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Survival after recurrent osteosarcoma: Data from 3 European Osteosarcoma Intergroup (EOI) randomized controlled trials ☆

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ABSTRACT

Background: Recurrence after osteosarcoma usually leads to death; thus prognostic factors for survival are of great importance.

Methods: Between 1983 and 2002, the European Osteosarcoma Intergroup accrued 1067 patients to 3 randomized controlled trials of pre- and post-operative chemotherapy for patients with resectable non-metastatic high-grade osteosarcoma of the extremity. Control treatment in all trials was doxorubicin 75 mg/m^2 and cisplatin 100 mg/m^2. The comparators were additional high-dose methotrexate (BO02), T10-based multi-drug regimen (BO03) and G-CSF intensified-DC (BO06). Post-recurrence survival (PRS) was investigated on combined data with standard survival analysis methods.

Results: Median recurrence-free survival was 31 months; 8 recurrences were reported more than 5 years after diagnosis. In 564 patients with a recurrence (median 13 months post-randomisation), there was no difference in post-relapse survival between treatment arms. Patients whose disease recurred within 2 years after randomization had worse prognosis than those recurring after 2 years. Patients with good initial histological response to pre-operative chemotherapy had better overall survival after recurrence than poor responders. Local relapse was more often reported after limb-saving procedures (2 versus 8%; amputation versus limb-saving), independent of primary tumour site. Site of first recurrence (local 20%, lung 62%, "other" 19%) affected survival, as patients recurring with non-lung distant metastases only or any combination of local relapse, lung metastases and non-lung

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metastases (=group "other") had significantly worse overall survival (local 39%, lung 19%, "other" 9% at 5 years).

Conclusions: These data describing a large series of patients with recurrent extremity osteosarcoma confirm the relationship between early recurrence and poor survival. There was better PRS in patients after good histological response to pre-operative chemotherapy, or with local-only recurrence.

1. Introduction

Non-metastatic high-grade osteosarcoma of the extremities is a disease that remains incurable in up to 30% of patients despite continuous efforts to improve outcome. Standard treatment includes wide margin resection of the tumour, either by limb-sparing procedure or by amputation, combined with pre- and post-operative multi-agent chemotherapy. Histological response of the resected tumour to pre-operative chemotherapy is strongly prognostic for long-term outcome, with patients who achieve a good histological response (usually defined as $\geqslant$90% necrosis) having a better prognosis than those who do not. Disease relapses, local and/or distant, are difficult to treat and often will eventually lead to death. Thus prognostic factors for overall survival after recurrence (post-recurrence survival or PRS) are of great importance.[1] Large scale studies with uniform treatment and follow-up data may enable us to gain insight into patterns of, and risk factors for, relapse which in turn may promote the development of more effective treatments.

The European Osteosarcoma Intergroup (EOI) is a network conducting such large scale studies since 1982 and a large database is available to study the clinical characteristics of this disease. To date, the EOI has completed 3 randomised controlled trials, involving over one thousand patients with localised extremity osteosarcoma. Each of the 3 trials used a "standard" treatment arm of 6 cycles of perioperative doxorubicin and cisplatin (DC) chemotherapy. The comparator arms were additional high-dose methotrexate (MRC-BO02/EORTC-80831),[2] T10-based multi-drug regimen (MRC-BO03/EORTC-80861)[3] and G-CSF intensified 6 cycles of 2-weekly DC (MRC-BO06/EORTC-80931).[4] Since no statistically significant post-relapse survival differences between treatments arms were reported in any of these trials we have used the prospectively collected EOI database concerning all 3 randomised trials to perform retrospective analyses focusing on the patterns of local and distant recurrence in patients with non-metastatic osteosarcoma of the extremities.

2. Patients and methods

2.1. Patients

In 1983–2002, EOI completed accrual to 3 consecutive randomized controlled trials of pre- and post-operative chemotherapy for patients with resectable non-metastatic high-grade osteosarcoma of the extremity (MRC-BO02/EORTC-80831, MRC-BO03/EORTC-80861 and MRC-BO06/EORTC-80931); $n = 179$, 391 and 497 patients, respectively.[2–4] Patients were randomised through the MRC Clinical Trials Unit, formerly the MRC Cancer Trials Office (including United Kingdom (UK), Ireland and South America) or the EORTC Data Centre (mainland Europe and Saudi Arabia). Patients with histologically proven, localised, high-grade extremity osteosarcoma were eligible for randomisation. Other eligibility criteria included age $\leqslant$40 years, and adequate renal and cardiac function. Patients who had received prior chemotherapy or had a previous malignancy were ineligible. Ethics approval was granted at all institutions, and written informed consent was obtained from the patient or parent, in accordance with local regulatory guidelines.

Patients were randomised within 35 days after diagnostic biopsy, and the aim was a to review of all diagnoses by a member of the EOI pathology sub-committee. Control arm treatment in all trials was six cycles of doxorubicin 25 mg/m^2 daily for 3 days in combination with cisplatin 100 mg/m^2 as a continuous infusion at 3-weekly intervals (DC). The comparator arm in MRC-BO02/EORTC-80831 consisted of only 4 DC courses, each cycle preceded by high-dose methotrexate 8 g/m^2 (HD-MTX) with appropriate folinic acid rescue. In MRC-BO03/EORTC-80861, 6 cycles of DC were compared to a multi-drug regimen that was very similar to that given to the poor responders in the original T-10 protocol,[5] with additional treatment with doxorubicin at week 2, and cisplatin and doxorubicin given to all patients post-operatively. In MRC-BO06/EORTC-80931, both arms received the same total number of 6 cycles of DC, however, in the comparator arm was a dose-dense, G-CSF-supported, 2-weekly schedule. In all trials it was recommended that the resected specimen was examined histologically to assess response to pre-operative chemotherapy. Good histological response was defined as >90% necrosis. Available specimens were reviewed centrally by EOI pathologists.

After primary treatment all patients were subject to regular follow-up schemes that included clinical examination and chest X-ray every 3–8 weeks for the first 6 months, every 6–9 weeks until the end of year 1, every 2–3 months during year 2, every 3–4 months during year 3, and every 3–6 months until year 5. After year 5, follow-up was annually.

2.2. Statistical methods

This was a retrospective analysis, including all 1067 patients from the 3 trials, carried out on an intention-to-treat basis. Patients (29) with early recurrence in the first 90 days after surgery were included in the analysis. Separate analyses were undertaken to examine prognostic factors for post-relapse survival (PRS). Factors examined included: first site of recurrence, time of recurrence, surgery type, histological

response to pre-operative chemotherapy, study group, histological subtype of tumour, primary site of tumour and proximal versus distal tumour site (proximal site being defined as a proximal tumour of the humerus or femur; distal sites, all other). PRS was also analysed by trial, treatment regardless of trial and treatment within trial to determine whether the analysis of all patients together was reasonable. Frequency tables were used to show first site of recurrence by original site of tumour, and by type of surgery, and chi-squared tests were used to detect differences in distribution of site of recurrence across categories. A two-sided significance level of 5% was adopted for all analyses; all confidence intervals are presented at the 95% level. Stata 9 (StataCorp, College Station, TX) was used for the analysis.

The analyses of factors influencing PRS used standard time-to-event methodology (survival analysis). Survival was measured from the recorded date of first suspicious or confirmed disease recurrence, or from the date of follow-up where the recurrence was reported, if the date of recurrence was not explicitly reported.

Recurrences were grouped into the following three categories: (1) patients with local relapse only ("local only"), (2) patients with lung metastases only ("lung only"), and (3) patients reporting either non-lung distant metastases only or any combination of local relapse, lung metastases and non-lung metastases ("other site(s)"). Disease progression events before primary surgery were excluded. PRS was timed until death (from any cause) or patients were censored at the date of last follow-up if death had not been reported. Median follow-up was calculated by reverse censoring on PRS. The relative risks of each factor are summarised using hazard ratios (HR) from univariate Cox regression models. Multivariate Cox models were also used to determine which variables were independently prognostic. HRs are expressed relative to patients in the baseline category of the factor of interest; so an HR less than 1.0 indicates a lower risk of the event for patients in that category compared to the baseline category. Survival rates at 5 years after first recurrence are also presented for subgroups of patients. Variables were considered to be nominal; no ordering of the categories was assumed. Patients with missing data for the variable of interest were excluded from that particular analysis in the Cox models. All models were stratified by trial.

3. Results

3.1. Patient characteristics

The baseline characteristics of all 1067 patients are shown, by trial, in Table 1. Median follow-up time for all patients was 10 years; being 18 (quartiles 17, 19) years for BO02; 13 years[11,15] for BO03; and 5 years[3,7] for BO06. The patient characteristics were broadly similar for each of the 3 trials, although there was a slightly higher proportion of males in BO03, and chondroblastic osteosarcoma were more commonly reported in BO03 and BO06.

3.2. Incidence of recurrence

Median recurrence-free survival was 31 months. Overall, 564 recurrences were reported of which only 8 were reported more than 5 years after randomisation.

For 307/564 (54%) of patients who recurred, the first site of recurrence was lung only; for 67 (12%) it was local only and for 190 (34%) other site(s). There was no evidence of a relationship between site of first recurrence and site of primary tumour (χ^2 $p = 0.653$) (Table 2A). Considering all 1067 patients, local recurrence was reported in 54/707 (8%) after limb salvage and 5/305 (2%) after amputation. Now considering only the 564 patients who reported a recurrence, 54/356 (15%) of those who had limb salvage, and 5/176 (2%) of those who had amputation, reported local recurrence (Table 2B).

3.3. Post-recurrence survival

In the 564 patients who reported a recurrence, median time to recurrence was 13 months from randomisation. There was no evidence of a difference in PRS between the four first-line treatment arms (13–19% at 5 years; 6 cycles of conventional 3-weekly DC versus 3 investigational comparator arms). Separate analyses were also conducted per trial, by treatment arm; no statistically significant differences were observed (data not shown), which further justifies the analysis of the three trials as a combined dataset.

Median survival after recurrence was 14 months (quartiles 7, 30 months), and PRS at 5 years was just 18% (95% confidence interval (CI) 15%, 22%) (Fig. 1; Table 3). Patients whose disease recurred within 2 years after randomization had worse prognosis than those recurring after 2 years (hazard ratio (HR): 0.53; 95% CI: 0.41, 0.69) as shown in Fig. 2. This factor remained prognostic in the multivariate model, with effect size and statistical significance remaining similar (HR: 0.58; 95% CI: 0.41, 0.83) (Table 4).

The site of first recurrence affected PRS, as patients recurring with only lung metastases-only had significantly worse survival after recurrence than patients with local recurrence (HR: 1.64; 95% CI: 1.16, 2.31). Additionally, those patients with first recurrence at a non-lung distant site or a combination of sites had a still worse prognosis compared to those with local recurrence only (HR: 2.75; 95% CI: 1.93, 3.94). Five year PRS in the local-only group was 39%, in the lung-only group 19%, and in the other site(s) group 9% (Table 3). The site of first recurrence was also shown to be independently prognostic as both terms remained significant in the multivariate model (Table 4).

Patients with good histological response to the original pre-operative chemotherapy had better survival after recurrence than poor responders as shown in (HR: 0.70; 95% CI: 0.53, 0.93) (Table 4).

Whether patients had an amputation or limb salvage surgery affected PRS, with 21% (95% CI: 17%, 26%) of limb salvage patients still alive at 5 years from first recurrence, compared to 13% (8%, 19%) of patients who had amputation (Table 3).

There was no evidence of any difference in survival after recurrence due to the site of the primary tumour; either considering the bone affected or the proximal versus distal location of the tumour in the bone. Histological subtype of tumour also did not appear to affect survival after recurrence.

Table 1 – Baseline characteristics by trial for 1067 patients recruited to 3 consecutive EOI studies.

	Trial							
	BO02 (80831)		BO03 (80861)		BO06 (80931)		Total	
	No.	%	No.	%	No.	%	No.	%
Collaborative group								
UK/MRC	112	63	267	68	228	46	607	57
EORTC/SIOP	67	37	64	16	151	30	282	26
Other	0	0	60	15	118	24	178	17
Age at randomisation (years)								
0–10	20	11	47	12	95	19	162	15
11–15	68	38	134	34	195	39	397	37
16–20	67	37	134	34	141	28	342	32
21–30	20	11	61	16	47	9	128	12
31+	4	2	15	4	19	4	38	4
Median (IQR)	16 (13–18)		16 (13–19)		15 (12–18)		15 (12–18)	
Min–max	3–40		3–38		3–40		3–40	
Sex								
Male	102	57	261	67	293	59	656	62
Female	77	43	130	33	201	41	408	38
Classification of sarcoma								
Common type	144	81	260	66	271	63	675	68
Chondroblastic	9	5	45	12	51	12	105	11
Fibroblastic	10	6	43	11	15	3	68	7
Osteoclast rich	3	2	8	2	9	2	20	2
Anaplastic	8	4	16	4	21	5	45	5
Small cell	1	1	2	1	5	1	8	1
Telangiectatic	0	0	10	3	29	7	39	4
Other	2	1	7	2	29	7	38	4
Missing	2	*n/a*	0	*n/a*	67	*n/a*	69	*n/a*
Site of tumour								
Femur	100	56	215	55	296	60	611	58
Tibia	47	26	101	26	116	24	264	25
Fibula	9	5	20	5	25	5	54	5
Humerus	23	13	49	13	48	10	120	11
Radius	0	0	3	1	5	1	8	1
Ulna	0	0	3	1	1	0	4	0
Missing	0	*n/a*	0	*n/a*	6	*n/a*	6	*n/a*
Location of tumour on bone								
Proximal	77	44	164	42	190	39	431	41
Midshaft	0	0	20	5	12	2	32	3
Distal	100	56	205	53	288	59	593	56
Missing	2	*n/a*	2	*n/a*	7	*n/a*	11	*n/a*
Type of surgery								
Amputation (incl. rotationplasty)	78	44	108	28	119	26	305	30
Limb salvage	100	56	273	72	334	74	707	70
Missing	1	*n/a*	10	*n/a*	44	*n/a*	55	*n/a*
Histological response								
Poor	14	40	189	70	224	57	427	61
Good	21	60	80	30	171	43	272	39
Missing	144	*n/a*	122	*n/a*	102	*n/a*	368	*n/a*
Total	179	100	391	100	497	100	1067	100

4. Discussion

The large EOI database with prospective and systematically collected follow-up data enabled us to gain insight into patterns of recurrent disease after primary treatment of non-metastatic high-grade osteosarcoma. This information might be useful for further improvement of treatment of a disease that is still incurable in almost 30% of cases. Strengths of these analyses are the large number of non-selected recurrences of non-metastatic osteosarcoma of the extremity;

Table 2 – Site of recurrence versus (A) original site of tumour (B) surgery type for 564 recurrent, originally non-metastatic, high-grade extremity osteosarcoma patients of 3 consecutive EOI studies.

Site of recurrence	Site of tumour											
	Femur		Tibia		Fibula		Humerus		Radius/Ulna		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A												
Local recurrence only	42	13	12	10	1	4	11	14	1	20	67	12
Lung mets only	178	54	71	56	11	45	43	54	4	80	307	54
Other site(s)[a]	108	33	43	34	12	50	26	33	0	0	190	34
Total reporting recurrence	328	100	126	100	24	100	80	100	5	100	564	100

Site of recurrence	Type of surgery							
	Amputation		Limb salvage		Missing		Total	
	No.	%	No.	%	No.	%	No.	%
B								
Local recurrence only	5	3	54	15	8	25	67	12
Lung mets only	108	61	187	53	12	38	307	54
Other site(s)[a]	63	36	115	32	12	38	190	34
Total reporting recurrence	176	100	356	100	32	100	564	100

[a] Other site(s) = either non-lung distant metastases only or any combination of local relapse, lung metastases and non-lung metastases.

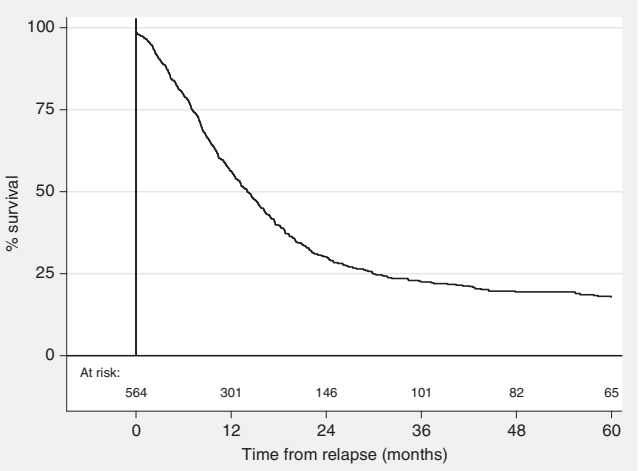

Fig. 1 – Kaplan–Meier curve of survival after first recurrence in 564 recurrent, originally non-metastatic, high-grade extremity osteosarcoma patients of 3 consecutive EOI studies.

construction of a single prospectively collected dataset with uniform main inclusion criteria and detailed information on primary treatment; half the patients uniformly treated with 6 courses of DC. This study includes all events – local, lung and other distant recurrences. The survival outcomes cannot be directly compared to other papers just describing either survival after local recurrence only or survival after (repeated) resection of lung metastases only (e.g. 6). The time to recurrence and rate of local recurrences is in line with the available literature.

Amongst the limitations is the limited information on how the recurrences were treated. However, all patients were treated in experienced sarcoma centres and it is likely that all patients received the best available treatment for their recurrence. This includes, whenever possible, complete resection of a local recurrence and/or surgical treatment of all distant recurrences in case of resectable disease.

All other published series of patients with recurrent osteosarcomas confirm the importance of complete surgical resection of a recurrence.[1,6–10] The role of chemotherapy for resectable recurrences is much more controversial, since randomised prospective studies in this setting are lacking. A retrospective study by Saeter et al.[11] in 60 patients suggests a favourable role for chemotherapy in this setting, while other larger retrospective studies only show event-free survival benefit[8] or even overall survival benefit in situations when a complete surgical remission could not be achieved.[1]

This analysis shows that good pathological response of the primary tumour to pre-operative chemotherapy has independent prognostic value for survival after recurrence, irrespective of the time to recurrence. Reasons for this can only be speculated, but may relate to increased chemosensitivity of the tumour at relapse downsizing and allowing complete resection of the recurrence(s) or, as an alternative explanation, due to eradication of micrometastatic disease related to proven chemosensitivity in the past. However, the limited availability on prognostic covariates may have obscured our observed good pathological response–survival prognostic relationship.

Our study confirms findings from most other studies, e.g. early recurrences and multifocal recurrences (local with lung and/or other recurrences; presented as “other” group in this paper) are related to worse survival, which seems logical as this corresponds with more aggressive behaviour of the disease. We also confirmed that local recurrence was more often observed after limb-saving procedures and was related to better survival compared to distant recurrence. Another important limitation of our study is the fact that positive prognostic factors identified in other series, such as completeness of surgery for the recurrence, number of lesions,

Table 3 – Median survival and survival rates for selected patient subgroups for 564 recurrent patients.

Subgroup	N patients[b]	Median survival (IQR) (months)	% Surviving by 5 years after recurrence (95% CI)
All patients	564	14.1 (7.1, 30.0)	18 (15, 21)
Timing of recurrence			
<2 years from randomisation	454	12.5 (6.7, 24.4)	14 (11, 18)
⩾2 years from randomisation	110	22.2 (11.8, 181.4)	35 (25, 44)
Site of first recurrence			
Local only	67	32.2 (10.8, NYR)	39 (27, 52)
Lung only	307	16.9 (8.7, 31.0)	19 (14, 24)
Other site(s)[a]	190	9.1 (5.2, 17.4)	9 (6, 14)
Histological response			
Poor	272	13.7 (7.0, 29.8)	18 (13, 23)
Good	99	21.5 (10.8, 41.2)	22 (14, 32)
Surgery type			
Amputation	176	12.3 (6.0, 23.4)	13 (8, 19)
Limb salvage	356	15.4 (7.9, 37.5)	21 (17, 26)

NYR = 75th percentile not yet reached in this subgroup.

[a] Other site(s) = either non-lung distant metastases only or any combination of local relapse, lung metastases and non-lung metastases.

[b] Total of subgroups may be <564 due to missing data.

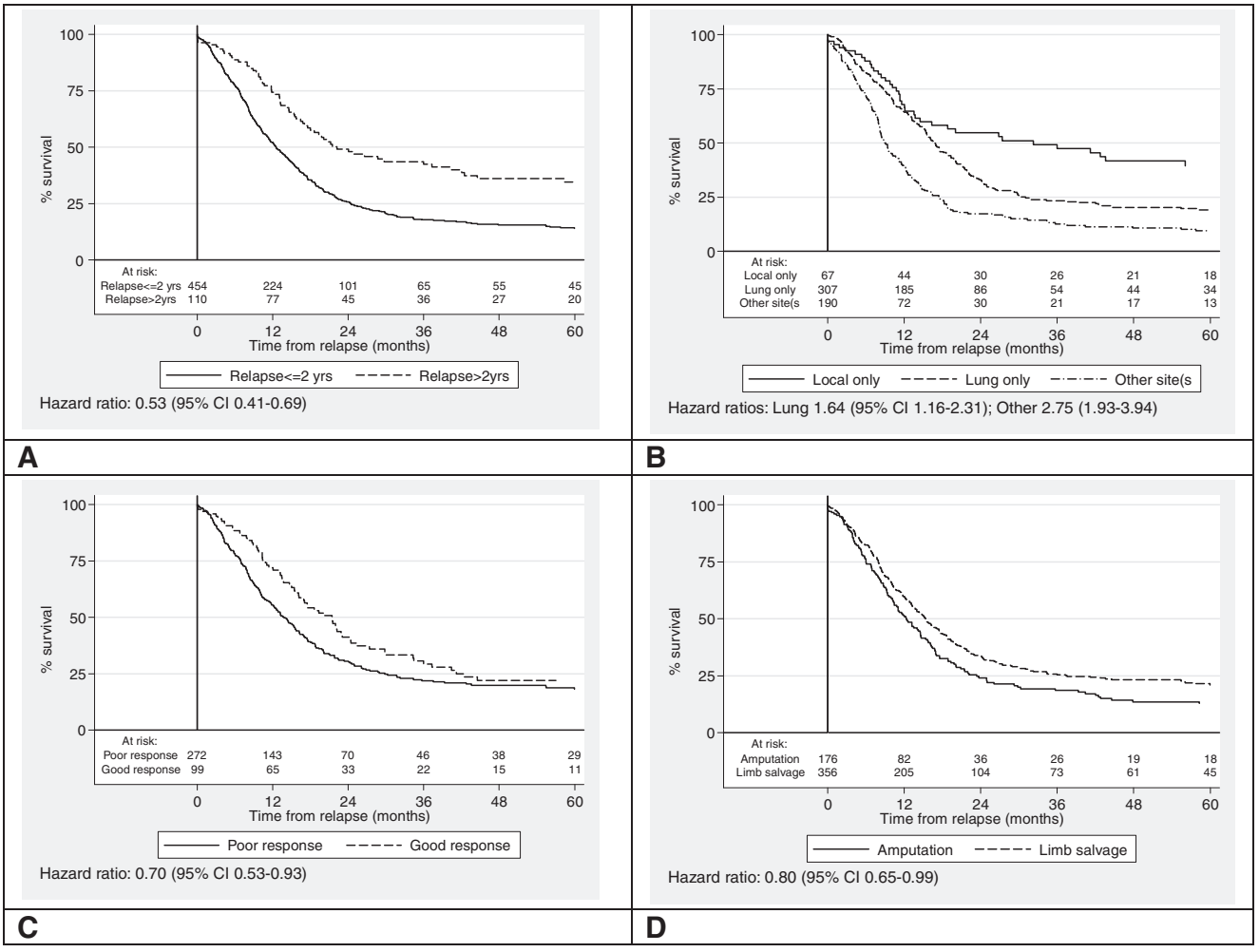

Fig. 2 – Kaplan–Meier curve of survival after first recurrence by (A) early (within 2 years after randomisation) versus late (more than 2 years from randomisation) recurrence, (B) site of recurrence, (C) histological response to pre-operative chemotherapy, and (D) surgery type in 564 recurrent patients.

Table 4 – Specifications of univariate and multivariate Cox models for 564 recurrent patients.

Model term	N	Univariate models		Multivariate model (N = 365)	
		HR (95% CI)	p	HR (95% CI)	p
Timing of recurrence	564				
<2 years from randomisation					
⩾2 years from randomisation		0.53 (0.41, 0.69)	<0.001	0.58 (0.41, 0.83)	0.003
Site of first recurrence	564				
Local only					
Lung only		1.64 (1.16, 2.31)	0.005	1.56 (1.02, 2.39)	0.039
Other site(s)		2.75 (1.93, 3.94)	<0.001	2.58 (1.64, 4.07)	<0.001
Randomising group	564				
MRC					
EORTC		1.22 (1.01, 1.49)	0.044	1.14 (0.85, 1.51)	0.383
Site of tumour[a]	563				
Femur					
Tibia		0.90 (0.71, 1.13)	0.357		
Fibula		0.98 (0.61, 1.57)	0.932		
Humerus		1.01 (0.76, 1.33)	0.962		
Radius/ulna		0.44 (0.11, 1.75)	0.242		
Site/location of tumour	559				
Proximal femur/humerus					
Distal site		0.89 (0.70, 1.14)	0.365	0.91 (0.66, 1.25)	0.553
Type of osteosarcoma	521				
Common type					
Chondroblastic		0.86 (0.61, 1.19)	0.362	0.72 (0.48, 1.09)	0.124
Fibroblastic		0.84 (0.57, 1.26)	0.404	1.23 (0.75, 2.00)	0.415
Anaplastic		0.85 (0.51, 1.41)	0.524	0.69 (0.36, 1.33)	0.272
Telangiectatic		1.57 (0.96, 2.58)	0.075	1.62 (0.87, 3.04)	0.131
Other		1.32 (0.91, 1.91)	0.141	1.56 (1.01, 2.41)	0.044
Histological response	371				
Poor					
Good		0.70 (0.53, 0.93)	0.015	0.72 (0.53, 0.97)	0.031
Surgery type	532				
Amputation					
Limb salvage		0.80 (0.65, 0.99)	0.042	0.94 (0.71, 1.26)	0.693

All models stratified by trial.

[a] Not included in multivariate model due to overlap with other variables.

unilateral lung metastases instead of bilateral, absence of pleural disruption and second complete surgical response could not be derived from this current study as this information was not recorded. Most of these other series were small retrospective studies, with the exception of the studies on osteosarcoma relapses by the Cooperative Osteosarcoma Study Group (COSS) and Rizzoli Institute, both based on prospectively collected databases.[1,8]

As in other series, we found a high number of local recurrences after limb-saving procedures compared to amputations. The surgical outcomes in a subgroup of our dataset were assessed with respect to their surgical treatment. Local recurrence was closely related to the adequacy of the margins of excision and to the chemotherapeutic response.[12] This implies that limb-saving procedures should only be performed when adequate surgical margins are deemed possible, despite the fact that isolated local recurrences have a better prognosis than distant recurrences (28 versus 10% 5 year survival after recurrence).

Only 8 recurrences were reported 5 years or more after randomisation which accounts for less than 2% of all recurrences. In the COSS dataset, including axial osteosarcomas and primary metastatic osteosarcoma, there were 5% recurrences in years 6–10 and 0.7% thereafter. Clinico-histologic parameters of late relapse were recently analysed: there was a trend that patients with a chondroblastic subtype or a location in the tibia or fibula had a higher risk for late relapse.[13] In a single centre retrospective study only 4 out of 8 late asymptomatic lung recurrences were detected by follow-up chest X-ray, from which only 1 patient was cured.[14] All other patients with late recurrences presented with symptoms. The low number of late recurrences in our group of non-metastatic extremity osteosarcomas questions the role of routine intensive radiological examinations to screen for (asymptomatic) recurrences later than 5–10 years after primary diagnosis. However, this observation should be confirmed in other large and more detailed cohort before this may lead to practice change. Yearly follow-up after 5 years should, continue with chest X-ray and for

orthopaedic follow-up as well as for screening, treatment and awareness of risk factors for cardiovascular disease (e.g. hyper/dyslipidaemia, obesity and smoking), secondary tumours and screening and consultation for other late side-effects of chemotherapy.[15] These issues have gained interest in recent years with the increasing number of patients being cured after intensive and long chemotherapy regimens.

Our analyses found that cooperative study group had a small effect on survival in the univariate model, with patients randomised through the MRC having longer median PRS than those randomised through the EORTC. However, study group is a proxy for a variety of indefinable clusters of clinical practices.

As well as the lack of data on post-recurrence treatment, another limitation of our study is the broad time period over which factors such as pathology techniques, assessment of disease recurrence and surgical methods may have changed, although the minimum requirements were prospectively defined in the 3 protocols. Despite having a common control arm, the different research arms used across the trials are a potential limitation, but before commencing analyses we determined that there was no good evidence of differences in PRS between treatment arms. Some possible prognostic factors as mentioned above were not available for analysis in this dataset, and histological response to chemotherapy was missing for 368/1067 patients in total, and in particular was present was for only 35 BO02 patients. This meant that multivariate models including this factor could only include about two thirds of the patients available.

In conclusion, this study, despite its limitations, shows that histological response to primary treatment of a high-grade osteosarcoma positively influences survival after a recurrence, even when other factors are taken into account. This study confirms that early recurrences are related to worse survival and that very late recurrences are rare. EOI is now participating in the world-wide EURAMOS-1 trial (www.euramos.org). Although the primary aim of the trial is to compare approaches to first-line chemotherapy, it will generate important further information on outcomes of patients after recurrence. Further prospective studies of recurrent disease, for instance randomised studies on the role of (neo)adjuvant chemotherapy for resectable recurrences, studies incorporating new agents and new surgical and radiotherapy techniques, are needed to improve treatment outcome for the substantial proportion of patients than cannot be cured after primary treatment.

Conflict of interest statement

None declared.

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