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## Original Article

# Evaluation of prognostic factors and survival among patients with osteosarcoma attended at a philanthropic hospital in Teresina, Piauí, Brazil

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## A B S T R A C T

**Objective:** Make an analysis of the factors that influence their survival and prognosis of patients with osteosarcoma treated at a Charity Hospital in Teresina-PI. **Methods:** We analyzed medical records of 32 patients diagnosed with osteosarcoma in the period January 2005 to December 2010. **Results:** Patients were aged between 6 and 73 years, with 56.2% men and 43.7% women. The prevailing color was black, with 62.5% of cases. With regard to histological subtype, the majority were osteoblastic type (71.8%). The anatomical location of the tumor was prevalent region of the knee (distal femur and proximal tibia). Regarding the size of the tumor, tumors were 43.8% bigger than 15 cm. Degree of necrosis Huvos concentrated primarily among the types I and II, 53.1% and 25% respectively. The overall survival at two and four years was 45.5% and 39% respectively and event-free survival at two and four years was 39.8% and 19.9% respectively. **Conclusion:** We considered the worst prognosis, the presence of metastases at diagnosis and tumors larger than 15 cm. And the criteria of Huvos did not reach statistical significance for the prognosis of patients.

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## Introduction

Neoplasia occupies second place among Brazilian mortality rates, only behind circulatory diseases, which therefore makes cancer a public health problem.<sup>1</sup>

Among all forms of neoplasia in general, primary bone tumors constitute 3% to 4%. Furthermore, in the Brazilian setting, the definitive diagnoses for cases of primary bone tumors tend to be delayed. Early diagnosis for these forms of neoplasia is fundamentally important, especially in relation to malignant tumors, for which local control and therapeutic management aimed at increasing these patients' survival are needed.<sup>1</sup>

Osteosarcoma is the commonest type of bone tumor with a primary malignant bone matrix, accounting for 0.2% of human malignant neoplasia. It was first described by Dupuytren in 1805, and its main characteristic consists of production of osteoid matrix by neoplastic cells. It mainly affects children and adolescents during their first two decades of life and its favored anatomical position is the metaphyses of long bones. The distal femur and proximal tibia are the locations most frequently affected by osteosarcoma, followed by the proximal humerus.<sup>1</sup>

Today, it can be said that the prognosis for patients with osteosarcoma depends on the size of the tumor, the surgical margins achieved during the operation and any presence of pulmonary metastases.<sup>2</sup>

It is also known that factors such as sex and anatomical location of the lesion are not associated with local recurrence or with the prognosis, while the percentage induction of necrosis by chemotherapy and the surgical margins are factors associated with local control.<sup>2</sup>

This study had the aims of analyzing the factors that were influencing prognosis and survival among patients attended at a philanthropic hospital in Teresina, Piauí, and epidemiologically and clinically characterizing the sample. Each factor was evaluated separately and together, with the aim of finding a better diagnostic and therapeutic approach for the patients affected by this disease.

## Sample and methods

After gaining approval from the Research Ethics Committee of UFPI, with CAAE registration no. 0399.0.045.000-11, and approval from the National Research Ethics Commission (CONEP), with registration number 045, a descriptive-analytical quantitative retrospective cross-sectional study was begun, covering the period from January 2005 to December 2010. The medical files of 32 patients who had been diagnosed with osteosarcoma at a philanthropic hospital in Teresina, Piauí, were analyzed.

In evaluating the medical files, the following data were gathered: age, sex, color, occupation, date of diagnosis of osteosarcoma, Huvos criterion (Table 1), size and anatomical location of the tumor, histological subtype, presence of lymph fluid and/or blood invasion, surgical treatment used, surgical limits found from histopathological evaluation, presence or

**Table 1 - Incidence of complaints per category.**

Types	Huvos criteria
Grade I	No effect from chemotherapy
Grade II	Partial response with necrosis of more than 50%
Grade III	Necrosis of more than 90%, with viable tumor present
Grade IV	No viable tumor

absence of metastasis over the course of the study, location of the metastasis and data of appearance, tumor staging at the time of diagnosis, presence or absence of local recurrence after the surgical treatment, and date of the patient's death, if this occurred during the period of the study.

The patients of the present study were treated based on the Brazilian protocols for chemotherapy treatment for osteosarcomas (both metastatic and non-metastatic). The statistical analyses were performed using the SPSS statistical software (version 9.0). Initially, the simple frequencies of all the variables studied were calculated. Subsequently, the accumulated survival probabilities were calculated by means of the Kaplan-Meier technique. All the variables were analyzed regarding their importance in relation to the prognosis, for event-free survival (percentage of patients who up to a given date, remained free from local and/or systemic manifestations) and for overall survival (percentage of patients who were still alive up to a given date). The Huvos grade (I, II, III or IV), tumor size (< 15 or > 15 cm), presence of metastasis at diagnosis and surgical treatment used (radical or salvage) were evaluated as variables to determine their prognostic value, in relation to survival, using the log-rank test.

## Results

The patients' ages ranged from 6 to 73 years, with a median of 15 years; 56.2% were aged less than or equal to 15 years and 43.7% were over 15 years of age. In relation to sex, 56.2% were men and 43.7% were women. The most prevalent color was black, accounting for 62.5% of the cases, followed by mixed (21.8%) and white (15.6%). Regarding the variable of occupation, 90.6% of the patients were students.

In relation to histological subtype, 71.8% were osteoblastic, 21.8% were chondroblastic and 6.2% were rich in giant cells.

The anatomical location of the tumor had the following distribution: 50% distal femur, 21.8% proximal tibia, 9.4% proximal femur and 9.4% proximal humerus. The distal tibia, proximal fibula and distal fibula presented one case each (percentage of 3.1%).

The tumor sizes were divided into less than or equal to 15 cm (56.2%) and greater than 15 cm (43.8%). In relation to the Huvos necrosis grade, 17 patients (53.1%) presented Huvos I, 8 (25%) had Huvos II, 7 (21.8%) had Huvos III and none had Huvos IV.

Regarding metastasis, 20 patients (62.5%) developed this at some time over the course of the disease. Of these, seven (21.8%) already had a metastasis at the time of the diagnosis.

Among the metastasis sites were the following: lung (100%), bone (25%), liver (5%) and others (15%).

In relation to the surgical treatment, 65.6% of the patients underwent radical surgery (amputation), while 34.4% were able to benefit from salvage surgery on the limb. Among the patients with larger-sized tumors (> 15 cm), 85.7% underwent radical surgery.

Two cases of local recurrence were observed (6.2%) and 62.5% of the patients died due to osteosarcoma.

The overall survival curve is shown in Fig. 1 and the two and four-year rates were 45.5% and 39%, respectively. The event-free survival curve is shown in Fig. 2 and the two and four-year rates were 39.8% and 19.9%, respectively.

The factor that significantly influenced overall survival in the univariate analysis was the surgical treatment ( $p = 0.0002$ ), as illustrated in Fig. 3. Radical surgical treatment was considered to be an adverse factor, in comparison with salvage treatment, since it presented a higher mortality rate. Other factors such as sex, age, tumor location, histological subtype, tumor size, metastasis at the time of diagnosis and surgical limits, did not reach statistically significant limits, for  $p$ -values < 0.05.

The factors that had an influence on the risk of an event (metastasis and/or local recurrence) in the univariate analysis were the following: surgical treatment ( $p = 0.0037$ ; Fig. 4), metastasis at the time of diagnosis ( $p = 0.0016$ ; Fig. 5) and tumor size ( $p = 0.0502$ ; Fig. 6). Radical surgical treatment was considered to be an adverse factor for events to appear (metastasis and/or local recurrence), in comparison with salvage treatment. Presence of metastasis at the time of diagnosis showed a greater rate of events (metastasis and/or local recurrence), in comparison with its absence, and tumor size greater than 15 cm along its major axis was considered to be an adverse factor for event-free survival. The other factors studied did not present significance levels for  $p$ -values < 0.05 (sex, age, tumor location, histological subtype and surgical limits).

The degrees of tumor necrosis following chemotherapy (Huvos) did not reach statistical significance levels for the two survival types: overall ( $p = 0.2903$ ) and event-free (0.5327), as shown in Figs. 7 and 8. Huvos grades were not considered to be prognostic factors for either overall or event-free survival.

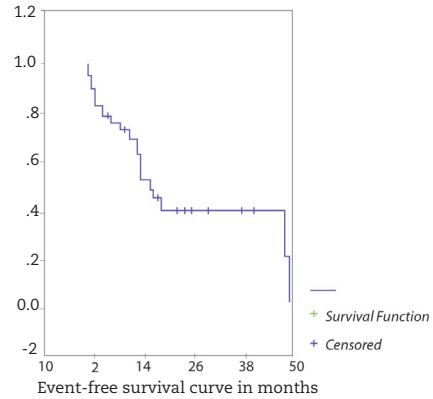


Fig. 2 - Event-free survival curve.

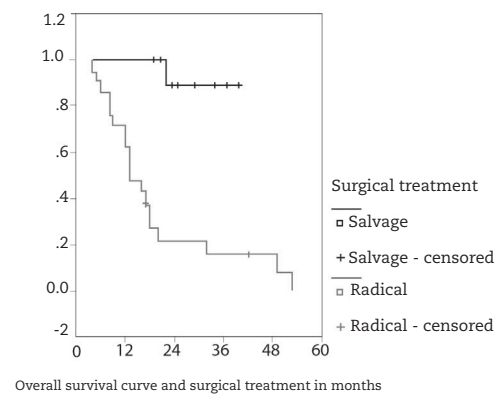


Fig. 3 - Overall survival curve according to surgical treatment.

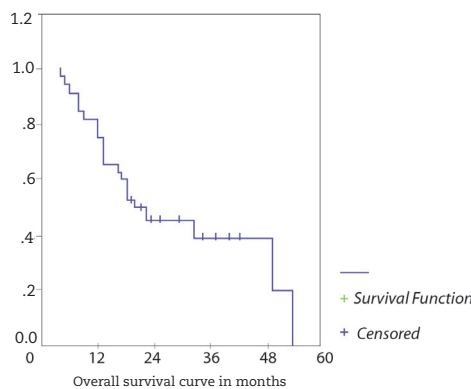


Fig. 1 - Overall survival curve.

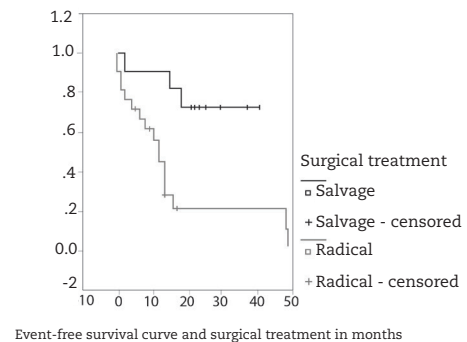
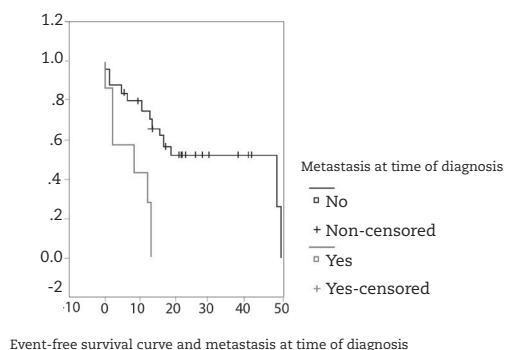
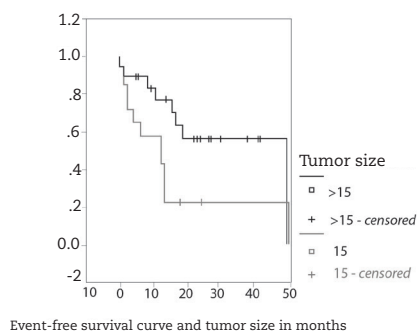


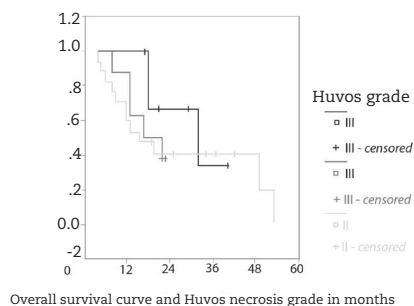
Fig. 4 - Event-free survival curve according to surgical treatment.



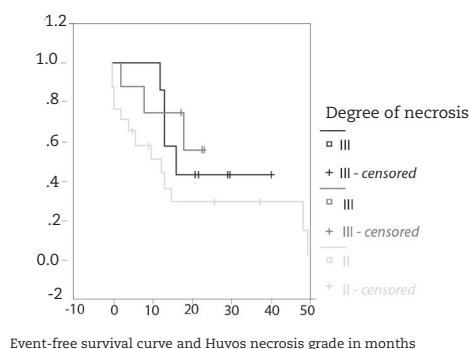
**Fig. 5 - Event-free survival curve according to metastasis at the time of diagnosis.**



**Fig. 6 - Event-free survival curve according to tumor size**



**Fig. 7 - Overall survival curve according to Huvos necrosis grade.**



**Fig. 8 - Event-free survival curve according to Huvos necrosis grade.**

## Discussion

The epidemiological and clinical characterization in the present study was concordant with the literature.<sup>1-3</sup>

The unfavorable prognostic factors were metastasis at the time of diagnosis, tumor size larger than 15 cm and radical surgical treatment. During the follow-up among these patients, metastases were identified in 62.5% of them, among whom 21.8% had already presented metastasis at the time of diagnosis. This percentage was, in turn, higher than values reported from other countries (15% to 20%), but it was within the range reported in Brazil, which has been as high as 38%.<sup>4</sup> In evaluating its significance for event-free survival, we found that it was related to worse prognosis. Rech et al.<sup>5</sup> also came to this conclusion, through demonstrating that less than 20% of these patients present five-year disease-free survival.<sup>5</sup> These patients probably demonstrated worse survival results because they had larger-sized tumors during the initial stages of the disease and because these cases were diagnosed at a late stage.<sup>4,5</sup>

In our study, 43.8% of the patients presented tumor sizes larger than 15 cm, and these patients had worse event-free survival results. This corroborates the data of Bispo Júnior,<sup>6</sup> in a doctoral thesis, and the findings of Castro et al.<sup>4</sup>

The patients' overall survival after two and four years was 45.5% and 39%, respectively. Other studies<sup>4,6</sup> have reported overall survival rates higher than those found in our study.

In evaluating event-free survival, we observed two and four-year rates of 39.8% and 19.9%, respectively. Similar studies have revealed higher rates.<sup>4-6</sup>

The type of surgical treatment (amputation or limb preservation) was chosen for the patients in accordance with the concomitant conditions presented. In other words, the decision was made according to the degree to which the disease had already evolved. Patients whose diagnoses were made at a late stage, with metastatic disease and/or large-volume tumors, almost always underwent radical surgery. In this manner, 65.6% of the patients underwent amputation.

Although the patients with an indication for salvage surgery on the limb had a greater chance of presenting local recurrence, depending on the surgical technique and the learning curve, they presented overall and event-free survival rates greater than those of patients who underwent amputation.<sup>7,8</sup> This was because the patients with voluminous tumors (with the implication of impossibility of limb preservation) presented worse prognosis even at the time of diagnosis.<sup>8,9</sup>

We evaluated the Huvos criteria but found that they did not present any significance in relation to the patients' prognoses. In a doctoral thesis, Bispo Júnior<sup>6</sup> reported that the stratification into groups I and II was unnecessary because of the similar behavior presented by these two groups, and also demonstrated that the prognostic behavior was similar between the groups.

Other criteria for prognostic evaluation and staging have already been proposed in the worldwide literature.<sup>10,11</sup> Magnetic resonance imaging may in the future be used for assessing the degree of tumor necrosis following neoadjuvant chemotherapy.

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## Conclusion

According to this study, presence of metastasis at the time of diagnosis and tumor size larger than 15 cm were factors for worse prognosis. On the other hand, the Huvos criteria did not reach statistical significance for the patients' prognoses.

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## Conflicts of interest

The authors declare that there was no conflict of interests in conducting this study.

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