Surgical management of spinal osteblastomas

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OBJECTIVE Osteoblastoma is a rare primary benign bone tumor with a predilection for the spinal column. Although of benign origin, osteoblastomas tend to behave more aggressively clinically than other benign tumors. Because of the low incidence of osteoblastomas, evidence-based treatment guidelines and high-quality research are lacking, which has resulted in inconsistent treatment. The goal of this study was to determine whether application of the Enneking classification in the management of spinal osteoblastomas influences local recurrence and survival time.

METHODS A multicenter database of patients who underwent surgical intervention for spinal osteoblastoma was developed by the AOSpine Knowledge Forum Tumor. Patient data pertaining to demographics, diagnosis, treatment, cross-sectional survival, and local recurrence were collected. Patients in 2 cohorts, based on the Enneking classification of the tumor (Enneking appropriate [EA] and Enneking inappropriate [EI]), were analyzed. If the final pathology margin matched the Enneking-recommended surgical margin, the tumor was classified as EA; if not, it was classified as EI.

RESULTS A total of 102 patients diagnosed with a spinal osteoblastoma were identified between November 1991 and June 2012. Twenty-nine patients were omitted from the analysis because of short follow-up time, incomplete survival data, or invalid staging, which left 73 patients for the final analysis. Thirteen (18%) patients suffered a local recurrence, and 6 (8%) patients died during the study period. Local recurrence was strongly associated with mortality (relative risk 9.2; $p = 0.008$). When adjusted for Enneking appropriateness, this result was not altered significantly. No significant differences were found between the EA and EI groups in regard to local recurrence and mortality.

CONCLUSIONS In this evaluation of the largest multicenter cohort of spinal osteoblastomas, local recurrence was found to be strongly associated with mortality. Application of the Enneking classification as a treatment guide for preventing local recurrence was not validated.

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KEY WORDS osteoblastoma; primary spine tumor; spinal oncology; Enneking classification; surgical treatment; prognostic factors; local recurrence; survival

ABBREVIATIONS EA = Enneking appropriate; EI = Enneking inappropriate; WBB = Weinstein-Boriani-Biagini.

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OSTEOLASTOMA is a rare and benign primary bone tumor that accounts for approximately 1%–5% of all benign primary bone tumors;¹ 28%–36% of all osteoblastomas occur in the spinal column.^{1,20} Despite being benign tumors, osteoblastomas often behave more aggressively than other benign tumors, and in some cases malignant transformation or extensive local recurrence that cannot be controlled occurs.^{5,15,16} Osteoblastomas present radiographically as osteolytic lesions more than 20 mm in diameter, and they have a range of aggressiveness toward the surrounding tissues.¹⁷ These tumors are staged on the basis of the degree of aggressiveness found with CT, MRI, and histology.^{17,20} Accurately classifying these tumors can be a challenge based on the subjective interpretation of imaging and accepted histological limitations.⁴

The Enneking classification was developed for the surgical staging and management of primary musculoskeletal tumors.⁶ It is based on the grade and extent of the tumor and uses histological, radiographic, and clinical features to aid in the determination of resection margins.⁶ According to the Enneking classification, benign tumors can be divided into 1 of 3 stages: latent (S1), active (S2), or aggressive (S3) (Table 1).^{6,18} Use of the Enneking classification in the management of patients with a primary bone tumor of the appendicular skeleton has led to improved survival rates.^{7,13,22} Nevertheless, implementation of this classification in the management of primary spine tumors has not been widely accepted because of complexities of the spine for which the Enneking classification does not account, such as involvement of the epidural compartment, involvement of neurological structures, and the need for restoring spinal stability.¹² Therefore, the Weinstein-Boriani-Biagini (WBB) system, which takes the complex anatomy of the spine into account, was developed to stage spinal tumors and recommend surgical procedures to treat them.¹¹

Because of the low incidence of primary spine tumors, there are limitations to performing clinical research, which results in a lack of evidence-based treatment guidelines.^{3,19,21} Subsequently, the management of these tumors has been inconsistent and possibly has led to unnecessary mortality and morbidity. An evidence-based approach was developed recently by the AOSpine Knowledge Forum Tumor, which gathers evidence to guide the surgical management of primary spine tumors.⁸ The primary purpose of this study was to use this approach to determine whether application of the Enneking classification in the management of spinal osteoblastomas influences local recurrence and survival rates.

Methods

Design

This study was part of an international multicenter retrospective review of primarily prospectively collected data with cross-sectional follow-up; 10 of the 13 participating spine centers contributed osteoblastoma case data from Europe and North America. The patients were not consecutively included at all centers. The research protocol was approved by the local ethics board of each participating spine center. Patients were included if they were admitted to a participating spine center with a diagnosis of spinal osteoblastoma, underwent surgical intervention between November 1991 and June 2012, and had at least 12 months of follow-up. Patients were excluded if they were admitted for treatment of a metastatic spinal tumor, were diagnosed with a primary spinal cord tumor, had insufficient data available, or had insufficient follow-up time.

Demographic data, tumor histology results, resection margins, Enneking stage, WBB stage, information on use of adjuvant therapies and local recurrence, and survival data were collected from clinical charts and institutional databases. When necessary, governmental databases were accessed to retrieve information concerning death. Data were captured in a secure Web-based application (RED-Cap, Vanderbilt University).

Definitions

Two groups of patients were analyzed, those who underwent an Enneking-appropriate (EA) procedure, and those who underwent an Enneking-inappropriate (EI) procedure.^{8,9} EA was defined by the final pathology margin (pathologist's final report) matching the Enneking-recommended surgical margin, and EI was defined by the final pathology margin not matching the Enneking-recommended surgical margin.⁹ For example, if final pathology results indicated an intralesional resection of an S3 tumor, the procedure the patient underwent to treat it would be considered EI, because a wide/marginal margin was recommended (Fig. 1). For an S1 or S2 tumor, intralesional resection was recommended, so if the final pathology reports indicated an intralesional resection, the procedure the patient underwent would be considered EA.

Surgical Technique

Different surgical procedures were performed as a result of variations in pathology characteristics and surgeon experience and preferences.^{8,10} Surgical procedures consisted of excision, including intralesional excision and

TABLE 1. Enneking classification of benign tumors*

Stage	Characteristics
S1	Latent or inactive tumor surrounded by a well-circumscribed capsule; grows very slowly
S2	Active tumor surrounded by a thin capsule and a reactive tissue layer; grows slowly
S3	Aggressive tumor surrounded by a very thin incomplete or absent capsule; a wide reactive hypervascular pseudo-capsule invades neighboring tissue; grows very rapidly; associated with high recurrence rate; histological features include large epithelioid osteoblasts either rimming the osteoid or forming a clustered matrix

* Enneking classification.^{6,12,14}

FIG. 1. Left: EA resection of S3 osteoblastoma with a wide surgical margin that matches the recommended surgical margin. **Right:** EI resection of S3 osteoblastoma with an intralesional surgical margin that does not match the recommended surgical margin.

curettage, or en bloc resection with reconstruction of the spinal column when necessary.

Pathology Results

The surgical pathology results, which differentiated EA from EI procedures, were provided by an experienced musculoskeletal pathologist. Wide and marginal resection margins were combined into 1 category because sparing of critical anatomical structures was preferred over achieving the recommended surgical margin, including excision of these critical anatomical structures.¹⁰

Statistical Analysis

Descriptive statistics (mean $\pm$ standard deviation and frequency [percentage]) were used to summarize demographic data. Kaplan-Meier curves were created to illustrate time to tumor recurrence and mortality data. For evaluating differences between groups, the Fisher exact test was used for categorical variables, and the Student *t* and Mann-Whitney tests were used for continuous variables. Significance was defined as a *p* value of < 0.05 . All statistical analyses were performed using Stata 12.0.

Results

A total of 102 nonconsecutive cases of spinal osteoblastoma were identified. Twenty-seven were excluded because follow-up was less than 12 months, 1 case was removed because of incomplete survival data, and 1 case was removed because of invalid staging. Therefore, 73 patients were included in the final analysis; 25 (34%) were female and 48 (66%) were male, and their mean age at the time of surgery was 24.6 ± 12.8 years. Patient demographics and clinical characteristics are summarized in Table 2.

When we studied the characteristics of the Enneking appropriateness cohorts (Table 3), we found no statistically significant sex or age differences between the EA and EI groups. The mean follow-up for the EA group was 4.3 ± 3.1 years and that for the EI group was 4.3 ± 2.8 years. We found no differences between the EA and EI groups

regarding the WBB classification; 2 (3%) patients received adjuvant therapy, and they both belonged to the EI group. There was statistical significance at baseline for spinal location (mobile versus fixed) and tumor grade; more EA-treated patients presented with a lesion in the fixed spine than did EI patients ($p = 0.045$). The EI group presented with only aggressive (S3) tumors ($p < 0.001$).

Local Recurrence

A total of 13 (18%) local recurrences occurred in the 73 patients (Fig. 2 left). In the EA cohort, 8 (26%) of 31 had a local recurrence, and in the EI cohort, 4 (11%) of 35 had a local recurrence. We found no statistical significance for local recurrence and postoperative treatment course between the 2 groups. In the EA group, 5 (63%) of the recurrences were of S2 tumors, and 3 (38%) were S3 tumors. None of the patients who suffered a local recurrence had a history of previous spine surgery.

Mortality

During the study period (mean follow-up 4.1 ± 2.9 years), a total 6 (8%) deaths occurred (Fig. 2 right), 3 (10%) in the EA group and 3 (9%) in the EI group. Five of these 6 deaths occurred in patients with an S3 osteoblastoma, 3 of 6 patients had an osteoblastoma-related cause of death, and the cause of death was unknown in the remaining 3 patients.

There was a strong relationship between local recurrence and death (relative risk 9.2; $p = 0.008$). A separate analysis, in which we adjusted for Enneking appropriateness (relative risks 6.0 [EA group] and 15.5 [EI group]), did not significantly alter the results. The frequencies of local recurrence and death according to Enneking appropriateness are listed in Table 4.

Discussion

Osteoblastoma is a rare benign primary bone tumor with a predilection for the spinal column. The Enneking classification has been used historically for the surgical

TABLE 2. Summary of demographic and clinical characteristics

Variable	Value
Age (yrs) (n = 73)	
At diagnosis	23.5 ± 11.1
At surgery	24.6 ± 12.8
Sex (n = 73)	
Female	25 (34)
Male	48 (66)
Previous spine tumor op (n = 73)	
No	64 (88)
Yes (intralesional resection)	9 (12)
How the diagnosis was made (n = 41)	
Open biopsy	11 (27)
CT-guided biopsy	18 (44)
Intraop biopsy	12 (29)
Preop embolization (n = 67)	
No	51 (76)
Yes	16 (24)
Adjuvant therapy (n = 72)	
No	69 (96)
Yes	3 (4)
Spinal location (n = 73)	
Mobile	64 (88)
Cervical	16 (25)
Cervical-thoracic	1 (2)
Thoracic	23 (36)
Thoracic-lumbar	1 (2)
Lumbar	23 (36)
Fixed	9 (12)
Lumbar-sacrum	2 (22)
Sacrum	5 (56)
Sacrum-coccyx	2 (22)
WBB tissue sectors (n = 64)	
Anterior (Sectors 5–8)	2 (3)
Posterior (Sectors 9–12, 1–4)	31 (48)
Both	29 (45)
Complete (Sectors 1–12)	2 (3)
Tumor grade (n = 68)	
S2, active	17 (25)
S3, aggressive	51 (75)
Enneking appropriateness (n = 66)	
EA	31 (47)
EI	35 (53)
Pathology results from the surgical specimen (n = 66)	
Wide or marginal	25 (38)
Intralesional	41 (62)
Local recurrence (n = 73)	
No	60 (82)
Yes	13 (18)

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TABLE 2. Summary of demographic and clinical characteristics

Variable	Value
Survival (n = 73)	
Alive	67 (92)
Dead	6 (8)

Data are presented as number (percentage) or mean ± SD.

staging and management of primary bone tumors in the appendicular skeleton.⁶ Yet, no clear treatment guidelines for the management of primary spine tumors have been available.^{3,19,21} As a result, spinal tumors have been treated inconsistently and mainly based on surgeons' clinical experience rather than evidence-based treatment guidelines. To our knowledge, this study is the largest multicenter cohort of spinal osteoblastomas to have evaluated the Enneking classification as the main treatment guideline.

Boriani et al.² previously studied the role of the Enneking classification system and their related surgical consequences in the outcomes of patients with a spinal osteoblastoma. A total of 51 patients were identified, with an average follow-up duration of 90 months; 1 patient died 1 day after surgery. These authors found no local recurrence in patients with an S2 (active tumor) osteoblastoma when treated with intralesional resection. Local recurrence was found in 23% of the patients who underwent intralesional excision for their S3 tumor and in 67% (2 of 3) of the patients with an S3 osteoblastoma who underwent en bloc resection and had a previous spine operation. In contrast, we found local recurrence in 5 patients with an S2 osteoblastoma treated with intralesional (4 patients) and wide or marginal resection (1 patient); the treatment for all these patients was considered EA. Furthermore, 7 patients with an S3 osteoblastoma suffered local recurrence; 4 of them were treated with intralesional resection (EI), and 3 were treated with wide or marginal resection (EA). None of the patients who suffered a local recurrence had undergone previous spine surgery. It is interesting that overall recurrence rates in our study and in the Boriani et al. study were similar (18% and 17.5%, respectively). Boriani et al.² concluded that the Enneking classification seemed to be an excellent guide to selecting the appropriate treatment for spinal osteoblastomas; however, the results might not be generalizable, because theirs was a single-center study.

Based on our multicenter results, the Enneking system might be questioned as a treatment guide for spinal osteoblastomas; however, a number of potential considerations and limitations exist. The first consideration is the reliability of grading S2 and S3 osteoblastomas. A study by Chan et al.⁴ investigated the reliability of the Enneking and WBB staging systems. They found fair agreement (Fleiss $\kappa = 0.267$, 61% agreement) on the Enneking staging of benign primary tumors and only 49% agreement on the Enneking staging of osteoblastomas.⁴ These results highlight the notion that both radiographic and histological grading can be difficult, even for experienced clinicians and pathologists. A single-center study would minimize this variability but also would limit generalizability. Final

TABLE 3. Study characteristics according to Enneking appropriateness

Variable	EA (n = 31)	EI (n = 35)	p Value
Age (yrs) (n = 66)			
At diagnosis	23.8 ± 11.4	23.8 ± 11.7	0.926*
At surgery	24.7 ± 11.4	25.5 ± 14.7	0.822*
Sex (n = 66)			
Female	10 (32)	12 (34)	0.862†
Male	21 (68)	23 (66)	
How the diagnosis was made (n = 35)			
Open biopsy	7 (29)	2 (18)	0.810‡
CT-guided biopsy	10 (42)	5 (45)	
Intraop biopsy	7 (29)	4 (36)	
Spinal location (n = 66)			
Mobile	25 (81)	34 (97)	0.045‡
Fixed	6 (19)	1 (3)	
No. of vertebral levels spanned by the tumor (n = 66)			
1	21 (68)	28 (80)	0.256†
≥2	10 (32)	7 (20)	
WBB tissue sectors (n = 62)			
Anterior (Sectors 5–8)	0 (0)	1 (3)	0.312‡
Posterior (Sectors 9–12 & 1–4)	16 (59)	14 (40)	
Both	11 (41)	18 (51)	
Complete (Sectors 1–12)	0 (0)	2 (6)	
Tumor grade (n = 66)			
S2, active	17 (55)	0 (0)	<0.001‡
S3, aggressive	14 (45)	35 (100)	
Tumor vol, ellipsoid body (n = 57)	4.2 (1.8, 34.1)	4.7 (2.6, 19.6)	0.463§
<5 cm ³	15 (60)	17 (53)	0.604†
≥5 cm ³	10 (40)	15 (47)	
Adjuvant therapy (n = 65)			
No	30 (100)	33 (94)	0.495‡
Yes	0 (0)	2 (6)	
Local recurrence (n = 66)			
No	23 (74)	31 (89)	0.201‡
Yes	8 (26)	4 (11)	
Survival (n = 66)			
Alive	28 (90)	32 (91)	1.000‡
Dead	3 (10)	3 (9)	

Data are presented as number (percentage), mean ± SD, or median (25th, 75th percentiles).

* Student t-test.

† Pearson chi-square test.

‡ Fisher exact test.

§ Mann-Whitney-Wilcoxon test.

vigilance and detail in follow-ups can also vary among different centers. Second, despite our study being the largest cohort to date, the extensive variability involved in tumor research suggests that this study is underpowered. Finally, the mean follow-up duration in our study was 4.1 ± 2.9 years. For a tumor such as osteblastoma, this follow-up time is average; patients can live for many years after tumor resection. A follow-up time of at least 5–10 years (preferred) should result in improved insight into survival and local recurrence of osteblastomas. Follow-up time is a distinct limitation of this study, along with the fact that 27 patients had to be excluded because they had undergone less than 1 year of follow-up. We partially controlled for this limitation by analyzing the excluded patients, and no significant differences between the excluded patients and patients included in the final analysis were found.

Although osteblastoma is a benign tumor, it can behave aggressively with extensive uncontrollable local recurrence, and even malignant transformation with metastatic disease has been reported.^{5,15,16} Furthermore, osteblastoma has a high incidence of local recurrence after incomplete resection; recurrence rates between 10% and 24% for S2 osteblastoma and up to 50% for S3 osteblastoma have been reported.^{1,2,14} A study by Lucas et al.,¹⁵ which included an analysis of 75 extremity osteblastomas, found recurrence rates of 19% after intralesional excision, 5.6% after marginal en bloc resection, and 20% (1 of 5 patients) after wide local excision with disease-free margins. These results are in agreement with those of our study, in which we found a total recurrence rate of 18% and recurrence rates of 17% after intralesional resection and 20% after wide or marginal resection.

The epidemiological and imaging parameters of our study population were consistent with those in the literature. Both a male-dominant cohort (66%) and a mean age of 22.5 ± 10.2 years agree with previous studies in which there was a male predominance and 90% of the patients were diagnosed with an osteblastoma between the ages of 20 and 30 years.¹⁷ Furthermore, we observed that the mobile portion of the spine was involved in 88% of the patients, which is in concordance with the findings of Berry et al.,¹ who reported this involvement in 75% of their study's patients.

Osteblastomas typically arise from the posterior element and can extend into the vertebral body.¹⁷ Our study found that only 48% of the tumors were truly confined to the posterior elements corresponding to WBB sectors 1–4 and 9–12, 3% of the tumors were found solely in the anterior part of the vertebral body corresponding to WBB sectors 5–8, 45% of the tumors had extensions in both the anterior and posterior elements, and 3% of the tumors involved the complete vertebral column corresponding to WBB sectors 1–12. Therefore, extension of an osteblastoma into the anterior part of the vertebral body might be more common than previously described in the literature.

Conclusions

Although this is, to our knowledge, the largest cohort study of spinal osteblastomas in the literature to date, the

pathology reports can vary from center to center, and a surgeon's impression of margins and the final pathology assessment of margins can be inaccurate. The degree of

FIG. 2. Left: Kaplan-Meier analysis of time to first local recurrence after surgery. **Right:** Kaplan-Meier analysis of survival after surgery. Number at risk indicates the number of patients included in the analysis.

absolute number of events was low, which limits extensive statistical analyses. Because of the low incidence of osteoblastomas, only low-quality, single-center research has been performed, which resulted in a lack of evidence-based treatment algorithms. With this study being the first large cohort of osteoblastomas to involve multiple centers, generalizability has been enhanced. The validity of the Enneking classification for the treatment of spinal osteoblastomas was not demonstrated in our study. Yet, local recurrence was found to be associated with an increased risk of death. Nevertheless, until further prospective evidence is gathered, treating aggressive osteoblastomas (S3) with en bloc resection (wide or marginal margins) is theoretically sound and supported by previous single-center studies.² In the spine, risk, anatomical restraints, and functional implications of neurological sacrifice do not always allow for an EA approach. In these cases, complete intralesional resection with or without adjuvant radiotherapy, including stereotactic radiotherapy, would seem reasonable. Future long-term prospective studies that focus on image-grading standardization and histological grading supplemented by molecular sequencing are needed to improve classification of these tumors and, ultimately, their treatment. Indeed, the results of our study show that optimal management (resulting in no local recurrence) is not obtained for active or aggressive osteoblastomas and that a more detailed, valid grading system to direct management must be pursued.

TABLE 4. Local recurrence and mortality of patients with osteoblastoma according to Enneking appropriateness

Recurrence	No. of Patients (%)				Total (n)
	EA*		EI†		
	Alive	Deceased	Alive	Deceased	
None local	22 (79)	1 (33)	30 (94)	1 (33)	54
Local	6 (21)	2 (67)	2 (6)	2 (67)	12
Total	28	3	32	3	66

* Thirty-one patients.

† Thirty-five patients.

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Disclosures

Dr. Dekutoski is a patent holder in the Mayo Office of Intellectual Properties and Medtronic; Dr. Fisher is a consultant for Medtronic and NuVasive; Ms. Germscheid is currently employed by AOSpine International, the study sponsor, but does not have a vested interest in the study's outcome; Dr. Gokaslan has direct stock ownership in Spinal Kinetics and has received clinical or research support (including equipment or material) for this study from AOSpine International; and Dr. Rhines is a consultant for Stryker and Globus.

Author Contributions

Conception and design: Fisher, Germscheid. Acquisition of data: Fisher, Dea, Boriani, Varga, Luzzati, Fehlings, Bilsky, Rhines, Reynolds, Dekutoski, Gokaslan, Germscheid. Analysis and interpretation of data: Fisher, Versteeg, Germscheid. Drafting the article: Fisher, Versteeg, Germscheid. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fisher. Statistical analysis: Fisher, Versteeg, Germscheid. Study supervision: Fisher.

Supplemental Information

Previous Presentations

Portions of this work were presented at the 2016 Canadian Spine Society Meeting held in Whistler, Canada, on February 24–27, 2016, and the Global Spine Conference held in Dubai, United Arab Emirates, on April 13–16, 2016.

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