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The effect of local recurrence on survival in resected osteosarcoma

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Abstract

The aim of this study was to assess the effect of local recurrence on survival in primary osteosarcoma. 559 patients entered into two randomised trials of the European Osteosarcoma Intergroup who received surgery for primary operable high-grade osteosarcoma of the extremities were included in this analysis. Proportional hazards modelling techniques were used to assess the relative importance of sex, age, site, surgery performed and local recurrence. The last of these was considered as a time-dependent covariate. 42/559 (8%) patients had a local recurrence. In the multivariate analysis, local recurrence was found to greatly increase the risk of death (hazard ratio (HR) = 5.10, 95% confidence interval (CI) 3.51–7.41). Site and surgery performed also had a significant influence within this model. Using the technique of landmark analysis, with the landmark time set at 18 months, local recurrence alone had a significant influence on survival (HR = 4.60, 95% CI 2.80–7.57). Local recurrence is an indicator of poorer survival for patients with operable primary osteosarcoma.

Keywords: Local recurrence; Osteosarcoma; Survival

1. Introduction

The aim of surgery for primary osteosarcoma is to balance the need to achieve local control of the tumour, and to retain as much function of the limb as possible. Until the mid-1970s treatment for osteosarcoma generally consisted of surgery alone, usually amputation. In recent years, as neoadjuvant chemotherapy has increased in usage [1,2], limb salvage has become the mainstay of surgical management [3,4]. It is thought that preoperative courses of chemotherapy reduce the tumour volume sufficiently to allow limb salvage surgery to be safely performed.

Although it allows greater limb function, a major drawback of limb salvage surgery is that it increases the risk of inadequate surgical margins. Several studies have shown that inadequate margins and poor histological response increase the risk of local recurrence [5–8]. Although the prognosis of patients experiencing local recurrence is said to be poor, the impact of local recurrence on survival has not been formally examined.

Local recurrence has been shown to lead to reduced survival in patients with soft tissue sarcoma, but its effect on resected primary osteosarcoma has not been examined. Traditionally local recurrence rates in soft tissue sarcoma are considered to be in the region of 30–40% [9,10], although rates of between 10 and 20% have been reported in recent series [11,12] and in a recent report on preoperative thermoradiotherapy [13]. In osteosarcoma, local recurrence rates are lower, usually approximately 5–10% [8]. Thus, in order for there to be sufficient information to explore the influence of local recurrence in osteosarcoma reliably, a large number of osteosarcoma patients would be needed.

In this study, data on 559 patients entered into two randomised controlled trials were used to examine the relationship between local recurrence and survival in operable primary osteosarcoma of the extremities. Examining survival by local recurrence requires careful

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statistical analysis, the techniques used in this study have been chosen to avoid bias in the analysis and are explained fully in the next section.

2. Patients and methods

2.1. Patients

All eligible patients randomised into the first two trials of the European Osteosarcoma Intergroup (EOI) who received surgery for primary osteosarcoma were included in this analysis. EOI consists of the Bone Sarcoma Working Party of the UK Medical Research Council (MRC), the UK Children's Cancer Study Group (UKCCSG), the Société Internationale d'Oncologie Paedriatrique (SIOP) and the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group.

The first EOI randomised trial, BO02/80831 [2], compared a two-drug regimen of doxorubicin plus cisplatin against the same combination preceded by high-dose methotrexate. Between July 1983 and December 1986, 307 osteosarcoma patients were entered into this trial, 179 of whom received neoadjuvant chemotherapy for operable extremity osteosarcoma and were thus considered for this analysis. The other 128 patients not included in this analysis had primary metastatic, axial skeletal or recurrent disease, received postoperative chemotherapy only or were ineligible for the trial. BO02/80831 showed no evidence of a benefit in the methotrexate arm.

The second EOI randomised trial, BO03/80861 [14], compared the same two-drug regimen with multi-agent therapy based on the T10 regimen developed by Rosen and colleagues [1]. Between September 1986 and February 1993, 407 patients with operable non-metastatic osteosarcoma were entered into this trial, of whom 391 were eligible. No evidence of a survival benefit was found in the multidrug arm.

The main causes of ineligibility in these trials were excessive delay between biopsy and chemotherapy (>35 days), incorrect pathology, no date of biopsy and previous chemotherapy. As these trials shared the same control arm and no clear evidence of a difference in survival between treatment was found in either trial it was considered reasonable to combine data from both trials in order to perform this analysis.

Data on histological response were included in this analysis in order to assess its relationship with local recurrence and survival. Good histological response, as defined as $\geqslant 90\%$ necrosis, was assessed by an expert pathological review panel.

For the purpose of this analysis, local recurrence was defined as recurrence of the tumour within the surgical field following definitive surgery. Local progression prior to surgery, lymph node relapse outside the surgical field and recurrence of tumour elsewhere in the body were not classified as local recurrence.

2.2. Statistical methods

The aim of this analysis was to establish whether local recurrence has a prognostic effect on the survival of patients with resected primary osteosarcoma after allowing for other baseline factors. The multivariate analysis was performed using Cox's proportional hazard method, with variables being chosen via a forward conditional stepwise approach. Survival time was calculated from the date of surgery.

Three methods have been used to analyse these data.

2.2.1. Cox model with recurrence as a fixed covariate

For this method, local recurrence was considered as a simple prognostic factor, i.e. patients who had local recurrence were compared with those who did not. This is the most common method for looking at the influence of a variable on survival, but it can introduce bias if the variable — in this case local recurrence — takes one value at the start of follow-up, but takes another at a later stage.

This bias exists as the length of survival itself influences the chance of a patient being classed as recurrent or non-recurrent [15]. Patients who are classed as recurrent must live long enough for the recurrence to be detected. This 'guarantee time' or 'lead time' is at least as long as the time until the first follow-up assessment. No such lead time is required for the non-recurrent group and patients who die before their first follow-up assessment will automatically be classed as non-recurrent. In particular, patients with poor prognosis who die soon after surgery without experiencing local recurrence will guarantee poorer survival for the non-recurrent group.

2.2.2. Cox model with recurrence as a time-dependent covariate

Time-dependent covariates are those whose value, for any given patient, may change over time [16,17]. Thus, locally recurrent patients can be considered non-recurrent in the analysis until the recurrence occurs, and recurrent thereafter. The proportional hazards method can be extended to incorporate such variables. This method is not subject to the bias incurred when local recurrence is analysed as a fixed covariate, as in the first method.

2.2.3. Landmark method

The third method used is a landmark analysis [15,18]. This involves choosing a fixed time-point after follow-up has begun as a 'landmark' for conducting the analysis. Patients who are still being followed at the landmark time are classified as having had a local recurrence

before that timepoint or not. Survival time is calculated from the landmark time, and standard survival analysis techniques can then be used. Patients who die or are lost to follow-up before the landmark time are excluded from the analysis. Patients who have a local recurrence later than the landmark time are classified as non-recurrent in the analysis.

Landmark analysis allows an unbiased logrank test to be conducted for length of survival from the landmark time by recurrence status at the landmark time. Meaningful graphical representation of survival by recurrence status can also be obtained using Kaplan–Meier curves. The major drawback of this method is the arbitrary choice of the landmark time. If the time chosen is too early in the follow-up period, an insufficient number of recurrences would have occurred to make the analysis worthwhile. If the time chosen is too late, many patients may be excluded. The landmark time should be chosen before any statistical analyses are conducted, and if possible should have some clinical relevance. Sensitivity analysis can be used to see if results are affected by the choice of landmark time.

Before any analyses were performed, members of the EOI Surgical Sub-Committee were invited to choose a timepoint that would form the basis of this analysis. They were asked to make this decision based on their own surgical experience. Although they felt that the majority of local recurrences would have taken place before 2 years, there was concern that many of these patients would also have died in this period and thus be excluded from the analysis. Consequently, the landmark time was chosen to be 18 months.

3. Results

3.1. Patient characteristics

Of the 570 eligible randomised patients available from the two EOI trials, it was possible to include 559 in this analysis (178 from BO02/80831, 381 BO03/80861). 11 patients (1 BO02/80831, 10 BO03/80861) were excluded as they did not have surgery for primary osteosarcoma. Data on histological response were available for 368/559 (66%) of patients.

The trial data suggested that 64 (11%) patients had a local recurrence. In order to verify this, the EOI Surgical Sub-Committee wrote to the clinicians responsible asking for details of the recurrence. 48/64 (75%) of these forms were returned, 29 of these 48 patients (60%) were confirmed to have had local recurrence. The other 19 patients had suffered other forms of recurrence such as local progression prior to surgery and lymph node relapse. For the 16 patients who did not have forms returned it was assumed that the report of a local recurrence was correct, although the impact of this assumption is examined as it is likely that not all of these patients would indeed have had a local recurrence. In three cases, the patients had actually progressed locally before surgery and were, therefore, considered non-recurrent. Thus, 42 patients (8%) were considered to have had a local recurrence in this group of patients.

The characteristics of the 559 patients included in this analysis are shown in Table 1. Table 2 shows these characteristics tabulated by local recurrence. In general, the two groups of patients are fairly similar, although, as expected, a much higher proportion of the recurrent patients had limb salvage surgery.

3.2. Univariate analysis

Results of the univariate survival analysis are shown in Table 1. There is no evidence of a survival difference between different sex or age groups. Patients whose primary tumour was in the tibia or fibula appear to have slightly higher survival after 5 years, although this result falls short of significance at the 5% level. Patients who received amputation experience significantly poorer survival than other surgical groups.

3.3. Multivariate analysis — local recurrence as a fixed covariate

The variables included in the multivariate analysis are sex, age, site and type of surgery along with the incidence of local recurrence. These are the baseline variables common to both trials used in this analysis. In the first instance, they were all fitted as fixed covariates. Having fitted the model, local recurrence, surgery

Table 1
Patient characteristics and univariate analysis relating characteristic to length of survival

	n (%)	5-year survival (95% CI)	Logrank statistic	df	*P* value %
Sex					
Male	357 (64)	55 (50–60)			
Female	202 (36)	57 (50–64)	0.11	1	0.75
Age (years)					
< 12	94 (17)	55 (45–66)			
12–16	228 (41)	56 (49–62)			
17+	237 (42)	56 (49–62)	0.05	1	0.82
Location					
Femur	310 (55)	54 (48–60)			
Tibia/fibula	176 (31)	61 (53–68)			
Humerus/radius/ulna	73 (13)	51 (39–63)	5.59	2	0.06
Surgery received					
Amputation	164 (29)	42 (35–50)			
Limb salvage	373 (67)	61 (56–66)			
Rotation plasty	22 (4)	59 (34–75)	18.89	2	< 0.01

df, degree of freedom; CI, confidence interval.

Table 2
Patient characteristics by local recurrence

	Local recurrence	
	No ($n=517$)	Yes ($n=42$)
Sex		
Male	328 (63)	29 (69)
Female	189 (37)	13 (31)
Age (years)		
<12	89 (17)	5 (12)
12–16	212 (41)	16 (38)
17+	216 (42)	21 (50)
Location		
Femur	291 (56)	19 (45)
Tibia/fibula	163 (32)	13 (31)
Humerus/radius/ulna	63 (12)	10 (24)
Surgery received		
Amputation	160 (31)	4 (10)
Limb salvage	335 (65)	38 (90)
Rotation plasty	22 (4)	0

received and site of the tumour were found to have a significant effect on survival. Hazard ratios (HRs) and 95% confidence intervals (CIs) for these variables are found in Table 3.

It can be seen from Table 3 that patients who received amputation have a significantly worse outlook than those who received other operations. Patients whose primary tumour was in the tibia or fibula had better survival figures than those with primaries in other sites. Patients who suffered local recurrence had a much poorer survival outlook than those who did not, but for reasons mentioned earlier this conclusion should be treated with caution due to potential bias.

3.4. Multivariate analysis — local recurrence as a time-dependent covariate

A proportional hazards model was fitted as before, but with local recurrence included as a time-dependent covariate. Again local recurrence, type of surgery received and site of tumour were found to have a significant effect on survival. Hazard ratios and confidence intervals for this model are shown in Table 4.

The effects of surgery and site of tumour are similar to those seen already. The interpretation of a hazard ratio for a variable fitted as a time-dependent covariate is different to when the covariate is fixed. The risk of death for patients who have had a local recurrence was five times worse than the risk for those who had not recurred at the time of last measurement.

3.5. Landmark analysis

The landmark time chosen for this analysis was 18 months. The number of patients available for analysis at 18 months was 440, 22 (5%) of whom have suffered local recurrence. Survival by whether recurrence has occurred at 18 months is shown in Fig. 1.

Table 3
Hazard ratios and confidence intervals (CI) for multivariate Cox model

Variable	Hazard ratio[a]	95% CI	*P* value
Local recurrence			
No	1		
Yes	3.30	2.26–4.80	<0.0001
Surgery received			
Amputation	1		
Limb salvage	0.48	0.36–0.62	<0.0001
Rotation plasty	0.57	0.29–1.10	0.0947
Site of tumour			
Femur	1		
Tibia/fibula	0.67	0.50–0.90	0.0079
Humerus/radius/ulna	0.98	0.68–1.41	0.8927

[a] A hazard ratio (HR) of <1 indicates a survival benefit to that group.

It can clearly be seen that survival is considerably worse in patients who have recurred locally in the 18 months following surgery. The hazard ratio for this univariate analysis is 4.51 (95% CI 1.74–11.67) so patients who survive for 18 months following surgery are subsequently at more than four times greater risk of death if they had a local recurrence during those 18 months.

A multivariate analysis using a proportional hazards model was undertaken using these landmark survival data. The variables of interest were sex, age (at landmark time), site of tumour, surgery received and whether recurrence had occurred within 18 months of surgery. Using a forward conditional method to select variables, the only variable to have a significant effect was local recurrence. The hazard ratio was 4.60 (95% CI 2.80–7.57), very similar to that seen in the univariate analysis.

Table 4
Hazard ratios and confidence intervals (CI) for multivariate Cox model, local recurrence fitted as a time-dependent covariate

Variable	Hazard ratio	95% CI	*P* value
Local recurrence			
No	1		
Yes	5.10	3.51–7.41	<0.0001
Surgery received			
Amputation	1		
Limb salvage	0.47	0.36–0.62	<0.0001
Rotation plasty	0.58	0.30–1.13	0.1084
Site of tumour			
Femur	1		
Tibia/fibula	0.70	0.52–0.94	0.0161
Humerus/radius/ulna	0.97	0.67–1.40	0.8602

A hazard ratio of <1 indicates a survival benefit to that group.

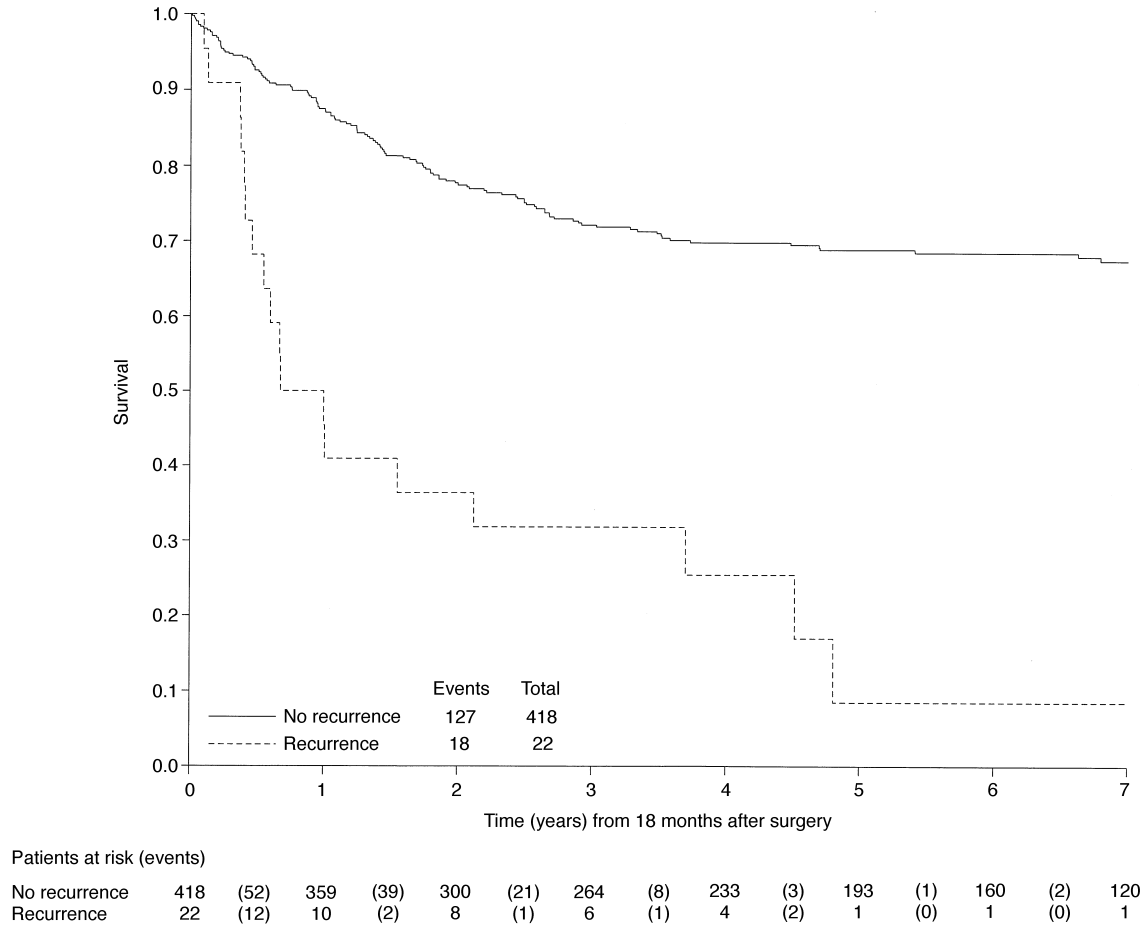

Fig. 1. Survival by recurrence status, calculated from 18 months after surgery. Log-rank statistic = 43.69 ($P = 0.0001$ on 1 degree of freedom (df)), hazard ratio = 4.51 (95% confidence interval (CI) 1.74–11.67).

In order to investigate whether the choice of time-point has an effect on the conclusions, similar analyses have been conducted with the landmark time set at 1 year and 2 years. The results of these are contained in Table 5.

Although the number of patients and recurrences varied, the proportion of recurrences remained fairly steady. The hazard ratios are not identical, but recurrence at landmark time does have a detrimental effect on survival in each case. The modest fluctuations in hazard ratio may be caused be the relatively low proportion of recurrent patients.

3.6. Local recurrence and histological response

Good histological response, defined as $\geqslant 90\%$ necrosis, was observed in 102/368 (28%) patients. In order to investigate the relative prognostic importance of histological response and local recurrence these variables, along with age, sex, site and surgery, were fitted in a multivariate proportional hazards model. 368 patients were included in this analysis, local recurrence was treated as a time-dependent covariate.

Local recurrence and histological response were both found to have a significant effect on survival (Table 6), as were surgery and site. The hazard ratio for local recurrence was lower than those observed in the previous analyses, but this was a much smaller group of patients. Local recurrence and histological response do appear to have independent roles in predicting survival for these patients.

Table 5
Hazard ratios (and 95% confidence intervals (CI)) for survival by recurrence status with different landmark times

Landmark time	Patients *n*	Recurrences *n* (%)	Hazard ratio (95% CI)
1 year	495	18 (4)	5.83 (1.97–17.25)
18 months	440	22 (5)	4.51 (1.74–11.67)
2 years	400	17 (4)	3.98 (1.33–11.92)

Table 6
Hazard ratios and confidence intervals (CI) for multivariate Cox model including histological response and local recurrence fitted as time-dependent covariate ($n = 368$)

Variable	n (%)	Hazard ratio	95% CI	P value
Local recurrence				
No	343 (93)	1		
Yes	25 (7)	3.26	2.03–5.24	< 0.0001
Histological response				
Good	102 (28)	1		
Poor	266 (72)	2.19	1.46–3.28	0.0002
Surgery received				
Amputation	100 (27)	1		
Limb salvage	249 (68)	0.50	0.36–0.69	< 0.0001
Rotation plasty	19 (5)	0.52	0.25–1.07	0.0758
Site of tumour				
Femur	204 (55)	1		
Tibia/fibula	112 (30)	0.57	0.39–0.83	0.0031
Humerus/radius/ulna	52 (14)	0.80	0.52–1.23	0.3037

A hazard ratio of < 1 indicates a survival benefit to that group.

The effect of incorporating histological response into the 18-month landmark analysis was also examined. Data on histological response were available for 288/440 (65%) patients. A multivariate proportional hazards model incorporating age, sex, site, surgery received, local recurrence and histological response was fitted to these data. Local recurrence (HR = 3.83, 95% CI 2.12–6.91) and histological response (HR = 1.70, 95% CI 1.08–2.68) were the only variables found to be significant. These results are consistent with those outlined above.

3.7. Assumptions regarding assessment of local recurrence

Before this analysis was performed, forms were sent to participating surgeons to verify all 64 suspected local recurrences within the two trials. Of the 48 patients for whom forms were returned, 29 were confirmed to have had a local recurrence. Sixteen of these forms were not returned, it was assumed in the analysis that these patients did suffer a local recurrence, apart from the 3 known to have progressed before surgery.

One potential criticism of this analysis is that this was a false assumption and that perhaps these patients did not have a local recurrence after all. However, if the multivariate model was fitted with local recurrence, as a time-dependent covariate, and patients considered as recurrent only if confirmed by the form, the results were very similar. Local recurrence, surgery performed and site were found to be significant, the hazard ratio for local recurrence was 4.55 (95% CI 2.94–7.04).

If the patients whose forms were not returned were considered non-recurrent in the 18-month landmark analysis then 16/440 (4%) were classed as having a local recurrence and the corresponding hazard ratio was 3.90 (95% CI 1.37–11.16).

4. Discussion

In this paper, three techniques of multivariate analysis have been used to investigate the prognostic effect of local recurrence on survival in operable osteosarcoma. Each has strongly indicated that patients who have a local recurrence are at a much greater risk of death than those who do not. Amputation was also associated with poor survival, which is understandable as within these trials it was usually performed on patients for whom limb salvage was considered too risky. Better survival was observed for tumours of the fibula and tibia than for the other sites.

One criticism of this analysis is that it fails to include other potentially important factors such as the size of tumour and resection margins. Unfortunately, these variables were not recorded for these trials, whose primary purpose was to evaluate the efficacy of different chemotherapy regimens. The effect of local recurrence on survival is very strong and independent of other factors, so it is likely that these unknown factors will only have a modest effect on the prognostic significance of local recurrence. Further collection of these factors will only quantify the relative importance of local recurrence, it is unlikely to alter the fact that local recurrence is an important event. This is certainly the case, for example, for histological response, which was recorded for two-thirds of the patients in the trial.

Data on tumour volume and resection margins have been collected by the three principal surgical centres for the second EOI randomised trial, BO03/80861. These centres performed surgery for 202 patients within the trial, and collected detailed surgical data on them. These data are currently being analysed, it is hoped that they will at least partially answer the question about the relative importance of local recurrence and other surgical variables in osteosarcoma, despite the inevitably small number of local recurrences in the dataset. Within this dataset there are sufficient numbers for each centre to examine whether outcomes differ between surgical institutions.

Another criticism of this analysis is that it has not been possible to verify local recurrence for 13 patients who were recorded as having had a local recurrence after definitive surgery, but for whom no form was returned. Analyses have been reported with these patients considered as recurrent and non-recurrent, and the results were consistent for the two cases; with local recurrence having a significant effect on survival.

There are numerous papers examining the relationship between local recurrence and survival in soft tissue sarcoma, however, the results and methodologies employed vary considerably. A review published in 1991 [19] concluded that many analyses concerning this relationship were invalid as they had not taken account of other important risk factors, and local recurrence was not often analysed using appropriate statistical methods, i.e. as a time-dependent covariate.

A literature search has revealed three papers in soft tissue sarcoma where local recurrence was included in a multivariate model as a time-dependent covariate. A series of 262 high-grade patients in the USA found local recurrence to be significantly associated with reduced survival in a multivariate model which also included stage, type of surgery, extent of resection, signs of sarcomatous skin invasion and presence of postoperative fever [9]. Results reported by the Royal Marsden Hospital in London also found local recurrence to be significant in a multivariate model, alongside size, grade and treatment with radiotherapy [10]. A more recent study from the Memorial Sloan-Kettering Hospital of primary soft tissue sarcomas of the extremities found that local recurrence fitted as a time-dependent covariate was an independent predictor both of subsequent metastasis and disease-specific survival in multivariate models containing other risk factors such as size and grade [20]. These results are comparable with those reported for osteosarcoma in this paper, namely that local recurrence, when analysed via the appropriate statistical methodology, has a significant effect on survival, independently of other important prognostic variables.

Although local recurrence is associated with reduced survival, it is impossible to say whether it causes poor outcome or is just a marker for it. Whatever the form of the relationship, in order to avoid distress to patients it would be sensible to try and minimise the risk of local recurrence. Several papers have suggested that the main factors which influence the development of local recurrence are inadequate surgical margins and poor histopathological response to chemotherapy [5,8]. The German COSS group recommend that limb salvage surgery is not attempted in poor responders as this leads to a greatly increased risk of local recurrence [7]. A French group also found that the risk of local recurrence was reduced if the biopsy was performed by the oncological surgeon and if preoperative chemotherapy lasted for less than 1 month [6].

One clear conclusion that can be drawn from this analysis is that work needs to be done to improve the long-term survival of patients who suffer local recurrence. The role of second-line chemotherapy in treating patients with locally recurrent osteosarcoma has yet to be evaluated. We have shown within this group of primary limb osteosarcoma patients that only approximately 5–10% suffer a local recurrence compared with approximately 50% developing metastases [2]. In order to have sufficient numbers, the role of chemotherapy would have to be evaluated for locally recurrent and metastatic patients together. Chemotherapy regimens for relapsed patients have shown good results in small series [21], but none have been evaluated in a randomised setting.

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