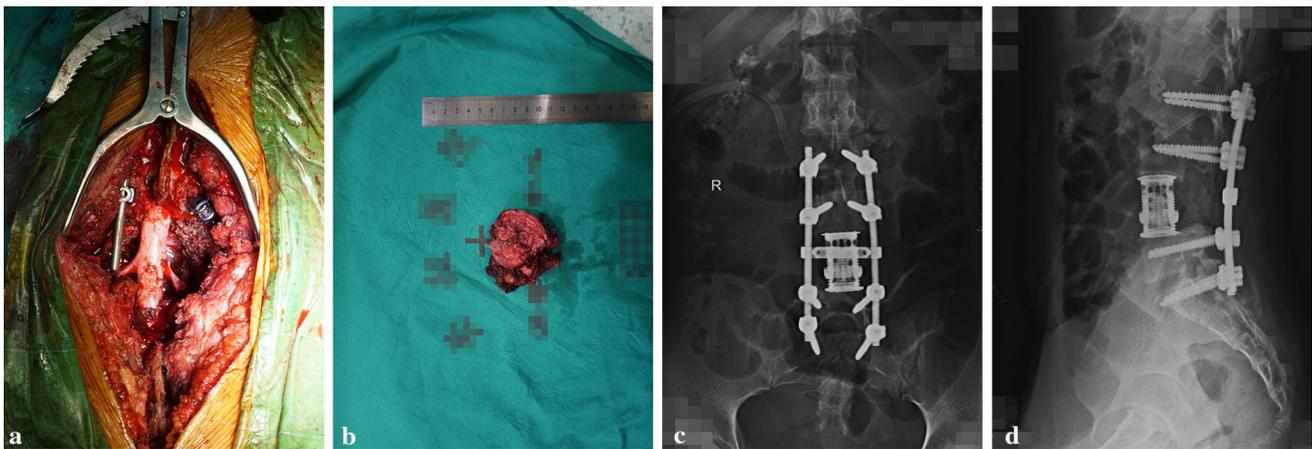


Fig. 4 The intraoperative and postoperative radiological images of the patient showed in Fig. 1. **a, b** En bloc L4 corpectomy was conducted with related nerve roots identified. **c, d** The postoperative

X-rays showed the fourth lumbar spine was removed and replaced by artificial vertebral body with pedicle-screw instrumentation

Table 2 Complications and prognosis of patients during the follow-up

Events	No. of patients	Percentage (%)
Neurologic function		
Promotion at least two levels	23	54.7
Promotion at one level	11	26.2
Not obvious	6	14.2
Deterioration	2	4.8
Complication		
CSF leakage	1	2.4
Pulmonary infection	2	4.8
Ureteral stenosis	1	2.4
Breakage of internal fixation	2	4.8
Wound infection	1	2.4
Outcome		
Lung metastasis	1	2.4
Death	3	7.1
Recurrence	8	19.0

CSF cerebrospinal fluid

after the initial surgery, while death occurred in 3 cases after 18, 40, and 42 months, respectively. While two patients suffered from pulmonary infection and hardware failure within 2 years, respectively, both of them died of pulmonary failure at last. The last one ABC secondary to giant cell tumor had progressed to multiple metastases and died of pulmonary metastasis eventually. The mean time from surgery to recurrence was 10.8 months (median 10, range 3–27), and 7 in 8 patients (87.5%) developed recurrence within 2 years.

Of all the 40 patients alive, 23 (59.0%) and 11 (28.2%) patients got a promotion of the Frankel score at least 2 or 1 grade(s), respectively. However, no improvement was observed in 6 patients while 2 cases even experienced

neurologic deterioration. Other postoperative complications include cerebrospinal fluid leakage (1 case), ureteral stricture (1 case), and wound infection (1 case), respectively. The detailed outcomes and related complications are illustrated in Table 2.

Univariate and multivariate analysis of prognostic factors

In our series, the estimated 5-year DFS and OS rate was 54.1% and 76.8%, respectively. Results of univariate analysis for both DFS and OS are shown in Table 3. With regard to DFS rate, a lower DFS rate was observed in patients with pathologic fracture ($p=0.021$), preoperative D-D level $>0.3 \mu\text{g/mL}$ ($p=0.019$), incomplete removal of the cystic walls ($p=0.012$), and not preoperative embolization ($p=0.016$). However, patients with postoperative Frankel A–C ($p=0.003$) and preoperative D-D level $>0.3 \mu\text{g/mL}$ ($p=0.003$) had a significantly lower OS rate. Other potential factors affecting OS rate included incomplete removal of the cystic walls ($p=0.041$) and combined radiotherapy ($p=0.011$). According to the multivariate analysis, both en bloc resection ($p=0.004$) and primary/secondary tumor status ($p=0.008$) were the independent predictors for DFS. Details are listed in Table 4, and the Kaplan–Meier survival curves of DFS for primary/secondary and surgical strategy are shown in Fig. 5.

Discussion

Aneurysmal bone cyst, accounting for 10–15% of benign spinal tumors, is an expansible pseudotumoral lesion which is more prevalent than any other benign tumor in the spine

Table 3 Univariate analysis of the prognostic factors affecting disease-free survival and overall survival

Factor	N	DFS		OS	
		%	<i>p</i>	%	<i>p</i>
Patient factors					
Age ^a : ≤20/>20	21/21	90.5/71.4	0.136	100.0/85.7	0.286
Male/female	17/25	76.4/84.0	0.904	100.0/88.0	0.101
Postoperative Frankel: D–E/A–C	38/4	94.7/25.0	0.059	100.0/25.0	0.003
Preoperative VAS: 0–2/3–5	22/20	86.4/80.0	0.976	95.5/90.0	0.607
Preoperative SINS: 7–12/13–18	32/10	90.7/50.0	0.027	96.9/80.0	0.162
Duration of symptom: ≤3 M/>3 M	21/21	81.1/81.1	0.625	95.2/90.5	0.937
Pain: (-)/(+)	5/37	80.0/81.1	0.511	100.0/91.9	0.756
Paralysis: (-)/(+)	25/17	92.0/64.8	0.719	100.0/82.4	0.133
Motor deficits: (-)/(+)	35/7	94.3/14.3	0.056	100.0/57.1	0.074
Sphincter disturbances: (-)/(+)	38/4	86.9/25.0	0.247	97.4/50.0	0.167
Pathologic fracture: (-)/(+)	25/17	72.0/94.1	0.021	88.0/100.0	0.101
Preoperative D-D level ≤0.3 µg/mL/>0.3 µg/mL	38/4	89.5/0.0	0.019	100.0/25.0	0.003
Tumor factors					
Primary/secondary tumor	22/20	90.9/65.0	0.036	100.0/85.0	0.443
Tumor site: C/T/L/S	15/2/20/5	86.7/100/70.0/80.0	0.609	93.3/100/95.0/80.0	0.763
Number of spinal lesions: single/multiple	37/5	86.5/40.0	0.396	91.9/80.0	0.687
Paravertebral soft tissue neoplasm: (-)/(+)	28/14	89.3/82.1	0.471	100.0/89.3	0.144
Treatment factors					
En bloc/intralesional excision	12/30	91.7/73.3	0.008	100.0/90.0	0.034
Complete removal of the cystic walls: (-)/(+)	16/26	46.2/94.9	0.012	77.0/100.0	0.041
Embolization: (-)/(+)	27/15	74.1/93.3	0.016	88.9/100.0	0.121
Blood: <2000/≥2000	30/12	93.3/50.0	0.188	96.7/83.3	0.135
Denosumab: (-)/(+)	40/2	80.0/10.0	0.592	92.5/100.0	0.694
Bisphosphonate: (-)/(+)	19/23	63.2/91.3	0.930	84.2/100.0	0.417
Radiotherapy: (-)/(+)	35/7	88.6/42.9	0.203	100.0/85.8	0.011

^aAge at observing spinal metastasis, *p* < 0.05 are all bolded

Table 4 Multivariate analysis of prognostic factors affecting DFS and OS

Factor	DFS		OS	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Postoperative Frankel: D–E/A–C	–	–	–	0.521
Primary/secondary tumor	19.70 (5.31–126.53)	0.008	–	–
Pathologic fracture: (-)/(+)	–	0.089	–	–
Preoperative D-D level ≤0.3 µg/mL/>0.3 µg/mL	–	0.445	–	0.232
Complete removal of the cystic walls: (-)/(+)	–	0.284	–	0.544
En bloc/intralesional excision	10.47 (2.27–173.52)	0.004	–	0.638
Embolization: (-)/(+)	–	0.151	–	–
Radiotherapy: (-)/(+)	–	–	–	0.339

CI confidence interval, HR hazard ratio, *p* < 0.05 are all bolded

[1, 4, 19, 20]. In our center, the mean age was 26.0 ± 15.0 (median 21, range 6–64) years, with a peak incidence in first two decades, which was conformed to the previous finding [1, 4, 21]. Slight female predominance (ratio 1.47:1) was observed in our center, which was consistent with the previous study [7, 9].

In terms of the proposed protocol for spine ABC treatment, intralesional excision with or without fusion, “en bloc” resection, radiation therapy, and selective arterial embolization are all good choices [14]. Current theory holds symptomatic ABC is aggressive with potential of bone destruction, spinal cord compression, pathologic fracture,

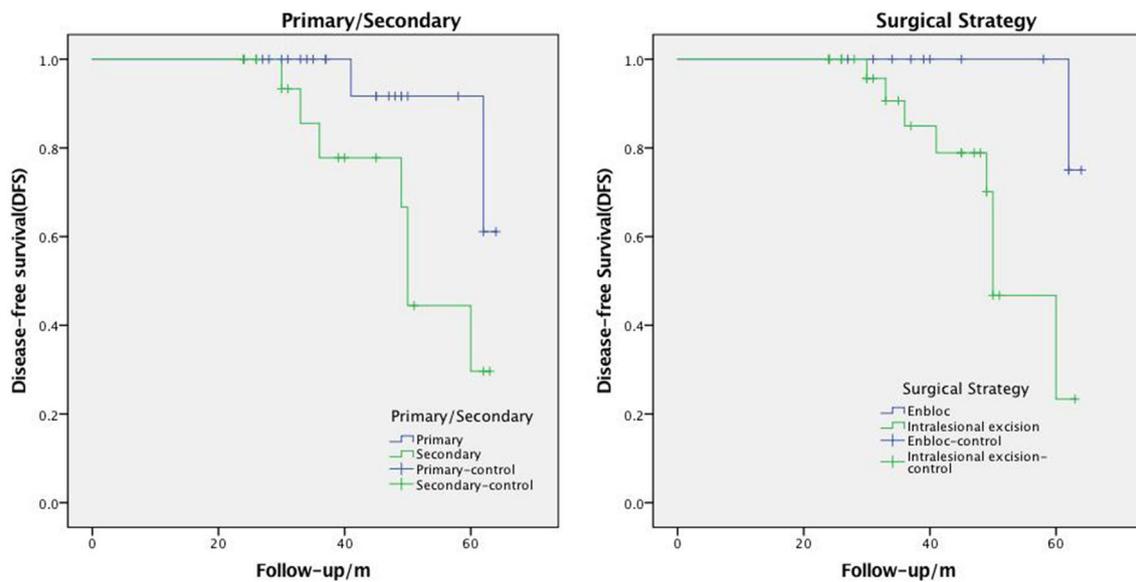


Fig. 5 Kaplan-Meier curves of disease-free survival (DFS) for primary/secondary tumor and different surgical strategies

spinal instability [1]. Complete surgical removal is still the first choice of symptomatic ABC in the presence of neurologic deficit and spinal instability [1, 4, 7, 8]. However, local recurrence has been reported as high as 60% after curettage with or without bone grafting [4]. In our center, the local recurrence rate was 19%, which was higher than the study reported by Boriani [4]. This is probably because of high proportion of “secondary” ABC included in our series. Besides, complications after surgical treatment were observed in our center as follows: pulmonary infection, breakage of internal fixation, cerebrospinal fluid leakage, lung metastasis, ureteral stenosis, and wound infection. Previous authors reported neurologic complications, surgical wound slough, and postoperative transient compression [1, 4, 8]. However, to our knowledge, detailed surgical outcomes and related prognostic factors remain unclear. In our research, the results suggested that en bloc resection and primary tumor status were favorable factors for DFS. Although en bloc resection is technically demanding in the spine, it is highly recommended in posteriorly located lesion because they can be less difficultly removed [18]. What is more, compared with intralesional excision accompanied by profuse intraoperative bleeding, en bloc resection, combined with preoperative embolization, could minimize the intraoperative bleeding and is the only treatment option with a minimum local recurrence incidence [1]. Previous studies demonstrated that only en bloc excision seems to be a good choice, but no severe complications, like massive intraoperative bleeding, profound neural deficit, cerebral stroke, and even death, were found in the follow-up. With rapid surgical and internal fixation techniques’ improvement, en bloc resection is performed for the treatment of non-malignant

but aggressive tumors of the spine [10, 21]. Based on our findings, we believe that the en bloc resection group could have a lower local recurrence rate to improve prolonged follow-up. Although total en bloc excision of tumor is a surgically demanding choice because of the tendency for intraoperative bleeding and the anatomic relation to the spinal cord, it is in line with the theory of complete excision of the relative compartment of the tumor to reduce the recurrence rate. Recurrence may aggravate the neurologic defects, exacerbate difficulty of the secondary surgery, and worsen tumor progression and eventually death [22]. Previous studies discovered the high local recurrence rate after intralesional excision when the cystic wall was incompletely removed [23–25]. The results in our study confirmed this finding as well.

In our study, the twenty secondary series were composed of giant cell tumor in 11 cases, fibroma 4 cases, osteoblastoma 3 cases, and chondroblastoma 2 cases. Compared with primary lesions, secondary ones seem to be more invasive after recurrence, causing angiogenesis, elevated vein pressure, and the change in hemodynamic. There were obvious differences between primary and secondary ABCs in DFS in our center. The theory of reactive vascular malformation may explain that based on osseous arteriovenous malformation initiated by the primary lesion, hemodynamic forces of the arteriovenous malformation thereby create secondary reactive lesion known as an ABC [7, 20]. Secondary ABCs become more invasive, thus causing angiogenesis, representing as an aggressive lesion because of the compression of the spinal cord.

Recent studies have focused on the prognostic role of preoperative plasma D-dimer in patients with spinal

tumors as it could be considered as not only a mediator of thrombosis but also a biomarker in tumor invasion, angiogenesis, and metastasis [26, 27]. Though our study could not indicate that elevated D-D level was an indicator of OS for patients with ABCs of the spine, we still believe that plasma D-D level, a marker of fibrinolytic state and high coagulation, may influence the relationship between tumor progression and activation of the hemostatic system [28].

In our center, successful preoperative arterial embolization was routinely performed for patients with tumors below T6. Patients with lesions in cervicothoracic spine were not performed for fear of the risk of cord ischemia and ectopic embolization [10, 29].

Seven cases with positive or uncertain tumor margin in our center underwent local postoperative conventional radiotherapy. However, three children were not recommended for radiotherapy for fear of the risk of complications including severe radiation-induced sarcoma. There is still some dispute regarding radiotherapy for spinal ABCs because of possible radiation-induced spinal deformity and radiation-induced sarcoma development and the risk of postlaminectomy kyphosis [30, 31].

Several previous findings indicated bisphosphonate therapy may minimize the lesion size and reconstitute eroded bone [32]. Nineteen victims in our center adopted bisphosphonate therapy (zoledronate 4 mg subsequently per month for the first year, every 6 months for the following 2 year). Two of them had local recurrence just due to the malignancy of primary tumors. The role of bisphosphonate is still controversial.

Although our research is the largest series of ABCs of the spine to date and highly homogeneous for patients from a single center, however, there are still some limitations. First, the limitation of our research is the nature of a retrospective study. Second, patients included in the study were all underwent surgery with neurologic deficits or spinal instability.

Conclusions

Our investigation suggests that secondary ABC status, compared with the primary one, may be correlated with worse prognosis because of their high tendency to recur locally. And en bloc resection could significantly improve the DFS for ABCs of the spine with neurologic deficits or spinal instability.

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Compliance with ethical standards

Conflict of interest We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript.

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