Prognostication including DNA analysis in osteosarcoma

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In a retrospective study of 83 osteosarcoma patients treated by surgery and adjuvant interferon from 1971 to 1986, the clinical course was related to different clinicopathologic features and tumor DNA content. DNA analysis was feasible in 60 cases. Four tumors were diploid and 56 hyperploid.

The 7-year survival rate, estimated by life-table analysis, was 0.44 for the whole series. Multivariate analysis disclosed that male sex, proximal tumor location, and histologic Grade IV were independent risk factors – all approximately of equal strength. DNA analysis did not provide prognostic information, except for tumors with extreme abnormality of the DNA content, which was associated with a very poor prognosis. A prognostication model was created, based on the number of risk factors present. The 7-year survival rate for patients with none, one, two, or three risk factors was 0.80, 0.59, 0.42, and 0.13, respectively.

The estimated 7-year rate of local recurrence was 0.29: 0.07 after ablative surgery and 0.54 after local surgery. Among patients who were free of metastasis 1 year after diagnosis, local recurrence reduced the 7-year survival rate from 0.86 to 0.48.

In high-grade osteosarcoma, conventional clinicopathologic features and local tumor control remain the most important prognostic factors.

Improved survival in osteosarcoma has been reported from several centers during the last decade (Bacci et al. 1986, Rosen and Nirenberg 1985, Simon et al. 1986). The results have mainly been attributed to the introduction of adjuvant chemotherapy. However, the few randomized studies comparing adjuvant chemotherapy with surgery solely present conflicting results (Edmonson et al. 1984, Eilber et al. 1987, Link et al. 1986). A problem in the evaluation of osteosarcoma treatment is the heterogeneity of the series with respect to different tumor features. To permit conclusions about treatment efficacy, it appears that improved tumor characterization, preferably by objective means, is needed.

For several tumor entities, it has been shown that cellular DNA analysis can provide prognostic information beyond that obtained by conventional clinicopathologic assessment. Thus, tumors with a normal (diploid) DNA content have a better prognosis than those with an increased (hyperploid) DNA content. In high-grade osteosarcoma, the vast majority exhibit a hyperploid DNA content (Bauer et al. 1987). Hence, the discrimination between diploid and hyperploid variants is not applicable for prognostic purposes. However, among osteosarcomas there is a great variation in the hyperploid DNA content (Hiddeman et al. 1987). Whether or not this reflects differences in degree of malignancy has not been investigated.

In the present study of osteosarcoma, based on a series receiving adjuvant interferon therapy, the prognostic significance of various clinicopathologic features and tumor DNA content was investigated.

Patients and methods

The study included 94 consecutive patients with primary osteosarcoma referred to our hospital between 1971 and 1986 (Bauer 1988). Eleven patients had lung metastasis on admission according to plain radiography. These were excluded, leaving 83 cases for analysis. There were 51 males and 32 females. Median age was 17 (5–74) years (Figure 1). Prior to admission, open biopsy had been performed in 20 cases.

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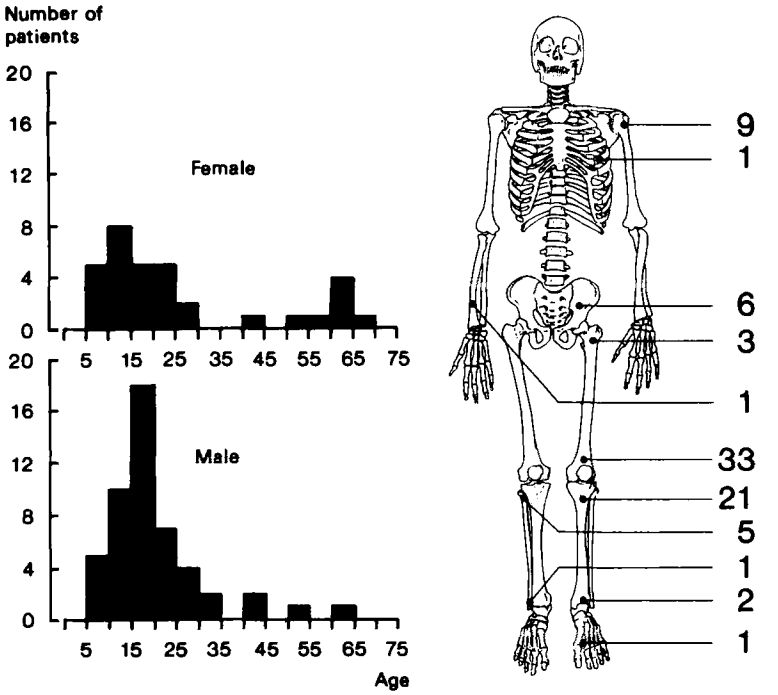

Figure 1. Tumor location and distribution according to age and sex.

The most common tumor locations were distal femur and proximal tibia (Figure 1). The median tumor size was 9 (2–20) cm, as defined by the largest diameter in macroscopic examination of the surgical specimen or in original radiographs. Histologic sections of open biopsy and surgical specimens were reviewed by one of us (CS) without access to clinical data. Histologic malignancy grading (I–IV) was performed according to Broders et al. (1939), and histologic subtyping (osteoblastic, chondroblastic, fibroblastic, and telangiectatic) according to Dahlin (1975; Table 1). Tumor staging and surgical margins according to Enneking (1986) were assessed retrospectively by reviewing radiographic, surgical, and histopathologic reports. There were 4 IB, 3 IIA, and 76 IIB lesions. The relationship between surgical procedure and surgical margin is shown in Table 2. However, stages and margins were not always described sufficiently detailed, in the reports reviewed, to permit accurate assessment. Hence, these data were not included in the prognostic analysis.

All the patients were treated by surgery and adjuvant interferon. Amputation or disarticulation was performed in 47 cases and local resection in 36. Natural leukocyte interferon-alpha was given by intramuscular injections starting at the time of diagnosis and continued for 18 months (Strander et al. 1984). The dose was 3 x 10^6 daily the first month, and then 3 x 10^6 three

Table 1. Histologic tumor grade and subtype

	Grade			
	II	III	IV	Total
Osteoblastic	1	22	27	50
Chondroblastic	0	13	5	18
Fibroblastic	3	5	6	14
Telangiectatic	0	0	1[1]	1
Total	4	40	39	83

[1] The single telangiectatic lesion was included in the osteoblastic group in the prognostic analysis.

Table 2. Surgical margins according to procedure

	Surgery	
	Local	Ablative
Intralesional	12	0
Marginal	11	2
Wide	13	24
Radical	0	21
Total	36	47

times weekly for the ensuing 17 months. Since January 1985, the daily dosage of 3 x 10^6 has been continued throughout the whole 18-month period.

Patients developing local recurrences or metastases were not treated according to a standardized protocol. The therapy for local recurrences was local or ablative surgery and for metastases it included interferon, Adriamycin, high-dose methotrexate, cis-platinum, and radiation in different combinations, and also surgery.

The mean follow-up time from diagnosis was 8 (0.3–16) years. No patient was lost to follow-up. Two patients committed suicide at 3 and 6 months after diagnosis; autopsy showed no evidence of disease and both patients were included in the survival analysis until the time of death. All other deaths, except one, were due to metastatic disease. The only exception was a patient who died of local pelvic recurrence after intralesional excision, radiation, and chronic infection.

DNA analysis

Determination of nuclear DNA content and size was feasible in 60 cases. Exclusion of 23 cases was due to deficient nuclear DNA stainability in 21 (Bauer and Kreicbergs 1987) and loss of paraffin blocks in 2.

DNA analysis was based on Feulgen-stained sections (4 µm) from paraffin-embedded specimens (Kreicbergs and Zetterberg 1980). The measurements were made in a rapid-scanning microspectrophotometer. The normal (diploid) DNA content was assigned the arbitrary value DNA Index (DI) 1.0. The following DNA variables were considered: percentage of tumor cells with DNA values > DI 1.25, percentage of tumor cells > DI 2.5, median DNA value (50th percentile), and extreme DNA value (90th percentile; Figure 2A; Kreicbergs et al. 1982). Tumors containing < 31 percent cells with DNA values exceeding DI 1.25 were classified as diploid and those containing > 31 percent as hyperploid (Bauer et al. 1986).

Nuclear size (projected area) in μm^2 was obtained from computerized transcripts of the microspectrophotometric DNA measurement of each nucleus (Kreicbergs et al. 1981). For each tumor cell population the median (50th percentile) and extreme (90th percentile) nuclear size was calculated (Figure 2B).

Statistics

The estimated 7-year survival and local recurrence rates were determined by Kaplan-Meier life-table analysis of censored data (Peto et al. 1977). Prognosis was related to the following clinicopathologic features: sex, age, tumor location and size, histologic subtype and grade. Age and tumor size were dichotomized into <18 and >18 years, and <10 and >10 cm, respectively. The prognostic significance of DNA content and nuclear size, treated as continuous variables, was analyzed separately without regard to the clinicopathologic features.

A bivariate log rank (Mantel-Haenzsel) test was applied to analyze survival and local recurrence in relation to the different clinicopathologic features. Multivariate Cox (1972) proportional regression analysis was used to test the relative significance of the different variables. Estimated survival for subgroups of patients with none, one, or several identified clinicopathologic risk factors was compared by a log rank test. Testing for trend in prognosis was performed according to Peto et al. (1977).

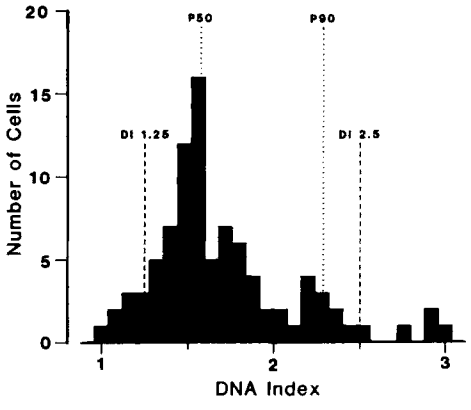

Figure 2A. DNA histogram of one osteosarcoma. In this example, the median DNA value (P50) was DI 1.6, the extreme (P90) value DI 2.6, 97 percent of cells > DI 1.25, and 5 percent of cells > DI 2.5.

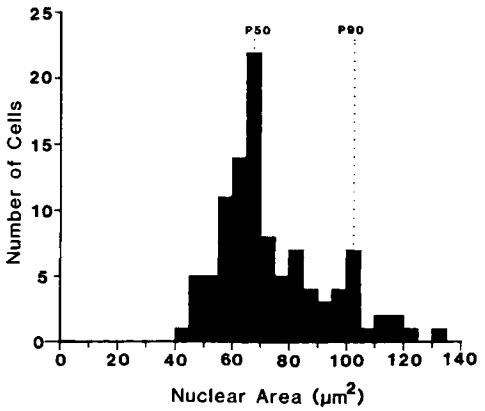

Figure 2B. Nuclear size histogram of the same tumor. Median (P50) nuclear size was 65 μm^2 and extreme (P90) 105 $m\mu^2$.

Results

Survival

The 7-year survival rate for the whole series of 83 patients was 0.44 (Figure 3). A comparison of survival for patients treated 1971–1979 and those treated between1980 and 1986 disclosed no difference. All the clinicopathologic features except age were related to survival (Table 3). Histologic grade appeared to be the strongest prognostic variable, Grade IV lesions being associated with a low survival rate. As to histologic subtype, patients with chondroblastic variants exhibited the lowest survival rate and those with fibroblastic the highest. Tumors located in the distal femur did not differ prognostically from those more proximally located, but clearly from the more favorable distal lesions. Based on the results of the bivariate analysis, dichotomies for tumor location and histologic subtype were formed for multivariate analysis. Tumors of the trunk, humerus, and femur were classified as proximal, and those of the lower arm and leg as distal. Analogously, chondroblastic and osteoblastic tumors were combined into one group for comparison with fibroblastic tumors.

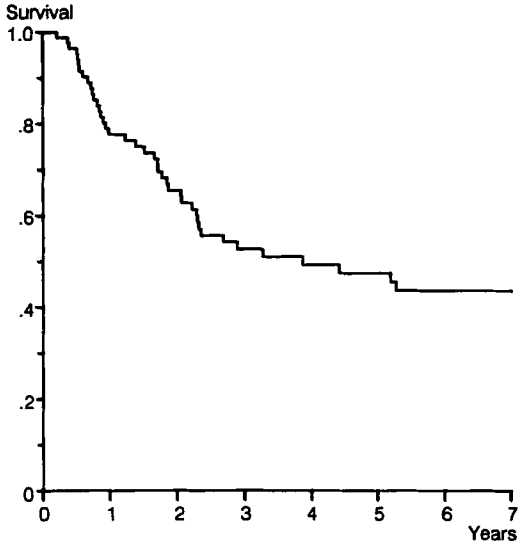

Figure 3. Life-table survival curve for the whole series of 83 patients. Twenty-one patients were still at risk at 7 years.

Table 3. Estimated 7-year survival rate in relation to clinicopathologic features

Variable		n	Estimated survival	P^1	P^1
Sex	Male	51	0.34	0.032	
	Female	32	0.60		
Age	≤18 years	45	0.35	0.12	
	>18 years	38	0.56		
Location	Trunk, shoulder, hip	19	0.37	0.90	
	Distal femur	33	0.32	0.007	0.032
	Distal to elbow/ knee	31	0.58		
Size	≤10 cm	58	0.49	0.018	
	>10 cm	25	0.30		
Grade	II–III	44	0.56	0.002	
	IV	39	0.30		
Type	Osteoblastic	51	0.44	0.15	
	Chrondoblastic	18	0.20	0.009	0.08
	Fibroblastic	14	0.70		

[1] Bivariate log rank test.

The significant factors associated with a poor prognosis were histologic Grade IV, proximal tumor location, and male sex (Table 4). Age, tumor size, and histologic subtype had no independent prognostic influence.

The identified risk factors were considered in different combinations to form 8 subgroups of patients in a Venn diagram (Figure 4). Life-table estimates of

Table 4. Multivariate Cox regression analysis of risk factors for tumor-related death

Covariate	Definition	Multiple regression coefficient	Relative risk	P
Sex	1 male; 0 females	0.74	2	0.042
Age	1 ≤ 18 yrs; 0 > 18 yrs.	0.53		0.11
Location	1 proximal; 0 distal	0.98	3	0.008
Size	1 > 10 cm; 0 ≤ 10 cm	0.04		0.91
Grade	1 IV; 0 II/III	0.96	3	0.005
Type	1 Osteo/Chondro; 0 Fibro	1.05		0.057

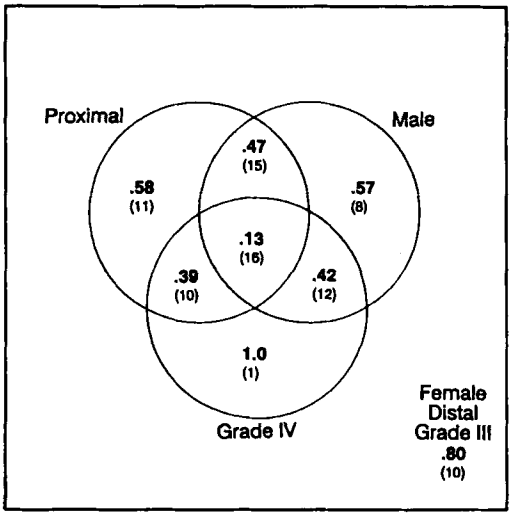

Figure 4. Estimated survival based on the risk factors male sex, proximal tumor location, and histologic Grade IV. Ten patients had none of these characteristics. Number of patients within parentheses.

7–year survival were determined for each subgroup. The survival rate was highest (0.80) for females with distal Grade III tumors and lowest (0.13) for males with proximal Grade IV tumors. As can be seen from the Venn diagram, the survival rate was approximately the same for subgroups with an equal number of risk factors. Hence, the series could be divided according to the number of risk factors present. The 7-year survival rate for patients with none, one, two, or three risk factors was 0.80, 0.59, 0.42, and 0.13, respectively (Figure 5).

DNA analysis was feasible in 60 out of 83 cases. The vast majority, i.e., 56 tumors, were hyperploid. The 7-year survival rate for the 56 patients with hyperploid lesions was 0.40. Three out of the 4 diploid cases remained free of disease at 4, 9, and 12 years; 1 died of local pelvic recurrence 10 months after the diagnosis. Bivariate Cox regression analysis disclosed that none of the tested DNA variables, nor nuclear size, gave prognostic information (Table 5). Only the extreme (P90) DNA value appeared related to survival. In fact, the estimated survival according to life-table analysis was 0.12 for the 9 patients with P90 > DI 4.0, as compared with 0.52 for the other 51 (log rank test: $P = 0.03$).

Local recurrence

The estimated 7-year local recurrence rate for the whole series was 0.29. Median time to local recurrence was 6 months; with the longest lag being 3 years.

According to surgical procedure, 3 out of 47 patients had a local recurrence after ablative surgery, and 17 out of 36 after local surgery (Figure 6). Taking into account the type of surgical procedure in the multivariate analysis, other factors such as tumor size, location, and histologic grade were not related to local recurrence.

To assess the significance of local recurrence for survival, patients who developed local recurrence within 1 year of diagnosis, but not metastasis, were compared with patients free of disease at 1 year. Hence, 38 patients were excluded from this analysis either because of death or metastatic disease within 1 year or because of a follow-up that was less than 1 year. The estimated 7-year survival rate for the 10 patients with local recurrence within 1 year of diagnosis was 0.48 as compared with 0.86 for the 35 patients free of disease at 1 year (log rank test: $P = 0.046$).

Table 5. Bivariate Cox regression analysis of DNA content and nuclear size in relation to death in tumor disease. Each covariate was analyzed separately

Covariate[1]	Regression coefficient	*P*
Median (P50) DNA value	0.24	0.42
Extreme (P90) DNA value	0.24	0.18
% cells > DI 1.25	0.006	0.51
% cells > DI 2.5	0.10	0.27
Median nuclear area	0.011	0.48
Extreme nuclear area	0.002	0.80

[1] All covariates were treated as continuous.

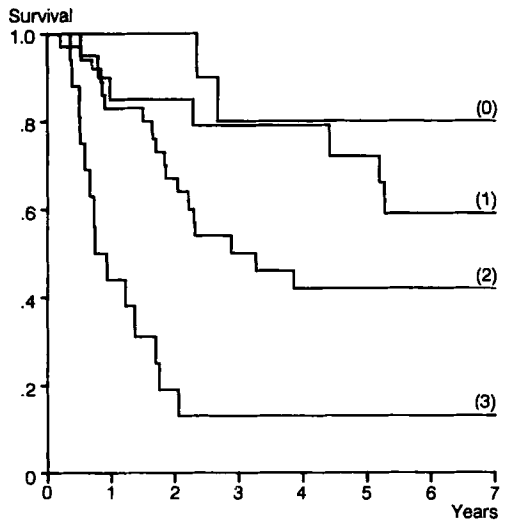

Figure 5. Life-table survival curves, based on the number (within parentheses) of risk factors, for subgroups of patients. There were 10, 20, 37, and 16 patients in the four subgroups. Chi-square test for trend in survival yielded 23.05; df = 1; $P < 0.001$.

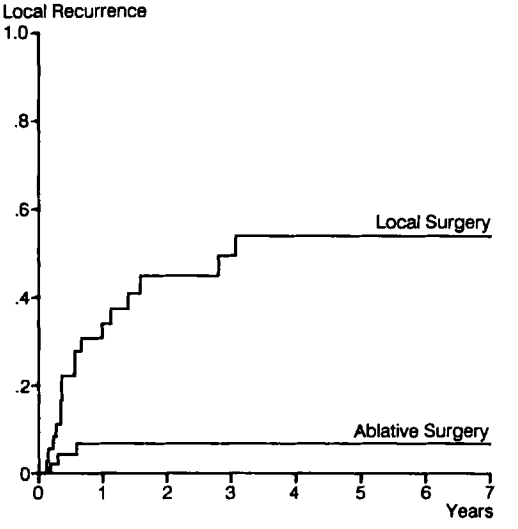

Figure 6. Life-table analysis of risk for local recurrence after local and ablative surgery, respectively. Log rank test for difference between curves $P < 0.001$.

Discussion

In the present series, treated by surgery and adjuvant interferon therapy, the estimated 7-year survival rate (0.44) is comparable to that reported from randomized trials with different adjuvant chemotherapy regimens in osteosarcoma (Bacci et al. 1986, Edmonson et al. 1984, Eilber et al. 1987, Link et al. 1986). Our study is of particular interest by representing a contemporary interferon-treated series for comparison with recent and current chemotherapy trials on osteosarcoma. Moreover, our study includes a consecutive series of patients, treated at one center over a period of 15 years, followed on an average 8 years. In fact, the number of patients still alive at 7 years and the course of the survival curve permitted reliable estimation of overall survival, instead of determining recurrence-free survival, which is more appropriate for short-term follow-up studies (Peto et al. 1977).

Although not based on a defined population, our series is representative with respect to different clinicopathologic features: there was a male predominance, peak age incidence around the second decade, and there was a preponderance of lesions about the knee. Histologically, the vast majority of tumors were high-grade, and the most common subtype was osteoblastic. Hence, in our opinion, our series permits conclusive prognostic analysis.

In studies of rare tumor entities, such as osteosarcoma, the limited series by necessity requires more or less artificial dichotomization of different variables to permit statistical analysis. In this study, tumors from different locations were divided into those involving the shoulder/hip/trunk, distal femur, and lower arm/leg. Because there was no difference in survival between the two former groups, these tumors were combined into one group of proximal lesions for comparison with distal lesions. Similarly, osteoblastic/chondroblastic lesions were compared with fibroblastic lesions, as the latter proved to be associated with a better, i.e., different, prognosis. Further, it appeared reasonable to group the few Grade II lesions with the Grade III lesions.

In the vast literature on osteosarcoma, various clinicopathologic features have been reported to be of prognostic relevance. However, the findings have been contradictory, particularly regarding the significance of age, sex, histologic subtype, and grade. To some extent, this may be explained by the lack of appropriate statistical methods. In a recent study from the Mayo Clinic, based on multivariate analysis, Taylor et al. (1985) were able to identify the following unfavorable characteristics: age less than 10 years, male sex, tumor diameter exceeding 15 cm, osteoblastic/chondroblastic subtype, involvement of femur or humerus, and less than 2 months' duration of symptoms.

In the present study, male sex, proximal tumor location, and histologic Grade IV were the only independent risk factors. Male sex has also been identified as a risk factor in soft tissue sarcoma (Rydholm 1983). Notably, males and females with osteosarcoma exhibit not only differences in survival, but also differences in incidence and age, the latter coinciding with puberty. Proximal location, but not large tumor size, was a risk factor. However, these two variables were interrelated. Excluding location from the analysis, tumor size emerged as a prognostic variable, as previously reported (Taylor et al. 1985). Although size may reflect biologic tumor properties to a greater extent than location, proximal lesions, presumably, are detected later than distal ones, and are more difficult to manage surgically. In the present study, histologic malignancy grading proved to be the most important prognostic factor. It may be assumed that there are tumors of both high- and low-grade malignancy among Grade II and III lesions. However, among Grade IV lesions, representing extreme neoplasia, the probability of low grade malignancy seems almost negligible. The observed significance of distinguishing between Grade III and Grade IV osteosarcomas appears somewhat surprising, because this particular distinction has been claimed to be almost impossible due to overlapping of different morphologic features (Dahlin and Coventry 1967).

DNA analysis by microspectrophotometry was not found to provide prognostic information, except for tumors with extremely high DNA values, which proved to be associated with a very low survival rate. Other variables such as percentage of hyperploid tumor cells and nuclear size were not prognostically discriminative, as demonstrated for chondrosarcomas, where the distinction between diploid and hyperploid variants was of considerable prognostic value (Kreicbergs et al. 1982). However, in osteosarcoma this distinction is not applicable, because the vast majority are hyperploid. By applying other DNA techniques, such as flow cytometry of cell suspensions, permitting accurate determination of peak DNA values and proliferative activity, it may prove feasible to discriminate prognostically among hyperploid osteosarcomas.

The three independent risk factors, i.e., male sex, proximal location, and histologic Grade IV, were approximately of equal strength according to multivariate analysis. By considering all conceivable combinations of these risk factors, survival was found to be related to the number, rather than the type, of risk factors present. Hence, the prognostication model was created according to the number of risk factors involved, all

reasonably well defined. The subgroups, representing four risk levels, were associated with a stepwise decreasing 7-year survival rate ranging from 0.80 to 0.13. Hence, in the present series of high-grade osteosarcomas, four prognostically different groups could be identified. Similar conclusions were reached by Taylor et al. (1985), although not considering histologic grade. The validity of the prognostication model applied has also been substantiated in soft tissue sarcoma (Rööser 1987). Interestingly, male sex and histologic Grade IV were of similar significance as now demonstrated in osteosarcoma; but, instead of tumor location, size was found to be of prognostic importance.

Local recurrence was strongly related to surgical procedure in the sense that it almost exclusively occurred after local surgery. The high rate, obviously, was due to inadequate surgical margins. In several studies, the local recurrence rate has been reported to be 5–15 percent after local surgery combined with chemotherapy (Bacci et al. 1986, Rosen et al. 1985, Simon et al. 1986). The superior results may be attributed to improved local tumor control by adjuvant chemotherapy. However, it must be emphasized that the present consecutive series included a few tumors that were virtually unresectable. Nevertheless, our findings imply that patients with a high-grade osteosarcoma should only be treated by local surgery when safe margins can be obtained.

The importance of local tumor control for survival was clearly reflected in the present study. In fact, the 7-year survival rate was 0.46 for patients with local recurrence as compared with 0.86 for those without local recurrence when considering specifically patients free of metastasis within the first year of diagnosis. Thus, local recurrence seems to be a significant factor related to survival, emphasizing the importance of safe surgical margins. In our opinion, relenting on the requirements for wide or radical procedures cannot be justified until adjuvant chemotherapy and local radiation are convincingly proven effective for local tumor control.

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Acknowledgments

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