Proximal Tumor Location and Fluid-fluid Levels on MRI Predict Resistance to Chemotherapy in Stage IIB Osteosarcoma

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Abstract

Background Primary tumor growth during neoadjuvant chemotherapy is believed to be a sign of resistance to chemotherapy (chemoresistance), and often is associated with poor histologic response, local recurrence, and poorer survival. Currently there are no proven indicators to predict poor response to chemotherapy at the time of diagnosis.

Questions/purposes We asked (1) what clinicopathologic factors present at diagnosis predict primary tumor growth during neoadjuvant chemotherapy, (2) what factors at presentation predict survival, and (3) when the factors at presentation and the treatment-related factors

are considered, what factors independently correlate with survival.

Methods We studied 567 patients with Stage IIB osteosarcomas. The factors assessed included age, sex, location, pattern on plain radiographs (radiodense, radiolucent, mixed), MRI findings, pathologic subtype, initial tumor volume determined by MRI, tumor volume change after chemotherapy, surgical margin, and histologic response to preoperative chemotherapy. Logistic modeling was used to identify risk factors.

Results Independent risk factors associated with primary tumor growth after neoadjuvant chemotherapy were proximal tumor location ($p < 0.01$; relative risk [RR], 2.41; 95% CI, 1.5–3.86) and fluid-fluid level on initial MRI ($p < 0.01$; RR, 5.56; 95% CI, 3.48–8.87). Among factors at presentation, large initial tumor volume ($p < 0.01$; RR, 1.58; 95% CI, 1.22–2.04), proximal tumor site ($p < 0.01$; RR, 1.61; 95% CI, 1.19–2.19), and presence of fluid-fluid level ($p < 0.01$; RR, 1.83; 95% CI, 1.37–2.5) independently predicted reduced event-free survival. When we consider the factors at presentation and treatment-related factors, large initial tumor volume ($p < 0.01$; RR, 1.54), tumor growth after neoadjuvant chemotherapy ($p < 0.01$; RR, 3.88), inadequate surgical margin ($p < 0.01$; RR, 2.42), and poor histologic response ($p = 0.03$; RR, 1.43) were independent poor prognostic factors of event-free survival.

Conclusions Proximal tumor location and the presence of the fluid-fluid level on initial MRI were predictors of tumor progression and poor survival in patients presenting with Stage IIB osteosarcomas. If confirmed in other studies, patients with these risk factors should be considered for trials of other treatment strategy.

Level of Evidence Level III, prognostic study. See the Instructions for Authors for a complete description of levels of evidence.

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Introduction

Prognostic factors for osteosarcoma can be categorized into factors evident at presentation and treatment-related factors. Factors at presentation include age, sex, initial tumor volume, tumor location, radiologic findings, histologic subtype, tumor stage, and serologic and molecular markers [1, 4, 6, 8, 10, 14, 17]. Treatment-related factors include histologic response to preoperative chemotherapy, change in tumor volume, and surgical margin [3, 7, 28]. Of these factors, histologic response after preoperative chemotherapy has been shown to be the most powerful prognostic indicator of survival in patients presenting without metastases at diagnosis [9]. Patients who respond poorly to chemotherapy show high propensity for worse outcome. Therefore, several approaches have been used to predict the response to chemotherapy including chemosensitivity analysis using biopsy samples, immunohistochemical analysis of protein expression (eg, TP53, multidrug resistance protein, and reduced folate carrier protein), transcriptome analysis using microarray technology, and proteomic approaches [11, 16, 22, 27, 32]. However, despite their predictive potential, these approaches are not readily available for clinical use.

Change in tumor volume after neoadjuvant chemotherapy, a factor relatively undervalued, might be a powerful independent prognostic indicator that supplements the limitations of the traditional assessment of histologic response and mirrors the oncologic outcomes. In two previous studies, tumor growth during chemotherapy was shown to predict poor histologic response, local recurrence, and reduced survival [20, 30]. We therefore aimed to determine the clinical characteristics assessable at the time of diagnosis that might predict an increase in tumor volume. In one study, tumor enlargement seemed to be positively related to age (≤ 15 years) and pathologic subtypes other than the osteoblastic type [20]. However, subsequent studies suggested that proximal humeral and pelvic locations tended to be associated with tumor enlargement after chemotherapy, and initial MRI of patients with local recurrence (most of whom showed tumor enlargement) gave us the impression that an increase in tumor volume was associated with the presence of the fluid-fluid level on MRI [8, 21, 29]. Therefore, by expanding the sample size and incorporating previously unexamined variables, we reassessed which initial factors might predict tumor enlargement after chemotherapy.

We aimed to determine: (1) the initial clinicopathologic factors that predict tumor enlargement after chemotherapy, (2) what factors at presentation predict survival, and (3) when the factors at presentation and the treatment-related factors are considered, what factors independently correlate with survival.

Patients and Methods

Patient Selection

Between 1990 and 2011, 922 patients with localized osteosarcomas were registered in our orthopaedic surgery database. We retrospectively reviewed 567 cases from these 922 according to the following criteria: (1) primary high-grade osteosarcoma; (2) no history of previous treatment except biopsy; (3) availability of prechemotherapy and postchemotherapy MRI; (4) surgery and chemotherapy performed at our institute; and (5) more than 2 years followup for patients who were event-free. The reasons for exclusion from the study were incomplete clinical data ($n = 91$), immediate surgery followed by adjuvant chemotherapy ($n = 60$), chemotherapy only ($n = 53$), prior surgery at another hospital ($n = 48$), previous curettage at a referral center ($n = 42$), Stage IIA disease ($n = 32$), osteosarcoma in the head and neck regions ($n = 15$), and less than 24 months of followup ($n = 14$). Therefore, the final study population consisted of 567 patients with Stage IIB osteosarcomas. This study was approved by our institutional research review board.

Three hundred sixty-eight male (65%) and 199 female (35%) patients with a median age of 19 years (range, 3–68 years) were included in this study (Table 1). The initial tumor volume was 150 mL or less in 304 patients (54%) and greater than 150 mL in 263 (46%). Four hundred seventy-one (83%) tumors were located around the knee and at other distal sites. The remaining 96 tumors (17%) were proximally situated (proximal femur, humerus, and pelvis).

Management and the Definition of Study Variables

The procedures used to define tumor extent included plain radiography and MRI of primary tumors, whole-body bone scanning, and chest CT. All 567 patients had Stage IIB disease according to the Musculoskeletal Tumor Society classification [10]. The factors assessed included age, sex, location of the primary tumor, plain radiographic pattern (radiodense, radiolucent, mixed), MRI findings (presence of the fluid-fluid level on T2-weighted axial image), pathologic subtype, tumor volume at presentation as seen on MRI, tumor volume change after chemotherapy (postchemotherapy/prechemotherapy tumor volume), surgical margin, and histologic response to preoperative chemotherapy.

All patients had preoperative chemotherapy, surgery, and postoperative chemotherapy and were followed up as previously described [18]. No patients received radiotherapy either preoperatively or postoperatively. All patients completed six cycles of the modified T10 protocol as described previously [26]. Briefly, each chemotherapy cycle

Table 1. Patient characteristics

Characteristic	Number of patients (n = 567)	Percentage
Age (years)		
≤ 15	269	47
> 15 to ≤ 40	270	48
> 40	28	5
Gender		
Male	368	65
Female	199	35
Initial tumor volume		
≤ 150 mL	304	54
> 150 mL	263	46
Location		
Distal femur	280	49
Proximal tibia	134	24
Humerus	55	10
Proximal femur	19	3
Distal tibia	14	3
Fibula	34	6
Forearm	9	2
Pelvis	22	4
Pattern on plain radiograph		
Lytic	176	31
Mixed	120	21
Blastic	271	48
Fluid-fluid level		
Absent	459	81
Present	108	19
Pathologic subtype		
Osteoblastic	450	79
Chondroblastic	70	12
Fibroblastic	27	5
Telangiectatic	6	1

consisted of high-dose methotrexate, Adriamycin (Pharmacia & Upjohn S.p.A., Milan, Italy), and cisplatin. The patients received one 8 to 12 g/m² dose on Day 1 and another 8 to 12 g/m² dose on Day 7. On Day 14, cisplatin was administered at 100 mg/m² during 2 hours. Subsequently, Adriamycin was administered at 60 mg/m² for 18 hours. Scheduled durations of chemotherapy ranged from 24 to 36 weeks.

For analysis, we divided patients into three groups according to their age. An age cutoff of 40 years was used to separate older and younger patients. For the younger age group, a cutoff of 15 years was used as the completion point of growth.

Osteosarcomas at proximal locations were compared with those at distal locations. For the upper extremity, the elbow was defined as the dividing point between proximal

and distal. For the lower extremity, a proximal location was assigned when the epicenter of the tumor was proximal to the midpoint of the femur. Plain radiographic patterns were classified as predominantly osteoblastic, predominantly osteolytic, or mixed [19].

All patients underwent MRI before biopsy and after completion of neoadjuvant chemotherapy. Fluid-fluid levels were considered to be present if two layers of varying signal intensity were identified on prechemotherapy T2-weighted axial images. The median interval between the first MRI and initiation of chemotherapy was 5 days, and the interval between the second MRI and surgery was 2 days. Intramedullary tumor extent (tumor length) was measured in coronal sections of unenhanced T1-weighted sequences. Tumor widths and depths were measured in axial sections of enhanced T1-weighted and T2-weighted sequences without fat suppression. MR images were independently reviewed by two of the authors (WSS, D-GJ). When there was a size discrepancy greater than 10%, images were reviewed simultaneously by the same two authors and decisions were made by consensus. Tumor volumes were determined using MR images as described by Gobel et al. [13] using the following formula: tumor volume (TV) = 0.53 × tumor length (TL) × tumor width (TW) × tumor depth (TD). We considered that a unidimensional size change greater than 5% could be reproducibly detected after taking into account interobserver variation. A unidimensional change of 5% corresponds to a three-dimensional change of 15% ($1.05^3 = 1.157$). Therefore, in this study, we defined an increase in volume using a cutoff of 15%. To determine the change in tumor volume, volumes after treatment were divided by volumes before chemotherapy, and these were expressed as tumor volume ratios [15]. Patients were assigned to one of two groups according to their tumor volume ratios. Specifically, tumor volume ratios greater than 1.15 were designated as increased and those 1.15 or less were designated as stable or decreased.

Slides of tumor tissue were reviewed by two pathologists (MSK, JSK) to determine the histologic subtype of the osteosarcoma. The subtype was determined according to the characteristics of the predominant matrix (greater than 50% in area) in the prechemotherapeutic biopsy specimen. Surgical margins were assessed using the method of Enneking et al. [10].

Histologic responses to preoperative chemotherapy were graded according to the percentage of tumor necrosis: good response (necrosis ≥ 90%) and poor response (< 90% necrosis) [24]. For survival analysis, the primary end point was time to event (metastasis or local recurrence). Event-free survival was measured from the date of initial diagnosis to date of the event. Data for patients who did not have metastases develop or who survived were censored at the final followup. The minimum followup was 6 months (mean, 103 months; range, 6–281 months).

Statistics

Fisher's exact test and Student's t-test were used to identify the correlation between tumor volume changes and clinico-pathologic variables. Logistic regressions were performed to identify variables at presentation that could predict tumor volume increase after chemotherapy. Multivariate analysis using the Cox proportional hazards model was performed on all factors found to be significant by univariate analysis. The Kaplan-Meier method and the log-rank test were used to analyze survival differences. Analyses were performed using SPSS Version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

What Factors at Presentation Predict Tumor Enlargement?

After preoperative chemotherapy, 215 patients (38%) showed a tumor volume increase greater than 15% and 352 patients (62%) showed unchanged tumor volume or a decrease in tumor volume (Table 2). The logistic model for tumor volume increase revealed that proximal location ($p < 0.01$; relative risk [RR], 2.41) and the presence of the fluid-fluid level on initial MRI ($p < 0.01$; RR, 5.56) were independent predictors of tumor volume increase after chemotherapy (Table 3). One hundred eight (19%) tumors showed fluid-fluid levels on T2-weighted prechemotherapy MR images. Seventy-seven (71%) of 108 tumors showed enlargement greater than 15% (Fig. 1). Fifty-five (57%) of 96 proximally located tumors showed tumor progression greater than 15% (Fig. 2), whereas 160 (34%) of 471 distal tumors showed tumor enlargement after chemotherapy.

What Factors at Presentation Predict Survival?

Among factors at presentation, a large tumor volume ($p < 0.01$; RR, 1.59; 95% CI, 1.22–2.04), proximal location of the tumor ($p = 0.01$; RR, 1.50; 95% CI, 1.19–2.19), and the presence of the fluid-fluid level ($p < 0.01$; RR, 1.84; 95% CI, 1.37–2.5) were independent predictors of a reduction in event-free survival (Table 4).

What Factors at Presentation and Treatment-related Factors Predict Survival?

Large tumor volume at presentation ($p < 0.01$; RR, 1.54; 95% CI, 1.19–2.00), tumor enlargement greater than 15% ($p < 0.01$; RR, 3.88; 95% CI, 2.87–5.24), an inadequate surgical margin ($p < 0.01$; RR, 2.42; 95% CI, 1.78–3.28),

Table 2. Univariate analysis of tumor volume change after chemotherapy

Variable	Tumor volume stable or increase $\leq 15\%$	Tumor volume increase $> 15\%$	p value
Age (years)			
≤ 15	164 (61%)	105 (39%)	0.060
> 15 to ≤ 40	176 (65%)	94 (35%)	
> 40	12 (43%)	16 (57%)	
Gender			
Male	225 (61%)	143 (39%)	0.531
Female	127 (64%)	72 (36%)	
Initial tumor volume			
Mean (range)	189.9 (3–2167)	181.3 (9–904)	0.608
≤ 150 mL	184 (60%)	120 (40%)	0.412
> 150 mL	168 (64%)	95 (36%)	
Location			
Distal femur	181 (65%)	99 (35%)	0.001
Proximal tibia	92 (69%)	42 (31%)	
Humerus	20 (36%)	35 (64%)	
Proximal femur	10 (53%)	9 (47%)	
Distal tibia	7 (50%)	7 (50%)	
Fibula	24 (70%)	10 (30%)	
Forearm	7 (78%)	2 (22%)	
Pelvis	11 (50%)	11 (50%)	
Pattern on plain radiograph			
Lytic	104 (59%)	72 (41%)	0.498
Mixed	79 (66%)	41 (34%)	
Blastic	169 (62%)	102 (38%)	
Fluid-fluid level			
Absent	321 (70%)	138 (30%)	< 0.001
Present	31 (29%)	77 (71%)	
Pathologic subtype			
Osteoblastic	285 (63%)	165 (37%)	0.530
Chondroblastic	38 (54%)	32 (46%)	
Fibroblastic	15 (55%)	12 (45%)	
Telangiectatic	4 (67%)	2 (33%)	
Others	10 (71%)	4 (29%)	
Histologic response			
Good	196 (84%)	36 (16%)	< 0.001
Poor	147 (46%)	171 (54%)	
Final outcome			
Alive	308 (71%)	125 (29%)	< 0.001
Dead	44 (33%)	90 (67%)	
Total	352 (100%)	215 (100%)	

and poor histologic response ($p = 0.03$; RR, 1.43; 95% CI, 1.03–1.99) were independent poor prognostic factors for event-free survival (Table 5). Ten-year overall and event-free survival rates were $68\% \pm 4.1\%$ and $57\% \pm 4.2\%$, respectively. Metastasis occurred in 235 patients (41%),

Table 3. Logistic models for tumor volume increase after chemotherapy

Variable	Univariate			Multivariate		
	RR	95% CI	p value	RR	95% CI	p value
Age (years)						
≤ 15	1			ND	ND	ND
> 15 to ≤ 40	0.83	0.59–1.18	0.31			
> 40	2.08	0.95–4.58	0.07			
Gender						
Male	1			ND	ND	ND
Female	0.89	0.62–1.28	0.53			
Initial tumor volume						
≤ 150 mL	1			ND	ND	ND
> 150 mL	0.87	0.62–1.22	0.41			
Location						
Distal	1			1		
Proximal*	2.61	1.67–4.08	< 0.01	2.41	1.50–3.86	< 0.01
Pattern on plain radiograph						
Lytic	1			ND	ND	ND
Mixed	1.15	0.78–1.69	0.49			
Blastic	0.86	0.55–1.35	0.51			
Fluid-fluid level						
Absent	1			1		< 0.01
Present	5.78	3.64–9.17	< 0.01	5.56	3.48–8.87	
Pathologic subtype						
Osteoblastic	1			ND	ND	ND
Chondroblastic	1.46	0.88–2.42	0.15			
Others	1.07	0.58–1.99	0.83			

RR = relative risk; * proximal = humerus, proximal femur, pelvis; ND = not done.

and of these 235 patients, 59 (25%) had local recurrence during their disease course. Four patients had local recurrence only. Primary metastases were located in the lung in 195 patients, in the bone in 25, in the lung and bone in eight, and in other locations in seven. The mean interval from diagnosis to metastasis was 23 months (range, 3–156 months; median, 17 months).

Discussion

Almost half of all patients with osteosarcoma respond unfavorably to chemotherapy [5]. Therefore, being able to predict responsiveness before the start of treatment would be of critical interest for physicians and patients. Previous trials have used three risk factors (tumor size, identification of a chondroblastic component on biopsy, and tumor/non-tumor ratio on bone scan) to predict poor response with controversial results in terms of being able to discriminate high-risk groups [12]. Tumor enlargement after chemotherapy is an independent prognostic factor in predicting

poor histologic response; therefore, we decided to focus on this factor. Of the clinical factors at the time of diagnosis, we identified that the proximal tumor location and the presence of the fluid-fluid level observed on MRI predicted tumor progression after chemotherapy. Moreover, further analysis showed that tumor enlargement has a greater relative effect on survival than any other factor, including initial tumor size, surgical margin, and histologic response.

There are several limitations to this study. Ideally, prognostic studies should be performed prospectively. However, patient recruitment to achieve a sufficient sample size takes several years and the duration of followup required to determine long-term outcomes makes such a study in one institution difficult to achieve. Therefore, we conducted a retrospective analysis of a large group of patients and included only patients with high-grade osteosarcoma who met the inclusion criteria. Although a relatively large number of patients were included, they were from one institution, and our results should be validated in a study with a larger number of patients. Second, we did not evaluate some known prognostic factors such as

Fig. 1A-B (A) A T2-weighted fat-suppression image of a distal femoral osteosarcoma shows a large extraosseous mass and fluid-fluid level (arrow). (B) The postchemotherapy T2-weighted image shows a marked increase in tumor size and further accentuation of multiple

fluid-fluid level (arrow). The initial tumor volume of 110 cc increased to 252 cc (130% increase). Histologic response to preoperative chemotherapy was 75%. The patient, a 24-year-old woman, had lung metastasis develop 15 months postoperatively.

Fig. 2A-B (A) A T2-weighted axial image shows a heterogeneously enhancing lesion in the proximal humerus. (B) The postchemotherapy T2-weighted axial image shows marked increase in tumor size. The initial tumor volume of 165 cc increased to 537 cc (3.3-fold

increase). Histologic response to preoperative chemotherapy was 30%. The 16-year-old female patient had lung metastasis develop 3 months after treatment, and despite aggressive metastasectomy, she died of disease 11 months thereafter.

serologic and molecular markers, because data were missing for some of our patients and the predictive power of serologic and molecular markers is controversial. Third, because oriental patients showed poor compliance with standard chemotherapy dosage, we made slight dose reductions. However, the observed 10-year event-free survival rate of 57% in our study is comparable to survival rates in other series [3, 5]. Finally, we characterized the small numbers of pelvic tumors as proximal site. When we eliminated them, the results did not change, therefore they were retained in this analysis.

Regarding the initial clinicopathologic factors, we expected patients who were older, had subtypes other than

the osteoblastic type, had a large tumor, showed an osteolytic type on plain radiography, and had tumors in proximal locations would show tumor enlargement after chemotherapy. Osteolytic osteosarcomas can be associated with pathologic fracture, telangiectatic or fibrous subtype, and Stage IIA lesions [2, 19, 31]. However, in patients with osteolytic osteosarcomas who subsequently had local recurrences, we sometimes observed rapid progression of the tumor after chemotherapy. Therefore, we suspected that the osteolytic pattern might be an expression of hidden aggressiveness. Nevertheless, the plain radiographic pattern failed to show a correlation with tumor enlargement. Instead, during review of the prechemotherapy and

Table 4. Survival analysis for factors at presentation

Variable	Univariate		Multivariate		
	5-year EFSR	p value	RR	95% CI	p value
Age (years)					
≤ 15 (n = 269)	61 ± 3.0	0.36	ND	ND	ND
> 15 (n = 298)	58 ± 2.9				
Gender					
Male (n = 368)	85 ± 1.8	0.27	ND	ND	ND
Female (n = 199)	71 ± 3.2				
Initial tumor volume					
≤ 150 mL (n = 304)	66 ± 2.7	< 0.01	1	1.22–2.04	< 0.01
> 150 mL (n = 263)	53 ± 3.1		1.58		
Location					
Distal (n = 471)	63 ± 2.2	< 0.01	1	1.19–2.19	< 0.01
Proximal* (n = 96)	43 ± 5.1		1.61		
Pattern on plain radiograph					
Lytic (n = 176)	65 ± 3.6	0.14	ND	ND	ND
Blastic or mixed (n = 391)	57 ± 2.5				
Fluid-fluid level					
Absent (n = 459)	64 ± 2.3	< 0.01	1	1.37–2.5	< 0.01
Present (n = 108)	43 ± 4.8		1.83		
Pathologic subtype					
Osteoblastic (n = 450)	61 ± 2.3	0.23	ND	ND	ND
Other (n = 117)	56 ± 4.6				
Total	60 ± 2.1				

EFSR = event-free survival rate; RR = relative risk; ND = not done; * proximal = humerus, proximal femur, pelvis.

postchemotherapy MR images of osteolytic osteosarcomas for patients with local recurrences, we found that tumors with the fluid-fluid level on initial MRI have a strong tendency for tumor enlargement after chemotherapy. In our current study, 31 (29%) of 108 tumors showing fluid-fluid levels at presentation did not have tumor progression. Further study focusing on the relationship between the extent of fluid-fluid levels in tumors and their response pattern after chemotherapy is necessary. Although proximal sites (27/96, 28%) showed a higher percentage of the fluid-fluid level on MRI than nonproximal sites (81/471, 17%), proximal location and MRI findings played independent roles in tumor enlargement. Currently, except for the proximal tumors with fluid-fluid levels, the reason why proximally located tumors are likely to enlarge after chemotherapy is not clear.

Among factors at presentation, proximal location, a large initial tumor, and the presence of fluid-fluid level were independent predictors of a reduction in event-free survival.

Apart from the axial sites, whether proximal sites are associated with poorer prognosis than distal locations remains controversial [23, 25], and if this is the case, the reasons are not yet understood. In a study of a series of

patients at Memorial Sloan-Kettering Cancer Center, the humerus was a favorable site; however, it has been shown that proximal sites are associated with unfavorable outcomes [5, 23, 25]. Bielack et al. [5] speculated that variations in chemosensitivity cannot explain the poor prognosis associated with proximal locations, because there was no correlation between various extremity sites and response. In contrast, in a previous study [8], the proximal humeral site was associated with a higher incidence of pathologic fracture and poor histologic response than other extremity locations. Regarding tumor size, we initially expected that a large tumor at presentation would predict volume increase after chemotherapy. However, we found that initial tumor size did not correlate with tumor enlargement, but a large initial tumor volume did show an independent role in worsening survival. Although the tumor enlargement after chemotherapy and poor histologic response were not identical, in a study with the largest series, Bielack et al. [5] reported no correlation between tumor size and response in osteosarcomas of the extremities. They assumed the higher relapse risk for patients with large primary tumors would be attributable to an increase in metastatic burden parallel to tumor size.

Table 5. Survival analysis including factors at presentation and treatment-related factors

Variable	Univariate		Multivariate		
	5-year EFSR	p value	RR	95% CI	p value
Age (years)					
≤ 15 (n = 269)	61 ± 3.0	0.36	ND	ND	ND
> 15 (n = 298)	58 ± 2.9				
Gender					
Male (n = 368)	85 ± 1.8	0.27	ND	ND	ND
Female (n = 199)	71 ± 3.2				
Initial tumor volume					
≤ 150 mL (n = 304)	66 ± 2.7	< 0.01	1	1.19–2.00	< 0.01
> 150 mL (n = 263)	53 ± 3.1		1.54		
Location					
Distal (n = 471)	63 ± 2.2	< 0.01	1	0.77–1.45	0.74
Proximal* (n = 96)	43 ± 5.1		1.06		
Pattern on plain radiograph					
Lytic (n = 176)	65 ± 3.6	0.14	ND	ND	ND
Blastic or mixed (n = 391)	57 ± 2.5				
Fluid-fluid level					
Absent (n = 459)	64 ± 2.3	< 0.01	1	0.78–1.44	0.72
Present (n = 108)	43 ± 4.8		1.06		
Pathologic subtype					
Osteoblastic (n = 450)	61 ± 2.3	0.23	ND	ND	ND
Other (n = 117)	56 ± 4.6				
Tumor volume change					
≤ 1.15 (n = 352)	78 ± 2.2	< 0.01	1	2.87–5.24	< 0.01
> 1.15 (n = 215)	29 ± 3.2		3.88		
Surgical margin					
Wide (n = 489)	89 ± 1.4	< 0.01	1	1.78–3.28	< 0.01
Other (n = 78)	21 ± 4.7		2.42		
Histologic response					
Good (n = 232)	76 ± 2.8	< 0.01	1	1.03–1.99	0.03
Poor (n = 318)	48 ± 2.8		1.43		
Total	60 ± 2.1				

EFSR = event-free survival rate; RR = relative risk; ND = not done; * proximal = humerus, proximal femur, pelvis.

After completion of chemotherapy and surgery, a large initial tumor, tumor enlargement after chemotherapy, an inadequate surgical margin, and poor histologic response were independent poor prognostic factors for event-free survival. Proximal location and the presence of fluid-fluid levels seem to be subordinate variables for tumor enlargement as they lost significance on the multivariate model. Tumor enlargement after chemotherapy remained the most powerful risk factor for reduced survival. On the contrary, using tumor volume change as a covariate, the relative risk of histologic response which has been regarded as the strongest prognostic factor for localized osteosarcoma, decreased to that of the initial tumor volume. This decrease in relative risk for survival may be

attributable to a strong correlation between volume change and histologic response. We considered that tumor volume change has more predictability in patients showing good histologic response with increased tumor volume and poor response with decreased tumor volume. Given the poor outcome of patients with local recurrence, our major concern is the correlation between local recurrence and location, surgical margin, and chemotherapy response. There were 59 local recurrences in our patients. Nineteen (20%) of 96 patients with proximal site tumors showed local recurrence whereas 40 (8.5%) of 471 patients with tumors in other locations had local recurrences. As a whole, 28 (47%) of 59 patients had inadequate surgical margins, 47 (80%) of 59 showed poor histologic response,

and 48 (81%) of 59 showed tumor volume increase greater than 15%. We presume that the increased rate of local recurrence in the proximal site would be more attributable to the high propensity for tumor volume increase (chemoresistance) rather than relative difficulty in resection.

We identified two (proximal location, presence of fluid-fluid levels on prechemotherapy MRI) easily assessable clinical factors that can predict chemoresistance in patients with localized osteosarcomas. These two factors plus larger volume tumors are associated with a decreased event-free survival. We also found that tumor enlargement after chemotherapy was a more powerful prognostic factor than tumor necrosis. If these findings can be confirmed in other studies, it might be reasonable to treat these poorer prognostic tumors differently. Considering that current efforts to treat these refractory groups are ineffective, alternative treatments such as novel drug regimens or a clinical trial evaluating immediate surgery followed by chemotherapy before these high-risk groups of patients will show chemoresistance might be reasonable approaches to consider.

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