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Original article

Effect of increases in tumor volume after neoadjuvant chemotherapy on the outcome of stage II osteosarcoma regardless of histological response

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Abstract

Background. We assessed volume changes after neoadjuvant chemotherapy and evaluated relations between tumor size changes and clinical characteristics. In addition, we sought to determine whether tumor size change influences patient outcome.

Methods. The records of 127 patients with stage II osteosarcoma who showed more than a 15% volume change after chemotherapy were retrospectively reviewed. Patients were divided into two groups depending on whether tumors increased or decreased in size. Fisher's exact test was performed to analyze correlations between tumor size changes and clinicopathological variables. Five-year metastasis-free survival and overall survival were evaluated using univariate and multivariate analyses.

Results. A total of 71 patients (55.9%) showed a decrease in tumor volume, and 56 patients (44.1%) showed an increase. An increase in tumor volume after neoadjuvant chemotherapy was found to be positively correlated with a poor histological response and subsequent metastasis. Univariate analysis identified the following parameters as poor prognostic factors: age ≤15 years ($P = 0.03$), American Joint Committee on Cancer (AJCC) stage IIB ($P = 0.02$), a subtype other than osteoblastic ($P < 0.01$), a poor histological response ($P < 0.001$), and increased tumor volume after preoperative chemotherapy ($P < 0.0001$). Multivariate analysis revealed that AJCC stage IIB ($P = 0.006$) and an increase in tumor volume after preoperative chemotherapy ($P < 0.001$) both independently shortened metastasis-free survival. However, a poor histological response lost its prognostic significance ($P = 0.34$).

Conclusions. Increased tumor volume after neoadjuvant chemotherapy independently shortened metastasis-free and overall survival in AJCC stage II osteosarcoma patients. Tumor volume changes may serve as a basis for risk-adapted therapy when used in combination with other prognostic factors.

Introduction

Tumor size change is one of the parameters used to evaluate solid tumor response to neoadjuvant chemotherapy.[1] However, tumor volume change after chemotherapy receives little attention as a viable prognostic factor in osteosarcoma patients because usually there is not a marked volumetric response.[2] Therefore, the Response Evaluation Criteria in Solid Tumors (RECIST) are seldom useful for assessing osteosarcoma response to chemotherapy.[3] Several studies have reported that increases in tumor volume are well correlated with a poor histological response to chemotherapy. However, a reduced or stable tumor size cannot guarantee a good response (positive predictive value <60%).[4–8] In their series, the cutoff point for a size change was 5%. However, no evaluation has been undertaken to identify a relevant cutoff in the context of predicting subsequent metastasis.

We previously reported that in terms of tumor necrosis rate and volume change a small portion of good responders who showed an increase in tumor volume after chemotherapy could be reclassified as poor responders.[9] However, little is known about the initial characteristics of patients who show marked size changes after preoperative chemotherapy. To identify such initial characteristics, we selected 127 patients who showed marked volumetric changes after chemotherapy (a volume cutoff of 15%).

In the present study, we evaluated the relation between size changes and clinical characteristics. In addition, we sought to determine whether size changes induced by chemotherapy influences patient outcome.

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Materials and methods

Patients

This retrospective study was conducted on 529 osteosarcoma patients who were registered at the Department of Orthopedic Surgery at our institution between 1992 and 2003. We retrospectively selected 347 cases from among the 529 that met the following criteria: (1) extremity osteosarcoma; (2) American Joint Committee on Cancer (AJCC) stage II; (3) age <40 years; (4) surgery and chemotherapy at our institution; (5) availability of pre/postchemotherapy magnetic resonance (MR) images; (6) a more than 3-year follow-up for event-free patients. Furthermore, 220 of the 347 patients who showed less than a 15% volumetric change on pre/postchemotherapy MR images were excluded. Therefore, the final study population consisted of 127 osteosarcoma patients. Informed consent was obtained from patients or legal guardians, as appropriate. This study was approved by our institutional research review board.

All patients underwent preoperative chemotherapy, surgery, and postoperative chemotherapy and were followed as previously described.[10] No patients underwent radiotherapy preoperatively or postoperatively. All patients completed six cycles of chemotherapy protocol. Briefly, each cycle of chemotherapy consisted of high-dose methotrexate, adriamycin, and cisplatin: Methotrexate 8–12 g/m^2 was administered intravenously twice, on days 1 and 7. On day 14, cisplatin 100 mg/m^2 was given for 2 h intravenously. Subsequently, adriamycin 60 mg/m^2 was delivered for 18 h. The scheduled duration of six cycles of chemotherapy ranged from 24 to 36 weeks. The calculated dose intensity of methotrexate ranged from 2.7 to 6.0 g/m^2/week, and those of cisplatin and adriamycin ranged from 17 to 25 mg/m^2/week and from 10 to 15 mg/m^2/week, respectively. The fractional dose intensity of methotrexate was 0.69, and those of cisplatin and adriamycin ranged from 0.6 to 0.8 and from 0.41 to 0.55, respectively.

The histological response was assessed at the time of surgery and was graded according to the percentage of tumor necrosis using grades III and IV (necrosis of ≥90%) indicating a good response or grades I and II (necrosis of <90%) indicating a poor response.[11]

All patients underwent magnetic resonance imaging (MRI) before diagnostic biopsy and after completion of neoadjuvant chemotherapy. The median time interval between the first MRI and initiation of chemotherapy was 6 days, and the interval between the second MRI and surgery was 2 days. MRI sequences included a standard (spin-echo) T1-weighted sequence (repetition time/echo time 400–900/10–20 ms) with or without gadolinium enhancement and an intermediate-weighted/T2-weighted sequence (1500–2500/70–100) without fat suppression. 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.[2] MR images were independently reviewed by two of the authors (J.Y.Y., D.G.J.). For cases that showed a size discrepancy of more than 10%, images were reviewed simultaneously by the same two authors, and decisions were made by consensus. Tumor volume was determined from individual MR images as described by Bieling et al.[12] (Fig. 1). Tumor volume was calculated by an ellipsoidal formula.

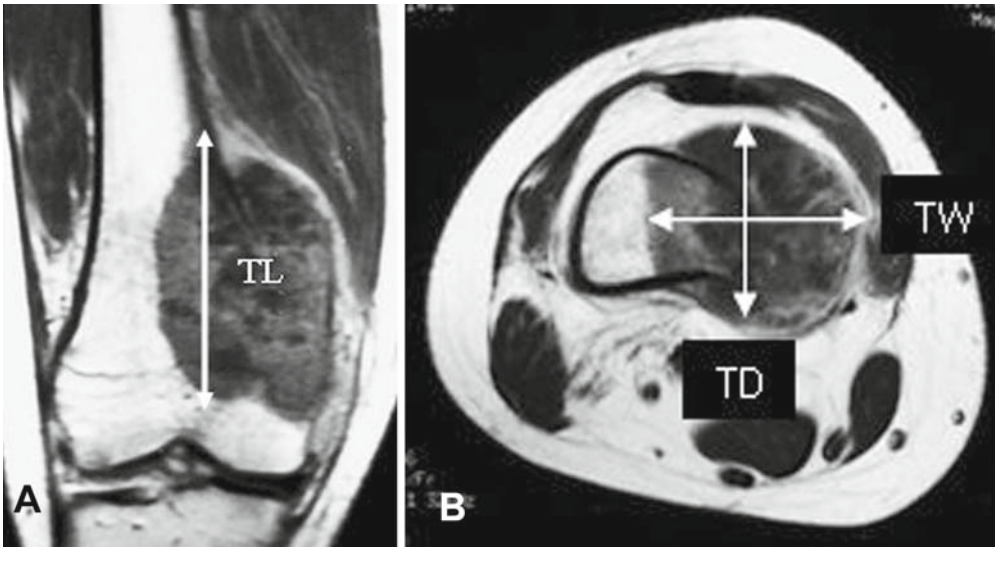

Fig. 1. **A** Tumor length (*TL*) was measured in coronal sections of unenhanced T1-weighted sequences. **B** Tumor width (*TW*) and depth (*TD*) were measured in axial sections of enhanced T2-weighted sequence without fat suppression. Tumor volume was calculated by an ellipsoidal formula: Tumor volume = $\pi \times TL \times TW \times TD/6$

Tumor volume = π × tumor length × width × depth/6

Statistics

We divided patients into two groups: increased tumor size and decreased tumor size. Fisher's exact test was performed to identify correlations between tumor size changes and clinicopathological variables. In the survival analysis, the primary endpoints used were time to metastasis and time to death. Metastasis-free periods were defined from the date of diagnosis to the last visit or the date of distant metastasis detection. Overall survival time was defined from the date of diagnosis until death (from all causes) or the last follow-up. The assessed variables were age, sex, AJCC stage, pathological subtype, tumor location, histological response to preoperative chemotherapy, and metastasis. Survival analysis with respect to clinicopathological variables, metastasis, or death was performed using the Kaplan-Meier method; and the significance of the differences was determined using the log-rank test. In addition, we divided patients into four groups by combining the two prognostic factors — volume change and histological response or AJCC stage — and performed survival analysis. Factors found to influence prognosis by univariate analysis were subjected to multivariate analysis using a Cox's proportional hazard regression model and a backward conditional stepwise procedure to determine whether these factors independently affected prognosis. The results of the Cox model analysis are reported as relative risk and 95% confidence interval. All calculations were performed using SPSS version 13.0 (SPSS, Chicago, IL, USA). Differences with associated $P < 0.05$ values were considered significant.

Results

Patient characteristics and correlations with tumor volume changes

Patient characteristics are summarized in Table 1. Briefly, 83 males (65.4%) and 44 females (34.6%) of median age 16 years (range 4–39 years) were included in this study. Based on the AJCC staging system, 42 patients (33.1%) had a stage IIA tumor, and 85 (66.9%) had a stage IIB tumor. After preoperative chemotherapy, 71 patients (55.9%) showed a tumor volume decrease, and 56 patients (44.1%) showed a tumor volume increase. An increased tumor volume was found to be positively correlated with the following clinicopathological variables: age ≤15 years ($P = 0.01$), subtypes other than osteoblastic ($P = 0.02$), a poor histological response ($P < 0.001$), and subsequent metastasis ($P < 0.001$).

Survival analysis

The median follow-up for all 127 patients was 71 months, and their 5-year overall survival rate, as determined

Table 1. Patient characteristics according to size change

Characteristic	No.	Increase	Decrease	*P*
Age				
≤15 years	61 (48.0%)	34 (55.7%)	27 (44.3%)	0.01
>15 years	66 (52.0%)	22 (33.3%)	44 (66.7%)	
Sex				
Male	83 (65.4%)	39 (47.0%)	44 (53.0%)	0.45
Female	44 (34.6%)	17 (38.6%)	27 (61.4%)	
AJCC stage				
IIA	42 (33.1%)	19 (45.2%)	23 (54.8%)	1.00
IIB	85 (66.9%)	37 (43.5%)	48 (56.5%)	
Subtype				
Osteoblastic	114 (89.8%)	46 (40.4%)	68 (59.6%)	0.02
Other	13 (10.2%)	10 (76.9%)	3 (23.1%)	
Location				
Distal femur	62 (48.8%)	26 (41.9%)	36 (58.1%)	0.58
Proximal tibia	30 (23.6%)	12 (40.0%)	18 (60.0%)	
Proximal humerus	13 (10.2%)	8 (61.5%)	5 (38.5%)	
Other	22 (17.3%)	10 (45.5%)	12 (54.5%)	
Histological response				
Good	56 (44.1%)	9 (16.1%)	47 (83.9%)	<0.001
Poor	71 (55.9%)	47 (66.2%)	24 (33.8%)	
Metastasis				
Yes	60 (47.2%)	41 (68.3%)	19 (31.7%)	<0.001
No	67 (52.8%)	15 (22.4%)	52 (77.6%)	
Total	127 (100%)	56 (44.1%)	71 (55.9%)	

AJCC, American Joint Committee on Cancer

using the Kaplan-Meier method, was 68.6% [95% confidence interval (CI) 64.3%–72.9%]. Metastasis occurred in 60 patients (47.2%), and the 5-year metastasis-free survival rate was 53.2% (95% CI 48.7%–57.7%). Metastases were located in lung in 50 patients, bone in 5, lung and bone in 2, and in other locations in 3. The mean interval from diagnosis to metastasis was 18.6 months (range 3–64 months; median 14.5 months).

Univariate analysis identified the following parameters as poor prognostic factors in terms of metastasis-free survival (Table 2, Fig. 2A); age ≤15 years ($P = 0.03$), AJCC stage IIB ($P = 0.02$), subtypes other than osteoblastic ($P < 0.01$), poor histological response ($P < 0.001$), and increased tumor volume after preoperative chemotherapy ($P < 0.0001$). Among these factors, AJCC stage, histological response, and tumor volume change also influenced overall survival. Multivariate analysis revealed that AJCC stage IIB ($P = 0.006$) and increased tumor volume after preoperative chemotherapy ($P < 0.001$) independently shortened metastasis-free survival (Table 3). However, a poor histological response lost its prognostic significance ($P = 0.34$). Similar results were obtained for overall survival.

Subgroup analysis

We divided patients into four groups by combining prognostic factors — histological response and volume

Table 2. Univariate survival analysis

Characteristic	No.	5Y-MFSR	*P*	5Y-OSR	*P*
Age					
≤15 years	61 (48.0%)	43.4 ± 6.5	0.03	62.8 ± 6.6	0.08
>15 years	66 (52.0%)	62.1 ± 6.0		73.7 ± 5.5	
Sex					
Male	83 (65.4%)	52.9 ± 5.5	0.76	71.4 ± 5.1	0.63
Female	44 (34.6%)	53.7 ± 7.6		63.7 ± 7.6	
AJCC stage					
IIA	42 (33.1%)	66.6 ± 7.3	0.02	83.0 ± 5.9	0.01
IIB	85 (66.9%)	46.5 ± 5.5		61.3 ± 5.5	
Subtype					
Osteoblastic	114 (89.8%)	56.0 ± 4.7	<0.01	68.1 ± 4.5	0.45
Other	13 (10.2%)	27.7 ± 13.1		76.9 ± 11.7	
Location					
Distal femur	62 (48.8%)	49.7 ± 6.4	0.45	69.3 ± 6.1	0.27
Proximal tibia	30 (23.6%)	56.7 ± 9.1		76.7 ± 7.7	
Proximal humerus	13 (10.2%)	29.9 ± 15.4		26.4 ± 15.5	
Other	22 (17.3%)	68.2 ± 9.9		72.4 ± 9.6	
Histological response					
Good	56 (44.1%)	71.4 ± 6.0	<0.001	81.5 ± 5.3	0.002
Poor	71 (55.9%)	38.7 ± 5.9		58.0 ± 6.2	
Tumor size					
Increase	56 (44.1%)	27.5 ± 6.1	<0.0001	53.9 ± 7.1	0.0002
Decrease	71 (55.9%)	73.2 ± 5.3		79.7 ± 4.9	
Total	128	53.2 ± 4.5		68.6 ± 4.3	

5Y-MFSR, 5-year metastasis-free survival rate; 5Y-OSR, 5-year overall survival rate

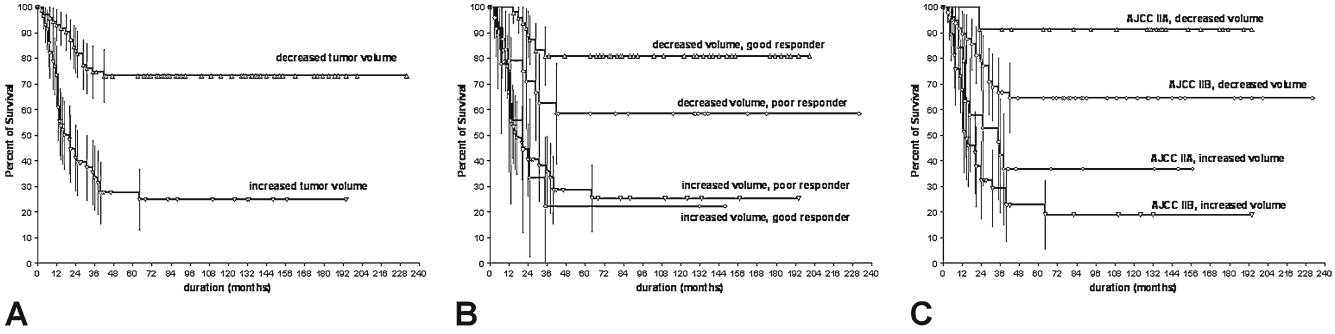

Fig. 2. Metastasis-free survival according to volume change (increased vs. decreased) (**A**), combined volume change and histological response (**B**), and combined volume change and American Joint Committee on Cancer (*AJCC*) stage (**C**)

Table 3. Multivariate survival analysis

	Metastasis-free survival			Overall survival		
Variables	RR	95% CI	*P*	RR	95% CI	*P*
Age ≤15 years	1.60	0.94–2.70	0.08	NA	NA	NA
AJCC stage IIB	2.38	1.29–4.38	0.006	2.93	1.29–6.65	0.01
Other subtype	1.06	0.52–2.18	0.87	NA	NA	NA
Poor histological response	1.41	0.70–2.85	0.34	1.86	0.83–4.17	0.14
Increased size	4.29	2.46–7.49	<0.001	3.41	1.77–6.57	<0.001

RR, relative risk; CI, confidence interval; NA, not assessed

change — and performed survival analysis. The groups were as follows: group 1, decreased volume and good histological response (n = 47); group 2, decreased volume and poor response (n = 24); group 3, increased volume and good response (n = 9); group 4, increased volume and poor response (n = 47). The 5-year metastasis-free survival rates of these groups were 80.9% (group 1), 58.3% (group 2), 22.2% (group 3), and 28.5% (group 4) (Fig. 2B). All groups showed survival difference except groups 3 and 4 (P = 0.77).

Second, we created another four groups according to volume change and AJCC stage, as follows: group I, decreased volume and AJCC stage IIA (n = 23); group II, decreased volume and AJCC stage IIB (n = 48); group III, increased volume and AJCC stage IIA (n = 19); group IV, increased volume and AJCC stage IIB (n = 37). The 5-year metastasis-free survival rates of these four groups were 91.3% (group I), 64.5% (group II), 36.8% (group III), and 22.7% (group IV) (Fig. 2C). All groups showed survival differences except for groups III and IV (P = 0.13).

Discussion

The prognostic factors of localized osteosarcoma can be divided into two categories: (1) clinicopathological variables at the time of diagnosis (e.g., tumor size, skip metastasis, old age, axial location) and (2) treatment-related variables (e.g., histological response and local recurrence).[13,14] Moreover, tumor volume changes after preoperative chemotherapy might serve as a prognostic factor.[15] A correlation between increased tumor volume and poor histological response has been reported, but the prognostic relevance of volume change remains to be verified.[5,16] In this retrospective study, we obtained the following results: A tumor volume increase after neoadjuvant chemotherapy was found to be positively correlated with a poor histological response and subsequent metastasis. However, we found it difficult to predict which patients would show an increase in tumor size based on their initial characteristics, such as initial tumor size or location. Furthermore, an increase in tumor volume was found to shorten metastasis-free and overall survival independently in AJCC stage II osteosarcoma patients.

This study has several limitations that deserve consideration. The study had a relatively small sample size, and it was not randomized or controlled. Ideally, this prognostic study should have been done prospectively; but it would have required a long patient follow-up. Therefore, we conducted this retrospective analysis on a cohort of patients who met our inclusion criteria. The second limitation is that tumor volumes were calculated from dimensions measured on MR images using a simplified mathematical formula rather than by using a built-in software package installed in the MRI scanner. Thus, although Shin et al. reported that tumor volumes measured by MRI using the ellipsoid mass formula are closely correlated with volumes calculated using built-in software packages,[8] there are potential risks of our over- or underestimating actual tumor volume and of the data not reflecting tumor extension.

Compared to Ewing's sarcoma, osteosarcoma produces an abundant extracellular matrix, and therefore marked volume change after preoperative chemotherapy cannot be easily determined.[17] We supposed that a unidimensional size change of more than 5% could be reproducibly detected after considering interobserver variation. A unidimensional change of 5% corresponds to a three-dimensional change of 15% (1.05^3 = 1.157; 0.95^3 = 0.857). Therefore, in this study, we defined an increase or decrease in volume using a cutoff of 15%. In the present study, increases in volume ranged from 115% to 432% (median 164%), whereas decreases in volume ranged from 17% to 85% (median 60%).

Initially, we expected that initial patient characteristics (e.g., tumor size) would predict a volume increase during chemotherapy, but unexpectedly it was found that initial factors were not correlated with volume changes, excepting age and histological subtype. However, an age of ≤15 years was related to increased tumor volume, and these patients also had poor metastasis-free survival by univariate analysis. Although histological subtypes other than the osteoblastic type commonly increase in volume after chemotherapy, the

small number of other subtypes enrolled (about 10% of total cases) limits the clinical usefulness of our findings.

Interestingly, the histological response, which has been regarded as the strongest prognostic factor for osteosarcoma,[13,18–21] and which showed statistical significance by univariate analysis in the present study, lost its prognostic relevance when multivariate analysis was performed using volume change as a covariate. This loss of relevance may be due to a strong correlation between volume change and histological response. In addition, we combined the prognostic factors (i.e., volume change and histological response or AJCC stage) and performed subgroup survival analysis. A survival difference was observed for reduced tumor volume with respect to histological response or AJCC stage. Intriguingly, for an increased tumor volume, no survival differences were observed with respect to histological response or AJCC stage. We considered that the patients showing increased tumor volume with good response had technical problems assessing the tumor necrotic rate by conventional histological methods. They usually showed hemorrhagic necrosis and fluid-fluid levels on MR image and high uptake on positron emission tomography, which might be underestimated by histological examination.

Conclusion

An increased tumor volume after neoadjuvant chemotherapy was found to shorten the metastasis-free and overall survival independently in AJCC stage II osteosarcoma patients. However, we were unable to identify patients who would exhibit a later tumor volume increase after chemotherapy using initial patient characteristics. Our findings suggest that tumor volume change could provide a basis for risk-adapted therapy if used in combination with other prognostic factors.

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