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Do pathological fractures influence survival and local recurrence rate in bony sarcomas?

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ARTICLE INFO

Article history:
Received 6 May 2007
Received in revised form 28 June 2007
Accepted 4 July 2007

Keywords:
Osteosarcoma
Ewing's sarcoma
Chondrosarcoma
Pathological fracture
Survival
Local recurrence
Prognosis

ABSTRACT

The influence of pathological fracture on surgical management, local recurrence and survival was established in patients with high grade, localised, extremity osteosarcoma ($n = 484$), chondrosarcoma ($n = 130$) and Ewing's sarcoma ($n = 156$). Limb salvage was possible in 79% of patients with a fracture compared to 84% of patients without a fracture ($p = 0.17$). No difference in local recurrence was found between fracture and control groups. In univariate analysis, survival in the fracture group was lower than in the control group for osteosarcoma (34% versus 58%, $p < 0.01$) and chondrosarcoma (35% versus 63%, $p = 0.04$), but not for Ewing's sarcoma (75% versus 64%, $p = 0.80$). In multivariate analysis, fracture remained a significant predictor of survival for osteosarcoma, but not for chondrosarcoma, where dedifferentiated subtype appeared to be decisive. Pathological fracture independently predicts worse survival in osteosarcoma, but not chondrosarcoma and Ewing's sarcoma. Limb saving surgery seems safe, if adequate resection margins are achieved.

1. Introduction

Pathological fracture through a bony sarcoma can theoretically worsen prognosis by spreading tumour via the fracture haematoma, or by spreading micro-metastases. It can also lead to joint involvement. If the fracture is not recognised as being pathological, there is a risk of inappropriate procedures, delaying diagnosis and potentially spreading the disease more than necessary. The literature is unclear about the implications of a pathologic fracture on the outcome for patients with bony sarcomas.[1–6] The aim of the current study was to establish whether pathological fracture had any influence on surgical management, local recurrence or survival in patients treated for a localised high grade extremity sarcoma of bone (osteo-, Ewing's or chondrosarcoma). For osteosarcoma and chondrosarcoma the influence of subtype was established as well.

2. Patients and methods

A retrospective survey was performed, using a prospectively kept database on which patient, tumour, treatment and outcome details were recorded. We included all patients, treated between 1983 and 2003, for a localised, primary, high grade, bony osteosarcoma, chondrosarcoma or Ewing's sarcoma of an extremity. All patients were treated in the Royal Orthopaedic Hospital in Birmingham (UK), which is a national referral centre for bone tumours. We excluded those patients who did

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.07.004

not receive 'standard treatment'. In osteosarcoma and Ewing's sarcoma this consisted of a pre-operative chemotherapy, followed by resection of the tumour and post-operative chemotherapy. For osteosarcoma chemotherapy was administered according to the protocol of the European Organisation for Research and Treatment of Cancer (EORTC) current at the time,[7,8] for Ewing's sarcoma according to the protocol of the UKCCSG or the EICESS groups.[9,10] Tumours, located in, or extending into the proximal half of the humerus and femur, were considered to be 'proximal', the others 'distal'. Radical and wide margins, according to Enneking,[11] were considered to be 'adequate' and marginal or intralesional margins 'inadequate'. Chemotherapy response was defined according to the protocol of the European Osteosarcoma Intergroup as good if less then 10% of viable tumour was found in the resection specimen.[12,13]

Outcome parameters were local recurrence and estimated 10-year overall survival. We compared the outcome in patients with and without a pathological fracture through the tumour, occurring before or during treatment. To evaluate the safety of limb saving surgery in patients with a fracture, the type of surgery was evaluated in respect to local recurrence and survival.

Other evaluated prognostic variables included proximity of the tumour, surgical margins and chemotherapy response (for osteo- and Ewing's sarcomas). The influence of subtype on the occurrence of fracture and on survival was established for osteosarcoma (telangiectatic as opposed to 'other' subtypes), and for chondrosarcoma (dedifferentiated as opposed to grade 2 or grade 3).

In a total of 620 eligible patients who were treated for osteosarcoma in the mentioned period, 83 had metastatic disease at diagnosis and were excluded. The fraction of patients with metastasis at diagnosis was equal in the fracture and non-fracture group (15% and 13%, respectively, $p = 0.58$, χ^2). A futehr fifty-three patients were excluded, 45 because they did not receive standard treatment (41 had no or incomplete chemotherapy, 4 had no resection) and 8 because they died of an unrelated cause. Thus, 484 patients were analysed. The mean follow-up in survivors was 117 months (7–252 months). Completeness of follow-up was 97% after 2 years and 94% after 3 years.

For chondrosarcoma, 152 patients were treated, 13 of them had metastatic disease at diagnosis. Again no difference in the percentage of patients with and without fracture was found between these 2 groups (13% and 7%, $p = 0.30$, χ^2). A further 9 patients were excluded, 2 because resection was impossible and 7 because of unrelated death. This left 130 patients with localised, primary, high grade chondrosarcoma of an extremity to analyse. All included patients were diagnosed with a chondrosarcoma grade 2 or 3, or a dedifferentiated chondrosarcoma. The mean follow-up in survivors was 81 months (3–263 months). Completeness of follow-up was 88% after 2 years and 76% after 3 years.

Of the 223 patients with Ewing's sarcoma, 52 had metastatic disease at the time of diagnosis. The percentage of metastatic disease in the fracture and no-fracture groups did not differ significantly (14% and 11%, $p = 0.56$, χ^2). Fifteen patients were excluded because they did not receive standard treatment (5 had palliative chemotherapy, 7 had chemo- and radiotherapy but no surgery, 3 did not have chemotherapy). This left 156 patients with Ewing's sarcoma to analyse. The mean follow-up in survivors was 120 months (19–253 months). Completeness of follow-up was 99% after 2 years and 92% after 3 years.

2.1. Statistical analysis

Comparability of the groups with and without fracture was assessed with the χ^2 test for nominal variables and with a Mann/Whitney test for age. Local recurrence was compared between the groups with a χ^2 test as well. Overall survival was determined by Kaplan Meier survival analysis and compared between groups with a log rank test. For the assessment of (independent) predictive value of factors, a Cox proportional hazards model was used (level of significance $p \leqslant 0.05$).

3. Results

3.1. Osteosarcoma: patient and tumour characteristics and treatment. Comparability of fracture- and control groups (Table 1)

Of the 484 patients in the osteosarcoma group, 56 had a fracture (12%). The groups with or without a fracture were comparable regarding sex and age at diagnosis. The site of the osteosarcoma in both groups was predominantly in the distal femur. The second most common place was the proximal tibia, followed by the humerus (Fig. 1a). Location of the tumours in the bone was different in both groups: in the fracture group 41% of the tumours were proximal, compared to only 13% of tumours in the control group ($p < 0.01$). The fraction of telangiectatic subtype was higher in the fracture group (23% versus 6% in the control group, $p < 0.01$). In the group of patients with a telangiectatic osteosarcoma the incidence of fracture was higher (34%) than in the group with other subtypes (10%).

Treatment in both groups was comparable. Adjuvant radiotherapy was given in 9% of patients in the fracture group and in 8% in the non-fracture group ($p = 0.90$). All fractures were treated conservatively apart from one which was treated with osteosynthesis elsewhere, which did not influence further treatment. Limb saving surgery was done in the majority of cases and percentages of ablative and limb saving surgery were comparable between the 2 groups, as were surgical margins and chemotherapy response.

3.2. Chondrosarcoma: patient and tumour characteristics and treatment. Comparability of fracture- and control groups (Table 1)

Of the 130 analysed chondrosarcoma patients, 33 (25%) had a fracture. The groups of patients with or without a fracture were comparable concerning age, sex, treatment and surgical margin. The fracture group showed a tendency towards more proximal tumours and towards a higher fraction of dedifferentiated subtypes, but these differences did not reach the level of significance.

Table 1 – Comparability of fracture and no-fracture groups in osteosarcoma, chondrosarcoma and Ewing's sarcoma

	Osteosarcoma fracture ($n = 56$)	Osteosarcoma no fracture ($n = 428$)	p Value	Chondrosarcoma fracture ($n = 33$)	Chondrosarcoma no fracture ($n = 97$)	p Value	Ewing's fracture ($n = 16$)	Ewing's no fracture ($n = 140$)	p Value
Sex (male/female)	36/20	254/174	0.48	20/13	63/34	0.65	8/8	87/53	0.35
Median age (years + range)	16 (4–57)	16 (5–57)	0.52	59 (28–78)	53 (15–84)	0.90	18 (6–37)	15 (2–48)	0.18
Proximal tumour (%)	23 (41)	54 (13)	<0.01	21 (64)	54 (56)	0.42	9 (56)	38 (27)	0.02
Teleangiectatic subtype[a] (%)	13 (23)	25 (6)	<0.01	–	–	–	–	–	–
Grade[b]	–	–	–	–	–	0.49	–	–	–
Dedifferentiated (%)	–	–	–	10 (30)	21 (22)		–	–	–
Grade 3 (%)	–	–	–	5 (15)	12 (12)		–	–	–
Grade 2 (%)	–	–	–	18 (55)	64 (66)		–	–	–
Limb salvage (%)	44 (79)	357 (83)	0.37	23 (70)	79 (81)	0.16	16 (100)	125 (89)	0.17
Adequate margin (%)	35 (63)	288 (67)	0.58	17 (51)	41 (42)	0.31	11 (67)	81 (59)	0.55
	(1 unknown)	(3 unknown)		(3 unknown)	(20 unknown)		(2 unknown)	(34 unknown)	
Poor Chemotherapy response (%)	43 (78)	320 (75)	0.91	–	–	–	7 (44)	51 (36)	0.72
	(1 unknown)	(15 unknown)					(3 unknown)	(35 unknown)	
Adjuvant radiotherapy (%)	5 (9)	36 (8)	0.90	–	–	–	1 (6)	29 (21)	0.16

a For osteosarcomas.
b For chondrosarcomas.

Tumour site was different from that in osteosarcoma, the majority being localised at the proximal, rather than the distal femur or proximal tibia (Fig. 1b).

3.3. *Ewing's sarcoma: patient and tumour characteristics and treatment. Comparability of fracture- and control groups (Table 1)*

In the Ewing's sarcoma group, 16 of 156 (10%) had a fracture. Again, the groups with or without a fracture were comparable for age, sex, treatment and surgical margin. Also in Ewing's sarcoma the fracture group showed significantly more proximal tumours (Fig. 1c).

3.4. *Local recurrence and overall survival in osteosarcoma (Tables 2 and 3)*

The local recurrence rate was similar (e.g. 14%) in the fracture group and the control group in osteosarcoma patients ($p = 0.96$). Comparing local recurrence between patients in the fracture group only, treated with ablative or limb saving surgery, revealed no statistically significant differences with local recurrence in 17% of the ablative group and 14% of the group treated with limb saving surgery ($p = 0.79$ in χ^2 test).

The estimated 10-year overall survival in the entire group of osteosarcoma patients was 55%. The overall survival in the group with a fracture was lower (34%) than in the control group (58%; $p < 0.01$). Table 2 shows the results of univariate analysis. It appears that, apart from fracture, proximal tumour location, poor chemotherapy response, inadequate margin, and ablative surgery are correlated with worse survival. Comparing survival in fracture and control groups shows that fracture is a predictor of worse survival in most subgroups, but not in patients with proximal tumours, telangiectatic subtype, good chemotherapy response, or ablative surgery. In multivariate analysis (Table 3), fracture, proximal tumour location, ablative surgery, inadequate margin, and poor chemotherapy response appear to be independent predictors of worse survival.

3.5. *Local recurrence and overall survival in chondrosarcoma (Tables 4 and 5)*

The local recurrence rate was not statistically different between the fracture and the control group in chondrosarcoma, although a tendency towards more local recurrence in the fracture group seemed to exist (local recurrence in fracture group 33%, in control group 20%, $p = 0.11$). No statistical difference in local recurrence was found in the fracture group comparing ablative and limb saving surgery (39% in the ablative group and 20% in the group treated with limb saving surgery; $p = 0.28$ in χ^2 test).

The estimated 10-year overall survival in the entire group with chondrosarcoma was 57%. The overall survival in the fracture group was lower (35%) than in the control group (63%) ($p = 0.04$). Apart from fracture, only dedifferentiated and grade 3 subtypes were correlated with worse survival in univariate analysis (Table 4). As in osteosarcoma, patients treated with ablative surgery showed a worse survival, but

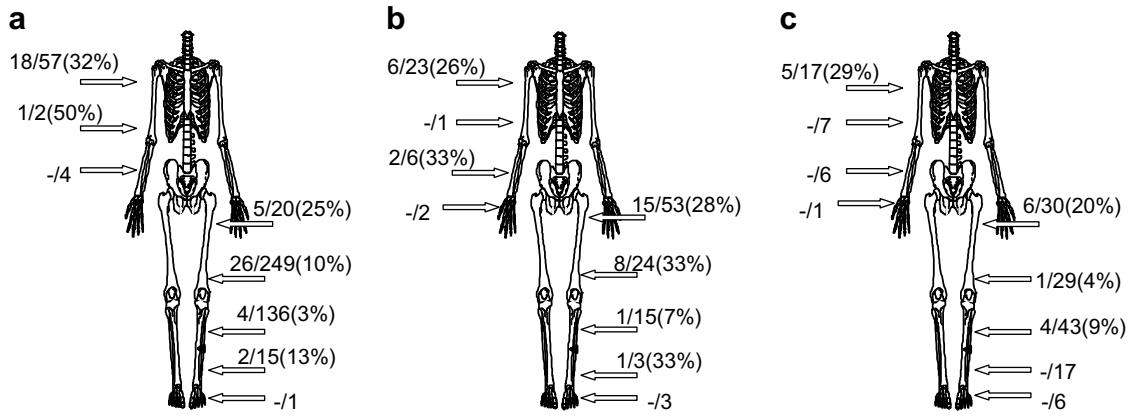

Fig. 1. Number of fractures and total number of tumours on specified sites (% of fractures between brackets) in the eligible patients: 484 with osteosarcoma (a), 130 with chondrosarcoma (b), and 156 with Ewing's sarcoma (c).

Table 2 – Estimated 10-year survival in osteosarcoma (%); univariate analysis

	All patients (n = 484)	Fracture (n = 56)	No fracture (n = 428)	p Value ←
All patients	55	34	58	0.0002
Proximal tumours	39	33	42	0.24
Distal tumours	58	36	60	0.006
p Value ↑	0.0002	0.3757	0.0043	
Telangiectatic	47	43	52	0.221
Other subtype	56	33	58	0.0004
p Value ↑	0.6284	0.7886	0.9975	
Poor chemo response	48	24	51	0.0002
Good chemo response	79	66	81	0.112
p Value ↑	<0.0001	0.0233	<0.0001	
Inadequate margin	43	21	46	0.043
Adequate margin	61	42	63	0.0043
p Value ↑	0.0024	0.3752	0.0045	
Limb saving surgery	59	37	62	0.0001
Ablative surgery	35	21	37	0.5278
p Value ↑	<0.0001	0.3181	<0.0001	

Table 3 – Overall survival in osteosarcoma; multivariate analysis

Factor	Odds ratio	Confidence interval	p Value
No fracture	0.59	0.401–0.869	0.0076
Distal tumour	0.649	0.456–0.924	0.0166
'Other' subtype[a]	1.25	0.749–2.087	0.3937
Ablative surgery	2.48	1.743–3.528	<0.0001
Adequate margin	0.56	0.412–0.761	0.0002
Good chemo response	0.336	0.208–0.543	<0.0001

a As opposed to telangiectatic subtype.

this difference was not statistically significant. Studying subgroups, fracture correlated with worse survival only in distally located tumours, although a tendency existed in all subgroups. In multivariate analysis, subtype appeared to be the only independent predictor of survival (Table 5).

3.6. *Local recurrence and overall survival in Ewing's sarcoma (Tables 6 and 7)*

In patients with Ewing's sarcoma, no difference between the groups was found for local recurrence, which was 0% and

9% for fracture and no-fracture groups, respectively ($p = 0.22$). All patients in the fracture group were treated with limb saving surgery.

Fracture in Ewing's sarcoma was not correlated with estimated 10-year overall survival, which was 75% and 64% for fracture and no-fracture groups ($p = 0.50$). None of the studied factors showed any statistically significant correlation with survival in univariate (Table 6) or multivariate analysis (Table 7).

Table 4 – Estimated 10-year survival in chondrosarcoma (%); univariate analysis

	All patients ($n = 130$)	Fracture ($n = 33$)	No fracture ($n = 97$)	p Value ←
All patients	57	35	63	0.04
Proximal tumours	50	33	56	0.3556
Distal tumours	65	50	70	0.0268
p Value ↑	0.2378	0.5432	0.1919	
Dedifferentiated	36	20	45	0.2531
Grade 3	48	80	48	0.89
Grade 2	67	42	71	0.13
p Value ↑	<0.0001	0.0164	0.0017	
Inadequate margin	60	52	63	0.0749
Adequate margin	53	47	55	0.9207
p Value ↑	0.3093	0.6933	0.1664	
Limb saving surgery	60	41	65	0.0595
Ablative surgery	43	27	46	0.7206
p Value ↑	0.1208	0.6779	0.1896	

Table 5 – Overall survival in chondrosarcoma; multivariate analysis

Factor	Odds ratio	Confidence interval	p Value Wald test
No fracture	0.948	0.453–1.982	0.8868
Distal tumour	0.787	0.370–1.675	0.787
Subtype[a]			
Dedifferentiated	1.868	0.698–4.999	0.2135
Grade 2	0.367	0.133–1.014	0.0532
Global Wald test			<0.0001
Ablative surgery	1.922	0.831–40443	0.1267
Adequate margin	1.382	0.623–3.066	0.4257

a Wald test related to grade 3.

Table 6 – Estimated 10-year survival in Ewing's sarcoma (%); univariate analysis

	All patients ($n = 156$)	Fracture ($n = 16$)	No fracture ($n = 140$)	p Value ←
All patients	65	75	64	0.5
Proximal tumours	70	78	69	0.8216
Distal tumours	63	71	62	0.5817
p Value ↑	0.2887	0.7749	0.319	
Poor chemo response	64	71	63	0.6736
Good chemo response	62	67	61	0.8464
p Value ↑	0.2878	0.9944	0.273	
Inadequate margin	68	67	69	0.8915
Adequate margin	67	73	66	0.7539
p Value ↑	0.4396	0.8815	0.5159	
Limb saving surgery	66	75	65	0.5378
Ablative surgery	66	na	66	
p Value ↑	0.428	na	0.4571	

Table 7 – Overall survival in Ewing's sarcoma; multivariate analysis

Factor	Odds ratio	Confidence interval	*p* Value
No fracture	1.186	0.403–3.492	0.7564
Distal tumour	0.833	0.394–1.763	0.6333
Ablative surgery	1.082	0.243–4.823	0.9179
Adequate margin	0.851	0.369–1.965	0.7053
Good chemo response	0.687	0.336–1.406	0.687

4. Discussion

Although a fracture through a bony sarcoma may theoretically have an adverse effect on the outcome of the disease after treatment,[14,15] this is not consistently reflected by the literature. Zeifang and colleagues studied 336 patients with bony sarcomas of different type and stage, 30 of which had a fracture. They found a similar local recurrence rate but a worse survival in patients with a fracture. Limb saving surgery was considered safe if an adequate resection margin can be obtained.[5] This is confirmed by Ebeid and colleagues, who presented a series of 31 patients with a fracture through different types of stage IIB tumours of bone, who were all treated with limb saving surgery. Local recurrence in this series occurred in 6%. Survival was 81% and seemed worse for patients who sustained their fracture during chemotherapy as opposed to those who presented with a fracture. The follow-up period, however, in this study was short and the type of tumour differed, making this comparison rather weak.[16]

For osteosarcoma, the literature is contradictory on the implications of pathological fracture. In 1996, Abudu et al. presented a series of patients with a fracture who showed similar survival to a comparable group in the literature without a fracture.[1] Glasser and colleagues reported worse survival for patients with a fracture.[17] Scully et al. showed an unfavourable influence of fracture on both local recurrence and survival in a multicentre evaluation.[4] This study could be biased by the fact that a considerable part of the patients did not receive pre-operative chemotherapy, as was correctly noted in a comment by Bacci.[18] Bacci himself did not find a difference for either local recurrence or survival.[3] Both Abudu et al.[1] and Scully et al.[4] compared oncological outcome between patients who presented with a fracture, and those who sustained it during treatment, and both did not find any difference. Abudu reported a higher chance of local recurrence if patients with a fracture were treated with limb saving surgery. This difference disappeared, however, after correction for surgical margin. Scully et al.[4] as well as Bacci et al.[3] compared limb saving and ablative surgery in their studies and did not find any difference in oncological outcome between them.

In the current study, fracture- and control group consisted of osteosarcoma patients, treated in the same period in one institution. All had similar treatment. The groups were comparable, apart from the fact that tumours in the fracture group were located more proximally, and that telangiectatic subtype was more frequent in the fracture group. This is consistent with the concept that proximal tumours, as well as telangiectatic subtypes, are more aggressive.[19] Fracture was found to be an independent predictor for worse survival, but no difference in local recurrence was found. This seems to indicate that it is probably not the spreading of tumour cells in the fracture haematoma that leads to a worse prognosis. More likely, the fracture is a symptom of a more aggressive tumour, and therefore heralds a lower survival chance.

For chondrosarcoma, several authors highlighted the importance of local control,[20–25] but few mentioned the influence of pathological fracture. Lee et al.[2] reported on 227 patients with chondrosarcoma, 141 of which were of high grade. Pathological fractures occurred predominantly in the group with high grade tumours (38 compared to 46 in the entire group). In their series, fracture did not have an influence on oncological outcome, although it is not clear how exactly this analysis was done. The authors did not comment on the type of surgery in comparison to local recurrence or oncological outcome. They did find a correlation between achieved surgical margin and survival in high grade lesions, as is reported in other publications. In most publications, histological grade is found to be an independent, prognostic factor in chondrosarcoma. In our patients with high grade non-metastatic chondrosarcoma, surgical margins were comparable between fracture and control groups. No difference in local recurrence was found. Patients with a fracture did show a lower survival rate. In multivariate analysis, however, only subtype appeared to be and independent predictor of survival, which decreased with increasing grade of malignancy. This fits with the idea that a fracture is more likely to occur in a more aggressive tumour, which would also be supported by the above-mentioned literature. The fact that more patients with dedifferentiated chondrosarcomas are in the fracture group in our study supports this theory.

For Ewing's sarcoma, Wagner et al. reported that tumours in the proximal femur are at higher risk for fracture and that late fracture, occurring after completion of therapy, should raise the suspicion of local recurrence. They did not report on the difference in survival or local recurrence between patients with or without a fracture.[26] Fuchs et al. found similar results concerning location, and reported no significant difference in survival or local recurrence comparing 14 patients with a fracture through Ewing's sarcoma, sustained before or during treatment, with the entire group of patients. It is not clear in this paper whether the fracture patients are included in the control group and whether fracture and no-fracture groups were matched for treatment, stage, and other characteristics.[27] Hoffmann and colleagues compared 42 fracture patients with a control group of 350 patients with Ewing's sarcoma or PNET stage 2, and found no difference in relapse free or overall survival.[6]

Our study seems consistent with the above mentioned. None of the studies compares ablative and limb saving surgery in fractured Ewing's sarcoma patients, which in our study does not reveal a difference. The explanation why Ewing's sarcoma does not show a difference in overall survival between fracture and no-fracture groups, whereas osteo- and chondrosarcoma do show worse survival in fractured patients, could be that Ewing's sarcoma generally is more chemotherapy sensitive.[28] This idea is strengthened by our finding that in osteosarcoma, good chemotherapy

responders do not show a difference in survival between fracture and control groups.

Another factor that might influence both survival and the chance of pathological fracture in all of the three studied tumours is tumour volume. Bacci and colleagues found tumour volume to be an independent predictor for survival in osteosarcoma, but in their patients pathological fracture did not correlate with survival, not even in a univariate analysis.[29] Scully et al. found exactly the opposite, worse survival for fractured patients, but no influence of tumour size.[4] For chondrosarcoma, Lee and colleagues report a correlation of larger tumour volume with a worse prognosis, but they did not find fracture to be of influence.[2] Hoffmann and colleagues found no influence of fracture in Ewing's sarcoma, and worse survival for patients with larger tumours. Volume, however, lost its predictive value in the fracture group.[6] Unfortunately, we did not have sufficient information about tumour volume in the three studied patient groups to establish the influence of tumour volume.

We conclude that a pathological fracture in a bony sarcoma does not increase the chance of local recurrence, provided oncological principles are adhered to and the tumour and fracture sites can be excised with clear margins. Overall survival is worse in patients with a fracture in osteo- or chondrosarcoma, but not in Ewing's sarcoma. Fracture is an independent predictor of survival in osteosarcoma only. The fracture is probably not in itself the cause of the lower survival, but rather a symptom of a more aggressive tumour. The influence of tumour volume should be further studied. Limb saving surgery in fractured patients does not seem to have an influence on local recurrence or survival and therefore is thought to be safe, as long as adequate margins can be obtained. We recommend that patients with a pathological fracture through a bony sarcoma be treated by non-operative stabilisation of the fracture (e.g. by means of a splint) and appropriate analgesia, followed by chemotherapy according to the standard protocol. After this, resection of the tumour should, as usual, be done with wide margins. We have not been able to clarify the benefit, or otherwise, of adjuvant radiotherapy following limb salvage after a pathological fracture.

Conflict of interest statement

None declared. No financial or personal relationships with any of the authors exists that could inappropriately influence this work.

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