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ORIGINAL PAPER

The relation of tumour necrosis and survival in patients with osteosarcoma

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Abstract
Purpose We investigated whether tumour necrosis was associated with disease-free survival (DFS) and overall survival (OS) of osteosarcoma patients treated in our institution.
Methods We retrospectively studied the predictive value of percentage of necrosis in 40 cases of IIB osteosarcoma treated from 1999 to 2008 in our institution. Patient and treatment factors such as age, gender, tumour site, surgery type, pathological type, tumour size, margin status, percentage of tumour necrosis, chemotherapy regimens and cycles were recorded. The average follow-up was 85.9 months (range, 25–135 months).
Results Two patients had local recurrence (LR) alone, five patients had both LR and metastasis, 14 patients had metastasis alone. Twenty-four patients were alive and 16 had died. The five-year DFS and OS were 47.8% and 65.9%, respectively. Tumour necrosis grouped by 90% was not associated with DFS and OS. Patients with greater than 70% necrosis rate had a significantly higher DFS than those with less than 70%.
Conclusion We found no survival advantage at 90% tumour necrosis in our study. Further study with more patients should be performed to evaluate the predictive value of necrosis rate at the cutoff of 70%.

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Introduction

Since the introduction of chemotherapy into the multimodal treatment regimen of high-grade osteosarcoma, its prognosis has impressively improved, with long-term survival being achieved in two-thirds of all patients [1]. In addition to the eradication of micrometastases, neoadjuvant chemotherapy allows the evaluation based on the histological response to chemotherapy. Many studies have shown that the histological response to preoperative chemotherapy is one of the most important predictors for clinical outcome of osteosarcoma [2–11]; in most of these studies, less than 90% of chemotherapy induced tumour necrosis rate was graded as "poor", and 90% or more tumour necrosis rate was defined as "good". Compared with poor responders, good responders had significantly higher event free survival (EFS) [2, 7–10], disease free survival (DFS) [3, 4, 11] and/or overall survival (OS) [2–7, 11]. Histological response with cutoff of 90% tumour necrosis seemed to become the surrogate measure of outcome.

Because good responders had a better survival, the improvement of tumour necrosis rate was theoretically capable of improving the clinical outcome. Inclusion of new drugs (such as ifosfamide) [12], different drugs (methotrexate plus doxorubicin versus methotrexate plus etoposide and ifosfamide) in preoperative chemotherapy [13] or intensification of chemotherapy [14] improved the percentage of good responders, but did not improve EFS, progression free survival and/or OS [12–14]. These results called into question the use of histological response (cutoff of 90% necrosis) as a surrogate outcome measure for this disease. One study argued that response is not an all or nothing phenomenon and that it must not be assumed that the arbitrary 10% viability cutoff line by many investigators represents an absolute value beyond which chemotherapy is

no longer effective. When response was not only divided between good and poor but also according to six regression grades, a more gradual impact became apparent, with stepwise improvement of survival from grade 6 to grade 1 [7]. In a retrospective study including 438 osteosarcoma patients, those with less than 50% necrosis rate had a poorer OS than the other groups with different necrosis grade (50–75%, 75–98% or 98–100%) [15].

Results of some earlier studies showed that histological response was not associated with improved survival of osteosarcoma patients. Replacement salvage chemotherapy with etoposide/ifosfamide combination for poor responders failed to improve metastasis free survival in a clinical trial by the Scandinavian Sarcoma Group [16], while this study showed no difference in metastasis free survival between good and poor responders. In addition, the results of some other nonrandomised clinical trials did show that there was no difference in EFS, OS or DFS between poor responders and good responders when postoperative salvage chemotherapy with addition of ifosfamide or ifosfamide/etoposide was administered for poor responders [17–19]. The results of these studies seemed to suggest that histological response with cutoff of 90% tumour necrosis lost its predictive significance for survival when salvage chemotherapy is administered postoperatively for patients with poor histological response.

This study aimed to evaluate the relation of percentage of tumour necrosis and DFS/OS in osteosarcoma patients treated at our institution following IRB approval.

Patients and methods

From 1999 to 2008, 67 consecutive osteosarcoma patients were treated at our institution. All diagnoses were confirmed histologically. Patients lost to follow-up or without preoperative chemotherapy and those with unconventional types of osteosarcoma including extraskeletal osteosarcoma, radiation-induced osteosarcoma, Paget's disease based osteosarcoma, low grade centre osteosarcoma and parosteal osteosarcoma were excluded from this study. Patients with MSTS stage IIIB were also excluded from this study.

The remaining 40 consecutive patients met the inclusion criteria. They were treated with neoadjuvant chemotherapy, resection or amputation, with or without adjuvant chemotherapy. This group included 21 males and 19 females ranging in age from 12 to 76 years (median, 22 years). The pathological varieties included: 32 osteoblastic type, seven chondroblastic type and one fibroblastic type. Location of osteosarcoma included: 24 distal femur, three proximal tibia, five pelvis or acetabulum, one humerus, one proximal femur, two distal tibia, two fibular bone, one rib and one radius.

All patients had two to six cycles of preoperative chemotherapy following biopsy. The three-drug regimen of cisplatin, adriamycin and high dose methotrexate was used in 26 patients (26/40: 65%), while other regimens were used in the other 14 patients preoperatively. Definitive surgery was performed within four weeks following completion of the preoperative chemotherapy. After surgical healing, 35 patients underwent postoperative chemotherapy; the three-drug regimen of cisplatin, adriamycin and high dose methotrexate was used in 18 patients, while other regimens were used in another 17 patients. Five patients did not have postoperative chemotherapy, among them, one patient had six cycles of preoperative chemotherapy, and the other four patients had no postoperative chemotherapy for delayed healing, infection or life-threatening toxicity. Among patients with postoperative chemotherapy, 20 patients received the same preoperative regimen postoperatively, while the drug regimen was changed in 15 patients. Thirty-five patients underwent limb salvage surgery or resection and five patients had amputation including one external hemipelvectomy, one hip disarticulation, two below knee amputations, and one above knee amputation. Radical resections with prosthesis reconstruction were performed in 27 cases. Radical resections without prosthesis reconstruction were performed in eight cases. Patients were followed-up with both imaging studies and physical examination.

Medical charts of all patients were carefully reviewed to collect clinical and pathological data. Tumour size was measured as the maximal diameter of tumour in the resection specimen in 37 patients; it was estimated according to the maximum diameter in the preoperative MRI reports in two patients, and the size of tumour was not available in one patient. A positive margin was defined as tumour present at the inked surgical margin. A negative margin was defined as no tumour present at the inked surgical margin. The tumour necrosis rate was recorded from the pathological reports, all of which were reviewed and confirmed by a senior pathologist in our hospital. Different cutoff standards were used for classification of tumour necrosis rate; 90% was used as the first cut-off parameter such that equal or greater than 90% of necrosis was defined as good histological response, and less than 90% was defined as poor histological response. The second cut-off parameter was 70%, which is the median tumour necrosis rate of all patients. According to tumour necrosis rate of 70%, all patients were divided into two groups, one had less than 70% necrosis, the other had 70% or more necrosis.

Statistics

The time zero was the date of diagnosis (biopsy date). The follow-up time ranged from 25 to 135 months (mean

85.9 months, median 92 months) for all patients. All clinical and pathological factors including age (younger versus older than 22 years), gender, tumour site (trunk versus extremities), surgery type (amputation versus resection), pathological type (osteoblastic versus other types), tumour size (<8 cm versus≥8 cm), margin status (negative versus positive), histological response (<90% versus≥90%; <70% versus≥70%), chemotherapy regimens (the three drug regimen including cisplatin, adriamycin and methotrexate versus other regimens) and completed cycles of chemotherapy (less than five cycles of chemotherapy versus five or more cycles of chemotherapy) were first investigated by univariate techniques. *T*-test was used to compare tumour necrosis rate between different groups. The disease-free survival (DFS) and overall survival (OS) were calculated by Kaplan-Meier method with log-rank test. Cox proportional hazards model was used for multivariate analysis to identify independent predictive factors. $P \leq 0.20$ in univariate analysis and some selected covariates were included in multivariate analysis. $P \leq 0.05$ was considered statistically significant. The SPSS software was used for all statistical analysis.

Results

Twenty-four patients were still alive including 23 patients with no evidence of disease and one with disease. Sixteen patients had died. The five-year DFS and OS were 47.8% and 65.9%, respectively. Two patients had local recurrence (LR) alone. Five patients experienced both LR and metastasis (sites were in the lung in three cases, lung and bone in one case and multiple bone in one case). The median time to LR was 21 months (range 8–133 months). Among the seven patients with LR, six died and one was alive with no evidence of disease. Fourteen developed metastasis alone, among them, nine patients had lung metastasis, two patients experienced both lung and bone metastasis, one patient had multiple bone metastasis, one patient developed lung and lymph note metastasis, and one patient had tongue and chest metastasis. The median time to metastasis was 18 months (range 2–98 months); among them three patients were still alive with no evidence of disease, one patient was alive with disease, and the other ten patients died of disease.

The tumour necrosis rate ranged from 1 to 100% (median 70%). Tumour necrosis rate was greater than 90% in ten patients, 70–90% in 11 patients and less than 70% in 19 patients. Negative margins were achieved in 34 patients, positive margins in six patients. The tumour size ranged from 2.5 cm to 18 cm (median, 8 cm).

Tumor necrosis rates were not significantly different when patients were grouped by age, gender, tumour site, tumour size, surgery type, pathological type, margin status or preoperative chemotherapy regimens (Table 1).

Kaplan–Meier analysis showed that the DFS of 66.7% was higher for patients who achieved 70% or more tumour necrosis versus 26.3% for those with less than 70% tumour necrosis ($P=0.036$, Fig. 1). Age, gender, tumour site, surgery type, pathological type, tumour size, tumour necrosis rate with cutoff of 90%, margin status, chemotherapy regimens and completed cycles of chemotherapy were not correlated with DFS in univariate analysis (Table 2). Among 35 patients who received postoperative chemotherapy, no significant difference was found in DFS ($P=0.348$) between patients using the same regimen postoperatively (12/20; 60%) and those who changed their postoperative regimens (6/15; 40%). Tumour necrosis rate grouped by 70%, age grouped by 22 years, and margin status (positive vs. negative) were selected into multivariate analysis. Only tumour necrosis rate grouped by 70% remained significant as an independent predictor for DFS ($P=0.044$; relative risk, 2.555; 95% confidence interval, 1.026–6.356).

Kaplan–Meier analysis showed no correlation of tumour necrosis grouped by 90% or 70% and OS. Age, gender, tumour site, surgery type, pathological type, tumour size, margin status, chemotherapy regimens and completed cycles of chemotherapy were not correlated with OS in univariate analysis (Table 3). Among 35 patients who received postoperative chemotherapy, no significant difference was found in OS ($P=0.694$) between patients using the same regimen postoperatively (10/15; 66.7%) and those who changed their postoperative regimens (13/19; 68.4%). Completed cycles of chemotherapy and tumour necrosis rate grouped by 70% were selected into the multivariate analysis, but none of them remained significant in the Cox model.

Discussion

Many previous studies have shown histological response to preoperative chemotherapy to be an important predictive factor for survival of osteosarcoma [2–11]. There are different systems grading the tumour response to preoperative chemotherapy, such as those by Rosen et al. [20] and Salzer-Kuntschik et al. [21], but most studies chose to define a good response as 90% or more tumour necrosis. Although good histological response was reported to predict better survival compared with poor histological response, many studies have shown that increasing the proportion of patients with good histological response did not result in improvement of survival [12–14]. In our study, only 25% (10/40) of patients achieved 90% or more tumour necrosis, which is much lower than 63% [2], 58.7% [6] and 55.6% [7] of good responders in some prior studies with

Table 1 Comparison of tumour necrosis rate according to different clinical, pathological factors

Characteristics	Patient groups	Tumour necrosis rate (% mean ± SD)	*P* value
Age	<22	58.86±28.70	0.171
	≥22	70.00±20.68	
Gender	Male	65.48±24.90	0.735
	Female	62.68±26.82	
Tumour site	Extremities	64.74±24.45	0.735
	Trunk	60.83±33.53	
Tumour size	<8 cm	63.59±27.17	0.847
	≥8 cm	65.23±25.24	
Surgery type	Resection	64.46±26.32	0.843
	Amputation	62.00±21.39	
Pathological type	Osteoblastic	66.28±22.62	0.297
	Other	55.63±21.95	
Margin status	Negative	63.71±24.73	0.797
	Positive	66.67±32.20	
Preoperative chemotherapy	CDDP, ADRIA, MTX	66.19±27.34	0.498
	Other	60.36±22.23	

SD standard deviation, *CDDP* cisplatin, *ADRIA* adriamycin, *MTX* methotrexate

larger sample size, but the five-year OS of 65.9% in our study group was similar to the 65.3% [7], 66.2% [2] and 68.1% [6] reported in those studies. These contradictory results make the histological response (cutoff, 90% necrosis) as a surrogate measure of outcome questionable. In one study including 1,702 patients, it is argued that the histological response should not be misinterpreted as an all or nothing phenomenon; it must not be assumed that the arbitrary 10% viability cutoff line represents an absolute border beyond which chemotherapy is no longer effective; in this study, tumour necrosis showed a gradual effect on survival [7].

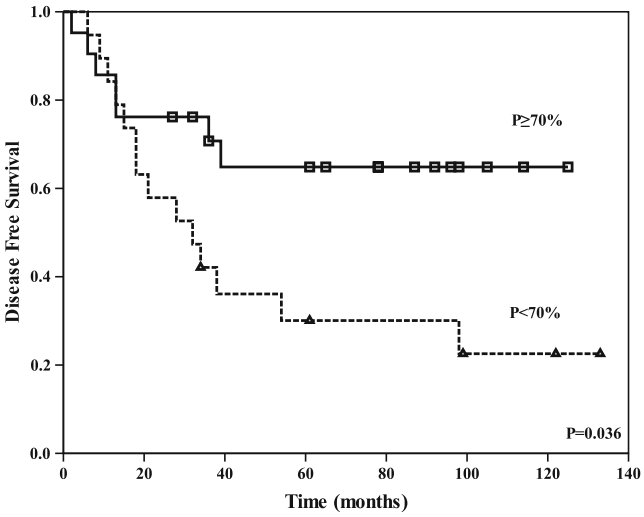

Fig. 1 This Kaplan-Meier survival curve shows disease-free survival for patients grouped by tumour necrosis rate of 70%. The DFS of 66.7% was higher for patients who achieved 70% or more tumour necrosis versus 26.3% for those who had less than 70% tumour necrosis (*P*=0.036)

The results of our study show that there was no significant difference between patients with more than 90% tumour necrosis and those with less than 90% tumour necrosis (60% versus 43.3%, *P*=0.474). Patients who achieved 70% or more tumour necrosis had a higher DFS rate of 66.7% compared with 26.3% for those who had less than 70% tumour necrosis (*P*=0.036). Multivariate analysis showed that tumour necrosis rate grouped by 70% remained significant as an independent predictive factor for DFS (*P*=0.044). This result may be possibly explained since patients who had 70–90% tumour necrosis achieved the same DFS rate as those showing greater than 90% tumour necrosis. In a retrospective study including 438 osteosarcoma patients, patients with less than 50% necrosis rate had a poorer OS than the other groups with different necrosis grade (50–75%, 75–98% or 98–100%) [15]. It is hard to draw a conclusion that 70% or more tumour necrosis rate is the new border for predicting DFS because of the limited sample size in our study group. But together with results of previous studies [12–14], the use of 90% necrosis as a surrogate outcome measure is controversial.

Our results showed that histological response with cutoff of either 70% or 90% tumour necrosis was not correlated with OS. Results of some studies also showed that 90% tumour necrosis did not correlate with survival [16–19]. A clinical trial by the Scandinavian Sarcoma Group showed that the etoposide/ifosfamide replacement combination did not improve outcome in the poor histological responders, but it should be noted that histological response was not associated with metastasis-free survival in this study [16]. Several non-ransomised clinical trials and retrospective studies have shown similar results in terms of correlation of histological response and survival when postoperative salvage chemotherapy with addition of ifosfamide or

Table 2 Univariate analysis on disease free survival (DFS)

Factor	Patient group	DFS (%)	*P* value
Age	<22	36.8	0.158
	≥22	57.1	
Gender	Male	47.6	0.979
	Female	47.4	
Tumour site	Extremities	47.1	0.948
	Trunk	50	
Surgery type	Resection	48.6	0.720
	Amputation	40	
Pathological type	Osteoblastic	46.9	0.940
	Other type	50	
Tumour size	<8.0	52.9	0.375
	≥8.0	45.5	
Tumour necrosis grouped by 90%	≥90%	60	0.474
	<90%	43.3	
Tumour necrosis grouped by 70%	≥70%	66.7	0.036[a]
	<70%	26.3	
Margin status	Negative	50	0.193
	Positive	33.3	
Chemotherapy regimens	CDDP, ADRIA, MTX	56.3	0.426
	Other regimens	41.7	
Completed cycles ofchemotherapy	<5 cycles	36.4	0.237
	≥5 cycles	51.7	

CDDP cisplatin, *ADRIA* adriamycin, *MTX* methotrexate

[a] Indicates statistical significance

Table 3 Univariate analysis on overall survival (OS)

Factor	Patient group	OS (%)	*P* value
Age	<22	52.6	0.394
	≥22	66.7	
Gender	Male	57.1	0.956
	Female	63.2	
Tumour site	Extremities	61.8	0.441
	Trunk	50	
Surgery type	Resection	57.1	0.438
	Amputation	80	
Pathological type	Osteoblastic	56.3	0.334
	Other type	75	
Tumour size	<8.0	64.7	0.602
	≥8.0	59.1	
Tumour necrosis grouped by 90%	≥90%	70	0.437
	<90%	56.7	
Tumour necrosis grouped by 70%	≥70%	71.4	0.155
	<70%	47.4	
Margin status	Negative	58.8	0.992
	Positive	66.7	
Chemotherapy regimens	CDDP, ADRIA, MTX	62.5	0.901
	Other regimens	58.3	
Completed cycles ofchemotherapy	<5 cycles	45.5	0.069
	≥5 cycles	65.5	

CDDP cisplatin, *ADRIA* adriamycin, *MTX* methotrexate

ifosfamide/etoposide was administered [17–19]. In these studies, no significant difference was found between poor responders and good responders in EFS, DFS or OS. All these studies seemed to suggest that histological response (cutoff of 90% tumour necrosis) lost its predictive value for clinical outcome when salvage chemotherapy was administered postoperatively for poor responders. In our study, 20 patients received the same preoperative regimen postoperatively, while the drug regimen was changed in 15 patients. No significant difference was found in DFS and OS between patients using the same regimen postoperatively and those who changed their postoperative regimens. But it is difficult to draw a conclusion from our study that salvage chemotherapy could not improve survival because of the retrospective nature of our study. To date, attempts to modify postoperative chemotherapy based on response ("salvage chemotherapy") have not resulted in convincingly improved outcomes [1]. Further controlled prospective clinical trials should be taken to assess the efficacy of salvage chemotherapy by randomisation for poor responders. In our hospital, a randomised clinical trial has started for poor responders randomised to accept the same chemotherapy regimen in one group and salvage chemotherapy with ifosfamide/etoposide in another group. We are looking forward to the results.

There are several limitations to our study. First, it is not a randomised or controlled study. Secondly, it is limited to patient numbers because of the low incidence of this disease in the whole population (2–3/million/year [22]). But in our study group, no patients were lost to follow-up. Considering the time of relapse, the average follow-up time of 85.9 months is long enough to evaluate survival. Moreover, with our current multimodality treatment regimens, the five-year OS of 65.9% was similar to 65.3% [7], 66.2% [2] or 68.1% [6] in other studies with larger sample size. Additionally, we questioned the 90% tumour necrosis as a surrogate measure of clinical outcome not only based on our result, but also based on several other studies with larger sample size [17–19] in which no significant difference was found between poor responders and good responders in EFS, DFS or OS. Collectively, although our series was small, our results help to justify further study into the relationship between percent necrosis and survival of osteosarcoma patients.

In conclusion, we found no survival advantage at 90% tumour necrosis in our study. Together with studies that have questioned the importance of achieving 90% for predicting survival, our results help to justify further prospective, randomised and controlled studies with large samples investigating the relationship between percentage of tumor necrosis and survival of osteosarcoma patients. Further study with more patients should also be performed to evaluate the predictive value of necrosis rate at the cutoff of 70%.

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Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigators were conducted in conformity with ethical principles for research. This study was approved by the Institutional Review Board.

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