EXTREMITY AND NON-EXTREMITY HIGH-GRADE OSTEOSARCOMA

The Norwegian Radium Hospital experience during the modern chemotherapy era

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Of 103 patients with high-grade osteosarcoma, 27% had tumours localized outside the extremities. Non-extremity patients were significantly older at diagnosis than patients with extremity tumours (median 38 vs. 17 years). More than 90% of patients with extremity tumours received adequate treatment (aggressive chemotherapy plus at least marginal surgery), compared with only 25% of patients with non-extremity tumours. Failure of adequate treatment was due to inoperable tumour, intralesional surgery and age preventing aggressive chemotherapy. There was a highly significant difference in both local tumour control and overall survival, both favouring patients with extremity tumours. Within the extremity tumour group, patients who were treated in prospective multicentre trials had a significantly better outcome than non-trial patients. Our results show that the fraction of patients with high-grade tumours that fall outside trials designed for 'classical osteosarcoma' may be larger than is usually acknowledged, and that the results reported for the classical group are by no means representative of the whole patient population. Improved and new treatment approaches are needed for patients with non-extremity tumours, particularly in the older age groups.

During the past two decades, the long-term results in osteosarcoma of high-grade malignancy have improved dramatically, with survival rates gradually rising from the 20% to the 70% range. This improvement is attributable to aggressive (neo)adjuvant combination chemotherapy, where the principal ingredients have been high-dose methotrexate (HDMTX), doxorubicin, cisplatin and ifosfamide. Furthermore, in specialized centres the fraction of patients treated with limb salvage procedures instead of amputations has risen by the same order of magnitude, without increase in the rate of local recurrence (generally below 10%) (1–5). However, the reports documenting these advances have largely been limited to so-called 'classical' high-grade osteosarcoma, i.e. patients under 30–40 years of age with extremity tumours and no evidence of metastases at the time of diagnosis. Although this includes the majority of patients, the results of this selected subgroup cannot be considered representative for the group as a whole. On the contrary, small reports on osteosarcoma of the jaw (6) and pelvis (7) have indicated that both local control and survival may be significantly inferior to that of patients with 'classical' tumours.

We have reviewed all patients with osteosarcoma of high-grade malignancy treated at the Norwegian Radium Hospital (NRH) from 1981 to 1995, which corresponds to the period in which modern aggressive chemotherapy protocols have been available in our institution. During the study period approximately 70% of all Norwegian patients with high-grade osteosarcoma were treated at the NRH. The purpose of this study was primarily to compare patients with extremity and non-extremity tumours with respect to patient characteristics, treatment, local control, development of metastases and overall survival, and to identify group-specific problems and challenges.

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Material and Methods

Patients

From February 1981 to December 1995, 103 patients with high-grade osteosarcoma were treated at NRH, 75 (73%) with extremity tumours and 28 (27%) with non-extremity tumours. Patient characteristics and tumour sites are summarized in Table 1. The most usual tumour sites for non-extremity patients were the jaw bones (40%), pelvis (25%) and ribs (18%). Extremity tumour patients had typical distributions for tumour site and age, and were significantly younger than non-extremity patients. Notably, 3 (4%) of the extremity patients versus 12 (43%) of the non-extremity patients were over 40 years of age ($p < 0.0001$), which is often considered the upper age limit for aggressive HDMTX-containing chemotherapy. The fraction of patients with detectable metastases at diagnosis was similar in both groups, as evaluated by CT scan of the lungs and bone scintigraphy (Table 1).

The diagnosis was established by open surgical biopsy in all cases. For diagnosis, staging and choice of treatment plan, each patient was evaluated in the NRH's multidisciplinary sarcoma group, which included dedicated specialists within orthopaedic, general and head and neck surgery, medical oncology, radiotherapy, radiology and nuclear medicine.

Surgery

In all patients considered operable at diagnosis or following preoperative chemotherapy, surgery with wide or marginal margins was attempted. 'Wide surgery' was defined as a procedure with at least a 1.5 cm microscopically tumour-free margin, 'marginal surgery' as having a smaller, but tumour-free margin, and 'intralesional surgery' as the presence of tumour cells at the resection borders.

Patients with head and neck tumours underwent surgery at the Department of Otolaryngology, the National Hospital and the other patients were operated either at NRH or at the National Hospital Centre for Orthopaedic Surgery, depending on tumour localization and type of procedure.

Table 1

Patient characteristics

	Extremity (n = 75)	Non-extremity (n = 28)
Median age (range)	17 (6–72)	38 (12–87)[1]
Sex (M/F)	48/27 (1.8)	16/12 (1.3)
Metastatic at diagnosis	15 (20%)	4 (14%)
Primary tumour site		
femur	39 (52%)	
tibia	24 (32%)	
humerus	9 (12%)	
fibula	3 (4%)	
mandible		8 (29%)
pelvis		7 (25%)
rib		5 (18%)
maxilla		3 (11%)
skull		2 (7%)
vertebra		2 (7%)
scapula		1 (4%)

[1] $p < 0.01$ (Mann-Whitney test)

Chemotherapy

During the study period, three consecutive chemotherapy protocols were employed, all being official studies or pilot studies of the Scandinavian Sarcoma Group (SSG). The SSG II protocol (1981–1990) consisted of the T-10 regimen as described by Rosen et al. (8), and the results of the SSG study have been published (2). Pre-operative chemotherapy included 4 HDMTX-courses, with good histological responders continuing with a HDMTX-based regimen postoperatively, whereas poor responders crossed over to a cisplatin/doxorubicin-based regimen (Fig. 1). In the subsequent SSG VIII protocol (1990 onwards), cisplatin/doxorubicin was added preoperatively, and the MTX dose was increased from 8 to 12 g/m^2. In a third pilot series (SSG/IOR-P1), high-dose ifosfamide was added to HDMTX and cisplatin/doxorubicin (Fig. 1).

Patients not suitable for SSG protocol treatment were considered for individualized chemotherapy adjusted for age and toxicity. 'Adequate chemotherapy' was defined as treatment according to SSG protocols or modified treatment containing at least two of the drugs MTX, doxorubicin or cisplatin in SSG protocol dosage, and with a delivery of at least 50% of intended cumulative dose. 'Adequate primary treatment' was defined as adequate chemotherapy combined with at least marginal surgery.

Radiotherapy

Unless combined with a surgical procedure removing all macroscopic tumour, radiotherapy was considered to be palliative treatment. Following a marginal or intralesional procedure, particularly in the head and neck region, brachytherapy was considered as an adjunct to external irradiation.

Follow-up and definition of relapse

Following primary treatment, the most patients were followed up at NRH, generally every 3 months for 2 years, then every 6 months for 3 years and once yearly until 10 years from diagnosis. Follow-up routinely included clinical examination and x-rays of the lungs and primary tumour site. If relapse was suspected, CT scan and bone scintigraphy were performed. Four patients with non-extremity tumours were followed up at their local hospital along the

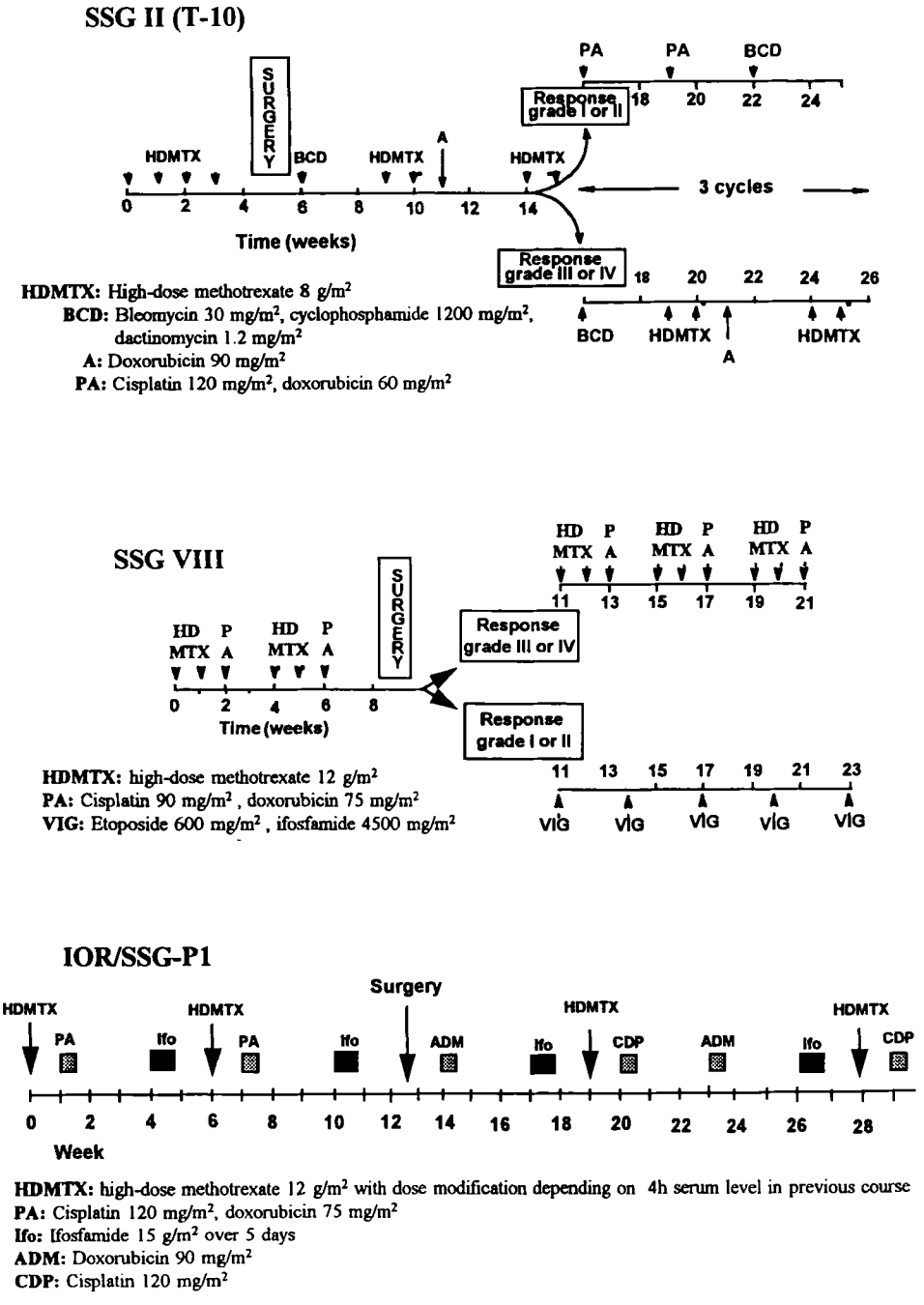

Fig. 1. Outline of the three osteosarcoma protocols conducted by the Scandinavian Sarcoma Group (SSG) during the study period. SSG II and SSG VIII were formal prospective SSG studies, IOR/SSG-P1 was a pilot protocol.

same guidelines, and reports from the follow-up visits were sent to the NRH.

Statistical analysis

Frequency tables of tumour response were analysed by the χ^2- or the Fisher's exact tests, depending on sample size. Age comparisons were done by the Mann- Whitney test. Survival data were analysed by the Kaplan-Meier method, utilizing the logrank test for comparisons. In the analysis of local control, patients in whom removal of the macroscopic tumour was not accomplished were considered to be local failures at the time of diagnosis.

Results

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Table 2

Primary treatment for patients with localized disease

	Extremity tumours (n = 60)	Non-extremity tumours (n = 24)
Wide or marginal surgery	58 (97%)	11 (46%)[2]
Intralesional surgery	1 (2%)	8 (33%)[2]
Radiotherapy to primary tumour site	1 (2%)	8 (33%)[2]
Adequate chemotherapy[1]	57 (95%)	14 (58%)[2]
Protocol SSG II	42	7
SSG VIII	13	3
SSG/IOR-P1	0	4
Modified	2	0
Adequate treatment[1]	56 (93%)	6 (25%)[2]

[1] See definitions in Material and Methods.
[2] $p \leq 0.0001$ as compared to extremity tumours.

patients with localized disease at diagnosis were considered as the presence of overt metastases influenced the choice of treatment, particularly in the older age groups.

Treatment administered

Extremity tumours. In excess of 90% of these patients received adequate primary treatment, i.e. wide or marginal surgery in combination with aggressive chemotherapy (Table 2). Of the four patients who received inadequate treatment, two received no treatment or surgery alone due to advanced age (76 and 72 years), one was not reoperated following intralesional surgery because of the rapid development of metastases, and one patient had no chemotherapy due to congenital renal impairment. The last mentioned 24-year-old patient subsequently received aggressive chemotherapy and lung resections on development of multiple metastases, and remains continuously disease-free 73 months after diagnosis and 68 months after the metastatic event.

Non-extremity tumours. Of the 19 patients (79%) who underwent surgery for removal of all macroscopic tumour, 8 (33%) had intralesional procedures (Table 2). Wide or marginal surgery was most often associated with tumours in the ribs (4/4 patients) or mandible (5/7), whereas no surgery or intralesional surgery was most often associated with tumours in the pelvis (5/5 patients), skull (2/2) or maxilla (2/3). Patients who received aggressive chemotherapy were significantly younger (median 31 years, range 12–45) than patients not receiving chemotherapy (65 years, range 18–87, $p < 0.05$). Only 25% received adequate multimodality treatment (Table 2). Two patients who started protocolled chemotherapy had serious toxicity after their first HDMTX course; one 45-year-old male had delayed MTX excretion with a moderate increase in serum creatinine prohibiting further treatment with HDMTX and cisplatin, and one 30-year-old male had fatal HDMTX toxicity.

Primary tumour control

Median follow-up for surviving patients is currently 81 months (range 7–176). One patient (2%) in the extremity group and five patients (21%) in the non-extremity group failed to obtain initial primary tumour control. Of the remaining patients, another three extremity and 12 non-extremity patients developed local recurrences after a median 18 months from diagnosis (range 8–60 months). Projected local recurrence-free survival for the two groups is shown in Fig. 2. Extremity and non-extremity patients had 3-year local control rates of 95% and 14%, respectively ($p = 0.0000$). In the non-extremity group, patients with wide or marginal surgery had significantly higher local control rates than patients with intralesional surgery ($p = 0.006$).

Development of distant metastases and survival

Of the patients with localized disease at diagnosis, 30 patients with extremity tumours and 12 patients with non-extremity tumours developed metastases, most of them to the lungs. Median time to metastases was similar in both groups (18 and 21 months, respectively), and the projected 4-year metastasis-free survival was comparable (Fig. 3).

Fig. 4 shows that patients with extremity tumours had a significantly better overall survival than patients with non-extremity tumours. Among the patients with localized extremity disease, those treated in prospective SSG studies had a significantly better survival than non-trial patients (72% vs. 50% at 5 years, $p = 0.03$). In the latter non-extremity group, although surgery and chemotherapy had no detectable impact on metastasis-free or overall survival when analysed separately, patients who had both protocol chemotherapy and at least marginal surgery had better survival ($p = 0.06$).

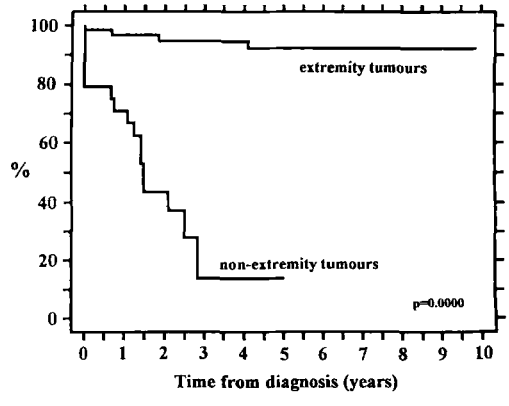

Fig. 2. Projected local recurrence-free survival in patients with localized extremity (N = 60) and non-extremity (N = 24) osteosarcoma.

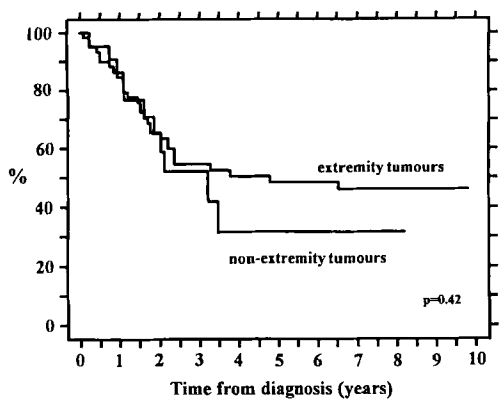

Fig. 3. Metastasis-free survival in patients with localized extremity and non-extremity osteosarcoma.

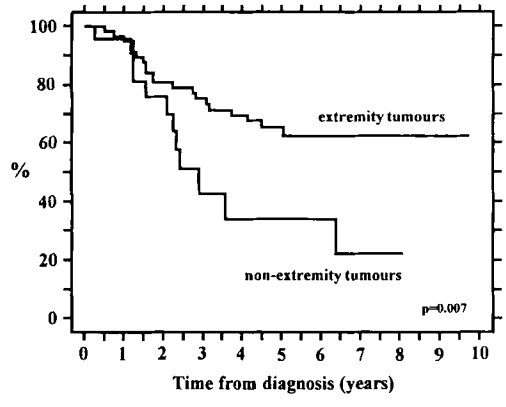

Fig. 4. Overall survival in patients with localized extremity and non-extremity osteosarcoma.

Discussion

Of all 103 patients with high-grade osteosarcoma treated at our institution during the 'modern chemotherapy era', only 42 patients (41%) were found eligible for prospective SSG protocols for 'classical' osteosarcoma. Table 3 shows that apart from the 28 patients who were excluded because of non-extremity tumour localization, 33 of 75 patients with extremity tumours (44%) were also treated outside formal studies. Table 3 shows the reasons for ineligibility, the commonest being metastases at diagnosis (16 patients) and protocol treatment before formal study activation (11 patients). These figures indicate that the results commonly reported in the literature for 'classical' osteosarcoma are not only non-representative for high-grade tumours in general, but may also be misleading concerning the group of non-metastatic extremity tumours. The latter point is illustrated by our finding that patients treated in formal prospective studies have significantly better survival than patients treated outside the studies (Fig. 5). The most important reason for this difference is probably differences in fulfilment of eligibility criteria, but another reason may be insufficient familiarity with the chemotherapy protocol

Table 3

Eligibility in official SSG studies

		Number
Eligible patients		
entered in: SSG II		32
SSG VIII		10
Ineligible patients		
Non-extremity tumours		28
Extremity tumours		33
metastases at diagnosis	16*	
treatment before formal protocol activation	11	
age >40 years	3	
renal impairment	2	
previous surgery to primary turnover	1	
Total		103

* One patient was incorrectly judged ineligible due to suspected metastases at diagnosis

before formal study activation, possibly leading to decreased dose intensity as compared to subsequent patients (Table 3).

Our results regarding long-term outcome for all patients with extremity osteosarcoma (5-year survival 66%), and particularly for those included in prospective studies (5-year survival 72%) compare favourably with those reported in the recent literature (2–5). Patients with non-extremity tumours had a much poorer prognosis, also in agreement with previously reported series (6, 7, 9). There appear to be two main reasons for this difference in outcome. Firstly, non-extremity tumour sites were associated with a high rate of local failure (Fig. 2), and 54% of localized tumours were either judged inoperable or resected with contaminated margins. The importance of local control was illustrated by three patients aged 12–28 years who died from relentless local progression of tumours in the skull, mandible and pelvis, without evidence

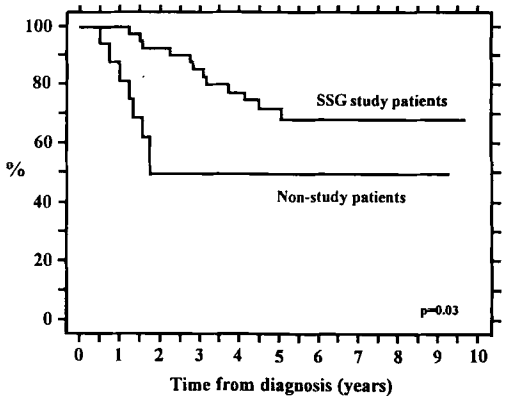

Fig. 5. Overall survival in patients with localized extremity tumours included in formal SSG studies (SSG II or SSG VIII, N = 42), and in patients treated outside study (N = 18).

of metastases. Secondly, the higher age associated with non-extremity tumours often prevented aggressive chemotherapy. The incidence of distant metastases was comparable in the two groups (Fig. 3), underlining the need for systemic treatment in the majority of patients with high-grade osteosarcoma, regardless of tumour localization and age. Nevertheless, it should be pointed out that a considerable number of patients with non-extremity tumours were treated with insufficient chemotherapy intensity that for extremity tumours would be associated with an even higher distant failure rate (1, 10) (Table 2), indicating that the systemic nature of non-extremity disease may be somewhat less pronounced.

How can the results for non-extremity osteosarcoma be improved? As failure in primary tumour control is a major problem and as osteosarcoma is a radiotherapy-resistant disease, surgical improvement is of paramount importance. Recently, advances have been made in resection and reconstruction techniques (11), and this development highlights the need for these patients to be referred to specialist centres with the appropriate experience. The introduction of growth factor support has reduced the neutropenia associated with aggressive chemotherapy, a development that has also to some degree facilitated therapy in the higher age groups. This is illustrated by the recent experience in our institution, where two patients with tumours in the mandible (age 37 and 40 years) and one 29-year-old patient with a maxillary osteosarcoma extending into the orbit were treated by the SSG VIII or IOR/SSG-P1 protocols (Fig. 1), with extensive growth factor support. These patients all had a good histological response following pre-operative chemotherapy, had radical surgery with a good functional result, and remain disease-free at 20, 22 and 29 months from diagnosis.

However, as the chemotherapeutic possibilities in the elderly are also limited by other organ-specific toxicities, there is a need for the development of novel treatment strategies. Novel approaches include radioimmunotherapy with isotopes coupled to monoclonal anti-osteosarcoma antibodies, and treatment with bone-seeking isotopes (12, 13). There are also indications of an effect of interferon in osteosarcoma, and although initial results have been conflicting, the potential of interferon in combination with chemotherapy should be explored (14, 15). Another biological response modifier of interest for clinical studies is muramyl tripeptide phosphoethanolamine (MTP-PE), which has shown promise in both animal and human studies (16).

ACKNOWLEDGEMENTS

The authors acknowledge the participation of the respective members of the NRH's multidisciplinary sarcoma group in the evaluation and treatment of each patient included in this study.

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