original report

Clinical Prognostic Factors and Outcome in Pediatric Osteosarcoma: Effect of Delay in Local Control and Degree of Necrosis in a Multidisciplinary Setting in Lebanon

Bilal Abou Ali, MD[1]; Maryssa Salman, MD[1]; Khaled M. Ghanem, MD[1]; Fouad Boulos, MD[1]; Rachid Haidar, MD[1]; Said Saghieh, MD[1]; Samir Akel, MD[1]; Samar A. Muwakkit, MD[1]; Hassan El-Solh, MD[1]; Raya Saab, MD[1]; Hani Tamim, PhD[1]; and Miguel R. Abboud, MD[1]

abstract

PURPOSE Outcomes in pediatric osteosarcoma have dramatically improved over the past few decades, with overall survival rates of 70% and 30% for patients with localized and metastatic disease, respectively.

PATIENTS AND METHODS We retrospectively reviewed clinical characteristics and outcomes of 38 patients treated between 2001 and 2012 at a single institution in Lebanon. All patients received a uniform three-drug chemotherapy regimen consisting of cisplatin, doxorubicin, and methotrexate. Ifosfamide and etoposide were added to the adjuvant treatment regimen in case of metastatic disease and/or poor degree of tumor necrosis (< 90%).

RESULTS After a median follow-up of 61 months (range, 8 to 142 months), patients with localized disease had 5-year overall and event-free survival rates of approximately 81% and 68%, respectively, whereas for metastatic disease, they were approximately 42%. The most common primary site was the long bones around the knee (n = 34; 89.5%). Six patients (15.8%) had metastatic disease to lungs, and three (7.9%) had synchronous multifocal bone disease with lung metastases. Adverse prognostic factors included nonlower extremity sites, metastasis, poor degree of necrosis, and delay of more than 4 weeks in local control. In bivariable analysis, only degree of necrosis was a prognostic predictor for survival and disease recurrence.

CONCLUSION Treatment of pediatric osteosarcoma in a multidisciplinary cancer center in Lebanon resulted in survival similar to that in developed countries. Delay in local control was associated with worse outcome. The only statistically significant inferior outcome predictor was poor degree of necrosis at the time of local control.

INTRODUCTION

Osteosarcoma is the most common malignant bone tumor in children and adolescents. Survival for these patients is poor with use of surgery and/or radiotherapy. The introduction of multiagent chemotherapy has dramatically improved outcomes over the past few decades, with overall survival (OS) rates of 70% for patients with localized disease and 30% for those with metastatic disease in developed countries.[1-3]

The current management strategy for pediatric osteosarcoma is on the basis of a combined approach consisting of neoadjuvant and adjuvant chemotherapy, together with surgical resection. Cisplatin, doxorubicin, and methotrexate constitute the backbone of chemotherapeutic regimens used for localized disease[4]; however, addition of an ifosfamide-containing regimen to these agents is tolerable and effective in the treatment of patients with osteosarcoma who present with lung metastases.[5] The strong correlation found between histologic response of the primary tumor and metastases supports the strategy of tailoring postoperative chemotherapy on the basis of histologic response of the primary tumor to preoperative chemotherapy.[6] However, there is no current evidence supporting the benefit of additional available chemotherapeutic agents regarding outcomes of patients with poor necrosis at surgical resection.

Multiple prognostic factors have been shown across several studies to influence outcome in pediatric osteosarcoma, including site and size of the primary tumor, presence of clinically detectable metastatic disease, surgical resectability and remission state, and response to chemotherapy as assessed by degree of tumor necrosis.[7,8]

The purpose of this study was to analyze prognostic factors and treatment outcome in pediatric osteosarcoma at a multidisciplinary center in Lebanon, because these have not been adequately described to date in developing countries.

Author affiliations and support information (if applicable) appear at the end of this article.

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PATIENTS AND METHODS

We conducted a retrospective review of the medical records of pediatric patients (age < 18 years) diagnosed with osteosarcoma at the American University of Beirut Medical Center (AUBMC) between August 2001 and May 2012. The following information was collected: age, sex, tumor site, pathology, stage of disease, treatment, degree of tumor necrosis, clinical course, complications of therapy, and outcome. This study was approved by the American University of Beirut Institutional Review Board. Histologic diagnosis was performed at the AUBMC for all patients. Site and local extent of tumor were assessed by either computed tomography or magnetic resonance imaging, depending on disease site. Initial metastatic workup for all patients included computed tomography scan of the chest and bone scan.

All patients with localized disease received uniform chemotherapy as per the POG (Pediatric Oncology Group) 9351 protocol (regimen A), which included two courses of neoadjuvant induction chemotherapy and four courses of adjuvant maintenance chemotherapy, administered every 5 weeks. Each course consisted of one cycle of a combination of cisplatin and doxorubicin (60 mg/m^2 of cisplatin per day via continuous intravenous [IV] infusion over 4 hours on days 1 and 2 and 25 mg/m^2 of doxorubicin per day via IV infusion over 1 hour on days 1, 2, and 3), followed by two cycles of methotrexate (12 g/m^2 per dose via continuous IV infusion over 4 hours). Leucovorin rescue was used after methotrexate infusion. Total treatment duration was 31 weeks.

Four cycles of ifosfamide (2.8 g/m^2 per day via IV infusion over 1 hour on days 1 to 5) and etoposide (100 mg/m^2 per day via IV infusion over 1 hour on days 1 to 5) were incorporated into the adjuvant treatment regimen for patients who had a poor degree of tumor necrosis (< 90%) and/or metastatic disease. Total treatment duration in this group of patients was 36 weeks. Mesna was used for uroprotection with ifosfamide infusion. Definitive local control using surgical resection was attempted at week 10 of treatment. Incidence and patterns of toxicity were reviewed retrospectively and graded according to Common Terminology Criteria for Adverse Events (version 4.0).

OS was defined as the time interval from date of diagnosis either to death resulting from any cause or last follow-up. Event-free survival (EFS) was defined as time to disease progression, relapse, or death resulting from any cause, whichever occurred first, or to date of last follow-up for patients without events. Survival analysis was carried out, and Kaplan-Meier curves were constructed for the different groups. In bivariable analysis for OS and EFS, we excluded patients who had upfront local control (n = 2) and patients with multifocal bone disease who did not achieve surgical local control during therapy (n = 3). Statistical significance was considered at the .05 level. SPSS software (version 23) was used for data management and analyses.

RESULTS

Thirty-eight pediatric patients with newly diagnosed osteosarcoma at the AUBMC between August 2001 and May 2012 were identified. Mean age at diagnosis was 12.9 years (range, 1 to 18 years), with 10 patients (26.3%) age younger than 10 years. Male-to-female ratio was 1:1. Six patients (15.8%) had metastatic disease to the lungs, and three patients (7.9%) had synchronous multifocal bone disease with lung metastases. The most commonly affected primary site was the long bones around the knee (n = 34; 89.5%). Other tumor sites included the humerus (n = 2; 5%), vertebral body (n = 1; 2.6%), and calcaneus (n = 1; 2.6%). At the time of this report, median follow-up time was 61 months (range, 8 to 142 months; Table 1).

Local control using surgical resection was planned for week 10, after two courses of induction chemotherapy; surgery was performed in 33 patients (86.8%). Type of surgery depended on site and extent of disease, feasibility of surgical resection, and patient age, and it included limb salvage with insertion of prosthesis in 25 patients, tumor resection with bone graft in five patients, amputation in two patients, and tumor resection with hip rotation plasty in one patient.

TABLE 1. Patient Demographic and Clinical Characteristics (N = 38)

Characteristic	No. (%)
Sex	
Male	19 (50)
Female	19 (50)
Age, years	
Mean	12.9
SD	± 3.8
< 10	10 (26.3)
≥ 10	28 (73.7)
Tumor site	
Lower extremity	34 (89.5)
Other*	4 (10.5)
Metastasis	
Localized	29 (76.3)
Lungs	6 (15.8)
Multifocal	3 (7.9)
Degree of necrosis, %	
< 90	16 (48.5)
≥ 90	17 (51.5)
Delay of surgery, weeks	
≤ 14	11 (33.3)
> 14	22 (66.7)

Abbreviation: SD, standard deviation.

*Humerus in two patients, vertebral body in one, and calcaneus in one.

Upfront surgical resection was performed in two patients; the three patients with synchronous multifocal bone disease did not undergo surgical resection. Thoracotomy was performed in six patients who presented with metastatic lung disease.

Overall, 22 (66.7%) of 33 patients had a delay in local control by more than 4 weeks (beyond week 14). Range of the delay was 5 to 20 weeks, corresponding to weeks 15 to 30 of treatment, with a mean delay of 7 weeks, corresponding to week 17 of treatment. Reasons for delay in local control included delay in procurement of limb prosthesis, neutropenia, febrile illness, and/or presence of mucositis. Therapy schedule for patients with delayed local control was adjusted; however, total duration of treatment and cumulative doses of chemotherapeutic agents were not different between patients with delayed local control and those who achieved local control on time.

Twelve patients (31.5%) had a poor degree of necrosis (< 90%) at the time of local control. A total of 21 patients (55.3%) had received ifosfamide and etoposide as part of the adjuvant treatment regimen, either because of poor necrosis at local control or metastatic disease.

Five-year OS and EFS rates for all patients were approximately 74% (95% CI, 55% to 84%) and 62% (95% CI, 46% to 76%), respectively (Fig 1). Relapse occurred in 14 patients (36.8%), at a median time of 22 months from diagnosis (range, 4 to 91 months). Tumor recurrence was local in three, distant in eight, and combined in three patients. Five patients (13%) experienced disease progression while receiving treatment. At the end of study, 27 patients (71%) were alive, with 23 patients (60.5%) in first complete remission, three (8%) in second or later complete remission, and one (2.6%) alive with disease.

Patients with localized disease had 5-year OS and EFS rates of approximately 81% (95% CI, 63% to 92%) and 68% (95% CI, 49% to 82%); those with metastatic disease had OS and EFS rates of approximately 42% (95% CI, 14% to 72%; Figs 2A and 2B). Regarding tumor site, patients with lower-extremity tumors had 5-year OS and EFS rates of approximately 75% (95% CI, 57% to 87%) and 62% (95% CI, 46% to 78%), respectively; those with non–lower-extremity tumors rates of approximately 50% (95% CI, 6% to 84%). Patients with a good degree of tumor necrosis (≥ 90%) had 5-year OS and EFS rates of approximately 88% (95% CI, 61% to 97%); patients who had a poor degree of tumor necrosis (< 90%) had rates of approximately 68% (95% CI, 40% to 86%) and 42% (95% CI, 20% to 66%), respectively (Figs 3A and 3B). Patients who had no delay in local control (at ≤ 14 weeks) had 5-year OS and EFS rates of approximately 80% (95% CI, 45% to 95%); patients who had a delay of more than 4 weeks in local control had rates of approximately 78% (95% CI, 53% to 90%) and 58% (95% CI, 36% to 76%), respectively (Figs 4A and 4B).

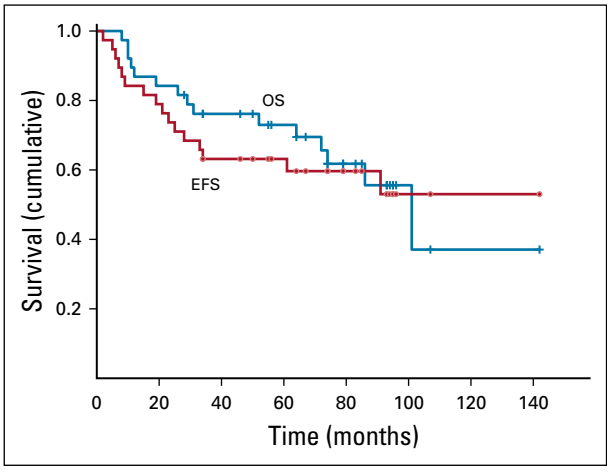

FIG 1. Kaplan-Meier analysis of overall survival (OS) and event-free survival (EFS) for all patients.

The prognostic importance of age, sex, metastatic disease, tumor site, delay in local control, and degree of tumor necrosis with regard to OS and EFS was analyzed. In bivariable analysis, only degree of tumor necrosis constituted an adverse prognostic factor for EFS ($P = .001$) and OS ($P = .002$; Table 2).

Hematologic toxicity was frequent. We recorded 77 episodes of febrile neutropenia occurring in a total of 29 patients, all managed by prompt inpatient IV antibiotics. Three episodes of septic shock occurred in three patients, and one episode of septicemia occurred in one patient, all of which responded to appropriate management. Other encountered toxicities were neutropenia without fever in 24 patients (58 episodes) and non-neutropenic fever in 27 patients (63 episodes). Two patients had secondary acute myeloid leukemia and myelodysplastic syndrome at 19 and 61 months from initial diagnosis, respectively, and both died as a result of secondary disease. Both patients received etoposide during therapy for poor degree of necrosis at local control. There was no life-threatening mucositis, and no deaths resulting from toxicity occurred during treatment. In addition, no instances of deafness, heart failure, long-term renal complications, or Fanconi-like syndrome were recorded.

DISCUSSION

A significant decline in mortality of patients with osteosarcoma has been observed over the past few decades. Five-year survival rate increased over the period between 1975 and 2010 from 40% to 76% in children younger than age 15 years and from 56% to approximately 66% in adolescents age 15 to 19 years.[2] Our study shows that patient outcomes after treatment for pediatric osteosarcoma in a high middle-income country might be comparable to outcomes reported in the United States and Europe.

Multiple prognostic factors have been shown across several studies to influence outcome in pediatric osteosarcoma,

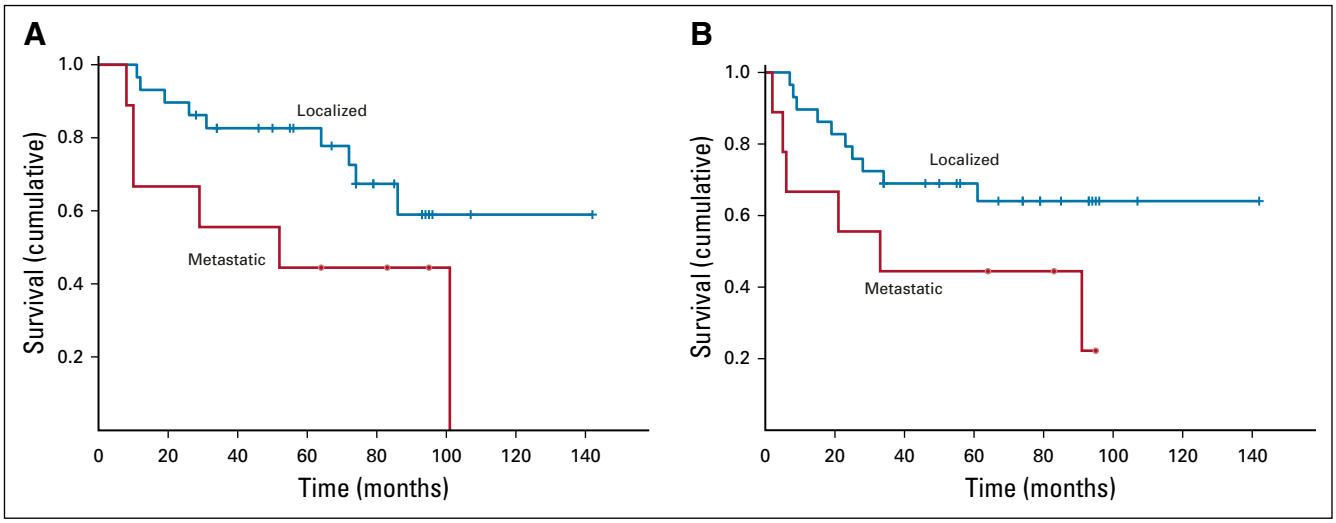

FIG 2. (A) Overall survival and (B) event-free survival for patients with localized and metastatic disease.

including primary tumor site and size, presence of clinically detectable metastatic disease, surgical resectability and remission state, and response to chemotherapy as assessed by degree of tumor necrosis.[7,8] Our analysis showed that non–lower-extremity site, metastasis, degree of necrosis, and delay of more than 4 weeks in local control were associated with worse prognosis. However, only degree of necrosis was a prognostic determinant of outcome in bivariable analysis.

The prognostic importance of disease stage has been clearly demonstrated in several studies. As many as 20% of patients with osteosarcoma have radiographically detectable metastases at presentation,[3,9] with the lungs being the most common site of initial metastatic disease.[10,11] Prognosis for patients with metastatic disease seems to be determined mainly by metastatic site, number of metastases, and surgical resectability of metastatic disease.[5,12] Prognosis seems more favorable for patients with fewer pulmonary nodules and for those with unilateral rather than bilateral pulmonary metastases.[3,5] Patients with metastases limited to the lungs have better outcomes than those with metastases to other sites or to the lungs combined with other sites.[3,12]

Our analysis showed that patients with localized disease have a much better prognosis than patients with overt metastatic disease. The results of a study by Bacci et al[13] confirmed that the prognosis of patients with metastatic osteosarcoma remains poor despite use of aggressive treatments, with 2-year EFS and OS rates of 21% and 55%, respectively, as compared with 75% and 94%, respectively, for patients with localized disease. Another study by Kager et al[3] showed that approximately 20% of patients with metastatic osteosarcoma will remain continuously free of disease and approximately 30% will survive

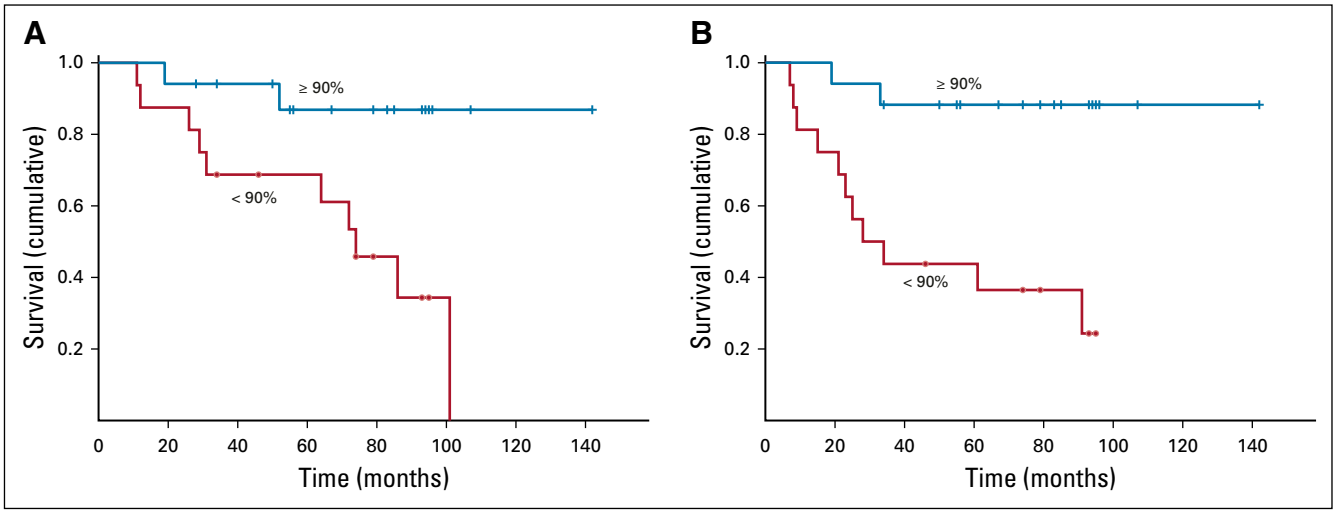

FIG 3. (A) Overall survival and (B) event-free survival for patients with a degree of tumor necrosis < 90% and ≥ 90%.

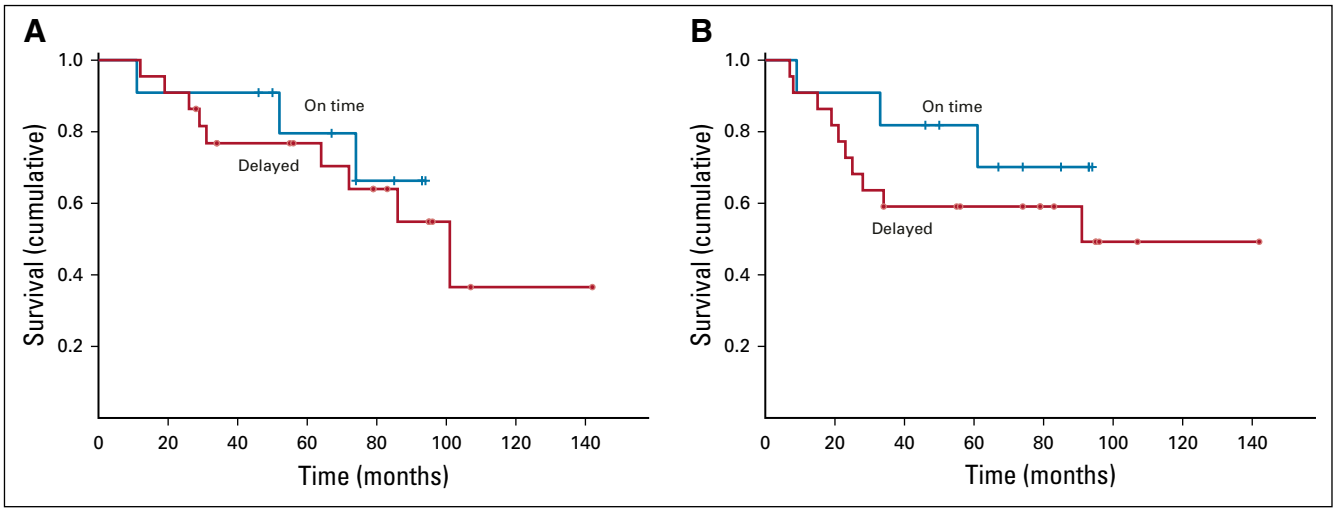

FIG 4. (A) Overall survival and (B) event-free survival by timing of local control (on time [≤ 14 weeks] or delayed [> 14 weeks]).

5 years from diagnosis. A study by Goorin et al[14] showed that projected 2-year progression-free survival for patients with lung metastases was 39%, whereas it was 58% for patients with metastases to other bones (with or without pulmonary metastases). The OS and EFS difference in our study for patients with localized versus metastatic disease did not reach statistical significance in bivariable analysis, likely because of the small number of patients.

Our study revealed the dismal prognosis of patients with synchronous multifocal osteosarcoma; there were no survivors among the three patients with multifocal disease. In the Italian experience, only three of 46 patients who

TABLE 2. Bivariable Analysis of Prognostic Factors

Variable	5-Year OS			5-Year EFS		
	No. (%) Alive (n = 21)	No. (%) Dead (n = 12)	*P*	No. (%) in Remission (n = 20)	No. (%) Relapsed (n = 13)	*P*
Sex			.48			.73
Male	9 (42.9)	7 (58.3)		9 (45.0)	7 (53.8)	
Female	12 (57.1)	5 (41.7)		11 (55.0)	6 (46.2)	
Age, years			1.00			1.00
< 10	6 (28.6)	3 (25.0)		5 (25.0)	4 (30.8)	
≥ 10	15 (71.4)	9 (75.0)		15 (75.0)	9 (69.2)	
Tumor site			.54			.55
Lower extremity	20 (95.2)	10 (83.3)		19 (95.0)	11 (84.6)	
Other	1 (4.8)	2 (16.7)		1 (5.0)	2 (15.4)	
Metastasis			.33			.36
Localized	19 (90.5)	9 (75.0)		18 (90.0)	10 (76.9)	
Metastatic	2 (9.5)	3 (25.0)		2 (10.0)	3 (23.1)	
Degree of necrosis, %			.004			.001
< 90	6 (28.6)	10 (83.3)		5 (25.0)	11 (84.6)	
≥ 90	15 (71.4)	2 (16.7)		15 (75.0)	2 (15.4)	
Delay of surgery, weeks			.70			.46
≤ 14	8 (38.1)	3 (25.0)		8 (40.0)	3 (23.1)	
> 14	13 (61.9)	9 (75.0)		12 (60.0)	10 (76.9)	

NOTE. Excluding patients who had upfront local control (n = 2) and those with multifocal bone disease who did not achieve surgical local control during therapy (n = 3).

Abbreviations: EFS, event-free survival; OS, overall survival.

presented with primary extremity tumors and synchronous metastases to other bones remained continuously disease free 5 years later.[15] Other studies have shown that no patients with synchronous multifocal osteosarcoma have been cured, but systemic chemotherapy and aggressive surgical resection may achieve significant prolongation of life.[5,16]

In our analysis, chemotherapy-induced necrosis was the single independent prognostic determinant of outcome. Several trials have shown that patients with favorable necrosis (≥ 90%) in the primary tumor after induction chemotherapy have a better prognosis than those with inferior necrosis (< 90%).[7,17,18] In a study by Kim et al,[19] patients with less necrosis in the primary tumor after initial chemotherapy were shown to have a higher rate of recurrence within the first 2 years compared with patients with a more favorable amount of necrosis. However, poor histologic response showed a gradual decline in prognostic value, and degree of necrosis lost its importance after 2 years; therefore, investigation of new predictive strategies and follow-up protocols was recommended for patients experiencing late relapse.

Addition of ifosfamide and etoposide to the standard chemotherapy regimen of methotrexate, cisplatin, and doxorubicin, on the basis of poor necrosis after induction therapy, has led to increased toxicity without any benefit with regard to OS or disease-free survival, as per the results of the recent international randomized controlled study, European and American Osteosarcoma Study Group (EURAMOS-1).[20]

Site of the primary tumor in osteosarcoma has been shown to be a significant prognostic factor in several reports. Many studies have previously shown that distal sites have a more favorable prognosis than do proximal sites among extremity tumors and that axial skeleton primary tumors are associated with the greatest risk of progression and death, primarily related to the inability to achieve complete surgical resection.[7,8] In our series, patients with lower-extremity tumors did well, with 5-year OS and EFS rates of approximately 75% and 62%, respectively, whereas those with non–lower-extremity tumors had 5-year OS and EFS rates of approximately 50%. However, tumor site did not retain prognostic significance in bivariable analysis with regard to OS and EFS, likely because of the small number of non–lower-extremity tumors (10.5%).

Resectability of the tumor is also a critical prognostic feature, because osteosarcoma is relatively resistant to radiation therapy. Complete resection of the primary tumor and any skip lesions with adequate margins is generally considered essential for cure. In our study, 33 patients (86.8%) underwent surgical resection, and the six patients with metastatic lung disease underwent thoracotomy. Studies have shown that patients who have complete surgical ablation of primary and metastatic tumors (when confined to the lung) may attain long-term survival, although EFS remains approximately 20% to 30% for patients with metastatic disease at diagnosis.[5,12,17,21] In the study by Kager et al,[3] number of metastases at diagnosis and completeness of surgical resection of all clinically detected tumor sites were of independent prognostic value in patients with primary metastatic osteosarcoma. A retrospective review of patients with craniofacial osteosarcoma performed by the German-Austrian-Swiss Osteosarcoma Cooperative Group reported that incomplete surgical resection was associated with inferior survival probability.[22] In the Multi-Institutional Osteosarcoma Study, the only factor predictive of survival after relapse was the ability to achieve complete surgical resection of primary tumor and metastases.[21]

Regarding type of surgery, 31 of our patients underwent a limb-sparing procedure, whereas two patients underwent amputation. Bacci et al[23] showed that more than 80% of patients with extremity osteosarcoma can be treated by a limb-sparing procedure and do not require amputation. The Italian Sarcoma Group/Scandinavian Sarcoma Group study showed that more than 90% of patients with osteosarcoma of the extremity can undergo conservative surgery.[24] One study from the European Osteosarcoma Intergroup found that limb-salvage surgery with effective chemotherapy remains the optimal treatment of osteosarcoma and that local recurrence was closely related to adequacy of the margins of excision and chemotherapeutic response. Their results showed that patients who had undergone limb-salvage surgery and who developed local recurrence still had better survival than those who had primary amputation (37% *v* 31% survival at 5 years).[25] However, in a study by Andreou et al,[26] limb-sparing surgery was significantly associated with a higher local recurrence rate, together with other factors, including no participation in a study, pelvic tumor site, soft tissue infiltration beyond the periosteum, poor response to neoadjuvant chemotherapy, failure to complete the planned chemotherapy protocol, and biopsy at a center other than the one performing the tumor resection, whereas no differences were found for varying surgical margin widths.

The ability to establish a limb-salvage program for our patients with osteosarcoma was the result of collaboration between the Children's Cancer Center, which raised funds, and government and third-party insurance plans.[27] This could be a model for pediatric oncology programs in other low- and middle-income countries where limb-salvage surgeries are not yet being performed.

In our study, we also investigated the effect of the timing of local control on outcome. To our knowledge, no study to date has specifically investigated the effect of delay in local control beyond the planned timing on outcome. In our cohort, 22 patients (66.7%) had a delay in local control beyond week 14 of chemotherapy. There was no difference in OS between patients who had delay in local control as

compared with patients who had timely local control, with 5-year OS rates of approximately 78% and 80%, respectively. However, the relapse rate was higher in patients who had delay in local control, with a 5-year EFS rate of 58%, as compared with 80% in patients who had timely local control. This factor lost significance in bivariable analysis with respect to both overall survival and disease recurrence. The lack of significance of the timing of local control in bivariable analysis might have been a result of the small cohort of studied patients.

In conclusion, treatment of pediatric osteosarcoma in a multidisciplinary cancer center in Lebanon resulted in survival similar to that in developed countries. Delay in local control was associated with worse outcome. The only statistically significant inferior outcome predictor was poor degree of necrosis at the time of local control.

AFFILIATION

[1]Children's Cancer Institute, American University of Beirut, Beirut, Lebanon

CORRESPONDING AUTHOR

Miguel R. Abboud, Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Center, P.O. Box 11-0236, Riad El Solh 1107 2020 Beirut, Lebanon; Twitter: @khaledghanem; e-mail: ma56@aub.edu.lb.

AUTHOR CONTRIBUTIONS

Conception and design: Bilal Abou Ali, Mayessa Salman, Said Saghieh, Samar A. Muwakkit, Raya Saab

Administrative support: Raya Saab

Provision of study material or patients: Bilal Abou Ali, Said Saghieh, Samir Akel, Samar A. Muwakkit, Raya Saab

Collection and assembly of data: Bilal Abou Ali, Fouad Boulos, Rachid Haidar, Samir Akel, Mayessa Salman, Samar A. Muwakkit, Hani Tamim

Data analysis and interpretation: Bilal Abou Ali, Hani Tamim, Mayessa Salman, Samar A. Muwakkit, Hassan El-Solh, Miguel R. Abboud

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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