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Case Study

Establishment of a New Radiological Prognostic Score in Patients with Osteosarcoma

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Abstract

Introduction: Osteosarcoma (OSS) is the most common primary malignant bone tumor. Treatment includes surgery and chemotherapy. Various prognostic factors have been identified, but the influence of tumor bone densification on chemotherapy response remains uncertain. **Objective:** This study aims to determine the impact of tumor bone condensation in OSS on therapeutic response to establish a potential new prognostic score. **Methods:** This retrospective single-center study involved 20 patients (adults and children) diagnosed with OSS between August 2006 and December 2018, treated at Cliniques Universitaires Saint-Luc (Brussels, Belgium). A tumor bone densification score was established, and chemotherapy response was evaluated. Follow-up data were collected, and statistical analysis was conducted. **Results:** The study included 20 patients (11 males, 9 females) with a median follow-up of 110 months (range 61-199 months). The femur was the most common tumor site (65%). At diagnosis, 95% had localized disease, and 45% were classified as good responders to chemotherapy (= 90% tissue necrosis). The 5-year overall survival was excellent, with a 5-year disease-free survival of 70% (± 10.2%). Patients with metastatic disease had poorer survival. Poor response to preoperative chemotherapy was the main independent poor prognostic factor associated with disease-free survival. **Conclusion:** This study confirmed a good prognosis for OSS patients in the localized stage treated with surgery and perioperative chemotherapy. Patients with metastases and poor response to preoperative chemotherapy had poorer survival. However, the study does not validate tumor bone condensation as a prognostic tool. Further research into other prognostic factors, such as the tumor microenvironment, is suggested.

Keywords: Osteosarcoma; Tumor Density; Prognostic Factor; Tumor Necrosis; Radiological Score; Disease-Free Survival

Background

Osteosarcoma (OSS) is the most common primary malignant bone tumor in children and adults, characterized by the production of immature bone [1-14]. It accounts for less than 1% of tumors in adults and 3-5% of tumors in children [3,5,10,12,15]. The worldwide incidence is 0.3 per 100.000 inhabitants per year, with a higher incidence among adolescents (0.8-1.1 per 100.000 between 15-19 years) [1,3,4,7-9,12]. There are two peaks in incidence: the first occurs in adolescents/young adults (AYA), between 10-24 years, while the second peak occurs in older patients, over 60 years [1,3,6,8,15]. This tumor is more prevalent in males with a sex ratio of 1.4 [1,3,5-8,15].

Initially, the treatment for OSS was surgery alone [2,5,8]. However, this was not very effective, with 3-year event-free survival rates of 20% [8]. Since the 1980s, the introduction of perioperative polychemotherapy, including high-dose Methotrexate (12g/m²), Doxorubicin (75 mg/m²), and Cisplatin (120 mg/m²) (MAP regimen), has significantly improved survival rates [1–5, 7-11]. The 3-year event-free survival rates increased from 20% to 45-70%, depending on the studies and patient types [2,11-14,16-18].

Various prognostic factors associated with osteosarcoma and validated by the literature have been identified: disease stage at diagnosis (localized versus metastatic), histological grade (high versus low grade), surgical resection margins (R0 versus R1), sex (higher incidence in males and better long-term survival rates in females), age (higher incidence and better prognosis in children),

and tumor location (limb bones versus spinal axis) [1,5-7,10,16].

Finally, the tumor's response to preoperative chemotherapy has also proven to be an important prognostic indicator. Based on studies and the analysis of the percentage of tumor necrosis induced by chemotherapy, two groups of responders have been distinguished: good responders (= 90% tissue necrosis) and poor responders (< 90%). Literature data indicates a lower 3-year event-free survival (45-55%) in poor responders compared to good responders (60-70%) [2,11-14,16-18]. Similarly, 5-year overall survival is 75-80% in good responders versus 45-55% in poor responders [9,11,13,16].

Furthermore, given that OSS is a primary malignant bone tumor characterized by the production of immature bone in varying quantity and quality, it could be hypothesized that including initial tumor bone densification as an additional prognostic factor, along with the chemotherapy response based on this degree of densification, might be interesting. However, to date, no data on this subject has been published.

In this context, we conducted a study aimed to evaluate the impact of tumor density on survival, as well as the correlation between tumor density and response to neoadjuvant chemotherapy. Our hypothesis was to establish a prognostic score that could determine patient survival based on tumor density. This study is retrospective and single-centered, based on a review of medical records of adult and pediatric patients with OSS who underwent surgery at Cliniques Universitaires Saint-Luc (Brussels, Belgium).

Materials et Methods

Patient Selection

This study included adult and pediatric patients with high-grade limb osteosarcoma (OSS), confirmed by biopsy and diagnosed between August 2006 and December 2018, for whom bilateral comparative CT scan imaging of limbs was available. Inclusion criteria required that all patients were treated with a combination of perioperative chemotherapy and surgical resection. Patients with secondary, parosteal, low-grade OSS or those without available bilateral comparative imaging were excluded from the study. The medical records of the selected patients were systematically reviewed, and the following data were collected:

- Demographic data: age at diagnosis and sex.
- Clinical and biological tumor characteristics: primary site, loco-regional and/or metastatic extension, LDH and alkaline phosphatase levels at diagnosis, and histological data.
- Treatment-related characteristics: type of chemotherapy administered, status of surgical resection margins obtained, and evaluation of the percentage of tumor necrosis induced by preoperative chemotherapy.
- Occurrence of OSS tumor recurrence: local recurrence and/or metastatic progression.

Medical and Surgical Treatment

Patients included were all treated with 2 cycles of neoadjuvant polychemotherapy following the MAP regimen (high-dose Methotrexate 12g/m², Doxorubicin 75 mg/m², and Cisplatin 120 mg/m²) according to the EURAMOS protocol [2,11,12].

Following these 2 cycles, a therapeutic response assessment to preoperative chemotherapy was performed. In case of response or stability of the disease, patients were systematically referred to the orthopedic department of Cliniques Universitaires Saint-Luc for surgical resection within a median time of 19.5 days (range, 7-30). All patients underwent limb-sparing surgery with wide-margin resection followed by reconstruction.

Postoperatively, patients continued their treatment with 4 cycles of MAP.

Radiological analysis

In order to evaluate and compare the volumes and bone densities of OSS to those of healthy bones, only patients who underwent comparative imaging of the contralateral healthy limb were included.

MIM imaging analysis software (MIMSoftware, Cleveland, OH, USA) was used to perform comparisons of mineralized volumes of the tumor versus the normal contralateral limb.

CT scan images of the affected limb and the healthy limb were compared. The objective was to assess the degree of mineralization of the tumor by comparing it to the same area on the healthy limb. An identical volume positioned on the same healthy bone segment was deverlineated. Soft tissues were subtracted from this volume using a threshold of 250 Hounsfield units, allowing for the determination of mineralized bone volume in the region of interest. A comparison of the two volumes – tumor mineralized volume versus normal bone volume – was performed by subtracting the tumor bone volume from the normal bone volume. A positive result indicated a tumor more osteolytic than osteosclerotic.

Endpoints

The primary endpoint is the evaluation of the impact of tumor bone density on disease-free survival (DFS), defined as the duration (in months) between surgical treatment and potential tumor recurrence.

The secondary endpoint was to establish a possible correlation between tumor bone density and the pathological response to neoadjuvant chemotherapy.

Statistical Analyses

Standard descriptive statistical analyses were performed. Quantitative variables were expressed as their central tendency (mean or median) and dispersion (standard deviation (SD) or range). Categorical variables were expressed as their absolute frequency (N) and relative frequency (%).

Survival and prognostic curves were established using Kaplan-Meier methods to estimate the probability of tumor recurrence-free survival (in months). Additionally, data analysis considered censoring, defined by patients lost to follow-up, those without tumor recurrence, or those deceased from other causes before the study closure date. The Log-Rank test was used to compare survival functions between groups.

Pearson correlation was used to verify the existence of a relationship between normally distributed quantitative variables, and Cramer's V was used for binary categorical variables. The Chi-square test was used to compare categorical variables. Unlike the Student's t-test, which compares continuous quantitative variables between two groups. The normality of data distribution was checked using QQ plots and the Shapiro-Wilk test.

SPSS software (SPSS Software, v.28.0.1.1(15), SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. All tests were two-sided, and p-values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

Based on all predefined inclusion criteria, a total of 20 eligible patients were included in this study.

Of 104 patients meeting the initial criteria of OSS surgery at CUSL, only 20 patients had imaging records (comparative imaging of contralateral healthy limb) and follow-up compatible with this study. The characteristics of these patients are presented in Table 1.

	Frequency (n=20)
Age at diagnosis (years)	
≤ 10	4
Nov-19	11
20-29	3
≥ 30	2
Sex	
Male	11
Female	9
Tumor Site	
Femur	13
Tibia	0
Fibula	2
Humerus	4
Radius	1
WHO Sarcoma Classification at diagnosis (biopsy)	
Conventional osteoblastic	14
Conventional chondroblastic	1
Conventional telangectiasic	2
Conventional mixed	3
Disease extent at diagnosis	
Localized disease	19
Metastatic disease	1
Biological data	

LDH ≤ UNL (≤ 250)	13
LDH > UNL	7
Alk Ph ≤ UNL (35-105 UI)	9
Alk Ph > UNL	8
Alk Ph NA	3
Status of surgical rescetion margins	
R0	19
R1	1
R2	0
Histological tumor response to neoadjuvant chemotherapy	
≥ 90% tumor necrosis	9
< 90% tumor necrosis	11
LDH = lactate dehydrogenase, Alk Ph = alkaline phosphatase, R = resection margins, WHO = World Health Organization	

Table 1: Baseline characteristics of patients.

After receiving 2 cycles of chemotherapy according to the MAP protocol (treatment duration: 10 weeks), all patients underwent tumor resection. Surgery was deemed complete in 19 of them (R0 status).

Histological evaluation of tumor response to neoadjuvant chemotherapy concluded a good tumor response in 45% of cases (n = 9), defined by = 90% tumor necrosis.

Subsequently, all patients continued therapeutic management with additional 4 cycles of adjuvant chemotherapy according to the same protocol. In this study, patients received a total of 6 cycles of chemotherapy.

Endpoints Analysis

All patients were followed for a minimum of 5 years. The median follow-up is 110 months (range 61 – 199 months).

All included patients are alive at the end of the follow-up. However, 7 patients (35%) experienced local or distant recurrence after treatment. Pulmonary lesions were the most frequent distant metastases (75%).

Fig. 1 illustrates the 5-year recurrence-free survival. From 83 months, the rate of patients without recurrence reaches 63% (± 11.4%)

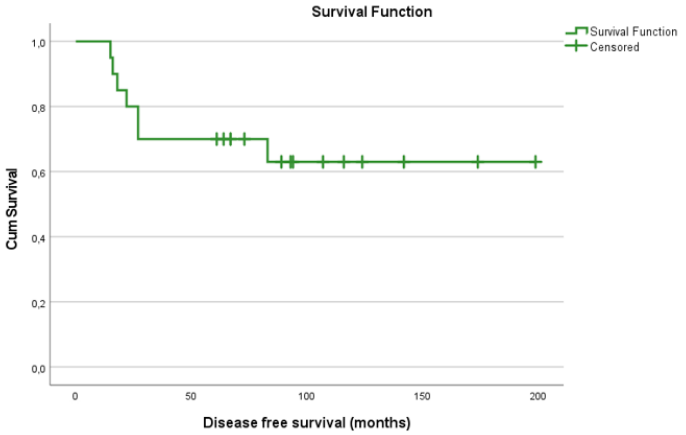

Figure 1: Kaplan-Meier curve for recurrence-free survival.

A specific analysis of survival and recurence data was conducted based on the endpoints. As shown in Fig. 2, DFS in patients with osteosclerotic OSS is not statistically different from the DFS of patients with lytic OSS (p=0.172). From a purely descriptive standpoint, lytic OSS even shows a trend towards a better prognosis. The 10-year (120-months) recurence-free survival rate for osteosclerotic OSS is 45% (± 17.4%) whereas for lytic OSS, it remains at 80% (± 12.6%) and appears to persist over time.

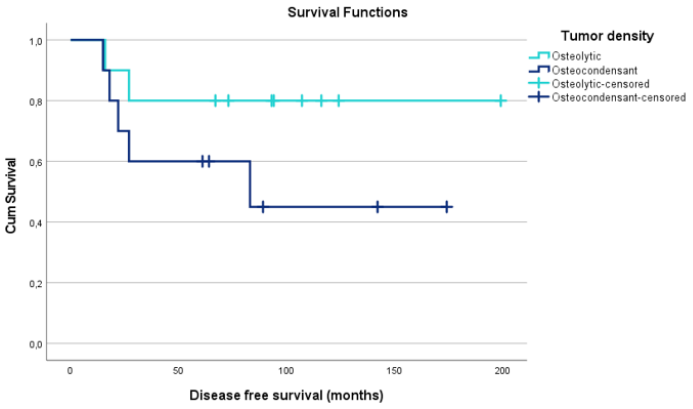

Figure 2: Kaplan-Meier survival curve based on bone density.

Similarly, Fig. 3 shows that there is no established correlation between tumor density status and the outcome of these patients (Pearson's r = -0.356, p = 0.123). However, these results clearly illustrate that patients without recurrence (dark blue circles) have a better prognosis than those with recurrence (circles of other colors). Finally, these results indicate that patients with recurrence tend to be preferentially osteosclerotic OSS (circles located above the Y-axis).

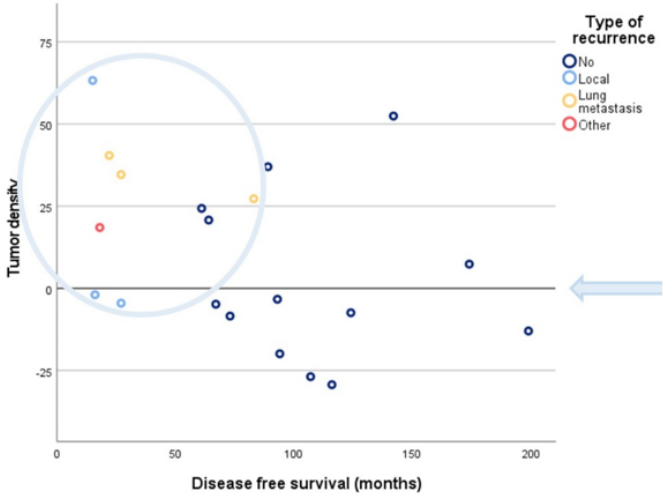

Figure 3: Scatterplot studying disease-free survival according to bone density and type of recurrence.

The DFS analysis based on recurrence status highlights a significant difference between the two curves (Chi^2=23.848 and p<0.001). This analysis also illustrates that most recurrences occur quite rapidly, between 15 and 27 months (Fig. 4 - green dashed lines).

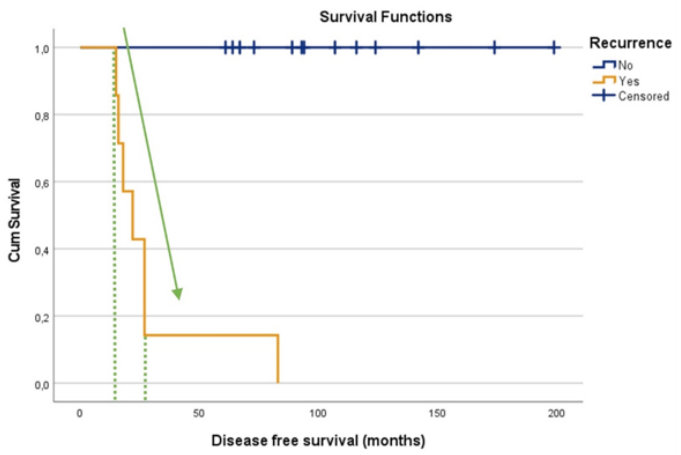

Figure 4: Kaplan-Meier survival curve based on recurrence status.

The influence of the preoperative chemotherapy response is illustrated in Fig. 5. The rate of patients without recurrence at 3 and 5 years in good responders (88.9% ± 10.5% at 3 and 5 years) is better than in poor responders (72.7% ± 13.4% and 54.5% ± 15%, respectively). However, this difference is not statistically significant (p=0.256). From a descriptive standpoint, good responders tend to have better survival. On the other hand, recurrences in poor responders occur early (during the first 27 months of follow-up), while for longer follow-up durations, the curve tends to conform with that of good responders. Additionally, there was no significant correlation between bone density and chemotherapy response (V=0.101, p=0.653).

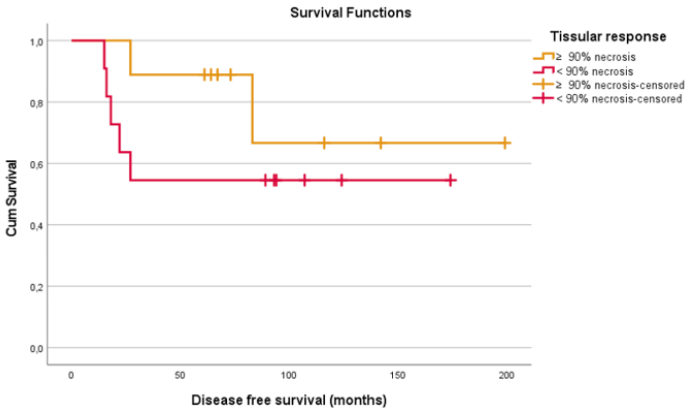

Figure 5: Kaplan-Meier survival curve based on tissue response to chemotherapy.

To compare patient groups with different bone density based on their response to chemotherapy, the data were examined from two perspectives. Firstly, tumor density was evaluated as a continuous quantitative variable (T-test), and secondly, as a categorical variable (lytic or sclerotic, Chi-square test). Regardless of the statistical analysis used, no statistical difference was demonstrated (T-test: p=0.645 and Chi-square: p=0.653). Indeed, there are as many lytic OSS tumors that respond well as those that respond poorly (Fig. 6). However, more sclerotic OSS tumors respond poorly to chemotherapy. Unfortunately, the differences are too small to draw statistically significant conclusions.

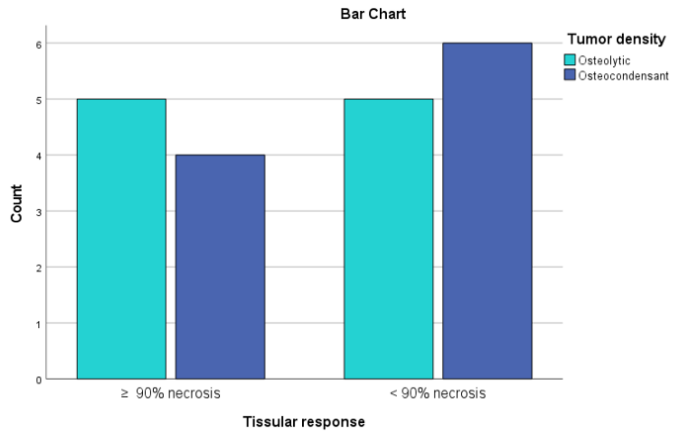

Figure 6: Bart Chart illustrated the correlation between bone density and chemotherapy response.

Discussion

This retrospective single-center study involving 20 patients with OSS aimed primarily to explore the correlation of several factor with recurrence-free survival, such as tumor bone density and chemotherapy response. Osteosarcomas are known to be more or less sclerotic or lytic. The main objective was to determine the impact of intratumoral bone density on chemotherapy response and consequently on recurrence-free survival, and to evaluate its prognostic role. This hypothesis is based on the work of Gomez-Brouchet et al. [4,13].

Since the advent of chemotherapy in the management of OSS, survival rates have not significantly improved over the past decades. The prognosis remains poor for 25% of patients who often experience early metastatic progression [3,5,8-10,15]. Therefore, improving overall management remains a major goal to increase the survival of these patients. This includes the need to establish prognostic factors to tailor therapeutic management.

There is a clear correlation between overall patient survival and the rate of response to neoadjuvant chemotherapy [19]. Therefore, a correlation between chemotherapy response and the radiological appearance, whether sclerotic or lytic, of the tumor could potentially be a predictive element for patient survival.

Unfortunately, our study was unable to demonstrate an impact of tumor bone density on recurrence-free survival (Figures 1 to 5). Additionally, no statistically significant correlation between tumor bone density and the histological response to neoadjuvant chemotherapy could be established (Figures 5 and 6), although a slight trend towards a poorer response of sclerotic osteosarcomas was observed.

In our study, the 5-year recurrence-free survival rate was 70% (± 10.2%), with patient demographics similar to those reported in the literature (Table 1). Additionally, the most frequently encountered histological subgroup was osteoblastic type.

All these characteristics and results are comparable to the data found in the literature [1-13,15]. Therefore, our study population exhibited a profile of characteristics consistent with those described for osteosarcomas. Thus, it appears that the quality of our sample is not the cause of the inability to prove the effect of bone density on osteosarcoma treatment.

However, besides the retrospective nature of this study, the limited number of included patients has restricted the statistical power of this analysis. The main reason for the small sample size was primarily related to the complexity of the radiological analysis, which required, among other things, a bone window CT scan and a magnetic resonance imaging (MRI) including the contralateral bones, which is not a standard imaging practice in the assessment of osteosarcomas. A more systematic integration of these two imaging examinations in the assessment of osteosarcomas in the future could overcome this limitation. Additionally, the inclusion of other patients with osteosarcomas, from our institution or other centers, could also resolve this sample size limitation. In addition to the small sample size, the limited difference in the number of patients between the two groups of bone density in osteosarcomas (osteoblastic versus lytic) could also explain the lack of significant difference in DFS, especially between patients with different bone density based on their tumor response to chemotherapy (Fig. 4). Only further studies including more patients will be able to determine the potential prognostic value of bone density in osteosarcomas.

Nervertheless, our study has demonstrated a trend for lytic osteosarcomas to have a better prognosis. In the study exploring the spatial distribution of the immune microenvironment in osteosarcomas and its correlation with imaging data, conducted by Cole G et al., it was shown that patients with highly lytic tumors had a better response to chemotherapy treatment [13]. From a purely descriptive standpoint, these findings are similar to ours.

Despite a limited number of patients, the DFS based on tumor response to chemotherapy appears to be better in good responders (Fig. 5). This trend, although not statistically significant, is consistent with and comparable to the results of other studies [2,3,7,8,16,19].

In this study, OS remains excellent (100%) despite a DFS of 70% (± 10.2%) at 5 years (Fig. 1). Uncontrolled diseases have a predominantly pulmonary metastatic progression (Table 2). In their study, Smeland et al. reported that 92% of their patients with OSS experienced relapses in the form of pulmonary metastatic nodules [12]. Very often, the progression is oligometastatic. Therefore, as described by Abdennadher et al. and Lehrer EJ et al., elective management through salvage surgery or stereotactic radiotherapy is often considered feasible [20,21]. These two locoregional ablative techniques have demonstrated therapeutic efficacy, leading to a favorable impact on the overall survival of these patients.

The analysis of DFS based on the recurrence status showed a significant difference between the two curves. However, these results should be interpreted with caution because our event of DFS is defined by the occurrence of a recurrence, which also defines the analyzed groups (Fig. 4).

Based on the fact that the majority of recurrences are early (Fig. 3), indicating a clear tumor aggressiveness, it could be interesting to postulate that this rapidity might be related to specific genomic profiles of some of these tumors. Our study, as well as that of Cole G. et al., demonstrated that molecular studies of OSS as well as the tumor microenvironment are essential. This type of evaluation could facilitate the categorization of patients with OSS into different risk groups and require adapted treatments to achieve better survival outcomes [4,9,13].

The establishment of a new prognostic factor could complement those already established (namely disease extent, resection margins, tissue response to chemotherapy, age, male gender, and tumor size). This could enable us to create a precise, sensitive, and specific predictive score, incorporating all these factors and, accordingly, adapt our future management. Finally, these results once again illustrate the importance of including the maximum number of patients in studies to gather a sufficient amount of data.

Conclusion

This retrospective unicentric review of osteosarcoma (OSS) gathered a cohort of adult and pediatric patients with characteristics similar to those reported in the literature. Our study confirmed the favorable prognosis in terms of disease-free survival (DFS) for these patients when they are at the localized stage and treated with surgery and perioperative chemotherapy. Despite local or distant recurrences, the overall survival of these patients remains excellent.

However, this study does not validate the impact of tumor bone condensation in OSS on therapeutic response and its use as a prognostic tool. The limited number of included patients and the inherent difficulty in measuring bone density are, until proven otherwise, the reasons for this lack of statistical validation. This study emphasizes the need for a larger sample to confirm the trend and attempt to establish a prognostic score.

Different trends have nonetheless been identified. Descriptively, patients with a poor response to preoperative chemotherapy have a worse survival outcome, as expected compared to the literature. Additionally, a trend also suggests a better response to chemotherapy for lytic OSS, while osteosclerotic OSS appears to have a higher recurrence rate than lytic OSS. Therefore, an analysis of a larger cohort could confirm a prognostic factor for the lytic or condensing aspect of an osteosarcoma. The search for other prognostic factors for OSS, such as genomic profiling and analysis of the tumor microenvironment, is also suggested.

Ethics Aapproval: We have received approval from the ethics committee.

Funding: Non funding was received for this study.

Conflict of Interests: We declare that we have no conflict of interests.

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