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European Journal of Cancer 41 (2005) 2806–2811

European Journal of Cancer

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Review

Periosteal osteosarcoma – a European review of outcome

Robert J. Grimer [a,*], Stefan Bielack [b], Silke Flege [b], Stephen R. Cannon [c], Gunnar Foleras [d], Ivan Andreeff [e], Todor Sokolov [e], Antonie Taminiau [f], Martin Dominkus [g], Mikel San-Julian [h], Yehuda Kollender [i], Georg Gosheger [j], from The European Musculo Skeletal Oncology Society (EMSOS)

[a] *The Royal Orthopaedic Hospital Oncology Service, Royal Orthopaedic Hospital, Bristol Road South, Northfield, Birmingham B31 2AP, UK*
[b] *The Cooperative Osteosarcoma Study Group (COSS), University Children's Hospital, Department of Paediatric Haematology and Oncology, Muenster, Germany*
[c] *Royal National Orthopaedic Hospital, London, UK*
[d] *The Norwegian Radium Hospital, Oslo, Norway*
[e] *University Hospital of Orthopaedics, Sofia, Bulgaria*
[f] *Leiden University Medical Centre, Leiden, Netherlands*
[g] *University of Vienna Medical School, Vienna, Austria*
[h] *University of Navarra, Navarra, Spain*
[i] *Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel*
[j] *University of Muenster, Muenster, Germany*

Received 23 March 2005; received in revised form 20 April 2005; accepted 20 April 2005
Available online 14 November 2005

Abstract

Periosteal osteosarcoma is a rare primary malignant bone tumour. Treatment is by surgical excision, but controversy remains about the value of chemotherapy. The members of the European Musculo Skeletal Oncology Society (EMSOS) collaborated to produce a dataset of 119 patients. The predominant site for the tumour was the femur, followed by the tibia. All but 2 patients underwent surgery, with 9 requiring amputation and the others having limb salvage. A total of 81 patients had chemotherapy, of whom 50 had neoadjuvant chemotherapy. There was no standard chemotherapy regime, but all patients receiving chemotherapy were given doxorubicin combined with at least one other agent. The overall survival was 89% at 5 years and 83% at 10 years. Eight patients developed local recurrence, of whom 5 died. Survival was related to appearance of local recurrence ($P < 0.0001$) but no other single factor. The use of chemotherapy was not shown to be a prognostic factor, but was used in two-thirds of the patients in this study.

Keywords: Periosteal osteosarcoma; Chemotherapy; Local recurrence; Outcome

1. Introduction

Periosteal osteosarcoma is one of the more uncommon types of osteosarcoma. It is characterised by its typical radiological and histological features (Fig. 1). It was first recognised by Ewing in 1939 and was further described by Lichtenstein in 1955, although a probable periosteal osteosarcoma has been described in a 14th century tibia retrieved from excavations in Hungary [1–3]. Subsequent series have confirmed the need for a wide excision of the tumour to maximise cure, but controversy remains as to whether chemotherapy is necessary [4–7]. Previous publications have produced mixed results in this regard, with some authors claiming

* Corresponding author. Tel.: +44 121 685 4150; fax: +44 121 685 4146.
E-mail address: rob.grimer@roh.nhs.uk (R.J. Grimer).

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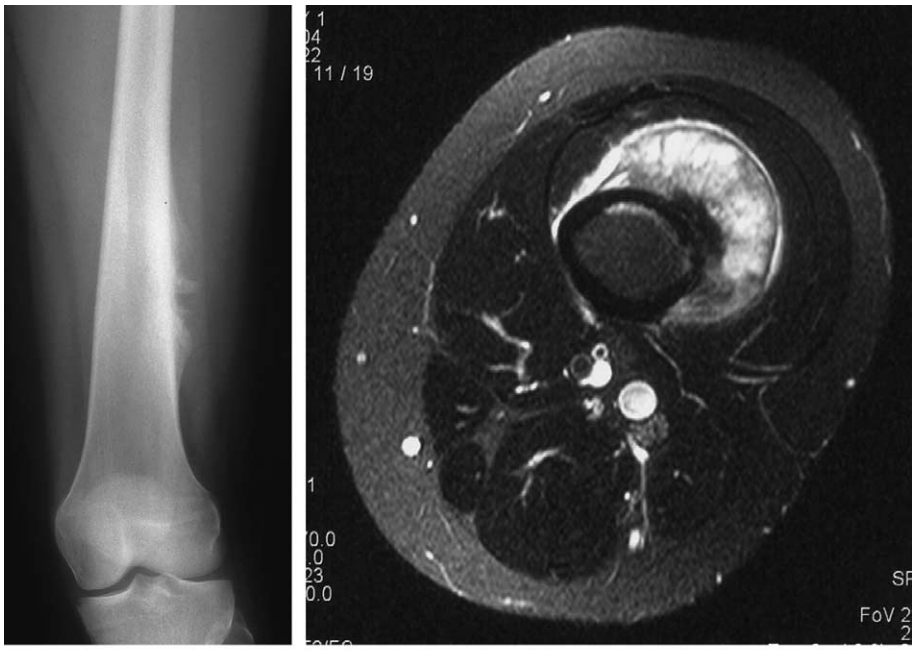
doi:10.1016/j.ejca.2005.04.052



a b

Fig. 1. Typical radiological appearances of a periosteal osteosarcoma of the femur demonstrating: (a) the raised periosteum with calcification and (b) the MRI appearance of a subperiosteal tumour encircling the femur.

100% survival in patients who have undergone adequate chemotherapy and surgery [8]. Unfortunately, however, there have been no recent large series which have been able to verify the need or otherwise for chemotherapy.

In order to try to resolve this problem, a group of European orthopaedic surgeons and oncologists agreed to collaborate by pooling their results from a number of specialist institutions and co-operative groups in order to try to identify the optimum treatment for this rare type of osteosarcoma.

2. Methods

The members of EMSOS were sent a letter inviting them to contribute cases to a review of patients treated for periosteal osteosarcoma. Because all of the centres invited to participate were large tertiary centres or co-operative groups for musculoskeletal oncology, it was agreed that there would be no central review of either the radiology or the histology of the retrieved cases. The authors accepted that there may be some cases of high-grade peripheral osteosarcoma that can look similar both radiologically and histologically, which may thus have been included in the overall series. It was made quite clear that cases of parosteal osteosarcoma should be excluded.

The main factors that differentiate a parosteal from a periosteal osteosarcoma is that a parosteal tumour arises on the surface of the bone and has a high degree of structural differentiation, with a densely ossified mass radiologically and a low-grade histological picture. Periosteal osteosarcoma, on the other hand, arises from under the periosteum and the typical radiological feature is the periosteal elevation encircling a good proportion of the bone (Fig. 1). Histologically, the tumour has the appearance of a well differentiated chondroblastic osteosarcoma.

Anonymised details of the patients, the tumour, the treatment and the outcome were requested and were entered into a database. The database was checked to exclude any duplicates and 6 cases with insufficient data either on the diagnosis or follow-up were not included in the final analysis.

Eight centres and one co-operative group contributed cases to this study, resulting in the inclusion of 119 cases, collected over a time period from 1974 to 2002.

The rates of local control, metastases and overall survival for this group of patients were investigated, in an attempt to identify potential patient and treatment factors that affected outcome, in particular whether the use of chemotherapy produced a significant survival advantage.

1. Overall survival was calculated using Kaplan–Meier survival curves and the impact of prognostic factors was assessed using the log-rank test [9,10]. Multivariate analysis was performed using Cox's proportional hazard method with variables being chosen using a forward conditional stepwise approach. Relative risks have been calculated using a proportional hazards model with only the noted covariate in the model.

Significance was set at $P < 0.05$ for two-sided tests. Survival time was calculated from the time of diagnosis. The end-point was taken as time of death or the last documented time the patient was known to be alive. Analyses were performed using Statview (Abacus Concepts Inc., Berkley, CA, 1996).

3. Results

Of the 119 patients, 64 were female and 54 male (1 unknown). Their median age was 18 years (range 8–72 years) (Fig. 2). The mean size of the tumours was 10 cm, but varied from 1 to 28 cm (Fig. 3). The median follow up was 7.2 years (Table 1).

The most common site for the tumour was in the femur (52 cases), followed by the tibia (46 cases). All other sites were far less common but included the humerus (8 cases), the fibula (4 cases), the pelvis (3 cases), ulna (3 cases) and single cases in the clavicle, radius and scapula. Two-thirds of the patients had diaphyseal as opposed to metaphyseal tumours. Only 1 patient had metastases identified at the time of diagnosis. Although the grade of tumour was requested this was only available for 43% of cases, with 7 patients being noted to have low-grade tumours and 44 high-grade tumours.

Eighty-one of the patients underwent chemotherapy, of whom 50 were documented to have neoadjuvant chemotherapy. Chemotherapy was more commonly used in younger patients (mean age of those with chemotherapy 19.4 years, those without chemotherapy 28.6 years, *t*-test $P = 0.003$), but was not apparently related to the size of the tumour or in patients who were noted to have high- or low-grade tumours. The treatment regimes used varied widely across centres, but the most common combination of drugs used was cisplatinum and doxorubicin (35 cases), whilst 11 patients had a three-drug regime and 29 patients had a four-drug regime based on doxorubicin, cisplatin, high-dose methotrexate and ifosfamide. The other patients had a variety of different regimes but all involved doxorubicin. Of the 38 patients who had the percentage necrosis documented following surgical resection, only 12 (32%) were documented to have >90% necrosis. There was no evidence that any one chemotherapy regime had better results than any other in terms of histological response or survival. Similarly, there was no difference in survival that could be identified between patients receiving ifosfamide, methotrexate or cisplatin or that there was any benefit for a four-drug *versus* three-drug *versus* two-drug regime.

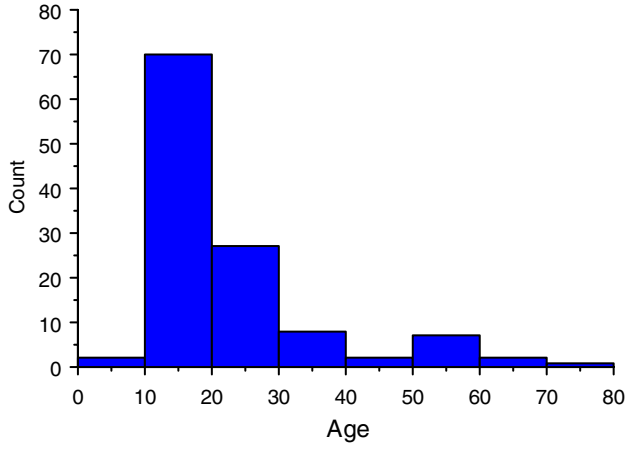


Fig. 2. Age distribution of the 119 patients.

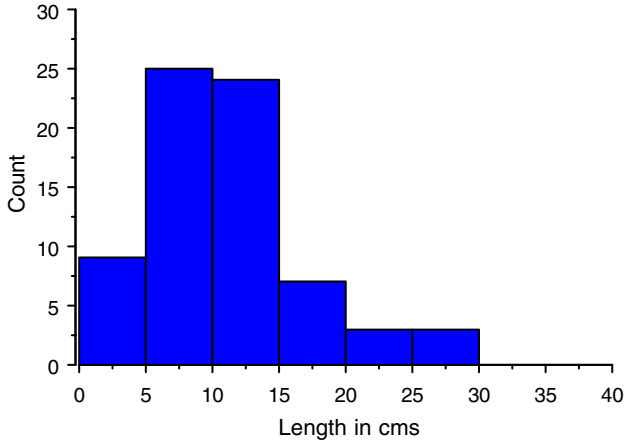


Fig. 3. Distribution of length of the tumours.

Table 1
Patient and tumour characteristics

	Mean	Median	Range
Age (years)	22.3	18.9	8–72
Size (cm)	10.6	10.0	1–28
Follow-up (years)	7.1	6.3	0.5–21

A total of 117 of the patients underwent surgical resection of their primary tumour. Fifty had excision alone, 30 had excision and some form of bone grafting, while 28 had excision and endoprosthetic replacement and 9 required an amputation. Of the 2 patients who did not undergo surgery, 1 died of chemotherapy toxicity and the other refused all treatment (dying after 18 months of metastatic disease). The excision margins were documented in 75 patients and were wide in 57, marginal in 17 and intralesional in 6.

Local recurrence (LR) arose in 8 patients (7%) and was not statistically related to any one factor. In those patients with documented margins of excision, it arose in 4 of 57 patients with wide or radical margins (7%) and in 3 of 21 (14%) with marginal or intralesional

margins. No patient with >90% necrosis following neoadjuvant chemotherapy developed LR, but in patients who did not have chemotherapy LR was no more common than in those who did receive it but in whom there was a poor response.

Of the 8 patients who developed LR, 6 underwent further surgical treatment, 3 having amputation and 3 further local excisions. Two had synchronous metastases at the time of LR and both received palliative treatment. Three more of the eight developed metastatses subsequently and all five of these patients died at a mean of 28 months after developing the LR (although 1 actually died of leukaemia). The 3 patients who have not been documented to have developed metastases in conjunction with LR all have very short follow-up (less than 12 months since development of LR). None of the 7 patients with a documented low-grade tumour developed LR.

A total of 17 patients developed metastases, 4 having had a previous local recurrence and 16 having lung metastases and 1 a bone metastasis in the opposite leg. Two patients had both lung and bone recurrences.

A total of 19 patients died, 15 of their disease (including 1 of chemotherapy-related complications) and 4 of other causes (colon cancer, a brain tumour (*post mortem* never done) and 2 from acute myeloid leukaemia). All 4 of these patients had received chemotherapy for their osteosarcoma. Two of the 7 patients with low-grade tumours died, compared with 5 of the 44 with high-grade tumours and 12 of the 56 where no grade was specified.

The overall survival of the 119 patients was thus 89% at 5 years and 83% at 10 years. (Fig. 4). The tumour-specific survival was only marginally different, with 89% 5-year survival and 85% 10-year survival. The only factor found to be statistically significant for overall survival was the presence of local recurrence (Fig. 5). There was no significant difference in survival between patients who did or did not have chemotherapy (Fig. 6), between those who had a good or bad response to neoadjuvant chemotherapy, between those with wide as opposed to marginal resections and there was no difference in outcome between patients when categorized by age, sex, site, grade or size of the tumour (Table 2).

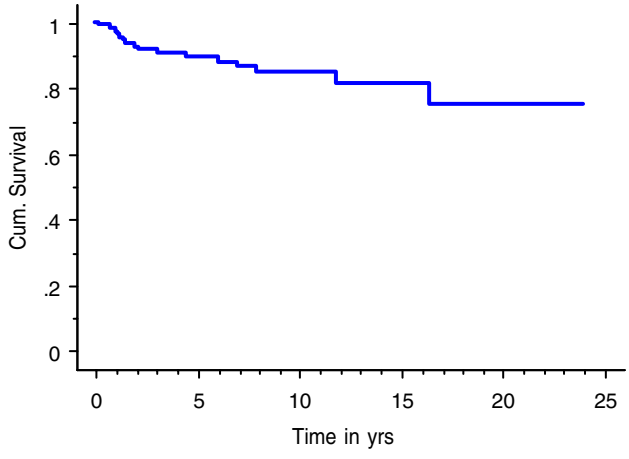


Fig. 4. Tumour-specific survival – all patients.

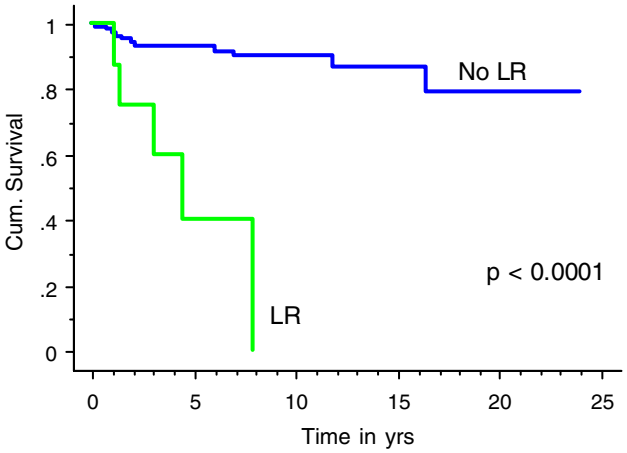


Fig. 5. Tumour-specific survival split by whether or not patients developed local recurrence (LR).

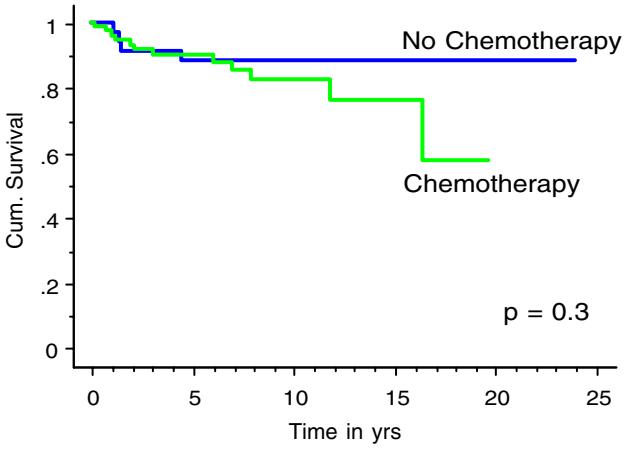


Fig. 6. Overall survival split by whether or not patients had chemotherapy.

Table 2
Factors affecting overall survival

Factor	HR	CI	*P*-value
Age (continuous variable)	1.015	0.983–1.047	0.3663
Size (continuous variable)	1.071	0.976–1.176	0.1480
No chemotherapy	0.562	0.199–1.588	0.276
<90% Necrosis	1.983	0.217–18.122	0.544
Inadequate margins of excision	0.643	0.138–2.999	0.574
Local recurrence	8.79	2.958–26.167	<0.0001

Hazard ratios (HR) with confidence intervals (CI) and *P*-value. Calculated using a Cox proportional hazard method with each factor being entered in isolation. Age and size were continuous variables. Multivariate analysis was not used as only one factor was significant on univariate analysis.

4. Discussion

Periosteal osteosarcoma is a rare variant of osteosarcoma and has represented 1–2% of all osteosarcomas in different series [11,12]. It has typical radiological and histological features and is classified as an intermediate grade osteosarcoma, exhibiting histological features of a moderately differentiated chondroblastic osteosarcoma. It often arises in the diaphysis of the tibia or femur, unlike conventional osteosarcoma, which only arises in the diaphysis in 5–10% of cases.

The data we have obtained have come from 8 European tertiary referral centres and 1 Co-Operative Osteosarcoma Study Group and we assumed that each centre confirmed the diagnosis to its own satisfaction. We have not independently had either the radiology or histology reviewed and this is a potential significant weakness of the study. It means, for instance, that it is possible that some parosteal osteosarcomas or some high-grade surface osteosarcomas may have been included in the series. We feel, however, that it is most unlikely that a parosteal osteosarcoma will have been included because of the very different radiological and histological appearances. High-grade surface osteosarcomas are very rare, even compared with periosteal osteosarcoma and although they may be difficult to differentiate and would be treated in an identical manner, they may have a slightly worse prognosis [13]. We had hoped to have a central review of the radiology and pathology of these cases, but after three requests only two centres had provided limited data. We felt that further attempts were not likely to produce enough responses for any useful conclusions to be drawn.

The patient population has included all patients presenting to the specialist centres for treatment apart from those excluded because of insufficient data. It is likely that the group selected is reasonably representative of those patients with the condition. Although the patient accrual extended over a period of almost 30 years (1974–2002), we felt that it was reasonable to include all these patients as it was unlikely that patients treated earlier would have had chemotherapy and thus might have acted as a control group for those treated in more recent years.

This is the largest collection of patients with periosteal osteosarcoma ever reported and the results parallel those previously reported apart from those by Revell *et al.* [8], in whose small series where chemotherapy was used in every patient there had been no tumour-related deaths. In other series, chemotherapy has been used unpredictably and no conclusion has been possible about its efficacy.

We tried to identify in what situations different centres would use chemotherapy, but there was no clear or consistent strategy across most centres. In some centres chemotherapy was used routinely and in others it was not. Some centres only gave it for larger tumours and some only if there was medullary involvement. It may be that chemotherapy was not used in patients with small well localized tumours who might have a better prognosis, but we were not able to confirm this. The chemotherapy regimes have also varied greatly, although all contained doxorubicin.

With a 5-year survival rate of 89% and a 10-year survival rate of 83%, these results are comparable with other series [6–8]. Despite the size of the series we have been unable to show convincingly whether chemotherapy is of benefit for this condition.

Although information about tumour grade was requested, it was supplied in less than half the cases. Grade appeared to have no bearing on whether the patient received chemotherapy and had no effect either on local recurrence or overall survival. Most authors consider periosteal osteosarcoma to be an intermediate grade tumour and the results of this study would tend to confirm this.

The extent of medullary involvement has not been assessed in this study. Unni [4], who originally described the condition, felt that medullary involvement precluded the diagnosis of periosteal osteosarcoma, but Hall [7] and others felt that this was simply the natural progression of the tumour if left untreated. Murphey and colleagues recently carried out a radiological–pathological review of 40 cases from the Armed Forces Institute of Pathology (AFIP) and concluded that although signal change in the medulla was not uncommon, this was usually reactive. They also identified that the tumour typically surrounded 50–55% of the cortex and that whilst the underlying bone was usually thickened it was also eroded by the tumour [14].

The surgical management of our cases has been fairly standard, with a wide variation in the methods of reconstruction following excision. We have not enquired further about the complications or functional outcomes of the various surgical treatments as there are already numerous publications on this topic [15,16]. We have documented, however, the margins of excision achieved and have found a poor correlation with local control. The reason for this is most likely due to the poor reporting of surgical margins from so many different institutions. There is no doubt that obtaining clear margins is essential for this, as for any other sarcoma, and we strongly recommend that periosteal osteosarcoma should be managed in specialist centres by experienced surgeons, pathologists and oncologists in order to obtain optimum results.

Local recurrence has proved relatively rare in this condition, but importantly was associated with a very high incidence of metastases and death.

Previous authors have commented on the possible high incidence of second malignancy in this condition [6,8]. In this study, with an average follow-up of 7.5

years, there were 4 second malignancies, 2 being leukaemia and 1 colonic cancer and 1 brain tumour. Whilst this is of some concern, it is not outwith the range of second malignancy for other tumours treated with similar chemotherapy [17,18]. It is, of course, conceivable that these patients may have had a variant of the Li-Fraumeni syndrome and a possible underlying genetic abnormality cannot be excluded. Unfortunately, no cytogenetics on either of the two cases with leukaemia were available. Analysis of any future case of second malignancy may, however, shed light on chemotherapy being a possible cause for that second malignancy. Clearly, if the treatment leads to a potential risk of a second malignancy, then any potential benefit of the initial treatment may be nullified by the increased risks of problems later on.

In conclusion, the main aim in treating periosteal osteosarcoma must be to achieve local control. This study has not proved conclusively one way or the other that chemotherapy is necessary for this condition, but it was used in the majority of patients. If chemotherapy is to be used it would appear from this series that there is no obvious advantage for a multi-drug regime over a simpler regime, but it may well be that chemotherapy does not significantly affect the outcome of this disease.

Conflict of interest statement

None declared.

Acknowledgement

Contributing institutions: Royal Orthopaedic Hospital, Birmingham, UK; Royal National Orthopaedic Hospital, London, UK; The Norwegian Radium Hospital, Oslo, Norway; The COSS group, Muenster, Germany; Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel; University Hospital of Orthopaedics, Sofia, Bulgaria; Clinic of Bone Tumours, Sofia, Bulgaria; University of Vienna Medical School, Vienna, Austria; University of Munster, Munster, Germany; University of Navarra, Navarra, Spain; Leiden University Medical Centre, Leiden, Netherlands.

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