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Research Article

Outcomes and Prognostic Factors for Non-metastatic Osteosarcoma of the Extremity

Manal A Zamzam[1], Emad Ali H Moussa[2], Ahmed El Ghoneimy[3], Magdy El Sherbiny[3], Mohamed S Zagloul[4], Hala Taha[5], Iman Goda[5], Sameera Ezzat[6] and Ranin Soliman[7]*

[1]*Department of Pediatric Oncology, Children's Cancer Hospital, Egypt*
[2]*Department of Clinical Oncology, Menufeya University, Egypt*
[3]*Department of Orthopedic Surgery, Children's Cancer Hospital, Egypt*
[4]*Department of Radiation Therapy, Children's Cancer Hospital, Egypt*
[5]*Department of Pathology, Children's Cancer Hospital, Egypt*
[6]*Department of Epidemiology and Preventive Medicine, Menoufia University, Egypt*
[7]*Health Economics and Outcomes, COO Office, Egypt*

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***Corresponding author**

Ranin Soliman, Health Economics and Outcomes, COO Office, Egypt,
Tel: (+02) 0100 326 3399;
Email: raninmagdi@hotmail.com

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Keywords Osteosarcoma; Prognostic factors; Pathological response; Outcome

Abstract

Purpose: To assess the impact of several patient-related and treatment-related prognostic factors in patients with localized osteosarcoma of the extremities treated at a single institution with the same chemotherapy protocol over a three-year period.

Patients and Methods: We reviewed 57 patients with localized osteosarcoma of the extremities treated at the Children's Cancer Hospital, Egypt, between July 2007 and December 2010, with a minimum follow-up of one year. Gender, age, tumor site and size, type of surgery, surgical margins, serum level of alkaline phosphatase and histologic response to preoperative treatment were retrospectively evaluated.

Results: With a median follow-up of 23 months, the three-year Event-Free Survival (EFS) and overall survival rates were 70.5% and 77.8 %, respectively. In univariate analysis, EFS was significantly related to the age of patients, serum level of alkaline phosphatase, and tumor volume but not to histologic subtype or histologic response to preoperative treatment. In multivariate analysis, only gender and serum alkaline phosphatase were statistically significant. Local and systemic recurrences occurred in 12 patients (21%) (10 developed pulmonary metastasis, one patient developed both bone and pulmonary metastases, and one patient had local recurrence). Median time to recurrence was 9.2 months, and recurrence correlated with the histologic response to preoperative treatment, tumor volume and serum alkaline phosphatase.

Conclusion: The three- year EFS and overall survival were 70.5% and 77.8%, respectively. Age, tumor volume, and the serum level of alkaline phosphatase significantly influenced EFS. These factors should be considered when deciding on risk-adapted treatments for osteosarcoma patients. However, gender and serum alkaline phosphatase were the only significant variables in the multivariate analysis.

Introduction

Until the 1970s, osteosarcoma had a very poor prognosis, but major progress in outcomes followed the introduction of adjuvant chemotherapy, with disease-free survival rates increasing from below 20% with surgery alone to more than 40% with adjuvant chemotherapy [1-3]. Nevertheless, recurrent disease still occurs in approximately 30%-40% of patients and more than 70% of these patients die despite second-line treatment.

Generally accepted prognostic factors related to surviving osteosarcoma are the presence of metastases at the time of diagnosis, the histologic response to neo-adjuvant chemotherapy, and adequate surgical margins. The prognostic relevance of other factors, such as tumor site and size, histologic subtype, elevated Alkaline Phosphatase (ALP), and age remain controversial [4]. Identification of the risk factors for recurrence would be of major importance for developing new and risk-adapted treatment strategies. However, they may be difficult to confirm because studies with homogeneous series from a single institution are usually too small to have reliable statistical significance [5-7]. In contrast, multi-institutional studies have two main limitations: a lack of unified standardized methods to evaluate prognostic factors and diversity of background experience in surgery for bone sarcomas, which yields unreliable results from different centers in multi-centered studies [8-10].

This study aims to assess the impact of several patient-related and treatment-related prognostic factors in patients with localized osteosarcoma of the extremities treated at a single institution with the same chemotherapy protocol over a three-year period.

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Patients and Methods

Subjects

Patients were considered eligible when fulfilling the following criteria: typical radiographic and histologic features of primary high-grade osteosarcoma, tumor located in the extremity, no previous history of cancer, no prior surgery or chemotherapy, age under 18 years, no coexisting disease contraindicating chemotherapy, and no evidence of metastases at diagnosis.

All eligible patients received MAP chemotherapy (high-dose methotrexate, doxorubicin and cisplatin) after providing informed consent. The diagnosis of osteosarcoma, established by clinical and radiologic findings, was always confirmed with tumor tissue from an open or Computed Tomography (CT)-guided needle biopsy. Tumor volume was evaluated according to the method described by Gobel et al. [11].

Patient Evaluation

A complete medical history and physical examination were obtained for all patients. Standard laboratory tests, including complete blood counts, liver and kidney function tests, electrolytes and serum ALP were obtained at baseline and at regular intervals until at least four years after the completion of therapy. The initial staging workup included plain radiography and Magnetic Resonance Imaging (MRI) of the primary tumor, technetium-99 methyldiphosphonate bone scanning and CT of the chest. These studies were repeated before definitive surgery (week 10), at week 20 and at the completion of therapy. For the first year, patients were monitored by CT- chest and radiography of the primary tumor site every two months and by bone scans every six months. Subsequently, patients underwent CT-chest every three to six months and radiography of the primary tumor site every six to 12 months for at least four years after the completion of therapy. Patients underwent echocardiography, audiometry and glomerular filtration rate assessment before starting treatment and serially thereafter.

Chemotherapy

The protocol consisted in 18 cycles of standard MAP chemotherapy over 29 weeks as shown in figure 1 (Appendix). Pre-operatively, chemotherapy comprised two cycles of cisplatin (60 mg/m2 days 1 and 2 over six-hour continuous infusion) and doxorubicin (37.5 mg/m^2 days 1 and 2 over four-hour continuous infusion) given at weeks 1 and 6, and four cycles of high-dose Methotrexate (MTX) at weeks 4, 5, 9 and 10 in a four-hour infusion at a dose of 12 g/m^2 with leucovorin rescue (15 mg every six hours, for 11 cycles, guided by MTX serum level). Hydration during and after MTX infusion followed the guidelines suggested by Rosen et al [12]. Patients underwent surgery at week 11. Postoperative chemotherapy was given as eight cycles of high-dose MTX as described above, two cycles of cisplatin/doxorubicin and two cycles of doxorubicin as shown in figure 1.

Evaluation of the Response

Clinical and radiologic responses were assessed at week 10. Achieving a response was defined as either decreased tumor volume (≥ 50% reduction in the product of the three perpendicular tumor diameters) or stable tumor volume (< 50% reduction or < 25% increase in the product of the three perpendicular tumor diameters) on MRI. Patients with significantly increased tumor size (≥ 25% increase in the product of the three perpendicular tumor diameters) or those with new lesions were considered to have progressive disease.

Surgery and Pathologic Evaluation of the Response to Chemotherapy

The type of surgery (amputation, rotationplasty, or limb salvage), as well as the type of reconstruction after resection of load-bearing bones, was chosen depending on the location and extent of the tumor, neurovascular structure involvement, skeletal maturity, desired lifestyle, and presence of complicating factors, such as displaced pathologic fractures or infected biopsy sites. Conservative surgery was considered mandatory if the preoperative staging assured the possibility of achieving wide surgical margins, preserving a limb that could at least be partially functional after reconstruction. After surgery, the surgeons and the pathologists together reviewed the macroscopic specimens to determine surgical margins according to the Enneking criteria [13]. Surgical margins were categorized as radical or wide (adequate), or marginal or contaminated (inadequate). The response to preoperative chemotherapy was evaluated following the criteria reported by Picci et al and graded as 'good' (≥ 90% tumor necrosis) or 'poor' (<90%tumor necrosis) [14].

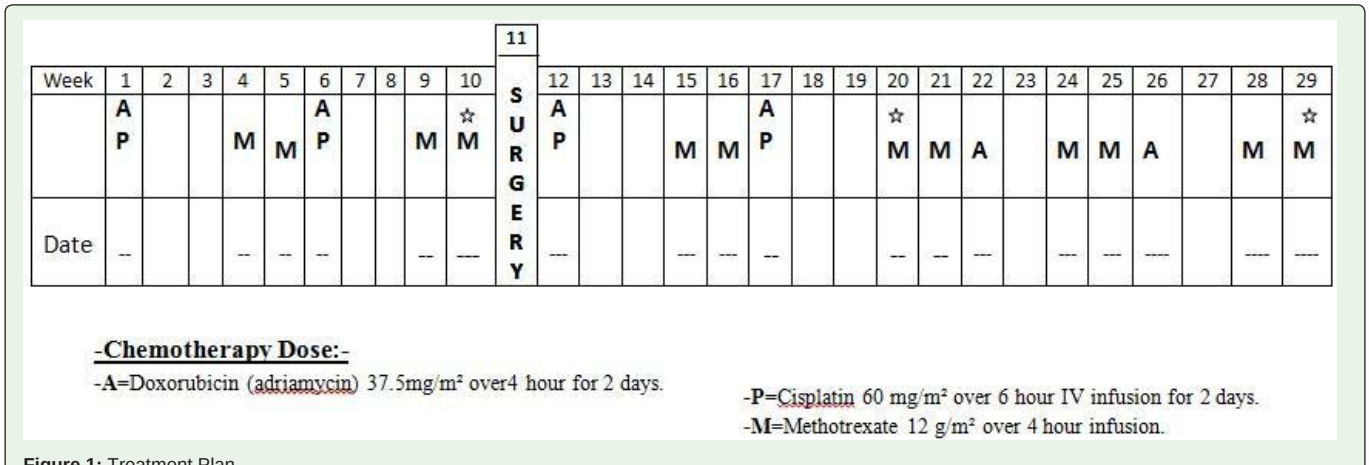

Figure 1: Treatment Plan.

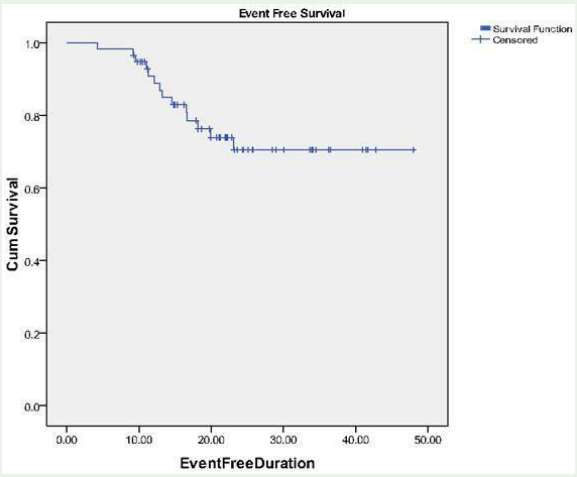

Figure 2: Three year overall survival, OS = 77.8%.

Statistical Analysis

Overall Survival (OS) was calculated from the first day of diagnosis to death from any cause or to the last follow-up visit. Event-Free Survival (EFS) was calculated from the date of diagnosis to the date of recurrence or death owing to toxicity or other causes or to the last follow-up visit. OS and EFS curves were plotted according to the Kaplan Meier method.

The following variables were evaluated: gender, age, tumor volume, tumor site, histologic subtype, type of surgery, and histologic response to preoperative chemotherapy using the log- rank test for univariate analysis. Factors found to influence EFS by univariate analysis were analyzed using Cox's proportional hazard regression model [15]. Significance was set at $p < 0.05$. Analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

Between July 2007 and December 2010, 57 eligible patients were retrospectively studied at the Children's Cancer Hospital, Egypt. The distribution of demographics, tumor-related variables and treatment related variables are listed in table 1. The male: female ratio was 1.2:1 and the median age at diagnosis was 13 years (range four to 18 years). The most common primary tumor site was the femur (n=36, 63%).

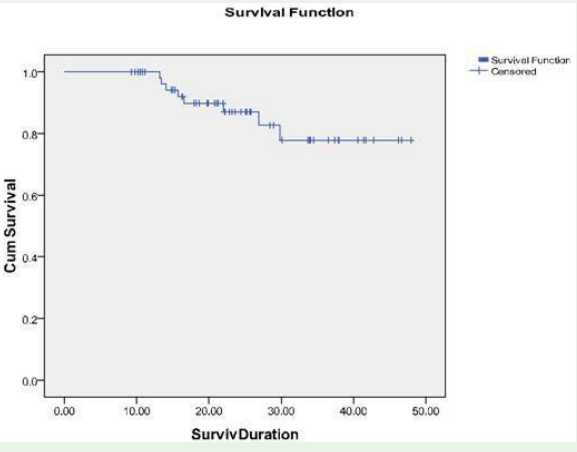

Figure 3: Three-year event-free survival, EFS = 70.5%.

Survival

At follow-up (median 23 months, range 12 to 54 months), 43 patients (75.5%) remained continuously event-free, 6 (10.5%) had recurrent disease, two (3.5%) had died from chemotherapy toxicity and 6 (10.5%) had died from disease progression. The three-year EFS were 70.5% and the OS was 77.8% (Figures 2 and 3) 12 patients (21%) developed recurrence: ten had isolated lung metastases, one had lung and bone metastases and one had isolated local recurrence. The

Table 1: Patient characteristics and three-year Event-Free Survival (EFS).

Variable	Number of patients(%)	3-year EFS (95% CI)	*p*-value
Gender			
Male	31 (54%)	78% (64.9-95)	
Female	26 (46%)	61% (43-87.6)	0.351
Age			
≤ 13 years	27 (47%)	80.6% (64.3-100)	0.036*
> 13 years	30 (53%)	60.1% (43.4-83)	
Site			
Femur	36 (63%)	71% (56.6-89.3)	
Tibia	15 (26%)	50% (25-100)	
Others	6 (11%)	100% (NA)	0.229
Histology			
Osteoblastic	23 (40%)	79% (63-99)	
Chondroblastic	10 (18%)	76% (52-100)	
Fibroblastic	7 (12%)	100% (NA)	
Telangiectatic	5 (9%)	60% (29.3-100)	0.194
Unspecified	12 (21%)	47% (25.7-88.2)	
Serum ALP^			
Normal	36 (80%)	86.9% (73.8-100)	< 0.001*
High	9 (20%)	33.9% (11.8-96.9)	
Tumor Volume			
≤ 150 cc	23 (40.3%)	80.5% (62.1-100)	0.017*
> 150 cc	34 (59.6%)	63.9% (48-83.7)	
Histologic Response			
Good	21 (37%)	77% (59.4-99.8)	0.39
Poor	36 (64%)	67.4% (52.3-87)	
Surgery			
Limb Salvage	47 (83%)	68.3% (54.6-85)	0.789
Amputation	7 (12%)	71.4% (44.7-100)	
Rotationplasty	3 (5%)	100% (NA)	

ALP: Alkaline Phosphatase

^Serum ALP was calculated for 45 patients.

*Statistically significant

NA: Not Applicable due to absence of events

median time to recurrence was 9.2 months (range 2.3 to 19 months); eight of these patients experienced recurrence in the first year and four relapsed later. The median time to recurrence was significantly longer for patients with normal values of serum ALP compared to those with high values (14 months *vs* 8 months, p = 0.034) and in good responders in comparison to poor responders (14.3 months vs. 8.2 months, p = 0.166). Nine of the relapsed patients had high tumor volume (>150 cc) and five had elevated serum ALP (p = 0.09).

Univariate analysis

The parameters and their prognostic significance for EFS are listed in table 1. No significant differences were seen according to the site of primary tumor, histology, gender, type of surgery, or histologic response to primary chemotherapy, where as serum alkaline phosphatase, tumor volume and age significantly influenced EFS.

Age: Prognosis was significantly better in younger patients. In those younger than the median age at diagnosis of 13 years, three-year EFS was 80.6%; in older patients it was 60.1% (p = 0.036) (Figure 4).

Gender: Gender was not a significant factor in our population: three-year EFS was 78% for males and 61% for females (p = 0.351).

Primary Tumor Site: The most common primary site was the femur, in 63% of the patients (three-year EFS, 71%), followed by the tibia in 26% (three-year EFS, 50%) and other sites in 11% (three-year EFS, 100%) (p = 0.229).

Histology: The osteoblastic subtype was found in 40% of our patients.

The three-year EFS values were osteoblastic 79%, chondroblastic 76%, fibroblastic 100%, telangiectatic 60% and non-specified 47% (p = 0.194). This suggests a lower risk of relapse for the fibroblastic subtype, but the number of patients with fibroblastic tumors was quite small (n = 7); further analysis is needed with a greater number of cases.

Tumor volume: The median tumor size was 187.2 cc (range 14.7-1135 cc). To compare our data with those reported by the COSS group [16] and the Rizzoli Institute [17], we applied a cut-off of 150 cc in our univariate analysis; 23 patients had a tumor volume < 150 cc (three-year EFS, 80.5%), and 34 had a tumor volume > 150 cc (three-year EFS, 63.9%) (p = 0.017) (Figure 5). The mean tumor volume of patients who had tumor recurrence was 393.16 (± 372) cc, compared with 258.4 (±174) cc in patients who remained continuously free of disease. 75% of patients who relapsed had tumor volume > 150 cc compared to 55% in those who remained continuously disease free (p = 0.023).

Histologic response: A good histologic response was reported in 37% of our patients. In this group, the three-year EFS was 77%, compared to 67.4% in patients with a poor histologic response (p = 0.390). No statistically significant differences were found in histologic response either for the patients with tumor volume < 150 cc (three-year EFS values for good and poor responders were 87% and 78%, respectively; p = 0.988), or for those with tumor volume > 150 cc (70% and 60%, respectively; p = 0.311). Elevated serum ALP was observed in 77% of patients with poor histologic response compared to 22% of patients with good histologic response (p = 0.449).

Surgery: The majority of patients (83%) underwent conservative surgery; only 12% patients had amputation and 5% underwent rotationplasty. The three-year EFS was 68.3% in patients who underwent limb salvage surgery, and 71.4% and 100% for amputation and rotationplasty, respectively (p = 0.789). The frequency distribution of gender, site, histologic subtype and serum level ALP, and the response to neoadjuvant chemotherapy, were not statistically significant in relation to type of surgery. However, the rate of limb salvage was significantly correlated with the tumor volume: 95% for smaller tumors versus 73% for larger tumors (p = 0.031). The surgical margins were adequate in 55 patients and inadequate in two patients, both treated with limb salvage; one of these received post-operative radiation therapy, whereas the other refused amputation or radiation and died of disease progression.

Serum ALP: Serum ALP was recorded in 45 of the patients, of whom 36 had normal levels and nine had elevated levels. ALP was predictive of EFS and a significantly better prognosis was found in patients with normal values than in patients with elevated values (3-year EFS 86.9% and 33.9%, respectively; p < 0.001) (Figure 6).

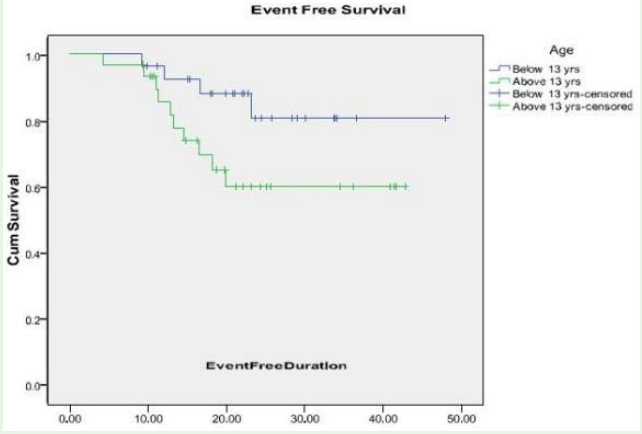

Figure 4: Three-year event-free survival comparing those aged above and below 13 years.
Note: ≤ 13 years= 80.6%, > 13 years = 60.1%, *p*-value = 0.036.

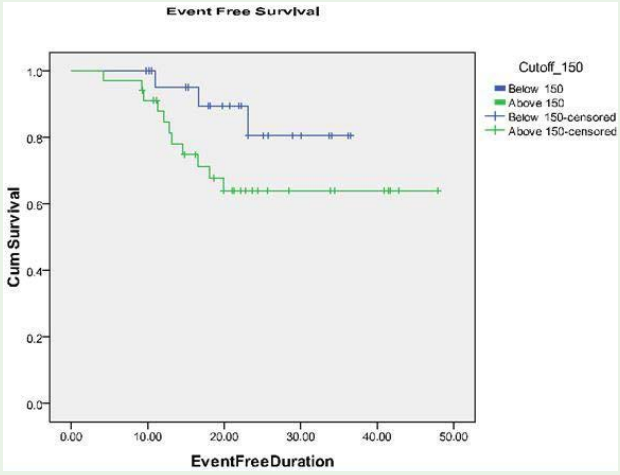

Figure 5: Three-year event-free survival comparing those with tumor volume above and below 150 cc.
Note: < 150 cc= 80.5%, > 150 cc = 63.9%, *p*-value = 0.017.

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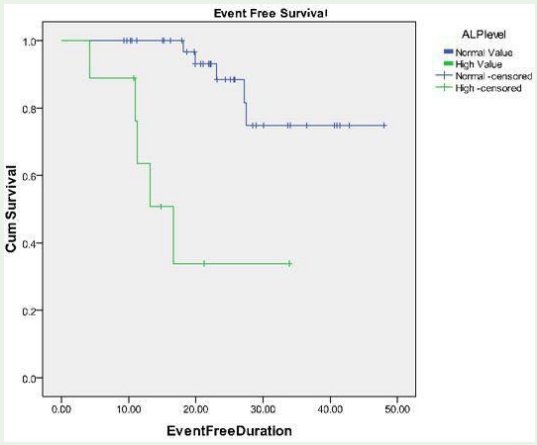

Figure 6: Three-year event-free survival comparing those with normal and high Serum Alkaline Phosphatase (ALP).
Note: Normal ALP= 86.9%, High ALP = 33.9%, *p*-value < 0.001.

Table 2: Multivariate analysis, Model 1.

Variable	RR	95% CI	*p*-value
Gender			
Male	1	1.73-98.8	0.013*
Female	13.078		
Age			
≤ 13 years	1	0.954-1.572	0.113
> 13 years	1.224		
SerumALP^			
Normal	1	4.53 -235.2	0.001*
High	32.657		

ALP: Alkaline Phosphatase

^ Serum ALP was calculated for 45 patients.

*Statistically significant

Table 3: Multivariate analysis, Model 2.

Variable	RR	95% CI	*p*-value
Gender			
Male	1	1.61-99.39	0.016*
Female	12.65		
Age			
≤ 13 years	1	0.90-1.55	0.026*
> 13 years	1.189		
Serum ALP level^			
Normal	1	4.75- 373.9	0.001*
High	42.16		
Tumor Volume			
< 150 cc	1	0.19-6.32	0.904
> 150 cc	1.113		
Histologic Response			
Good	1	0.33-1.75	0.473
Poor	1.89		

ALP: Alkaline Phosphatase

^Serum ALP was calculated for 45 patients.

* Statistically significant

Multivariate analysis

Using Cox's proportional hazard regression model, a first analysis was performed to investigate the prognostic significance of the factors predictive of EFS, including age, gender, and serum ALP. Serum ALP retained its statistical significance, age lost statistical significance, and gender showed statistical importance (Table 2).

Another Cox regression model was developed with the following covariates: age, gender, serum ALP, tumor volume and histologic response to chemotherapy (Table 3). The only two variables that remained statistically significant in the two models were gender and serum ALP.

Discussion

About 50% of patients with osteosarcoma of the extremity can be cured with a relatively non- aggressive regimen of chemotherapy [18-20]. Conversely, 40% of patients still die of the tumor, even if it is treated according to an extremely aggressive protocol [10,18,21,22]. A number of prognostic factors (such as: tumor site, size, subtype, gender, age, high ALP, high lactate dehydrogenase values, multidrug resistance and genetic variations), were noted to affect outcomes, but often with contradictory results owing to a lack of uniformity in patient analyses and methods [23].

A review article concluded that the most important prognostic variable for patients with osteosarcoma of the extremity was tumor necrosis following preoperative chemotherapy, whereas there was no consensus on the prognostic significance of gender, age, tumor location, or tumor size. In that report, no mention was made of the role of biochemical markers, such as serum ALP and lactate dehydrogenase, or of the role of histologic subtype [24].

The present study included a uniform group of 57 patients with non-metastatic osteosarcoma of the extremity, all treated at the Children's Cancer Hospital in Egypt, with the same chemotherapy protocol. Patient-related variables (gender, age, primary site, tumor volume, serum alkaline phosphatase, histologic subtype) and treatment-related variables (type of surgery and histologic response to neo-adjuvant chemotherapy) were analyzed. Univariate analysis identified tumor volume, age and serum ALP as predictive factors of patients' EFS. Multivariate analysis showed a significant adverse effect on prognosis for age greater than 13 years, high serum ALP and female gender.

A Cooperative Osteosarcoma Study (COSS) study of 128 patients with osteosarcoma of the extremity showed that the best way to evaluate the initial tumor volume was based on a three- dimensional measure, and that a cutoff point set at 150 cc distinguished groups with significantly different prognoses [16]. Adopting the same method and cut-off value of 150 cc in our study, we found a significantly poorer outcome for patients with a tumor volume greater than this cutoff than for patients with smaller tumors.

Our analysis involved a population ranging between 4 and 18 years of age, with a median value of 13 years. A significantly poorer prognosis was found in the subgroup of patients aged more than 13 years than in those of younger age. Contrary to our results, investigators at the Sloan- Kettering Cancer Center found a significantly poorer prognosis in younger patients with a cut-off set at 12 years of age [7]. Two further studies, conducted by the French Society of Pediatric Oncology (SFOP) [25] and Rizzoli Institute [23], found a poorer outcome in younger patients (12 years or younger). In these three studies, the population of patients included pediatric and adult patients up to 40 years of age. Conversely, two studies by MD-Anderson [10] and COG [26] included only pediatric patients and failed to find a different prognosis between patients grouped according to a cut-off age of 12 years. The importance of age as a

prognostic factor in osteosarcoma remains debatable; however, other studies concerning pediatric and adult tumors [27-29] have reported a different and more aggressive behavior of the tumor in children and young patients.

The results of our analysis showed that there was a lower risk of relapse for the fibroblastic and chondroblastic subtypes. However, in our study the number of patients with fibroblastic and chondroblastic tumors was relatively small (17 cases) and so these data need further analysis with a greater number of cases. These data are similar to those reported by Hudson et al. [26], who found a better prognosis for patients with the chondroblastic subtype and are contrary to those reported by Petrilh et al. [30] who reported a significantly worse prognosis for the non- osteoblastic subtypes. In a large study of an inhomogeneous group of patients with a diagnosis of osteosarcoma, no differences were found according to the histologic subtype [31].

The histologic response to the primary chemotherapy is considered an important factor influencing outcome. In several reports [7,8,10,26,32,33,34], a poor chemotherapy-induced tumor necrosis was associated with poor prognosis, suggesting that, in osteosarcoma, primary tumor and micrometastases can share the same chemosensitivity. In our analysis, the histologic response was not statistically significant in both univariate and multivariate analyses. This may be attributed to the small sample size in our study; more patients with longer follow-up duration are needed to reach significant results.

It is interesting to note the relationship between histologic response and tumor volume observed in our series. The outcome was not influenced by chemotherapy-induced necrosis; for patients with small tumor volume, the three-year EFS for good responders was 87%, whereas it was 78% for those with a poor histologic response. The difference was also not statistically significant for the group of patients with tumor volume >150 cc. The COSS study [16] reported the prognosis

of patients according to tumor volume and histologic response, finding an excellent prognosis for patients with a small tumor and good histologic response (five-year MFS 95%) and a very poor outcome for patients with a large tumor and poor histologic response (five-year MFS 25%). Serum ALP was found to be of significant importance in both univariate and multivariate analyses. In the report of the Memorial Sloan Kettering experience [7], serum alkaline phosphatase was a significant predictive variable of Disease-free Survival after multivariate analysis.

As reported in other studies performed in Italy [17], France [25], Germany [8] and the United States of America [7], gender was not found to be of significant importance in our univariate analysis. By contrast, a significant advantage for the female gender was described in studies performed in Brazil [30] and in Scandinavian countries [34].

Conclusion

Our data confirmed the prognostic significance of tumor volume, age and serum ALP, which influenced event-free survival in patients with non-metastatic osteosarcoma of the extremity treated with neo-adjuvant chemotherapy. On the basis of these results, we believe that future clinical trials for non-metastatic osteosarcoma of the extremities should identify appropriate therapeutic strategies for different risk groups based on prognostic factors in order to provide the best care to all patients and to reduce treatment-associated morbidity.

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