Prognostic Factors for Osteosarcoma of the Extremity Treated with Neoadjuvant Chemotherapy

15-Year Experience in 789 Patients Treated at a Single Institution

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Received 18 July 2005; revision received 25 August 2005; accepted 5 November 2005.

BACKGROUND. The evaluation variables influencing systemic and local recurrence and final outcome are extremely important in defining risk-adapted treatments for patients with nonmetastatic osteosarcoma of the extremity.

METHODS. A homogeneous group of 789 patients treated at a single institution between March 1983 and March 1999 with different protocols of neoadjuvant chemotherapy, with a minimum followup of 5 years, were retrospectively evaluated in relation to gender, age, serum levels of alkaline phosphatase, tumor site and size of the pathologic fracture, type of surgery, protocol of chemotherapy, surgical margins, and histologic response to preoperative treatment.

RESULTS. The 5-year event-free survival (EFS) and overall survival rates were 60.1% and 67.5%, respectively. Upon univariate analysis, EFS was significantly related to the age of patients, serum value of alkaline phosphatase, tumor volume, histologic subtype, type of surgery, surgical margins, histologic response to preoperative treatment, and chemotherapy protocol. Local recurrences (4.8%) were significantly correlated with surgical margins. The 5-year postrecurrence EFS survival was 17% and was significantly lower for patients who had a local recurrence and metastases than for those with metastases only. Patients who had a recurrence only in the lung had a postrecurrence survival rate significantly better than others, correlated with the number of metastatic nodules and the length of the disease-free interval.

CONCLUSIONS. Upon multivariate analysis, age $\leq$ 14 years, high serum levels of alkaline phosphatase, tumor volume $>$ 200 mL, a two-drug regimen chemotherapy, inadequate surgical margins, and poor histologic response to treatment maintained independent prognostic values on the outcome of nonmetastatic osteosarcoma of the extremities. These factors must be considered when deciding risk-adapted treatments for osteosarcoma patients. ***Cancer*** **2006;106:1154–61.**

KEYWORDS: osteosarcoma, treatment, prognostic factors, limb salvage.

Adjuvant and neoadjuvant chemotherapy, introduced in the early 1970s, have significantly improved the long-term survival rate for patients with osteosarcoma. Nevertheless, recurrent disease still occurs in about 30–40% of patients and more than 70% of them die of their tumor, despite second-line treatment. Intensified first-line chemotherapy regimens could improve prognosis, but the risk is overtreatment of patients who could benefit from less aggressive regimens. Therefore, the identification of risk factors for recurrence would be of major importance in the development of new and risk-adapted strategies of treatment. Since the early 1970s, several clinical studies have attempted to identify prognostic factors for survival in osteosarcoma after adjuvant and neoadjuvant treatment. However,

DOI 10.1002/cncr.21724
Published online 18 January 2006 in Wiley InterScience (www.interscience.wiley.com).

those studies generally have major defects. Homogeneous series from a single institution were usually too small to have reliable statistical significance.[1–3] Conversely, articles reporting multiinstitutional studies had two main limitations: no standard methods to evaluate prognostic factors, and a very different background and experience in surgery for bone sarcomas, providing very different results according to single centers within the multicentric studies.[4–8] The aim of this study was to asses the influence of several patient-related and treatment-related prognostic factors in a large series of patients treated at a single institution with neoadjuvant chemotherapy over a 16-year period, followed for at least 5 years.

MATERIALS AND METHODS

Patient Selection and Pathology

Records of the 789 patients who entered our institution with neoadjuvant studies of nonmetastatic osteosarcoma of the extremities between March 1972 and March 2000 were reviewed. The results achieved in the single studies, previously reported in detail,[9–12] were updated.

Patients were considered eligible when fulfilling the following criteria: typical radiographic and histologic features of primary, high-grade, central osteosarcoma, tumor located in the extremity, no previous history of cancer and no prior treatments, age under 40, no coexisting disease contraindicating chemotherapy, and no evidence of metastases at diagnosis.

Of the 1024 newly diagnosed cases of osteosarcoma observed at the authors' institution, 900 (88%) were eligible and included 32 patients where a thoracotomy was performed, after preoperative treatment for suspected pulmonary metastases on computer tomography (CT) of the chest revealed no tumor but benign lesions and 14 patients with histologically proven skip metastases without other signs of dissemination.

All the eligible patients were offered neoadjuvant chemotherapy after having been informed of the potential advantages and risks of this treatment. Of the 900 eligible patients, 111 declined to enter the study. The characteristics of the remaining 789 are reported in Table 1. The diagnosis of osteosarcoma, established by clinical and radiologic findings, was always confirmed on histologic slides of tumor tissue obtained from an open or needle biopsy, as well as from the resected specimen. According to Fletcher et al.,[13] osteosarcomas were classified as 'classic,' or conventional, telangiectatic, and small-cell osteosarcoma. On the basis of predominant cells and intercellular material, the 'classic' osteosarcomas were subclassified as osteoblastic, fibroblastic chondroblastic, and telangiectatic. This distinction, always made on surgical specimens, was possible in all but 71 cases of 'classic osteosarcoma' that were defined as 'not classifiable conventional osteosarcoma.' Tumor volume was retrospectively evaluated in 725 patients according to the

TABLE 1
Patients' Features, Treatments, and Cumulative Probability of 5-Year EFS

	Number of cases[a]	% of EFS	*P*
Gender			
Male	449	56.7	0.20
Female	334	64.3	
Age			
≤ 14 yrs	326	55.1	0.018
> 14 yrs	457	63.7	
Site			
Femur	410	56.6	0.32
Tibia	216	64.2	
Humerus	100	60.3	
Fibula	43	55.8	
Other sites	14	78.5	
Alkaline phosphatase			
Normal	492	69.2	0.0001
levated	291	44.7	
Tumor volume[b]			
< 200 mL	354	66.6	0.0001
≥ 200 mL	371	53.6	
Histology			
Osteoblastic	506	55.6	0.014
Chondroblastic	88	63.6	
Fibroblastic	71	76.1	
Telangiectatic	47	680	
Not classifiable	71	6.1	
Pathologic fracture			
Yes	65	56.9	0.34
No	718	60.7	
Surgery[c]			
Amputation	85	49.4	0.06
Limb salvage	661	62.0	
Rotationplasty	36	52.8	
Surgical margins[c]			
Adequate	63	61.5	0.03
Inadequate	719	47.6	
Histologic response[c]			
Good	496	66.9	0.0001
Poor	286	49.0	
Protocols of chemotherapy			
IOR/OS-N1	127	49.2	0.014
	IOR/OS-N2	164	64.6
	IOR/OS-N3	155	56.8
IOR/OS-N4	129	68.1	
IOR/OS-N5	208	66.8	

EFS, event-free survival.

[a] The 6 patients who died of unrelated causes were not considered.

[b] Evaluated only in 725 patients.

[c] One patient did not undergo surgery because of progression of disease since the preoperative phase.

TABLE 2
Protocols of Neoadjuvant Chemotherapy

Protocol	Period	No. of patients[a]	Preoperative treatment	Postoperative treatment
IOR/OS-N1	1983–1986	127	*HD*MTX-CDP vs.MTX-CDP	Good responders: MTX-CDP-ADM Poor responders: ADM-BCD
IOR/OS-N2	1986–1989	164	MTX-CDP-ADM	Good responders: MTX-CDP-ADM Poor responders: MTX-CDP-ADM-IFO-ETO
IOR/OS-N3	1990–1993	155	MTX-CDP-*LD*ADM	Good responders: MTX-CDP-*LD*ADM Poor responders: MTX-CDP-*LD*ADM-IFO-ETO
IOR/OS-N4	1994–1995	129	*HD*MTX-CDP-ADM-IFO	Good and poor responders: *HD*MTX-CDP-ADM-IFO
IOR/OS-N5	1996	208	*HD*MTX-CDP-ADM-*HD*IFO	Good responders: *HD*MTX-CDP-ADM-*HD*IFO (3 cycles) Poor responders: *HD*MTX-CDP-ADM-*HD*IFO (4 cycles)

MTX: methotrexate (*LD:* low doses, *HD:* high doses); CDP: cisplatin; ADM: doxorubicin (*LD:* low doses, *HD:* high doses); BCD: bleomycin + cyclophosphamide + dactinomycin; IFO: ifosfamide (*LD:* low doses, *HD:* high doses); ETO: etoposide.

[a] The six patients who died of unrelated causes were not included.

method described by Gobel et al.[14] on CT-scan measures of the three diameters of the lesion.

Preoperative Evaluation

A complete medical history was obtained for all patients, who also underwent a thorough physical examination and several chemical laboratory tests. The primary tumor was evaluated on standard radiographs and Technetium 99-MDP bone scans. CT was performed in the 767 patients treated after 1984. Magnetic resonance imaging (MRI) was also performed in about half of the latter patients. These exams were repeated before surgery. Bone metastases were investigated by total body scans, whereas standard chest radiographs and CT scans of the chest were used to exclude lung metastases for the 767 patients treated after 1984, and by full chest tomography for the 22 patients treated before.

Chemotherapy

Patients were treated by five different protocols of neoadjuvant chemotherapy (IOR/OS N1, N2, N3, N4, N5). In fact, between 1997 and 1999 there were two more protocols activated (IOR/OS-N6 and N7) and patients were actually randomized to receive the treatment scheduled for protocol IOR/OS-N2 or N4. For this analysis of prognostic factors, we grouped all patients receiving the same chemotherapy, so five protocols were considered and are summarized in Table 2. Details on all protocols have been previously published.[9–12]

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 (prosthesis, Kuntscher rod, or plate and cement, vascularized fibula combined with allograft, and allograft and autograft) were 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. Even if in the long span of time covered by these studies the surgical indications for local treatment might have changed, for conservative surgery it was considered always mandatory that 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 following Enneking indications.[15] The margins were classified as 'adequate' if radical or wide and 'inadequate' if margins were marginal, intralesional, or contaminated, regardless of histologic response, i.e., when margins still contained tumor cells even if completely necrotic. The response to preoperative chemotherapy was evaluated following the criteria previously reported[16] and graded as 'good' (90% or more tumor necrosis) or 'poor' (less than 90% tumor necrosis).

Postrecurrence Treatment

The type of treatment for metastases and/or local recurrence in relapsed patients was not standardized, but performed on an individual basis, considering the site and the number of metastases, the length of the free interval, if the local recurrence was isolated or combined with systemic recurrence, and the type of chemotherapy previously received by patients. None-

theless, the key point of treatment was generally the complete surgical removal of metastases and/or local recurrence whenever possible. A second line of chemotherapy, generally performed with drugs not used in the first-line treatment or with higher doses of the drugs previously used, was given to patients in whom it was not possible to achieve complete surgical removal of metastases, in patients with a disease-free interval between the first treatment and recurrence shorter than 2 years, and when there were more than two recurrences. It must be stressed that after the recurrence 57 patients were treated not at Rizzoli but at other institutions. Therefore, of the 313 patients who had a recurrence (see below), we know exactly the first type of treatment performed after recurrence in 256, whereas for the remaining 57 our data were drawn only from indirect information.

Statistics

Because of a lack of uniformity in the therapeutic regimen performed after recurrence, and considering that all but 47 patients of the 313 who had a recurrence died or are alive with uncontrolled disease, the prognostic significance of the variables investigated was evaluated only pertaining to event-free survival (EFS). The patients who died of causes unrelated to the tumor or to the treatment were excluded from the evaluation. The patients who developed a second neoplasm were censored at the time that the new tumor was diagnosed. The postrecurrence outcome and overall survival was also reported, but the relevant data should be considered with caution. When recurrent disease occurred, the postrecurrence treatment was not homogeneous and changed markedly over the 16 years of the studies. In addition, as reported before, of the patients treated after recurrence at other institutions we have only indirect data, and important details are often lacking. The EFS was established from the start of treatment to the date of recurrence (local recurrence or systemic). All patients were followed for at least 5 years. EFS curves were calculated according to the Kaplan–Meier method and compared by means of the log rank test. Significance was set at $P < 0.05$. The following variables were evaluated: gender and age of patients, tumor volume, tumor site, histologic subtype, presence or not of pathologic fracture at diagnosis, protocol of chemotherapy performed, type of surgery, and surgical margins and histologic response to preoperative treatment. Tumor volume was evaluated at different cut-offs. To allow a comparison with other authors' data, we used a cut-off of 14 years for age. The histologic subtypes were classified according to Fletcher et al.[13] A multivariate analysis was performed to identify factors predictive of EFS on those factors that proved significant in the univariate analyses by Cox regression.

RESULTS

Global Oncologic Results

At a followup of 5–22 years (median, 12.8), 440 patients (55.7%) remained continuously event-free, 313 had a recurrence (39.7%), 10 died from chemotherapy toxicity (1.3%), 6 died of reasons not related to osteosarcoma or chemotherapy treatment (2 suicides, 2 pulmonary embolism, 1 complication of central venous catheter, 1 car crash), and 20 developed a second neoplasm. Excluding the patients who died of unrelated causes, the 5-year EFS was 60.1% and the overall survival (OS) was 66.2%.

EFS by Univariate Analysis

The 5-year EFS rates according to patient characteristics and tumor variables are reported in Table 1.

Surgery, Surgical Margins, and Histologic Response to Chemotherapy

Surgery involved amputation in 85 patients (11.0%), including 7 patients initially treated with conservative surgery, then amputated due to early infectious complications; 661 patients were treated with limb salvage (84.5%), and 36 (4.5%) with rotationplasty. In one patient, due to systemic progression during the preoperative treatment, surgery was not performed. The rate of amputation was significantly different according to the years in which the patients were treated. For instance, this rate was 25.4% for the 126 patients treated with the first protocol (IOR/OS-1) between 83–86 and 7.7% for the 206 patients treated with the last protocol (IOR/OS-5) between 1995 and 1999 ($P < 0.0001$). The rate of limb salvage was unrelated to sex and age of patients or to the site of tumor. It was, however, correlated with the tumor volume (89.9% for smaller tumors vs. 81.2% for larger tumors; $P < 0.002$). The rate of rotationplasty was significantly higher in patients 14 years old or younger than in older patients (9.1% vs. 1.3%; $P < 0.005$). The surgical margins were inadequate (marginal, intralesional, or contaminated) in 62 patients (8.0%), and adequate (radical or wide) in 711 (92.0%). According to the type of surgery, the rate of inadequate surgical margins was significantly higher in patients treated with limb salvage than in patients treated with amputation (8.9% vs. 1.2%; $P < 0.02$). For the 35 patients treated with rotationplasty the rate of inadequate surgical margins was 8.6%.

The chemotherapy-related tumor necrosis was good in 496 (63%) patients and poor in 286 (37%). The rate of good responders was unrelated to tumor site, but significantly correlated with the histologic subtype

(63.9% for osteoblastic tumors: 50.6% for chondroblastic tumors, 25% for small-cell tumors, 61.7% for fibroblastic, and 86.7% for telangiectatic tumors; $P < 0.0005$), and with the tumor volume (68.6% for smaller tumors vs. 58.9% for bigger tumors; $P < 0.009$). According to preoperative chemotherapy the rate of good responders was 48.4% for the 127 patients on the IOR/OS-1 protocol treated with methotrexate (MTX) and cisplatin (CDP), 66.1% for the 319 patients (protocol IOR/OS-2, IOR/OS-3) treated with MTX, CDP, and adriamycin (ADM), and 65.7% for the 337 patients (protocols IOR/OS-4 and IOR/OS-5) treated with MTX,CDP, ADM, and ifosfamide. The differences between patients preoperatively treated with a two-drug regimen and patients treated with three-drug or four-drug regimens was highly significant ($P < 0.0001$).

Time-Dependent Variables

As mentioned, there were differences in some of the parameters evaluated in the present study due to its considerable length. In fact, diagnostic techniques, chemotherapy, and surgery evolution produced time-dependent results. Comparing the 291 patients treated between 1983 and 1990 (when MRI became a standard procedure for our patients), with those 492 who underwent treatment from 1990 to 1999, this resulted in a rate of limb salvage that significantly increased (78% vs. 90.6%; $P = 0.0001$). The rates of good histologic response to preoperative chemotherapy (60.1% vs. 67.8%; $P = 0.03$) and the 5-year OS (67.5% vs. 75.1, $P = 0.02$) were also significantly different. Nonetheless, no other variables showed time-dependency.

EFS by Multivariate Analysis

Through the use of univariate analysis, eight covariates seemed to be predictive of EFS: age of patients, serum alkaline phosphatase (AP), histologic subtype and volume of tumor, surgical margins, protocols of chemotherapy, type of surgery, and histologic response to preoperative treatment. Using the Cox proportional hazard model, multivariate analyses were performed to determine the variables that were independently predictive of EFS. As illustrated in Table 3, the risk of recurrence increased when the following characteristics were present: age $\leq$ 14, elevated AP serum at presentation, tumor volume $\geq$ 200 mL, inadequate surgical margins, and poor histologic response to preoperative chemotherapy. In addition to this, the first chemotherapy protocol (IOR/OS-1) was also an independent unfavorable prognostic factor. Conversely, the histologic subtype lost its statistical significance at multivariate analysis.

TABLE 3
Multivariate analysis

Variable	Relative risk	95% CI	Wald test
Age			
> 14 year	1		
≤ 14 years	1.3	1.0–1.7	$P = 0.044$
Alkaline phosphatase			
Normal	1		
Elevated	2.1	1.6–2.7	$P < 0.0001$
Tumor volume			
< 200 mL	1	1.1–1.8	$P = 0.01$
≥ 200 mL	1;4		
Protocol of chemotherapy	Wald test related to IOR-OS/N5		
IOR-OS/N5	1		
IOR-OS/N1	2.3	1.6–3.4	$P < 0.0001$
IOR-OS/N2	1.5	1.0–2.2	$P = 0.048$
IOR-OS/N3	1.6	1.1–2.5	$P = 0.015$
IOR-OS/N4	1.4	0.9–2.1	$P = 0.11$
Global Wald test			**$P = 0.0008$**
Surgical margins			
Adequate	1		
Inadequate	1.3	1.0–1.7	$P = 0.044$
Histlogic response			
Good	1	1.6–2.6	$P < 0.0001$
Poor	2.0		

Histologic subtype and tumor volume have not been considered because there are no data for all patients.
95% CI: confidence interval.

Pattern of Recurrence

In the 313 patients who experienced recurrence, the first recurrences were isolated lung metastases in 243 (77.6%) patients, isolated bone metastases in 26 (8.3%), lung and bone metastases in 5 (1.6%) cases, metastases in other sites in 3 (0.9%) (kidney, brain, heart), metastases in more than two sites in 2, isolated local recurrence in 20 (6.4%), local recurrences combined with bone metastases in 8 (2.6%), and local recurrence combined with lung metastases in 6 (1.9%). The average time to recurrence was 24.5 months (range, 2–204), 200 patients had a recurrence in the first 2 years (63.9%), and 113 later (36.1%). In the latter group of patients, 15 (4.8%) had a recurrence after 5 or more years from the beginning of treatment and 6 (1.9%) of them after 10 or more years. As reported before, median time to recurrence was significantly longer for patients with normal serum values of AP (18 mos vs. 25 mos for patients with high values; $P < 0.0001$), and in good responders in comparison with poor responders (22 mos vs. 17 mos; $P < 0.03$).

Local Recurrence

Local recurrence occurred in 44 (5.7%) of patients at 2–118 months (median, 23.7) from the beginning of treatment. In all but three cases local recurrence was

combined with systemic recurrence. In 20 patients local recurrence occurred at 3–28 months (median, 8 mos) before metastasis, in seven cases metastases were diagnosed at 4–32 months (median, 11 mos) before local recurrences, and in 14 cases local and systemic recurrences were contemporary events. Local recurrence was observed in 3 of 85 (3.5%) patients treated with amputation, in 39 of the 653 (6.0%) patients treated with limb salvage, and in 2 of 35 (5.7%) patients treated with rotationplasty. These differences were not statistically significant. According to the surgical margins, the rate of local recurrence was significantly higher for the 62 patients with inadequate surgical margins than in the 711 patients with adequate surgical margins (20.9% vs. 3.5%; $P < 0.0001$). In addition, the rate of local recurrence was higher in the 286 poor responders than in the 487 good responders (6.2% vs. 4.1%). This difference, however, is not statistically significant. If we consider patients with inadequate surgical margins and poor histologic response, the rate of local recurrence was 29.2%. The rate of local recurrence, however, was unrelated to sex and age of patients, site and volume of tumor, and presence or absence of pathologic fracture.

Postrecurrence Treatment Outcome

For the 313 relapsing patients, the first postrecurrence treatment was surgery alone in 171 (54.6%) cases, surgery combined with a second-line chemotherapy in 43 (13.7%), only chemotherapy in 24 (7.7%), and radiotherapy in 6 (1.9%). In the remaining 69 patients no therapies or only palliative treatments were performed. After the first postrecurrence treatment, 198 patients (63.2%) entered remission. It is interesting to note that the period of recurrence did not influence the type of postrecurrence treatment. For instance, for patients who had a recurrence with lung metastases the rate treated by surgery was 56.6% for the 53 who had a recurrence between 1983 and 1993 and 62.2% for those who had a recurrence between 1994 and 2004. Of patients who entered remission, 142 patients had a second recurrence, 50 a third, 13 a fourth, 6 a fifth, and 3 a sixth. Of the recurrence patients at present, 62 (19.8%) are alive and free of disease from 6 months to 19 years (median, 8 yrs) after the last treatment for recurrence, five are alive with uncontrolled disease, and 246 are dead. The mean survival of the latter patients was 37.4 months (2–220). Of the patients presently alive and free of disease, 47 had only one recurrence, 5 had two recurrences, 6 had three recurrences, and 4 had four recurrences. The rate of patients presently alive and free of disease was 19.8% for the patients who had only systemic recurrence and 6.8% for patients who had a local and systemic recurrence ($P < 0.03$). According to the sites of first metastases, the rate of patients presently free of disease was 21.9% for patients who had isolated lung metastases and 11.1% for the patients who had isolated bone metastases. None of the patients who had a recurrence in other sites or with metastases in more than two sites is presently alive and free of disease. For the 247 patients who initially had a recurrence with isolated lung metastases, the rate of the ones actually alive and free of disease was significantly correlated with the number of lung nodules at the first recurrence (42.0% for the 119 patients with one or two metastases vs. 3.1% for the 128 patients with 3 or more nodules; $P < 0.0001$) and to the time of recurrence (14.4% for the 159 patients who had recurrence in the first 2 years vs. 35.2% for patients who had a recurrence more than 2 years after the beginning of treatment; $P < 0.0005$). In other words, the mean time to recurrence was 41.9 months for patients currently alive and free of disease and 14.9 months for patients who died ($P < 0.0001$).

DISCUSSION

About 50% of patients with osteosarcoma of the extremity can be cured with a relatively nonaggressive regimen of chemotherapy.[17–19] Conversely, 40% of patients still die of the tumor, even if treated with extremely aggressive protocols.[2,5,8,12,17] The identification of prognostic factors to define different risk groups is very important. Despite the rarity of osteosarcoma, a number of clinical and pathologic features such as tumor site, size and subtype, patient gender and age, high alkaline phosphatase or high lactate dehydrogenase values, multidrug resistance, and genetic variations have been reported to have prognostic significance, but often with contradictory results due to the lack of uniformity in patient analyses and methods. Another possible bias is that most studies have reported their results only in terms of 5-year EFS probability, calculated on study populations whose minimum followup was often less than 3 years. We know that the new neoadjuvant treatments of osteosarcoma, besides increasing the cure rate, might also delay the time of recurrence.[20–22] Our present analysis evaluated a large number of patients according to the previously mentioned prognostic variables, followed for at least 5 years. The main strength of our study is that patients were treated at the same institution by the same medical staff, and data about the variables evaluated are available for almost all patients. The main shortcoming is that data do not come from a randomized study but were collected over a 16-year period. During this long period, new drugs, such as ifosfamide, new radiologic techniques (i.e., MRI), and new

surgical reconstruction procedures have been introduced. Moreover, our patients were treated with five different protocols of chemotherapy successively activated, with the possibility that prognostic factors significant for one type of treatment may no longer be predictive with improved treatment. Our study showed that six of the variables evaluated had an influence on patients' EFS treated with neoadjuvant chemotherapy. Multivariate analysis showed a significant adverse effect on prognosis for age less than 14 years, high serum AP, tumor volume greater than 200 mL, first chemotherapy protocol, inadequate surgical margins, and poor histologic response to preoperative treatment. Regarding the prognostic significance of age, a better prognosis for younger patients has been reported by Winkler et al.,[4] whereas other authors[22,23] found a better prognosis for older patients. In our study, patients 14 years old or younger had an independent worse prognosis than older patients. Nonetheless, due to different criteria of inclusion, a reliable comparison between studies is impossible. The prognostic significance of alkaline phosphatase in osteosarcoma, previously reported by us[24] and others,[3] is confirmed by this study in a larger number of patients. It is interesting to note that in our series serum AP is not only a significant prognostic factor, but its value also correlated with prognosis. In fact, the 5-year EFS was 24% for patients with serum AP values of more than 4 times higher than the normal values, and 46% for patients with high values below this limit ($P < 0.001$). Also, tumor size, significant in our series if based on the cut-off of 200 mL, has been reported to be a significant prognostic factor by univariate analyses in three other reviews.[4,25,26] Only for Spanier et al.[26] did it maintain its prognostic significance by multivariate analysis, even if the lack of standardization in measurement of tumor volumes makes the comparison inconsistent. In our study, patients with inadequate surgical margins had a significantly worse prognosis, with significance maintained by multivariate analysis. This was probably due to the very high rate of local recurrence in patients with inadequate surgical margins. The prognostic significance of histologic response to preoperative chemotherapy was confirmed by our series and its prognostic significance was maintained even after salvage chemotherapy given to poor responding patients. In fact, all our protocols except IOR/OS-N4 provided a different postoperative treatment for poor responders (Table 2), i.e., different drugs (IOR/OS-N1), addition of drugs (IOR/OS-N2 and N3), and additional cycles of chemotherapy (IOR/OS-N5). Despite those treatments, the outcome of poor responders was always worse than that of good responders, except with protocol IOR/OS-N2. Few randomized studies[18,27] have compared the effect of different regimens of chemotherapy: a two-drug regimen versus a three-drug one with contrasting results. In our nonrandomized five protocols, patients treated with a three-drug regimen (preoperative MTX, CDP, ADM) or four-drug regimen (preoperative MTX, CDP, ADM, and IFO) showed a better prognosis in comparison with the first, two-drug study (preoperative MTX and CDP). Among all the four drugs active against osteosarcoma, there were no differences between regimens using moderate versus high doses MTX and IFO. Our study also showed that some factors significant for EFS had an influence on recurrence and overall survival, i.e., serum AP values, histologic response to preoperative treatment, and protocols of chemotherapy. This finding should be considered when evaluating the preliminary results of new protocols. Another important fact resulting from the present review was the strict correlation between (in)adequacy of surgical margins and rate of local recurrence. According to this factor, we believe that when limb salvage surgery is not able to give adequate surgical margins, amputation must be considered, especially if inadequate margins are associated with a poor response to chemotherapy, because those patients have an intolerable chance of local recurrence. On the basis of these results, we believe that future clinical trials for nonmetastatic osteosarcoma of the extremities must identify appropriate therapeutic strategies for different risk groups based on prognostic factors in order to provide the best care to all patients and reduce treatment-associated morbidity.

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