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Clinico-histologic parameters of osteosarcoma patients with late relapse

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ABSTRACT

Primary high-grade intramedullary osteosarcoma of the extremities is a clinically aggressive bone tumour. There is an ongoing effort to further improve efficacy of neo-adjuvant chemotherapy and reduce chemotoxicity by trying to identify osteosarcoma patients who are at risk of treatment failure as well as to identify those who can do with less chemotherapy. In only 5% of patients, first distant metastasis or local relapse occurs 5 years or more after initial treatment for osteosarcoma. Patients and physicians can therefore easily erroneously consider a patient with osteosarcoma cured if he or she is disease-free for more than 5 years following diagnosis and treatment. To investigate if these rare late relapsing patients are characterised by specific clinico-pathological features, we examined clinical and histological variables of late relapse (first local recurrence or metastasis 5 years or more after initial diagnosis) out of a total of 2243 patients, with a special interest in the histological osteosarcoma subtype.

In total, 33 patients had a documented relapse 5 years or more after diagnosis. Half of the patients had good response ($\geqslant$90% necrosis) to pre-operative chemotherapy and the other half a poor response (<90% necrosis) and late relapses seemed to be more frequently proportionately in those who had a good initial response to chemotherapy. The occurrence of late relapse did not appear to be associated with age or gender. Although not statistically significant, there was a trend for patients with a chondroblastic subtype of osteosarcoma, or a location in the tibia or fibula, to have a higher risk for late relapse.

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1. Introduction

Osteosarcoma is the most frequent non-haematogenic malignant bone tumour.[1–3] A number of osteosarcoma subtypes are recognised, dependent on the site of the involved bone and the histomorphologic features. Among the high-grade central osteosarcomas, conventional, telangiectatic and small cell subtypes exist.[4] The conventional subtype comprises an osteoblastic, a chondroblastic and a fibroblastic variant. For research purposes, and comparison with data on osteosarcoma subtype in the literature, we restricted the term conventional to the osteoblastic variant, and the chondroblastic and fibroblastic variant are registered separately. Primary high-grade intramedullary osteosarcoma of the extremities is a highly aggressive bone tumour. Half of the patients are dead from disease 5 years after initial treatment for those with poor response (commonly defined as less than 90% necrosis) to pre-operative chemotherapy.[5–7] On the contrary, the 5-year overall survival ranges between 70% and 87% for patients with histological good response to chemotherapy ($\geqslant$90% necrosis).[6–9] There is an ongoing effort to further improve efficacy of chemotherapy and reduce chemotoxicity by identifying, at the time of diagnosis, those patients who will be at risk of treatment failure as well as those who need less intensive chemotherapy. Such prognostic factors are under investigation in the clinical, pathologic and molecular field. Information has been obtained on prognostic factors for overall and event-free survival,[10–12] the risk for local relapse[13] and the predictive factors for outcome after relapse[14,15] from several large randomised studies on osteosarcoma using different chemotherapy regimes. In the group of osteosarcoma patients with relapse, up to 5% still have their first distant metastasis or local relapse 5 years after their initial, seemingly successful treatment.[14,16] Prognosis in case of relapse is poor. The post relapse 5-year survival estimate is only in the range of 25%.[14,16] Here, we have looked at clinical and histological variables that could be predictive for patients at risk for late relapse, with a special interest in the histological osteosarcoma subtype.

2. Patients and methods

In both the control and study population, we included patients who were aged under 40 years at time of diagnosis. All patients had a biopsy showing high-grade intramedullary osteosarcoma of the extremities, with no evidence of metastasis at time of diagnosis, no previous history of other primary malignancy and no previous treatment with chemotherapy or radiotherapy. Late relapse was defined as first local recurrence or first metastasis occurring at least 5 years after initial diagnosis. The date of diagnostic biopsy was considered to be the date of diagnosis.

Patient data were retrieved from three sources: (1) EORTC 80831/MRC BO02[5] and EORTC 80861/MRCBO03[7] which were two randomised controlled trials run by the European Osteosarcoma Intergroup (EOI); (2) all patients under the age of forty at time of diagnosis with a primary, localised, high-grade central extremity osteosarcoma who were entered into the Cooperative OsteoSarcoma Study Group (COSS) database between the end of 1979 and October 1997; and (3) from a single surgical centre cohort in the UK, Birmingham. Patients in the Birmingham cohort had received chemotherapy similar to the EOI trials but had not formally been entered in the EOI trial, thus there was no duplication of patient entry. The EOI patients contributed to the late relapses and control group, the COSS and Birmingham cohort patients contributed only to the late relapses.

Therefore, for the EOI (1) there were a total of 557 osteosarcoma patients who were randomised to the trials between July 1983–December 1986 (BO02/80831: 179 patients)[5] and September 1986–December 1991 (BO03/80861: 391 patients).[7] This number excludes 13 patients without a reported progression but less than 5 years follow-up. Six (1%) of these patients had a late relapse and are considered cases for this paper, the remaining 551 form the control groups. The median follow-up in patients last alive is 14 years (min 5.2 years, max 20.5 years). For COSS this is a total of 1136 patients with a median follow up of 6.03 years (min 31 days, max 22.6 years) for all patients and 8.3 years (min 0.3–max 22.6 years) for 796 survivors. In the files from Birmingham there were a total of 550 patients.

Data analysed were age, gender and location of the tumour, histological subtype and response to chemotherapy. Since the COSS database did not record the histological subtype, this was retrieved from the original pathology reports by one of the authors (EH). The subtype was specified in the report in 17 (77%) patients. The criteria of subtyping and the method of assessment of necrosis has been extensively described elsewhere.[17,18] In short, an osteosarcoma was classified as one or other subtype if $\geqslant$90% of the lesion showed histological features specific for a given subtype. The exception was chondroblastic osteosarcoma, which was classified as such if more than 30% of the lesion was composed of a chondroid matrix. As for necrosis, in the EOI this was reported as a percentage of the total tumour. In the COSS database, necrosis is graded according to Salzer-Kuntschick criteria[18] as follows: (1) no viable tumour; (2) solitary viable cells or one islet of less than 0.5 cm; (3) less than 10% of viable tumour; (4) 10–50% of viable tumour; (5) more than 50% viable tumour; and (6) no effect of chemotherapy. For analysis, this was converted in accordance with the EOI data to good responders ($\geqslant$90%) for Salzer-Kuntschick grade 1, 2 and 3, and poor responders (<90%) for Salzer-Kuntschick grade 4 and higher.

In summary, patients with first relapse 5 years or more after diagnosis from two EOI trials, COSS database and the Birmingham cohort are included. Controls are patients with at least 5 years follow-up but no late relapse reported in the two EOI trials. With regard to evaluation of necrosis, data on the resected specimen was available in 364 patients.

3. Results

Out of a total of 1136 osteosarcoma patients in the COSS cohort, 22 patients (2%) had a first relapse or metastasis 5 years or more after their initial diagnosis. In the EOI group there were 6 (1%) cases from a total of 557 and in the patient group from Birmingham 5 (0.9%) cases out of a total of 550. This is a total of 33 patients with late relapse. Twenty-eight patients

(85%) relapsed with metastases, 4 (12%) with a local relapse and 1 (3%) with simultaneous local relapse and metastasis. Patient details are summarised in Table 1. The control group comprised the patients from the EOI trials, of whom 245 had 5 or more years of follow-up and no relapse and 306 who relapsed within 5 years.

3.1. *Late relapse and clinico-pathological features*

Of the patients with late relapse, 21 (64%) were male and 12 (36%) female (Table 2). Age at diagnosis ranged from 9 to 35 years with a peak incidence at 15–19 years. Age and sex distribution were similar in the control groups. Eighteen (54%) of the patients with late relapse had their osteosarcoma located in the tibia or the fibula in apparent contrast with 170 (31%) of osteosarcomas occurring in these locations in the control group (Table 3). There is some evidence that late relapses occurred more in patients with an initial localisation not in the femur or humerus (Pearson χ^2 5.08 (df = 1), $P = 0.024$).

Thirteen (46%) of the patients with late relapse had a non-conventional subtype of osteosarcoma compared with 158 (29%) of the patients in the EOI control (Table 3). The main difference was due to the higher proportion of chondroblastic tumours in the study group (21%) compared to the control group (9%). However, there was no good evidence of a difference in the number of patients with or without late relapse by pathological subtype (conventional vs chondroblastic vs. other non-conventional) (Pearson χ^2 4.1099 (df = 2), $P = 0.128$). There was no evidence of a relationship between subtype of osteosarcoma and localisation in the bone (Pearson χ^2 0.0069 (df = 1) $P = 0.934$, Fisher's exact = 1.000) (Table 4).

Table 1 – Late relapse patients

Patient	Age	Gender	Location	Site	Subtype	Response	IV to R (months)	Relapse	Site	Follow up since relapse (years)	Status at last follow up date
B1	16	M	Femur	D	Chondroblastic	Poor	81	Meta	Lung	14.1	Alive
B2	9	F	Tibia	D	Fibro/Osteobl	Unknown	110	Meta	Lung	5.2	Alive
B3	30	M	Femur	D	Fibroblastic	Poor	90	Local		4.5	Alive
B4	9	F	Femur	M	Pleomorphic	Poor	77	Meta	Lung	1	Dead
B5	9	F	Femur	D	Telangiectatic	Poor	66	Local		3	Dead
C1	10	F	Humerus	P	Conventional	Poor	73	Meta	Bone	16.5	Alive
C2	9	M	Ulna	D	Conventional	Good	72	Meta	Bone	4.3	Alive
C3	8	M	Tibia	D	Small cell	Good	63	Local + Meta	Bone	0.6	Alive
C4	26	M	Femur	D	Chondroblastic	Poor	103	Local		4.7	Dead
C5	13	M	Tibia	P	Fibroblastic	Good	66	Local		3.9	Dead
C6	22	M	Tibia	P	Conventional	Good	72	Meta	Lung	0.3	Alive
C7	15	M	Tibia	P	Unknown	Poor	74	Meta	Lung, bone, LN	0.8	Dead
C8	17	F	Fibula	P	Conventional	Good	123	Meta	Lung	2.7	Alive
C9	12	F	Tibia	P	Conventional	Good	101	Meta	Lung	0.4	Alive
C10	10	M	Tibia	P	Conventional	Good	65	Meta	Lung + CNS	0.2	Alive
C11	20	M	Tibia	P	Chondroblastic	Poor	118	Meta	Lung	2.9	Dead
C12	18	F	Tibia	D	Unknown	Good	89	Meta	Lung	6.6	Alive
C13	12	F	Femur	D	Unknown	Good	87	Meta	Lung	3.1	Dead
C14	13	M	Femur	D	Unknown	Good	84	Meta	Lung	11.6	Alive
C15	13	F	Tibia	D	Conventional	Good	75	Meta	Lung	3.3	Alive
C16	15	M	Femur	D	Unknown	Poor	71	Meta	Lung	2.8	Dead
C17	15	M	Fibula	P	Chondroblastic	Poor	69	Meta	Lung	3.3	Alive
C18	35	F	Femur	D	Conventional	Poor	69	Meta	Lung	4.1	Alive
C19	15	M	Humerus	P	Conventional	Good	65	Meta	Lung	0.0	Alive
C20	18	M	Tibia	P	Conventional	Poor	65	Meta	Lung	0.0	Alive
C21	23	M	Tibia	P	Chondroblastic	Poor	61	Meta	Lung	3.4	Alive
C22	17	M	Fibula	P	Chondroblastic	Good	90	Meta	Lung, bone	1.1	Dead
E1	18	M	Femur	D	Conventional	Poor	88	Meta	Lung	1.2	Dead
E2	15	M	Tibia	P	Conventional	Unknown	177	Meta	Lung	0.5	Dead
E3	13	F	Femur	D	Conventional	Good	62	Meta	Bone	1.2	Dead
E4	14	F	Tibia	D	Conventional	Poor	80	Meta	Bone	0.0	Dead
E5	32	M	Humerus	P	Conventional	Good	183	Meta	Lung	5.7	Alive
E6	19	M	Tibia	P	Fibroblastic	Unknown	65	Meta	Unknown	0.0	Dead

B, Birmingham; C, COSS; E, EOI; D, distal; M, midshaft; P, proximal; IV to R, interval to relapse in months; Meta, metastasis; LN, lymphnode; CNS, central nerve system.

Table 2 – Number of osteosarcoma patients by age group (age at entry/registration)

Age	Late relapses (all sources)			EOI control								
				EOI early relapses			EOI no relapse			EOI overall		
	M	F	T	M	F	T	M	F	T	M	F	T
0–4	0	0	0	1	1	2	2	0	2	3	1	4
5–9	2	3	5	11	11	22	11	9	20	22	20	42
10–14	3	6	9	55	47	102	34	36	70	89	83	172
15–19	10	2	12	87	31	118	63	30	93	150	61	211
20–24	3	0	3	31	7	38	32	11	43	63	18	81
25–29	1	0	1	11	3	14	3	4	7	14	7	21
30–34	2	0	2	2	4	6	1	3	4	3	7	10
35–40	0	1	1	3	1	4	5	1	6	8	2	10
Total	21	12	33	201	105	306	151	94	245	352	199	551
%	64	36	100	66	34	100	62	38	100	64	36	100

M, male; F, female; T, total.

Table 3 – Location of osteosarcoma and subtype

	Late relapses (all sources)		EOI control					
			Early relapse		No relapse		Overall	
	N	%	N	%	N	%	N	%
Location								
Femur	11	33	169	55	133	54	302	55
Tibia	15	45	73	24	70	29	143	26
Fibula	3	9	13	4	14	6	27	5
Humerus	3	9	48	16	21	9	69	13
Radius/Ulna	1	3	1	0	5	2	6	1
Other	0	0	2	1	2	1	4	1
Subtype								
Data missing	5		1		1		2	
Data available	28	100	305	100	244	100	549	100
Conventional	15	54	220	72	171	70	391	71
Chondroblastic	6	21	27	9	25	10	52	9
Fibroblastic	3	11	27	9	22	9	49	9
Anaplastic	1	3	13	4	10	4	23	4
Telangiectatic	1	3	5	2	5	2	10	2
Small cell	1	3	3	1	0	0	3	1
Other	1	3	10	3	11	5	21	4
Total	33		306		245		551	

Table 4 – Subtype in relation to involved bone

	Humerus and Femur		Tibia, Fibula, Ulna	
	N	%	N	%
Conventional	6	45	9	53
Non-conventional	5	54	8	47
Not available	3		2	
Total	14		19	

3.2. *Late relapse and response to pre-operative chemotherapy*

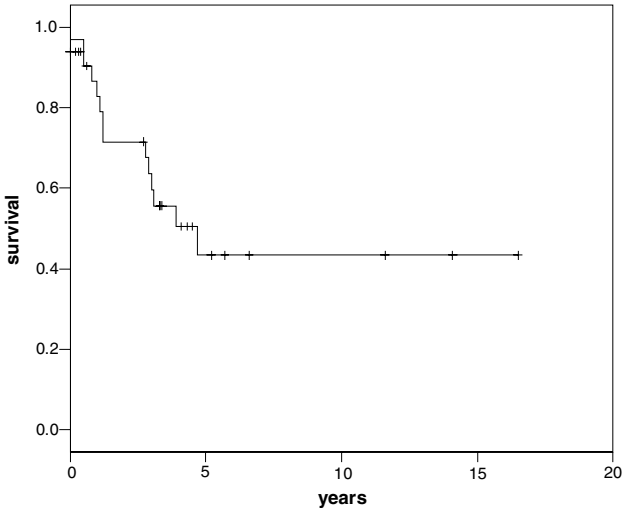
Half of the late relapse patients had good response (⩾90% of necrosis) to pre-operative chemotherapy and the other half a poor response (<90% of necrosis). Only 102 (28%) patients out of the 364 in the EOI control, for which the resected specimen was available for review, showed good response to chemotherapy. However, among the 1136 eligible COSS patients 580 had good (57%) and 433 (43%) had a poor response to pre-operative chemotherapy, with the rest of the patients having either primary surgery or no data available on response.

3.3. *Late relapse and survival*

The overall survival for patients with late relapse is depicted in Fig. 1. The overall survival at 1, 3 and 5 years following relapse was 83%, 60% and 43% respectively.

4. Discussion

When studying a disease in which there are multifactorial influences on progression and outcome such as



Kaplan-Meier: actuarial survival (standard error)
2-year 72% (SE 9%)
5-year 43% (SE 11%)

Fig. 1 – Kaplan–Meier survival curve of patients with first relapse more than 5 years after initial diagnosis and treatment.

osteosarcoma, large randomised trials are mandatory. Even then, due to the overall low incidence of osteosarcoma, the total number of cases can be too small when examining subsets of factors such as osteosarcoma subtype or studying events such as late relapse. For the purpose of our study, which tried to identify predictive factors for late relapse, we were thus obliged to merge data from EOI trial 80831 (BO02) and 80861 (BO03), the patients in the COSS cohort and patients from Birmingham. Even then there were only a small number of patients with late relapse making it difficult to comment reliably on prognostic markers. Merging of data poses the problem of looking at patients who had different chemotherapy regimes with different response to chemotherapy and different outcome in terms of disease-free survival (DFS) and overall survival (OS). Patients randomised in protocols with better DFS relapse statistically later than patients in protocols with significant worse DFS.[19] This is reflected by the 2% of patients with late relapse in the COSS cohort and 1% of patients with late relapse in the EOI patients. The 5 year disease-free survival in both groups is 62%[20] and 46%,[5,7] respectively. It is possible therefore that a "good" response to chemotherapy may in fact simply delay the onset of metastases in some patients.

With regard to age, location of the osteosarcoma and subtype, no significant differences were expected between the EOI and COSS study groups since these variables show similar distributions in diverse randomised trials[17,21–24] (Table 5). In our study group of osteosarcoma patients with late relapse, the peak incidence of diagnosis was between 15 and 19 years with a male predominance, which was the same as in the control group and data from the literature.[3,23] Normally, the bones around the knee and the proximal humerus are mostly involved with the distal femur being the site of predilection. Though not statistically significant there was an observed shift towards tibial or fibular involvement in patients with late relapse. There was also an over-representation of subtypes other than conventional osteoblastic in the late relapsing patients. This is probably largely due to the presence of a chondroblastic component, but the evidence is not as yet statistically significant. The histological subtype of osteosar-

Table 5 – Gender, localisation and subtype of high-grade intramedullary osteosarcoma in some large osteosarcoma study groups

Study group	Coss 80 [25]		Coss 86 [22]		Rizolli [21]		EOI[17,23]	
	N	%	N	%	N	%	N	%
Patients	116	100	171	100	510	100	570[a]	100
Male	69	59	107	63	292	57	361	63
Female	47	41	64	37	218	43	207	37
Location								
Femur	61	53	73	43	277	54	315	55
Tibia	38[b]	33	47	27	142	28	148	26
Humerus	12	10	18	11	56	11	72	13
Fibula	4[b]	3	12	7	0	0	27	5
Radius	2	2	0	0	0	0	3	1
Other	0	0	21	12	35	7	3	1
Unknown	0	0	0	0	0	0	0	0
Subtype[c]								
Conventional					348	68	71	65
Chondroblastic					63	12	10	11
Telangiectatic					44	9	2	8
Fibroblastic					39	8	9	7
Other							8	8
NOS					16	3		

a Gender not registered in two cases.
b One patient with two osteosarcomas.
c No details available on subtype in the COSS study database.

coma has been shown to be a predictive factor for response to chemotherapy.[17,21,25] Generally, chondroblastic osteosarcomas show poorer response to pre-operative chemotherapy as was already demonstrated by Kersjes in 1987.[26] In his report, a mean chondroid ground substance of 21% was seen in patients with poor response to pre-operative chemotherapy. In contrast, a chondroblastic subtype was related with better overall survival.[17] Whether patients with a chondroblastic subtype of osteosarcoma thus represent a high-risk or low-risk subgroup of osteosarcoma patients is open for further discussion and research. To determine with certainty whether chondroblastic osteosarcoma represents a separate entity with regard to clinical behaviour requires further investigation. However, the rarity of osteosarcoma and even more the diverse subtypes of osteosarcoma hamper this.

In conclusion, relapse 5 years after initial treatment of osteosarcoma is low, arising in between 1% and 2% of all osteosarcoma patients, and is consistently so in the three osteosarcoma study groups on which this study has been based. There is no evidence that late relapse is related to age or gender, but there is a trend for it to arise more commonly in chondroblastic subtypes, in patients with a primary in the tibia and fibula and seems to be proportionately more common in patients with initial good response to chemotherapy. These patients thus should be considered as at risk for late relapse, for which long-term follow up for detection of relapse is warranted.

Conflict of interest statement

None declared.

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