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Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup

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Abstract

Large randomised trials are mandatory when one wants to examine the effects of different aspects (such as the treatment modality) of a pathological condition on the overall outcome. This is especially true when studying a disease in which there is a multifactorial influence on progression and outcome such as osteosarcoma. Data on 570 patients with biopsy-proven primary central osteosarcoma of an extremity included in two consecutive studies of the European Osteosarcoma Intergroup (EOI) were analysed in order to evaluate if the histological subtype of the biopsy specimen correlated with the subtype of osteosarcoma represented in the resected specimen, if there was a relationship between the histological subtype and overall survival and if there was a relationship between the histological subtype and histological response to chemotherapy. High-grade osteosarcoma, as defined by established criteria, was subtyped as either conventional, chondroblastic, teleangiectatic, small cell, fibroblastic, osteoclast rich, anaplastic and sclerotic/osteoblastic well differentiated. A panel of experienced pathologists with a special interest in bone pathology was appointed to review the histological diagnosis and to assess the tumour response to chemotherapy on the resected specimen of each patient entered into the trials. Subtyping on the biopsy specimen proved to be highly representative for the subtype of the whole tumour. In 102 patients for which subtyping was performed on the biopsy and the resected specimens, there were only two discrepancies. Of the 568 patients for whom subtype was available, 404 (71%) were of the conventional type, 54 (10%) were chondroblastic, 53 (9%) had fibroblastic tumours and the remainder consisted of rare subtypes. A good response to preoperative chemotherapy was defined as 90% or more necrosis. The proportion of patients responding well to chemotherapy differed significantly between subtypes (Chi-square test statistics = 11.44, $P = 0.01$ on 3 degrees of freedom (d.f.)). In comparison with the conventional subtype, there was a higher proportion of good responders in the fibroblastic group and a lower proportion of good responders in the chondroblastic group. Good responders had a significantly better survival than patients who responded poorly to the pre-operative chemotherapy (logrank statistic = 25.20, $P < 0.01$ on 1 df). Survival did not differ significantly according to subtype (logrank statistic = 2.72, $P = 0.44$ on 3 df), although there was a suggestion that patients with chondroblastic tumours experienced a better long-term survival. This large set of prospectively-collected data provides important information on the relationship between pathological subtype, histological response and survival. Histological response has a known prognostic effect on survival, and we have shown that the rates of response differ by subtype. There is some evidence from this study that the specific histological subtypes, i.e. the chondroblastic subtype, experience better survival. However, despite this large multi-institutional study, we have insufficient numbers of non-conventional tumours to examine this unambiguously for these subsets.

Keywords: Osteosarcoma; Biopsy; Subtyping; Prognosis; Response to chemotherapy; Survival

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1. Introduction

Osteosarcoma is the most frequent malignant primary bone tumour [1–3]. Approximately 19.9% of all primary sarcomas [2] and 20–22% of all primary malignant bone tumours [3,4] are central high-grade osteosarcomas. A number of subtypes are recognised dependent upon the site of the involved bone and the histo-morphological features [5]. As such, among the high-grade central osteosarcomas osteoblastic, chondroblastic, fibroblastic, teleangiectatic, giant-cell rich, small cell, and sclerosing types are recognised [6–10]. The clinical and biological significance of these subtypes are controversial in literature, because data based upon large enough controlled randomised studies recognising these subtypes as separate entities are lacking. We used the data available from the first two studies of the European Osteosarcoma Intergroup (EOI) [11,12] containing 570 patients with biopsy-proven high-grade central osteosarcoma in order to evaluate the following three questions:

1. Does the histological subtype of the biopsy specimen correlate with the subtype of the resection specimen?
2. Is there a relationship between histological subtype and overall survival?
3. Is there a relationship between histological subtype and histological response to chemotherapy?

2. Patients and methods

Data available from the first two studies of the EOI were used. The EOI consists of the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group, the Bone Sarcoma Working Party of the UK Medical Research Council (MRC), the UK Children's Cancer Study Group (UKCCSG), and the Societé Internationale d'Oncologie Paediatrique (SIOP).

2.1. Patients

In both studies, patients included were aged 40 years or younger with a diagnosis of primary high-grade intra-osseous osteosarcoma of the extremities, with no evidence of metastasis at the time of diagnosis, with no previous history of malignancy and not yet treated with chemotherapy or radiotherapy. Periosteal and parosteal [13,14] osteosarcomas were excluded because of a different clinical behaviour.

In total, 570 patients were included for the studies running from July 1983 to December 1986 (study BO02/80831, 179 patients) [11] and September 1986 to December 1991 (study BO03/80861, 391 patients) [12]. Informed consent was obtained from the patients or their guardians before entering the study. Permission to enter patients into the studies had to be sought from the local ethical committee for each participating centre. The requirements for consent had to follow local practice.

2.2. Histological diagnosis

In order to be included in the study, patients had to have a biopsy-proven high-grade osteosarcoma, which was confirmed after reviewing the slides of the biopsy specimen by a member of the panel of reference pathologists. The initial biopsy to obtain material for histological evaluation and diagnosis was either an open biopsy or a closed (Jamshidi) biopsy and had to contain material from the intra-osseous tumour component, the cortex and the extra-osseous tumour component if this last one was present.

When a diagnosis of high-grade central osteosarcoma was confirmed, the subtype was classified according to the categories as given in Table 1, following the criteria of the World Health Organization (WHO) classification for conventional, teleangiectatic and small cell osteosarcoma [5]. For the others subtypes, criteria commonly in use were applied [1–4,6,7]. In short, the common denominator in all subtypes is the presence of osteoid or bone directly formed by the tumour cells. Teleangiectatic osteosarcoma is histologically defined by the presence of single or multiple aneurismatic spaces containing blood or degenerated tumour cells. The spaces are separated by septa containing anaplastic sarcoma cells with numerous mitoses. Osteoid formation is scant and has a lace-like filigree pattern. Small-cell osteosarcoma is composed of sheets of small cells comparable to Ewing's sarcoma, with small amounts of lacy osteoid. To be classified as chondroblastic, the tumour has to be composed of nodules of cartilage and a malignant population directly producing bone or osteoid. In the fibroblastic subtype, the tumour cells are spindle shaped and may take on a herringbone pattern. Only small amounts of osteoid are present. The osteoclast rich variant resembles very much the giant cell tumour in bone, but has definitive cytonuclear criteria of malignancy with osteoid production and is in contrast to the benign

Table 1
Histological subtypes of high-grade osteosarcoma recognised

- Conventional
- Chondroblastic
- Teleangiectatic
- Small cell
- Fibroblastic
- Osteoclast rich
- Anaplastic
- Sclerotic/osteoblastic well differentiated
- Others

giant cell tumour rarely localised in the epiphysis. The sclerotic well-differentiated type shows a bony matrix, filling the marrow spaces and showing maturation and normalisation of the malignant osteoblastic cells. The anaplastic subtype is characterised by highly pleomorphic cells, and can show malignant fibrous histiocytoma (MFH)-like features, but with once more focal direct bone production by the tumour cells. For a tumour to be classified as one or the other subtype, it had to be composed predominantly of tissue characteristic for this subtype. For a tumour to be of the chondroblastic subtype a cut-off of more then 30% of chondroid tissue in the resected specimen was set. Especially in the cases of non-conventional osteosarcoma in which it can be hard to find osteoid or bone formation in the initial biopsy the clinical history, age, localisation and radiographical findings had to be strongly concordant with a diagnosis of osteosarcoma and its subtype.

2.3. Treatment

The results of patient outcome in both trials incorporated in this analysis have been published previously [11,12]. In each trial patients were randomised between two regimens of neo-adjuvant chemotherapy. The first trial [11] compared a two-drug regimen of doxorubicin (DOX) and cisplatin (CDDP) with the same regimen preceded by high-dose methotrexate (MTX). The second trial [12] compared the same two-drug arm with a multidrug regimen based on the T10 schedule developed by Rosen and colleagues [15]. No significant difference in survival was found between the two arms in either trial. In both trials, surgery consisted of limb salvage if complete removal of the tumour with safe margins could be achieved. If not, an amputation was performed.

2.4. Assessment of histological response to chemotherapy

To assess the histological response to chemotherapy, the local pathologist was requested to make a longitudinal section in the plane of maximum tumour diameter through the resection specimen. After fixation and decalcification, the whole of this slab had to be divided into blocks and all of these blocks had to be embedded in paraffin blocks from which histological slides, haematoxylin and eosin stained, had to be sent in for review together with a diagrammatic map indicating the site of the individual blocks. The reviewer overlaid each slide with a 2-mm squares transparent graph paper on which the respective necrotic and viable areas were drawn. Having done this for each section, a composite reference map was made and percentage of viable and necrotic tumour could be calculated. Necrosis was defined as no detectable tumour or totally necrotic tumor intermingled with non-neoplastic reparative tissue or hyalinised relatively acellular tissue that contained sparse widely scattered pleomorphic cells with degeneration of the nucleus or totally pyknotic cells.

3. Results

3.1. Patients and data forms

Merging the data from the two studies resulted in a total of 570 eligible patients. From all of these patients, the biopsy material had been reviewed and a report of this was present. For 369 of these patients, material of the resected specimen was available and reviewed.

3.2. General results

As described in the reports of the EOI, there was no survival benefit for patients treated with the three-drug or multidrug regimen when compared with the two-drug arm [11,12]. This justifies the merging of the data from the two studies. Good response to chemotherapy was defined as 90% tumour necrosis or more, and poor response as less than 90% necrosis. For the combined data, this resulted in an overall good response to chemotherapy in 102 (28%) patients as illustrated in Table 2.

3.3. Subtyping and validity of subtyping on the biopsy specimen

Subtyping on the biopsy was done for all of the patients entering the studies (Table 3). In the first study, this was performed for 102 patients on the resected specimen as well. In only 2 cases (2%), there was a discrepancy between the subtype of the biopsy and that of the resected specimen. One case classified on the biopsy as chondroblastic and the other as fibroblastic both proved to be of the conventional subtype in the resected specimen. This was clearly the result of sampling error.

Table 2
Histological response as defined on the resection specimen

Histological response	BO02/80831 *n* (%)	BO03/80861 *n* (%)	Group total *n* (%)
Good ($\geqslant$90% necrosis)	22 (22)	80 (30)	102 (28)
Poor ($<$90% necrosis)	78 (78)	189 (70)	267 (72)
Total number	100	269	369

Good histological response of the resected specimen to chemotherapy, defined as $\geqslant$90% necrosis was assessed for 369 patients.

Table 3
Classification of osteosarcoma according to subtype

Classification	BO02/80831 *n* (%)	BO03/80861 n (%)	Group total *n* (%)
Conventional type	144 (80)	260 (66)	404 (71)
Chondroblastic	9 (5)	45 (12)	54 (10)
Fibroblastic	10 (6)	43 (11)	53 (9)
Anaplastic	8 (5)	16 (4)	24 (4)
Teleangiectatic	0 (0)	10 (3)	10 (2)
Osteoclast rich	3 (2)	8 (2)	11 (2)
Small cell	1 (1)	2 (1)	3 (1)
Other	2 (1)	7 (2)	9 (2)
Subtype not specified	2		2
Total	179	391	570

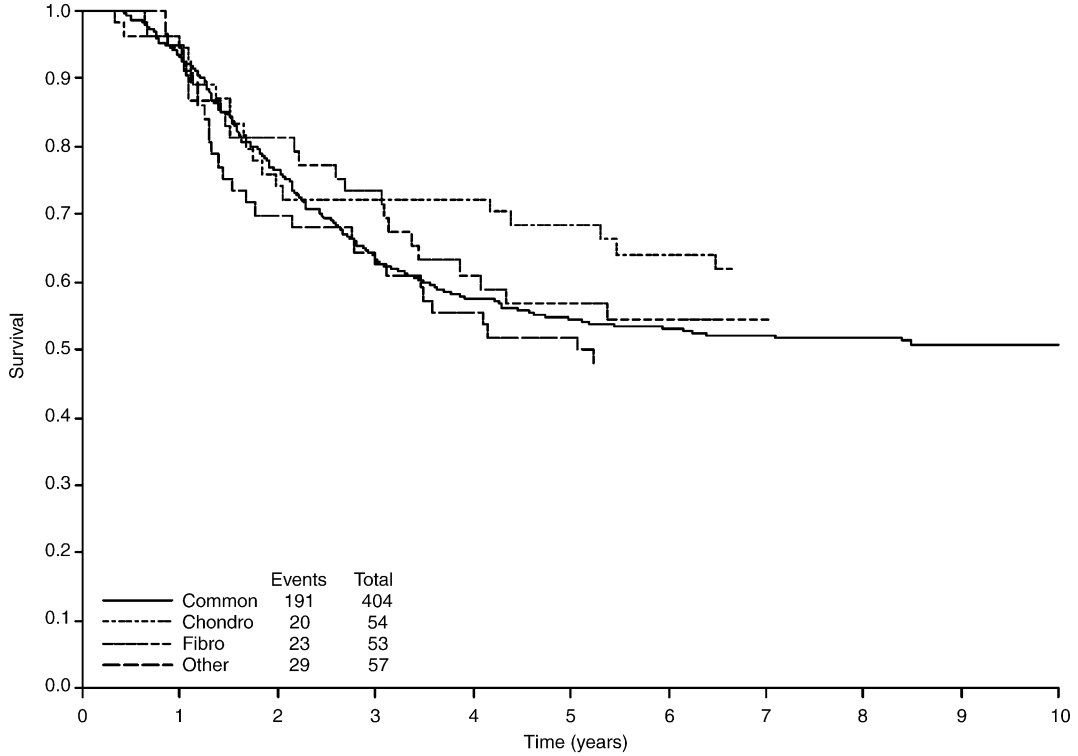
Of the patients recorded as 'Other', 8 were osteoblastic and 1 malignant fibrous histiocytoma (MFH)-like.

3.4. Histological response to chemotherapy by classification of osteosarcoma

The results are summarised in Table 4. Response differs significantly between subtype groups (χ^2 test statistic = 11.44, $P = 0.01$ on 3 degrees of freedom (df)). Due to the low numbers anaplastic, osteoclast rich, teleangiectatic, small cell and other subtypes were combined into one group for the test to be performed. The results showed a higher proportion of good responders in the fibroblastic group (41%) and a lower proportion in the chondroblastic group (9%) when compared with the conventional subtype (29%).

3.5. Histological subtype and survival

Fig. 1 shows the overall survival by subtype. Survival was calculated from the date of randomisation, as classification was determined from the biopsy specimens, which were collected before entry. Due to the low patient numbers, anaplastic, teleangiectatic, osteoclast rich, sclerotic/osteoblastic well-differentiated and small cell subtypes were combined into one group. There was no significant difference in survival between the histological subtypes (logrank statistic = 2.72, $P = 0.44$ on 3 df). There was a suggestion that patients with chondroblastic tumours experienced a better long-term survival, but there were insufficient patient numbers to confirm this. Hazard ratios (HRs) with 95% Confidence Intervals (CIs) for each histological subtype are shown in Table 5. A HR of less than 1 implies a survival benefit for that group. There is a statistically significant difference in the risk of death between the groups at the 5%



Patients at risk (Events)

Common	404	(27)	369	(66)	300	(52)	244	(21)	218	(12)	205	(5)	185	(4)	160	(1)	146	(2)	123	(0)	102
Chondro	54	(3)	51	(11)	40	(1)	39	(0)	37	(2)	33	(2)	29	(1)	26	(0)	24	(0)	19	(0)	15
Fibro	53	(3)	50	(7)	42	(4)	37	(6)	28	(2)	26	(1)	25	(0)	23	(0)	23	(0)	17	(0)	8
Other	57	(3)	54	(14)	39	(3)	36	(5)	31	(5)	31	(2)	23	(0)	20	(0)	15	(0)	10	(0)	9

Fig. 1. Survival curve by histological subtype showing a 15% difference in survival between conventional type and chondroblastic tumours. Logrank statistic = 2.72 ($P = 0.44$ on 3 degrees of freedom (df) Chondro, chondroblastic; Fibro, fibroblastic).

Table 4
Histological response by classification of sarcoma

Classification of tumour	Good response *n* (%)	Poor response *n* (%)	Total
Conventional type	76 (29)	183 (71)	259
Fibroblastic	16 (41)	23 (59)	39
Chondroblastic	3 (9)	32 (91)	35
Anaplastic	2 (14)	12 (86)	14
Osteoclast rich	1 (13)	7 (88)	8
Teleangiectatic	2 (40)	3 (60)	5
Small cell	0 (0)	3 (100)	3
Other	2 (33)	4 (67)	6
Total	102 (28)	267 (72)	369

Good histological response is defined here as $\geqslant$90% necrosis.

Table 5
Hazard ratios by histological subtype

Subtype	*n* (%)	5-year survival (%)	HR (95% CI)
Conventional	404 (71)	54	1
Chondroblastic	54 (10)	70	0.72 (0.48–1.08)
Fibroblastic	53 (9)	57	0.89 (0.59–1.35)
Other	57 (10)	52	1.12 (0.74–1.69)

HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

level if the 95% CI does not cross 1. It can be seen that there appears to be a large reduction (28%) in the risk of death for patients with chondroblastic tumours compared with common type tumours. However, this was not a statistically significant difference. In order to prove reliably that a difference of this magnitude in outcome exists between these groups, an excess of 150 patients in each subtype group would be required as calculated by a power analysis.

Histological response was determined from the resected specimen. Thus, for the analyses of survival by response to chemotherapy, survival was calculated from the date of surgery in order to avoid bias.

Survival for patients who responded well to chemotherapy was significantly higher than survival for poor responders (logrank statistic = 25.20, $P < 0.01$ on 1 df). Survival at 5 years for good responders was 75% compared with 45% for poor responders (Fig. 2). Due to low numbers of cases in most of the subtypes, survival in relation to the response to chemotherapy per subtype could not be determined.

The results were not biased by the choice of surgical procedure or patient's age, since there was a rather homogeneous distribution of subtypes over the different

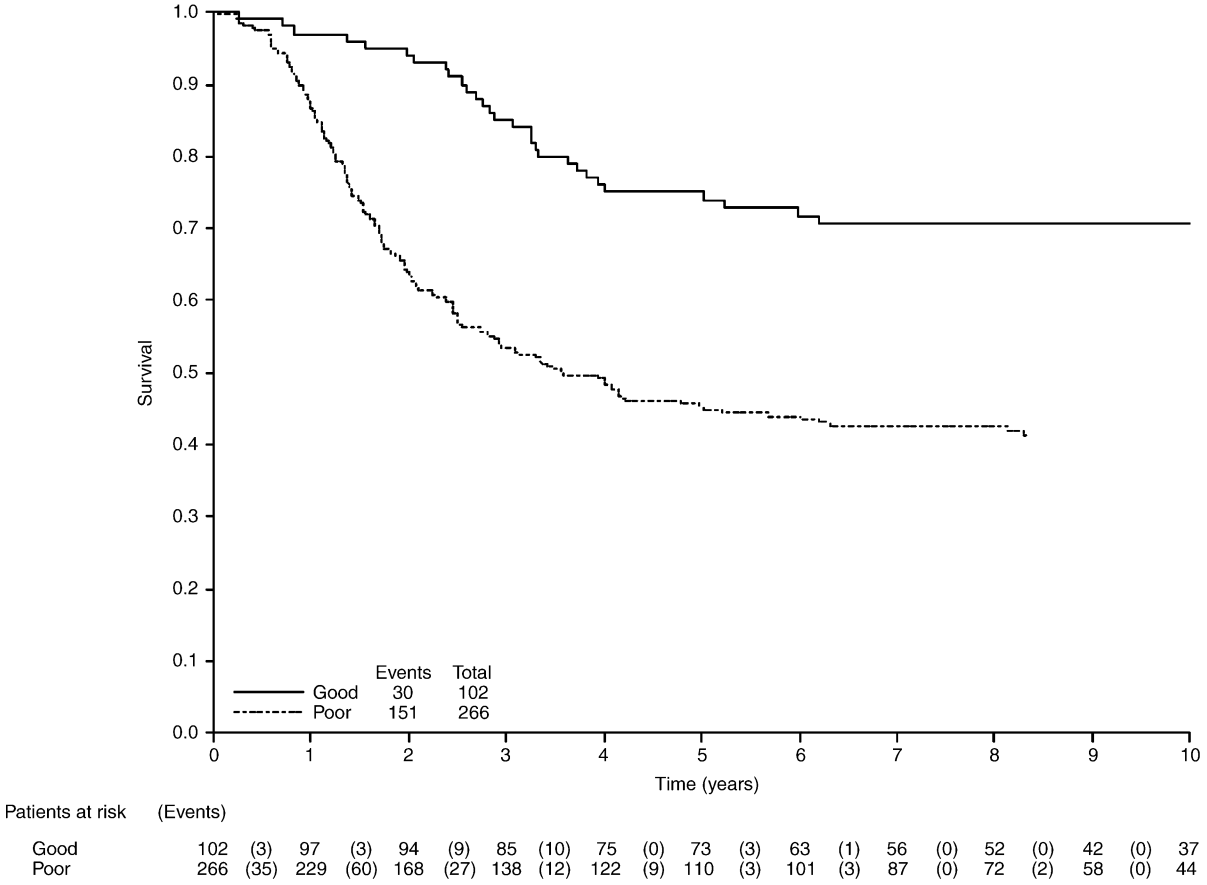


Fig. 2. Kaplan–Meier survival curve showing a significant better survival for patients with 90% or more tumour necrosis after preoperative chemotherapy. Logrank statistic = 7.68 ($P < 0.01$ on 1 degree of freedom (df)).

Table 6
Age and type of surgery by histological subtype

Subtype	Conventional *n* (%)	Chondroblastic *n* (%)	Fibroblastic *n* (%)	Other *n* (%)	Total *n* (%)
Age (years)					
<12	70 (72)	11 (11)	9 (9)	7 (7)	97 (100)
12–16	168 (73)	21 (9)	22 (10)	18 (8)	229 (100)
17+	166 (69)	22 (9)	22 (9)	32 (13)	242 (100)
Surgery received					
Amputation	112 (68)	19 (12)	12 (7)	21 (13)	164 (100)
Limb conservation	263 (71)	34 (9)	40 (11)	34 (9)	371 (100)
Rotation plasty	21 (95)	0 (0)	1 (5)	0 (0)	22 (100)
Not done	8 (73)	1 (9)	0 (0)	2 (18)	11 (100)
Total	404 (71)	54 (10)	53 (9)	57 (10)	568 (100)

age groups and there was a near even distribution in the choice of surgery for each subtype, as can be seen in Table 6.

4. Discussion

4.1. Subtyping and validity of subtyping on the biopsy specimen

The data available on 570 patients from two consecutive studies from the EOI were analysed.

In the first years of the study, the subtype was evaluated on the biopsy and the resection specimen. This information was available for a total of 102 patients. In only 2 cases (2%) was there a discrepancy. Since the correlation was so good, the subtype was not reported any more for the resection specimen in these trials. The method of biopsy was not specified and thus the numbers of open biopsies and closed biopsies are not known. However, we do not believe that the method of biopsy influenced the results. The validity of closed biopsy has been proven by a report on the use of the Jamshidi trocar biopsy in 258 patients with 270 biopsies. This revealed an accuracy of diagnosis in 95% of the patients and in 90.7% of the biopsies [16] which is comparable to the open biopsy.

The risk that a chondroblastic osteosarcoma is diagnosed on the biopsy as a chondrosarcoma is rather high as seen in a study by Geirnaerdt and co-workers [17]. In this study, 5 of 9 patients with proven chondroblastic osteosarcoma on resection had an initial diagnosis on biopsy of chondrosarcoma. However, this was not concordant with the clinical and radiological findings. In 3 patients, a second biopsy revealed the osteosarcomatous nature of the tumour leading to an accuracy of 80%. Whenever a diagnosis of chondrosarcoma is made on a biopsy, this has to be concordant with the clinical information and radiographical findings. The slightest discrepancy should alert the pathologists and the clinicians to the likelihood of a chondroblastic osteosarcoma. From this, it can be concluded that subtyping on the biopsy is reliable in expert hands. This is an important fact since, for patients who respond well to chemotherapy, subtyping on the resection specimen may prove to be impossible. The reliability of the subtyping on the biopsy specimen justifies the inclusion of cases with a complete response to chemotherapy in studies looking at the possible prognostic value of the subtype.

In a search of the literature back to the mid-1960s, only one report was found stating that a given area of chondroid ground substance gives a representative view of the complete tumour [18].

4.2. Histological response to chemotherapy by classification of osteosarcoma

For the 369 patients where information from the resected specimen was available, a good response was seen in 102 cases (28%). 75% of these were of the conventional subtype, 16% fibroblastic, 3% were chondroblastic and 7% other subtypes.

The chondroblastic subtype stands out from the other subtypes as these patients show a good histological response to chemotherapy in only 9% of the cases. The proportion of good responders varied significantly between the groups. Comparable results were seen in a study by the group of the Rizzoli Institute analysing 272 patients with primary osteosarcoma of the limb [19]. Criteria for including patients in their study were approximately the same as ours, with the exception that they also included 25 patients with resectable lung metastasis at the time of diagnosis. Their preoperative chemotherapy regimen included high-dose methotrexate, doxorubicin and cisplatin. Response was registered as total equalling 100% or incomplete. This was also assessed on complete inclusion of a longitudinal slab through the tumour. 19% of their patients showed a complete response. 16.3% of these were osteoblastic, 6.1% chondroblastic, 33.3% fibroblastic and 42.3%

teleangiectatic. In their study, subtype proved to be an independent predictive factor for histological response by multivariate analysis. However, subtype was not a predictable factor for local recurrence [20].

The fact that chondroblastic osteosarcomas show a poor histological response to chemotherapy is, however, not so surprising, since it is the chondroblastic component that does not or poorly responds resulting in a higher percentage of remnant viable tumour.

4.3. Histological subtype and survival

With regard to subtype being a prognostic parameter for survival, only two studies have been published since the use of neo-adjuvant chemotherapy. In the study of Pochanugool and colleagues [21], the subtype did not prove to be a prognostic factor. Their study group was composed of only 130 patients with stage IIA and IIB osteosarcoma that could be completely resected with tumour-free margins. The age of patients was not specified. The study of Petrilli and colleagues [22] was based on 92 patients between the ages of 4 and 28 years with non-metastatic primary osteosarcoma of the extremities of which the response to chemotherapy could be evaluated in only 62 cases. The non-osteoblastic subtype was a predictive variable for recurrence by uni- and multivariate analysis and proved to be an unfavourable prognostic factor for survival by univariate analysis. The non-osteoblastic subtype, however, was not further specified. Due to the low patient numbers, the heterogeneous composition of the two patient groups, the lack of data on patient age in one group and the lack of details on the non-osteoblastic subtype in the other, the results are of limited value and are not comparable.

The use of historical controls is also debatable, since with time the natural history of osteosarcoma may have changed [23]. Evolving techniques in the field of radiology have resulted in the earlier detection of osteosarcoma and have certainly led to an earlier detection of lung metastases. A solitary lung metastasis is nowadays resected in most centres, some patients having repeated metastasectomies over several years. All of these factors, apart from preoperative chemotherapy, have no doubt contributed to the longer survival of osteosarcoma patients [24]. In addition, the histological criteria for the diagnosis of osteosarcoma and their subtypes have been refined over time.

However, there are two major studies that can be used as a base-line for the pre-adjuvant chemotherapy period [25,26]. In a study of 184 patients operated upon for primary osteosarcoma of the extremity or limb girdles with or without metastasis, a regression analysis revealed a favourable outcome for the fibroblastic subtype [25]. Uribe and colleagues included 243 patients with primary high-grade central osteosarcoma. In this group, the fibroblastic subtypes had the best prognosis, followed by the chondroblastic subgroup. The osteoblastic subgroup had the worst prognosis [26]. This last result is in sharp contrast with a smaller study published in 1966 on only 54 patients in which the chondroblastic subtype has a remarkably bad prognosis when compared with the other subtypes [27].

As previously stated, the chondroid areas are probably the cause of a poor response to chemotherapy. It is therefore initially surprising that the chondroblastic subtype group have a better overall survival than the common subtype group, as seen in our study. We would have to presume that a near total necrosis in the non-chondroid areas occurs in all of the osteosarcomas of the chondroblastic subtype. Again, this would be an indication of their different nature.

We conclude that subtyping using the biopsy specimen is highly reliable and predictable for the composition of the whole tumour, chondroblastic osteosarcomas respond poorly to chemotherapy and this subtype can be a prognostic factor for survival. This last statement finds support from some of the larger studies, both in the period after, as well as before, the introduction of the use of preoperative chemotherapy [19,25,26].

Looking at the results of our study, where 28% of patients had a good response to chemotherapy, with only 9% of these patients having a chondroblastic type of osteosarcoma, raises questions about the current use of chemotherapy in patients with a chondroblastic subtype, especially in a preoperative setting with delayed surgery. The criteria for classifying an osteosarcoma to one or other subtype will also have to be redefined by the biological behaviour of that subtype. In a study of Kersjes and colleagues [18] on 22 osteosarcomas of the lower limb, a mean value of chondroid ground-substance of 4.4% was seen in patients with a good response (defined as more than 90% necrosis) to preoperative chemotherapy versus 21% in patients with a poor response. Currently, chondroblastic osteosarcoma is defined as an osteosarcoma with more than 30–90% chondrosarcomatous areas.

However, to determine if certain subtypes such as the fibroblastic and chondroblastic osteosarcomas are subtypes with a definitively different behaviour than the classic osteoblastic osteosarcoma that could justify a specific therapeutic approach, tailored studies are mandatory.

References

1. Huvos AG. *Bone Tumors. Diagnosis, Treatment and Prognosis*, 2nd edn. Philadelphia, WB Saunders, 1991, 85–155.
2. Unni KK. *Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases*, 5th edn. Philadelphia, Lippincott-Raven, 1996, 143–183.
3. Dorfman HD, Czerniak B. *Bone Tumors*, 1st edn. Mosby, St. Louis, 1997, 128–252.

4. Mirra JM. *Bone Tumors: Clinical, Radiologic and Pathologic Correlations*, 2nd edn. Philadelphia, Lea & Febiger, 1989.
5. Schajowicz F, Sobin LH. *World Health Organization. International Histological Classification of Tumours. Histological Typing of Bone Tumours*. Berlin, Springer-Verlag, 1993.
6. Simmons CC. Bone sarcoma: factors influencing prognosis. *Surg Gynaec Obstet* 1939, **68**, 67–75.
7. MacDonald I, Budd JW. Osteogenic sarcoma: I. A modified nomenclature and a review of 118 five-year cures. *Surg Gynecol Obstet* 1943, **76**, 413–421.
8. Ewing J. A review and classification of bone sarcomas. *Arch Surg* 1922, **4**, 483–533.
9. Ewing J. A review of the classification of bone tumors. *Bull Am Coll Surg* 1939, **24**, 290–295.
10. Sim FH, Unni KK, Beabout JW, Dahlin DC. Osteosarcoma with small cells simulating Ewing's tumor. *J Bone Joint Surg (Am)* 1979, **61**, 207–215.
11. Bramwell VHC, Burgers M, Sneath R, *et al*. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992, **10**, 1579–1591.
12. Souhami RL, Craft AW, Eijken JWvd, *et al*. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997, **350**, 911–917.
13. Unni KK, Dahlin DC, Beabout JW, Ivins JC. Parosteal osteogenic sarcoma. *Cancer* 1976, **37**, 2466–2475.
14. Unni KK, Dahlin DC, Beabout JW. Periosteal osteogenic sarcoma. *Cancer* 1976, **37**, 2476–2485.
15. Rosen G, Caparros B, Huvos AG, *et al*. Preoperative chemotherapy for osteogenic sarcoma. Selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. *Cancer* 1982, **49**, 1221–1230.
16. van der Bijl AE, Taminiau AHM, Hermans J, Hogendoorn PCW. Accuracy of the Jamshidi trocar biopsy in the diagnosis of bone tumors. *Clin Orthop* 1997, **334**, 233–243.
17. Geirnaerdt MJA, Bloem JL, van der Woude HJ, Taminiau AHM, Nooy MA, Hogendoorn PCW. Chondroblastic osteosarcoma; characterization by gadolinium enhanced MR imaging correlated with histopathology. *Skeletal Radiol* 1998, **27**, 145–153.
18. Kersjes W, Heise U, Winkler K, Delling G. Comparison of quantitative ground substance analysis in biopsy and resected tumor in osteosarcomas. *Virchows Arch A* 1987, **412**, 155–160.
19. Bacci G, Delepine N, Bertoni F, *et al*. Predictive factors of histologic response to primary chemotherapy in osteosarcoma of the extremity: study of 272 patients preoperatively treated with high dose methotrexate, doxorubicin and cisplatin. *J Clin Oncol* 1998, **16**, 658–663.
20. Bacci G, Ferrari S, Mercuri M, *et al*. Predictive factors of local recurrence in osteosarcoma. *Acta Orthop Scand* 1998, **69**, 230–236.
21. Pochanugool L, Subhadharaphandou T, Dhanachai M, *et al*. Prognostic factors among 130 patients with osteosarcoma. *Clin Orthop* 1997, **345**, 206–214.
22. Petrilli AS, Gentil FC, Epelman S, *et al*. Increased survival, limb preservation,and prognostic factors for osteosarcoma. *Cancer* 1991, **68**, 733–737.
23. Taylor WF, Ivins JC, Pritchard DJ, Dahlin DC, Gilchrist GS, Edmonson JH. Trends and variability in survival among patients with osteosarcoma: a 7 years update. *Mayo Clin Proc* 1985, **60**, 91–104.
24. Simon MA. Causes of increased survival of patients with osteosarcoma: current controversies. *J Bone Joint Surg (A)* 1984, **66-A**, 306–310.
25. Bentzen SM, Poulsen HS, Kaae S, *et al*. Prognostic factors in osteosarcomas. A regression analysis. *Cancer* 1988, **62**, 194–202.
26. Uribe-Botero G, Russell WO, Sutow WW, Martin RG. Primary osteosarcoma of bone. Clinicopathologic investigation of 243 cases, with necropsy studies in 54. *Am J Clin Pathol* 1977, **67**, 427–435.
27. Price CHG. The prognosis of osteosarcoma: an analytical study. *Br J Radiol* 1966, **39**, 180–188.