

## High-grade osteosarcoma (OS): the scope beyond the "classical" patient

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The term "classical osteosarcoma" has not been precisely defined, but is usually applied to patients under the age of 40 with extremity tumors of high-grade malignancy, and who do not have detectable metastases at the time of diagnosis. For this selected group of patients, treatment results have improved dramatically following the introduction of aggressive combination chemotherapy over the past two decades, and most large centers and cooperative groups now report metastasis-free and overall survival rates in the 60% and 70% ranges, respectively. In the international literature, the focus is almost entirely on this subgroup of "classical" patients, and one may be misled to believe that the results are comparable for most patients with high-grade OS. However, previous scattered reports have indicated that results for patients with metastatic disease (1) or non-extremity tumours (2) are significantly inferior. This report is a retrospective analysis of patient numbers, treatment administered and results for different categories of patients with high-grade osteosarcoma remitted to our institution during what may be termed the "modern chemotherapy era" (1980 onwards).

Norway is divided into five geographical health regions, each with a university hospital oncology department. As regards OS treatment, The Norwegian Radium Hospital (NRH) has the responsibility for all patients from the two largest health regions (50% of the 4 mill. population). In addition, NRH have a considerable number of selected referrals from the other health regions.

From January 1980 to December 1997, a total of 153 Norwegian patients with high-grade OS were referred to NRH, corresponding to approx. 70% of all patients with this tumor reported to the National Cancer Registry during the same time period. According to the definition given above, 45% of the patients belonged to the classical OS group, and a substantial 55% was non-classical (Table 1).

*Table 1. Patient categories*

Classical osteosarcoma	69 patients (45%)
Non-classical osteosarcoma	84 patients (55%)
Age >40 only	14
Non-extremity only	18
Metastatic only	20
Several factors	32

As shown, 38% of the non-classical patients had several features classifying them into this group. The most common overall non-classical feature was non-extremity localization (47 patients), followed by age >40 (42 patients), metastases at diagnosis (36 patients) and radiation-induced tumors (5 patients). The median age in the classical group was 16 years (range 6-40) as compared to 40 (6-87) in the non-classical group. The M/F ratio was 2.3 in the classical group and 1.4 in the non-classical.

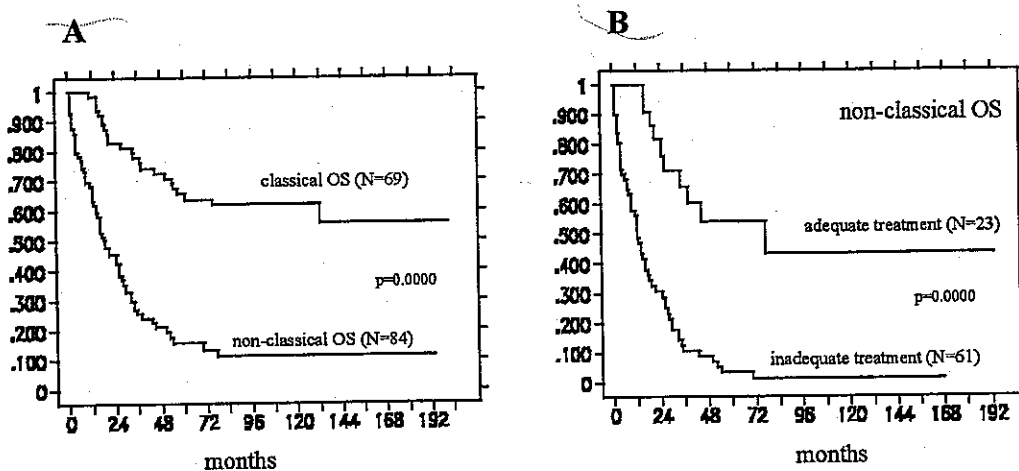
Table 2 outlines the adequacy of the treatment administered in the different patient groups. "Adequate treatment" was defined as surgical removal of all macroscopic disease with non-contaminated margins in combination with at least 6 courses of chemotherapy containing at least two of the following drugs: high-dose methotrexate  $\geq 8$  g/m<sup>2</sup>, doxorubicin, cisplatin or ifosfamide.

Table 2. Patients who received inadequate treatment

	Incidence	Reason for inadequacy		
		Surgery	Chemotherapy	Both
Classical osteosarcoma	6/69 (9%)	0	6 (100%)	0
Non-classical osteosarcoma	61/84 (73%)	18 (30%)	9 (15%)	34 (56%)
Age >40 only	11/14 (79%)	0	7 (64%)	4 (36%)
Non-extremity only	12/18 (66%)	8 (67%)	1 (8%)	3 (25%)
Metastatic only	10/20 (45%)	8 (80%)	0	2 (20%)
Several factors	28/32 (88%)	2 (7%)	1 (4%)	25 (89%)

In the classical group 91% received adequate treatment. Adequate surgery was performed in all cases; chemotherapy was not given or was inadequate in 6 cases (all treated in 1980). Forty six patients (67%) in the classical group were included in consecutive prospective studies run by The Scandinavian Sarcoma Group (from May 1982). None of the patients in the non-classical group were eligible for such studies, although some patients in both groups were included as pilot cases in the planning of SSG studies.

In the non-classical group, only 27% could receive treatment defined as adequate. As expected, the reasons for inadequacy was dominated by incomplete or absence of surgery in metastatic and non-extremity tumors, by inadequate chemotherapy in elderly patients, and by inadequacy of both modalities in patients with several non-classical features. Five-year metastasis-free and overall survival rates for classical OS were 46% and 66%, and the corresponding values for non-classical patients were 39% and 16%, respectively. In non-classical osteosarcoma survival was poor in all tumor patterns, but patients who received adequate treatment had significantly better survival than inadequately treated patients (54% vs. 4% at 5 years).



Overall survival for A: classical vs. non-classical osteosarcoma, B: non-classical patients receiving adequate vs. inadequate treatment

In classical OS results improved in the period from 1989, but no improvement with time was found for the non-classical group. In many of patients with non-extremity tumors failure of local control appears to be at least as important as distant failure.

### **Conclusions**

As many as 50% of high-grade OS patients may fall outside the "classical" category, and the results in this non-classical group are dismal. Many of these patients can not receive adequate surgery because of an inaccessible tumor site, and many can not tolerate aggressive chemotherapy because of age. In patients with metastatic disease at diagnosis chemotherapy resistance remains a major concern. In all of these patient categories new treatment modalities are needed, and prospective cooperative clinical trials should be initiated. In Norway a collaborative study with the National Cancer Registry is under way to examine patient profiles and results in a complete national cohort of OS patients. Retrospective studies on the outcome of non-classical osteosarcoma are also under way in SSG and EMSOS.

### **References:**

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2. Sæter G., Bruland Ø.S., Follerås G., Boysen M. and Høie J., Extremity and non-extremity high-grade osteosarcoma. The Norwegian Radium Hospital experience during the modern chemotherapy era. *Acta Oncol.*, 35 Suppl. 8, 129-134, 1996.