Tumour volume as a predictor of necrosis after chemotherapy in Ewing's sarcoma

A. Abudu, A. M. Davies, P. B. Pynsent, D. C. Mangham, R. M. Tillman, S. R. Carter, R. J. Grimer

From the Royal Orthopaedic Hospital, Birmingham, England

We studied the CT and MR scans, and the histology of 50 patients with primary Ewing's sarcoma of bone to determine the association between the change in tumour volume and necrosis after chemotherapy, and to ascertain their influence on prognosis. The mean age of the patients was 17 years. The limbs were involved in 40 and the axial bones in ten. The volume of the tumour at diagnosis varied from 31 to 1790 ml.

There was a significant relationship between necrosis and the measured change in volume of the tumour after chemotherapy. Progression of the tumour despite chemotherapy was seen only in patients with necrosis of grades 4 to 6. Necrosis significantly influenced survival ($p < 0.05$), but the effect of change in volume was less significant.

Change in volume of the tumour is a good predictor of necrosis induced by chemotherapy. Necrosis is a strong prognostic factor in Ewing's sarcoma.

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Ewing's sarcoma is a rare, primitive, highly cellular malignant round-cell tumour of bone and soft tissue, described by Ewing in 1921.¹ It is the second commonest primary malignant tumour of bone in children after osteosarcoma² and accounts for about 10% of all such lesions.^{3,4} Over the last two decades effective chemotherapy has been one of the most important advances in the management of patients with Ewing's sarcoma. Before this, treatment had consisted

of local irradiation or surgery alone, but less than 10% of the patients survived for more than five years.^{5,6} Modern treatment of Ewing's sarcoma with chemotherapy, surgery and/or radiotherapy results in a survival rate of 50% to 60% at five years in patients without metastases at diagnosis;⁷⁻¹¹ the prognosis is also influenced by the volume of the tumour at diagnosis^{12,13} and the amount of necrosis of the tumour after chemotherapy.⁹

Preoperative chemotherapy reduces the volume of Ewing's sarcoma,⁸ and this has been related to the prognosis.¹⁴ Reduction in the volume, if any, often occurs after the first cycle of chemotherapy, as shown by the Co-operative Ewing's Sarcoma Study (CESS),¹² and only minor shrinkage takes place after this. It is often dramatic and may be due to shrinkage of the neoplastic cell mass by necrosis, reduction in the volume of normal supporting stroma, resolution of inflammatory oedema or, more likely, a combination of these. The contribution of necrosis of tumour cells to the change in volume of the tumour is unclear. We have studied the relationship between the change in volume and necrosis of a tumour after chemotherapy, and the influence of these on the prognosis of patients with primary Ewing's sarcoma.

Patients and Methods

Between 1983 and 1993 we treated 152 patients with primary Ewing's sarcoma. For inclusion in the study patients were required to have complete staging studies performed at diagnosis, adequate CT or MRI of the tumour before diagnostic biopsy and after chemotherapy, no previous attempt at excision of the tumour before referral to our centre, the histological diagnosis confirmed by the pathologist (DCM) and no radiotherapy before excision of the tumour.

Of the 152 patients, 50 satisfied these criteria. There were 32 men and 18 women with a mean age at diagnosis of 17 years (5 to 40). Of the 50 tumours, 40 were located in the bones of the limbs, 11 in the femur, 16 in the tibia, four in the fibula, eight in the humerus and one in the calcaneum. Ten tumours were found in the axial skeleton, nine in the pelvis and one in the scapula.

Three patients had stage-IIA, 44 stage-IIB and three stage-III tumours at diagnosis, according to the Muscu-

A. Abudu, FRCS, Orthopaedic Specialist Registrar
A. M. Davies, FRCR, Consultant Orthopaedic Radiologist
P. B. Pynsent, PhD, Director of Research
D. C. Mangham, MRC Path, Consultant Pathologist
R. M. Tillman, FRCS, Consultant Orthopaedic Oncologist
S. R. Carter, FRCS, Consultant Orthopaedic Oncologist
R. J. Grimer, FRCS, Consultant Orthopaedic Oncologist
Royal Orthopaedic Hospital Oncology Service, Bristol Road South, Northfield, Birmingham B31 2AP, UK.

Correspondence should be sent to Mr A. Abudu.

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Fig. 1a

Fig. 1b

Diagram of the measurement of the volume of tumours with a) a discrete soft-tissue component and b) a large soft-tissue component.

loskeletal Tumor Society staging system.¹⁵ All patients had full staging studies with haematological and serum biochemical tests, whole-body bone scintigraphy and CT of the chest. In 46 patients we assessed the local extent of the tumours using CT scans obtained at diagnosis and before excision of the tumour after a course of chemotherapy. In the remaining four, seen after 1992, we assessed the extent of the tumour using MRI.

Measurement of the volume of the tumour was independent and blind, without any knowledge of the outcome of the patients. Assessment of the intra- and extraosseous component for each patient was made from the extension of the tumour in the longitudinal, lateral and anteroposterior planes. The calculations were as recommended by the CESS¹² depending on whether the soft-tissue component of the tumour was large or discrete (Fig. 1). The CT or MR scans taken before biopsy were used to measure the volume

of the tumour. After chemotherapy the volume was measured from the CT or MR scans taken after two cycles of preoperative chemotherapy, lasting for 18 weeks in those treated by the VACA regimen (vincristine, actinomycin D, cyclophosphamide and Adriamycin) or four cycles of VAIA or EVAIA (vincristine, actinomycin D, ifosfamide, Adriamycin with or without etoposide) lasting for 12 weeks, according to the CESS protocol.¹⁶

Necrosis of tumours was graded according to the criteria of Salzer-Kuntschik et al.¹⁷ There were six grades as follows: grade 1, no viable tumour cells in the excised tumours after chemotherapy; grade 2, a viable cluster of tumour cells of <0.5 cm; grade 3, viable tumour of less than 10% after chemotherapy; grade 4, viable tumour of between 10% and 50% after chemotherapy; grade 5, viable tumour of more than 50% after chemotherapy; and grade 6, no demonstrable necrosis after chemotherapy.

Table I. Details of the patients with Ewing's sarcoma according to the grade of necrosis

	Grade of necrosis						p value
	1	2	3	4	5	6	
Gender							
Female (n = 18)	5	3	5	2	3	0	0.4
Male (n = 32)	9	5	5	6	2	5	
Site							
Central (n = 10)	3	2	2	2	0	1	0.2
Extremity (n = 40)	11	6	8	6	5	4	
Surgery							
Amputation (n = 3)	1	0	0	2	0	0	0.6
Excision (n = 8)	3	1	2	1	0	1	
Excision + bone graft (n = 5)	2	1	1	0	1	0	
Excision + endoprostheses (n = 34)	8	6	7	5	4	4	
Surgical margins							
Intralesional (n = 3)	2	0	0	0	0	1	0.3
Marginal (n = 9)	2	0	3	2	1	1	
Wide (n = 35)	9	8	7	5	4	2	
Radical (n = 3)	1	0	0	1	0	1	
Median tumour volumes							
At diagnosis (ml)	338	359	408	477	276	399	0.28
(range)	54 to 830	31 to 842	69 to 1707	86 to 1790	56 to 1406	224 to 1238	
Reduction after chemotherapy (%)	-64	-67	-58	-38	-20	-11	<0.0001
(range)	-46 to -93	-56 to -80	-46 to -86	-61 to +18	-22 to +133	-64 to +63

Fig. 2

Box plot for the grade of necrosis and change in tumour volume after chemotherapy with median values and 95% confidence intervals ($p < 0.0001$).

All the patients had surgical excision of the tumours after preoperative chemotherapy. A full slice was examined histologically and the results stored on a database. Surgical treatment consisted of amputation in three patients (two below-knee and one hip disarticulation), simple excision of expendable bones in eight, excision and reconstruction with an autologous non-vascularised fibular graft in five and excision with endoprosthetic reconstruction in 34. The margins of tumour excision, according to the criteria of Enneking, Spanier and Goodman,¹⁵ were radical in three, wide in 35, marginal in nine and intralesional in three (Table I). Nine patients had

adjuvant postoperative radiotherapy because of intralesional or close margins.

We analysed disease-free and overall survival, according to the Kaplan-Meier method,¹⁸ in patients without metastases at diagnosis. Disease-free survival was defined as the time from diagnosis to either the date of review, or recurrence at local or distant sites. The overall survival was defined from the time of diagnosis to the date of review or date of death. Treatment-related death was counted as an event. Statistical comparisons of survival curves were by the Mantel-Cox log-rank test.¹⁹ The Cox proportional hazards regression model²⁰ determined the joint influence of factors which might influence survival time. The relationship between the change in volume after chemotherapy and histological necrosis of the tumour was studied using the Kruskal-Wallis test. Statistical significance was set at $p \leq 0.05$.

Results

The volume of tumours at diagnosis ranged from 31 to 1790 ml. After chemotherapy, the change in volume from diagnosis varied from a reduction of 91% to an increase of 133%.

Considering necrosis of the tumour, 14 patients were in grade 1, eight in grade 2, ten in grade 3, eight in grade 4, five in grade 5 and five in grade 6.

A statistically significant relationship was found between histological grading and the measured change in the volume of the tumour after chemotherapy ($p < 0.0001$) as shown in Figure 2. Reduction in tumour volumes, induced by chemotherapy, occurred in all patients with necrosis of grades 1 to 3 (Fig. 3). Progression of the tumour, despite chemotherapy, was observed only in patients with necrosis of grades 4 to 6 (Fig. 4). The volume of the tumour increased in four out of the 18 patients (22%) with necrosis of grades 4 to 6, one out of the eight patients (12.5%) with grade 4, one out of the five patients (20%) with grade 5 and two out of the five (40%) with grade 6.

Fig. 3a

Fig. 3b

The initial axial proton-density MR scan through the pelvis showing a) Ewing's sarcoma of the iliac bone with a large extraosseous tumour and b) a similar image at comparable level after four cycles of preoperative chemotherapy indicating complete resolution of the extraosseous tumour in a patient with necrosis of grade 1.

Fig. 4a

Fig. 4b

CT of the femur in a patient with Ewing's sarcoma with a) a large extraosseous component when first seen and b) after four cycles of chemotherapy showing no reduction of the tumour in a patient with necrosis of grade 6.

Fig. 5

Fig. 6

Fig. 7

Figure 5 – Length of relapse-free survival according to grade of necrosis. Figure 6 – Overall survival according to grade of necrosis. Figure 7 – Disease-free survival according to percentage reduction in tumour volume.

The median reduction in tumour volume was 64% for grade-1 necrosis, 67% for grade-2, 58% for grade-3, 38% for grade-4, 20% for grade-5 and 11% for grade-6. There was no statistical difference in the amount of reduction in volume for patients with necrosis of grades 1 to 3 ($p = 0.04$), and no difference was found when the measured change in volumes after chemotherapy for patients with necrosis of grades 4 to 6 were compared ($p = 0.26$). Table I illustrates the clinical details of all the patients according to the grade of histological necrosis.

Gender, the site of the tumour or the type of chemotherapy had no influence on the amount of necrosis observed or on the measured change in the volume of the tumour ($p > 0.05$). The observed change in volume was similar in the different regimens of chemotherapy.

The relapse-free survival and the overall survival were 69% and 75% at five years, respectively, for patients with necrosis of grades 1 to 3 compared with 34% and 49% for those with grades 4 to 6 ($p = 0.01$ and $p = 0.03$). Cox's proportional hazard regression model, using necrosis, tumour volume, change in tumour volume and site of tumour as variables, is shown in Figures 5 and 6. The influence of change in tumour volume on survival was less distinct. There was no statistically significant correlation between the measured change in tumour volume and the relapse-free and overall survival of patients. There was, however, a trend for patients with a large reduction in tumour volume to have a better survival figure. This was most significant at 40% reduction in the volume of the tumour. The five-year relapse-free survival in 12 patients with less than 40% reduction in tumour volume and without metastases at diagnosis was 46%, compared with 63% in the 35 patients who had reduction of tumour volume of 40% or more without metastases at diagnosis ($p = 0.09$) as shown in Figure 7.

Discussion

The histological examination of excised lesions remains the most accurate method of assessing the response of malignant tumours to chemotherapy, and the significance to the prognosis of patients with Ewing's sarcoma is well documented.^{9,11,12} Clinical evaluation, plain radiography and ultrasound have been used to measure the response of Ewing's sarcoma to chemotherapy.^{21,22} Clinical assessment and conventional radiography are cheap and easy to perform, but the results are often inaccurate. CT and MRI offer the most accurate imaging of the local extent of malignant bone tumours.²³

Ewing's sarcoma is a highly cellular tumour with a limited matrix and often shows marked changes in the extraosseous volume after chemotherapy. By contrast, osteosarcoma has a large extracellular matrix of bone and osteoid which requires active resorption by osteoclasts for its removal. Hence, the volume changes noted in Ewing's sarcoma may not be seen in osteosarcoma. Wellings et al²⁴

showed that quantitative changes in the volume of osteosarcoma measured by CT are an imprecise predictor of the response of the tumour to chemotherapy.

In order to ensure accurate assessment of volume or necrosis induced by chemotherapy we excluded a large number of patients from our study, including those whose initial pretreatment imaging scans had been performed after biopsy or any form of manipulation of the tumour, and those who had received preoperative radiotherapy before excision of the tumours after chemotherapy. The age, distribution of tumours and the survival of the patients excluded were similar to those who were studied.

This investigation shows that a change in the volume of Ewing's sarcoma after a course of chemotherapy is a good predictor of the histological response to chemotherapy. Progression in the volume of the tumour is seen only in patients with necrosis of grades 4 to 6 and the greatest reduction in volume is in those with grades 1 to 3. The change in tumour volume after chemotherapy and the survival of patients are similar in those with necrosis of grades 1 to 3 and also in those with grades 4 to 6. Necrosis within the tumour represents a significant prognostic factor. The relapse-free survival and overall survival of patients with necrosis of grades 1 to 3 are significantly better than those with grades 4 to 6. Patients with necrosis of grades 1 to 3 can therefore be regarded as good and those with grades 4 to 6 as poor responders.

The measured change in tumour volume is a good predictor of necrosis, but a less sensitive indicator of prognosis. This is probably because of other factors involved in changes in tumour volume after chemotherapy which may influence prognosis such as resolution of oedema or reduced vascularity of the tumour.²⁵ A statistical review of volume changes at different levels showed that the best correlation to prognosis was achieved when those with volume reduction of more or less than 40% were compared. The five-year relapse-free survival in patients showing reduction of 40% or more in tumour volume was 63% compared with 46% in those with reduction of less than 40%. This was not statistically significant ($p = 0.09$) in this small sample.

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