No improvement in the overall survival of 194 patients with chondrosarcoma in Finland in 1971–1990

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ABSTRACT We describe the clinicopathologic profile and survival of 306 patients with chondrosarcoma reported to the Finnish Cancer Registry in 1971–1990. 218 cases were available for reevaluation. Owing to their various clinicopathologic characteristics, we excluded the histologic variants of chondrosarcoma. Therefore, the final study population included 194 patients. The minimum follow-up was 9 years. The study population included 69 grade 1 tumors, 114 grade 2 tumors, and 11 grade 3 tumors. The commonest tumor sites were the chest, pelvis and femur. A local recurrence developed in 25% of the patients and metastatic lesions in 18%. The patients were treated in 31 hospitals (in 22 hospitals during the 1970s and in 26 in the 1980s), and the number of patients biopsied before the referral remained about the same from the 1970s (15%) to the 1980s (18%). The 5-and 10-year disease-specific survival rates were 70% and 57%, respectively. Multivariate analysis showed that the most important independent predictors of shortened survival were high histologic grade, age 50 years or older, and a diagnosis in the 1980s, as compared to the 1970s.

Most findings accorded with reports from specialist treatment centers, but to our surprise, the survival rate declined among patients diagnosed in the 1980s versus the 1970s. The failure to improve patient survival is probably due to treatment of the patients in 31 hospitals rather than in a few centers dealing with treatment of cancer.

Chondrosarcoma is the second commonest primary malignant bone tumor. It is characterized by a propensity for local recurrence and late metastases (Healey and Lane 1986, Dorfman and Czerniak 1995). In general, chondrosarcomas grow slowly; consequently meaningful survival analysis requires a long follow-up. On the basis of cellular atypia, mitotic figures and cellularity, chondrosarcomas are classified into 3 histologic grades (Huvos 1991, Inwards and Unni 1995). Although tumors of high grade are associated with an increase in the risk of metastases and shorter survival, the clinical course of chondrosarcoma can not always be predicted by histologic grade alone (Evans et al. 1977, Huvos 1991). This may be partly due to the difficulty in making a histologic distinction between benign and low-grade malignant cartilaginous tumors.

Chondrosarcomas are resistant to radiotherapy and chemotherapy, and therefore, surgical resection is the only curative treatment. They usually involve the pelvis, which makes it difficult to excise the tumor (Unni 1996). Consequently, local and systemic recurrences are common. Little is known about other factors that affect or predict failures in treatment.

Only a few studies are available on the prognostic factors in patients with chondrosarcoma (Evans et al. 1977, Pritchard et al. 1980, Sheth et al. 1996, Björnsson et al. 1998, Oshiro et al. 1998, Lee et al. 1999, Bergh et al. 2001). Most of them have been done in specialist treatment centers, which may involve a bias as regards referral of cases. The 3 population-based survival studies available concern tumors at specific anatomical locations

(Bovee et al. 1999, Mochizuki et al. 2000) or include all types of bone sarcoma (Hartley et al. 1992). We retrospectively examined the clinical pattern and survival of chondrosarcoma patients in Finland over a 20-year period. The data were collected from the nationwide Finnish Cancer Registry (FCR), which provides reliable records of all cases of cancer in the population.

Patients and methods

Patient data

This series comprised all 306 cases of chondrosarcoma of the bone diagnosed in Finland in 1971–1990 in 31 hospitals, retrieved from the files of the nationwide population-based FCR. The Registry was started in 1952, and it covers over 99% of all solid tumors diagnosed in Finland (Teppo et al. 1994). The study was approved by the Joint Ethics Committee of Turku University Central Hospital and University of Turku, and by the Ministry of Health and Social Affairs. Detailed clinical data—e.g., patient age at the time of diagnosis, and primary site, histologic diagnosis, grade, and treatment of the tumor—were collected about each case. Survival data were gathered, using nationwide death records through Statistics Finland. The closing date of the follow-up was 31 December, 1999, which ensured a follow-up of 9 years or more of all patients. The follow-up was complete.

On the basis of the treatment given, the patients were divided into 7 categories (Table 1). 98 patients were treated primarily by surgery alone, 42 by surgery combined with radiotherapy, 20 by surgery combined with radiotherapy and chemotherapy, and 16 by radiotherapy alone. In addition, 2 patients were treated by radiotherapy and chemotherapy, and 2 by radiotherapy alone. In 14 patients, only palliative treatment was given.

Histology

Histologic specimens from 218/306 cases were recovered for reevaluation. The original hematoxylin and eosin-stained slides were reviewed independently by 2 bone pathologists (TE and TB) to confirm the diagnosis and assess the grade of the tumor. The review was done without knowledge of the previous pathologic diagnosis or clinical outcome. Tumors were graded histologically, using the system described by Huvos (1991).

Table 1. Clinical characteristics of the 194 patients with chondrosarcoma

Clinicopathologic features	No. of patients
Gender	
Male	121 (62%)
Female	73 (38%)
Grade	
1	69 (36%)
2	114 (59%)
3	11 (6%)
Location	
Chest	41 (21%)
Pelvis	40 (21%)
Femur	37 (19%)
Hand	14 (7%)
Skull	15 (8%)
Humerus	15 (8%)
Spine	12 (6%)
Tibia	6 (3%)
Foot	6 (3%)
Scapula	5 (3%)
Radius	1 (1%)
Ulna	1 (1%)
Fibula	1 (1%)
Treatment	
Surgery alone	98
Surgery + RT	42
Surgery + RT + CT	20
Surgery + CT	2
RT + CT	2
RT alone	16
Palliative treatment	14

RT radiotherapy, CT chemotherapy.

Statistics

The overall disease-specific survival and survival without a local recurrence and metastases were estimated by the Life Tables method. The effect of each prognostic variable (tumor grade, age at diagnosis, gender, tumor location, treatment, and decade of diagnosis) was evaluated, using the Wilcoxon (Gehan) test. Multivariate analysis was done, using the Cox proportional hazards model to assess the effects of the variables when studied simultaneously, and identify independent prognostic factors. The criterion used to select covariates in the model was the Wald test statistics. Associations between categorical variables were studied, using the chi-square test. P-values less than 0.05 were considered statistically significant.

Table 2. Comparison of the original and reclassified diagnoses of 218 patients with chondrosarcoma

Review diagnosis	Original diagnosis Chondrosarcoma G1	G2	G3	Total
Chondrosarcoma G1	64	5		69
Chondrosarcoma G2	18	90	6	114
Chondrosarcoma G3		2	9	11
Clear cell chondrosarcoma	1			1
Mesenchymal chondrosarcoma	1			1
Myxoid chondrosarcoma	4	1		5
Osteosarcoma	1	9		10
Chondroma	7			7
Total	96	107	15	218

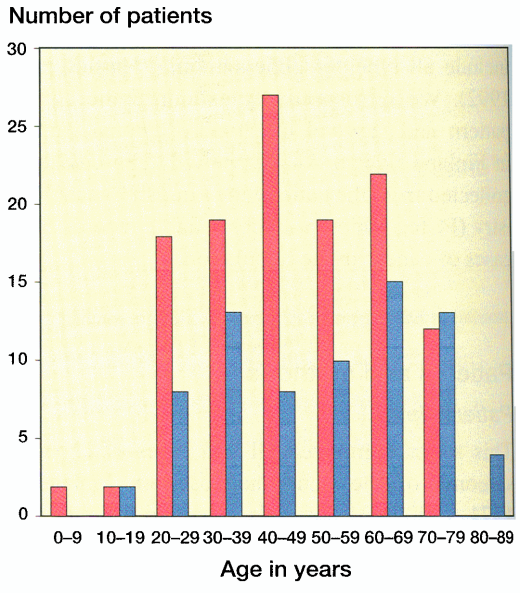

Figure 1. Age and gender distribution of the 194 patients with a confirmed diagnosis of primary chondrosarcoma.

Results

Clinicopathologic data

306 patients were diagnosed with chondrosarcoma in Finland in 1971–1990. Of the 218 tumors available for histopathologic reclassification, 201 were confirmed as chondrosarcomas, 10 were rediagnosed as osteosarcomas and 7 as benign chondromas (Table 2). The histologic chondrosarcoma variants—i.e., myxoid (5 cases), mesenchymal (1 case) and clear-cell chondrosarcomas (1 case)—were excluded from the cohort leaving 194 chondrosarcomas for the analyses.

The study population included 69 grade 1 tumors, 114 grade 2 tumors and 11 grade 3 tumors. Of the 194 patients, 121 were males and 73 females, with a median age (at the time of diagnosis) of 49 (0–84) years (Table 1). Most of the cases were diagnosed in the fourth, fifth and sixth decades of life (Figure 1). The commonest site was the chest wall, followed by the pelvis and femur. The relative frequency of the primary sites was similar in male and female patients and in the various age groups.

Hospitals

In the early 1970s, the Ministry of Social Affairs and Health of the Finnish government recommended that the treatment of malignant bone tumors should be given primarily in 2 University Hospitals, and that the patients be referred for treatment before biopsy. According to the present national survey, this recommendation was not followed because patients with chondrosarcoma had been treated in 22 hospitals during the 1970s and in 26 hospitals during the 1980s. Moreover, the number of patients undergoing biopsy of their chondrosarcoma tumors before referral did not decline with time: during the 1970s, 11/71 patients (15%) had a biopsy of their tumor before referral to the final treatment center, as compared to 22/123 patients (18%) in the 1980s. The number of patients who had the diagnostic surgical biopsy and the final surgical treatment in the same center was 60/71 (86%) in the 1970s and 83/123 (67%) during the 1980s. Although a biopsy of the tumor before referral to treatment was a significant negative prognostic factor for the patient's survival in the univariate analysis ($p = 0.006$), it did not reach a significant level in the multivariate analysis.

Survival analyses

Univariate analyses showed that the malignancy-grade was the most important risk factor for survival of the 194 patients (Table 3). To assess whether this group is representative of the entire original material of 306 patients, we compared the overall disease-specific survival curves in both groups. The 5-and 10-year overall survival

Table 3. Univariate analyses of factors predicting survival

	No. of patients	5-year survival (%)	10-year survival (%)
Age			
<50	98	83	79
50+	96	64	47
Gender			
Male	121	71	62
Female	73	77	70
Location			
Skull	15	80	67
Pelvis	40	62	49
Chest	58	72	59
Extremities	81	80	77
Grade			
G1	69	74	68
G2	114	79	68
G3	11	12	12
Time of diagnosis			
1970s	71	78	69
1980s	123	71	63
Chemotherapy			
No	172	75	68
Yes	24	41	18
Treatment			
Surgery alone	98	89	87
Surgery + RT	62	59	40
RT alone	16	16	–
Palliative treatment	14	–	–

RT radiotherapy

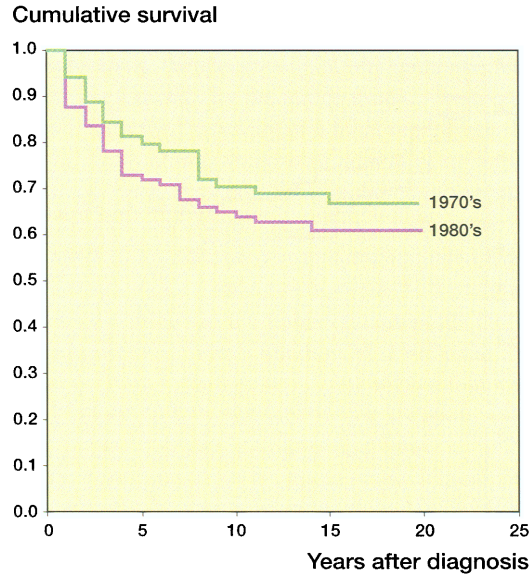

Figure 2. Disease-specific survival of patients with chondrosarcoma diagnosed in 1970–1979 and 1980–1990.

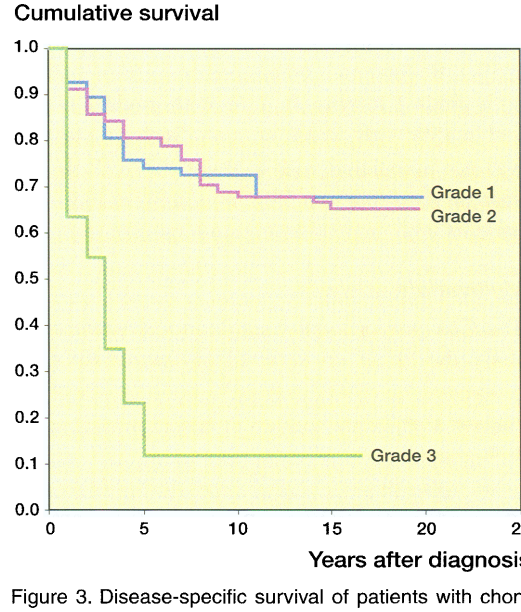

Figure 3. Disease-specific survival of patients with chondrosarcoma, according to histologic grade.

rates were 62% and 49%, respectively, in the 306 patients, and 74% and 66%, respectively, in 194 patients. Based on statistical analyses, this difference was not significant. Therefore, the selection process seemed not to distort the survival analysis. In 1971–1979, the 5-year survival rate was 78% and the 10-year rate 69%. In 1980–1990, the 5-year survival rate declined to 71% and the 10-year rate to 63% (Figure 2).

The survival rate of patients with a grade 3 tumor was much lower than that of patients with grade 1 or 2 tumors, which were similar (Figure 3). The survival rates of older patients were much worse than those of the younger ones, especially 10 years or more after the diagnosis. The 5-year survival rate of patients 50 years or older was 64%, and the 10-year rate 47%. In patients under 50 years of age, the 5-year survival rate was 83% and the 10-year rate 79% (Figure 5).

The 5- and 10-year survival rates of the 98 patients who underwent curative surgery were much better than those of the 42 patients treated with both surgery and radiotherapy. The survival rate of patients treated with adjuvant chemotherapy was even worse, 41% at 5 years and only 18% at 10 years.

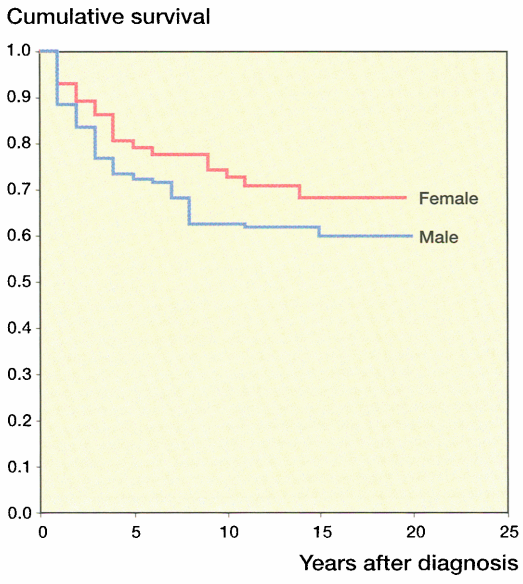

Figure 4. Disease-specific survival of patients with chondrosarcoma, according to gender.

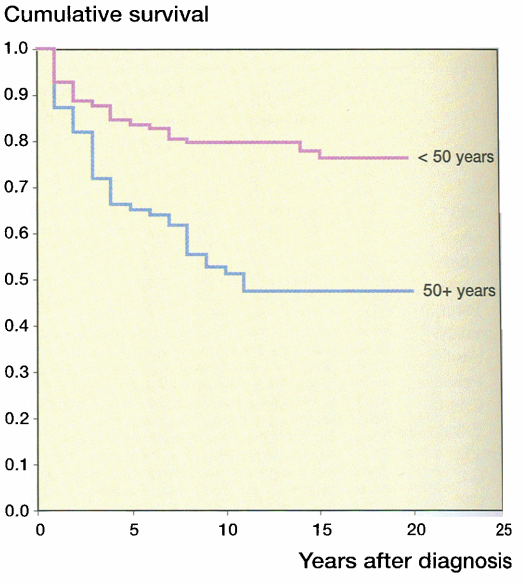

Figure 5. Disease-specific survival of patients with chondrosarcoma, according to age at the time of diagnosis.

A local recurrence developed in 42 patients (25%). Recurrences were seen in 17% of patients with grade 1 tumors, in 21% with grade 2 tumors and in 55% with grade 3 tumors. Such a recurrence was not associated with a lower survival: the 10-year survival rate was 58%, as compared to 62% in patients who did not develop a local recurrence.

Multivariate analysis

The Cox proportional hazards model was used to study the effect on survival of the patient's age and gender, tumor site and grade, use of adjuvant chemotherapy and radiotherapy in the initial treatment, and the decade of the initial diagnosis (Table 4). Age remained a significant risk factor ($p = 0.003$). Patients aged 50 years or older had a 2-fold probability of death, as compared to those who were under 50 years of age. Grade 3 indicated a poorer prognosis than grade 1 ($p < 0.01$).

Table 4. Multivariate analysis of factors predicting survival

Comparison of variables	P-value	RR	95% CI
Time of diagnosis			
1980s vs 1970s	0.009	2.1	1.2–3.6
Age			
50+ vs <50	0.003	2.3	1.3–3.9
Grade			
Grade 2 vs grade 1	0.9	–	–
Grade 3 vs grade 1	0.01	3.2	1.3–7.6
Treatment			
RT + surgery vs surgery	0.0001	7.7	3.8–16
RT vs surgery	0.0001	28	12–62

RR relative risk, CI confidence interval of the relative risk, RT radiotherapy

The decade of the initial diagnosis (1980s versus 1970s) proved to be a prognostic factor. The patients diagnosed during the 1980s had a significantly lower survival rate than those diagnosed in the 1970s, the relative risk of death being 2.1 ($p = 0.009$). When age, gender, grade, location of the tumor, treatment, metastasis and local recurrence were included in the multivariate analysis of the survival of patients during 1980s, only the occurrence of metastasis remained an explanatory factor. Neither gender nor location of the tumor was a significant prognostic factor.

Metastases

Of the 194 chondrosarcoma patients, 30 (18%) developed metastatic disease during the follow-up. Metastases developed in 3 patients with a grade 1 tumor (4% of cases), in 24 patients with grade 2 tumors (21%), and in 3 patients with grade 3 tumors

(27%). No statistical differences were found in the distribution of the tumor grades in patients with metastases who were younger or older than 50 years. In 14 cases, the metastasis occurred at the same time as the local recurrence. In 15 patients, chemotherapy was given as true adjuvant treatment and in 9 patients in response to the diagnosis of metastases. In the multivariate analysis, the grade ($p = 0.3$) and location of the tumor ($p = 0.5$) did not affect the metastases-free survival. The decade of diagnosis (1980s) was the only significant variable associated with an increased risk of metastases ($p = 0.03$, relative risk 2.5).

Discussion

7 of 218 tumors were reclassified as benign chondromas and 10 tumors as osteosarcomas, which illustrates the difficulty in evaluating and grading chondroid tumors. The distinction between enchondroma and chondrosarcoma is difficult (Healey and Lane 1986). In this study, 36% were grade 1, 59% grade 2, and only 6% grade 3 tumors among 194 patients. In contrast, Evans et al. (1977) reported 25% grade 3 tumors, which indicated that their grading system, based on mitotic activity differed from ours. However, Björnsson et al. (1998) and Pritchard et al. (1980) from the Mayo Clinic found a similar percentage of grade 3 chondrosarcomas as in this study but in Björnsson et al.'s study (1998) 61% were grade 1 tumors as compared to 36% in ours. This difference may be because our series is based on data from a national cancer register and not from a single referral center.

In our study, high tumor grade (grade 3) and patient age of 50 years or older proved to be independent indicators of a poor prognosis. The prognosis of patients with grade 1 and grade 2 tumors was similar, which suggests that this grading system is primarily of value in distinguishing between grade 3 tumors and the others. The grading system also predicted the occurrence of metastases, since grade 1 tumors were found to have a low tendency to metastasize. The importance of the grade in chondrosarcomas has also been shown by others (Pritchard et al. 1980, Sheth et al. 1996, Björnsson et al. 1998). Sheth et al. (1996) found that after surgical resection of pelvic chondrosarcomas, the prognosis of the patients was determined mainly by the tumor grade, which correlated with the frequency of a local recurrence. In our series of chondrosarcomas arising at different sites, the grade was not found to be of prognostic significance for local recurrence. Indicators of poorer than average prognosis have included high patient age, male gender, narrow surgical margins and tumor origin in the pubis (Evans et al. 1977, Kreicbergs et al. 1982, Sheth et al. 1996). On the other hand, Pritchard et al. (1980) did not find that the patient's age, gender or tumor location were statistically significant prognostic factors.

Our most interesting finding was the statistically significant reduction in the survival rate of chondrosarcoma patients diagnosed in the 1980s, when compared with those from the previous decade. The type of treatment and tumor biopsy before referral affect the recurrence rate (Kreicbergs et al. 1982, Mankin et al. 1982). We found that the national recommendations not to perform a biopsy of a suspected malignant bone tumor before referral had not been followed. The number of patients who had their tumors biopsied before referral did not decline with time. This alarming finding fortunately did not increase the local recurrence rate and did not affect the overall prognosis. Despite the recommendation by the Ministry of Social Affairs and Health of the Finnish Government, the surgical treatment of chondrosarcoma was not centralized since patients underwent operations in a total of 31 hospitals.

Chondrosarcomas are thought to be resistant to radiotherapy (Unni 1996). We observed, with multivariate analysis, that patients who were treated only by radiotherapy had a significantly worse survival than those treated by surgery. A simple explanation of this may be selection: radiotherapy was probably given to patients considered inoperable or to those who had large, high-grade lesions. Moreover, the fact that patients who were treated by surgery combined with radiotherapy had a significantly worse survival than those treated by surgery alone is probably due to differences in the patient characteristics.

Although the nationwide population-based Finnish Cancer Registry data have been successfully used for numerous studies of cancers, unfor-

tunately, information about the surgical margins used to treat the tumors or the size of the tumor is not available in the FCR. This is one of the disadvantages of the national register, which cannot be corrected afterwards. Although this information is available about some patients from their original hospital records, there is no reliable way to transfer this information retrospectively into a parameter which could be used for statistical analyses. A prospective study is needed to assess this. Such studies are facilitated by prospective registration, as initiated by the Scandinavian Sarcoma Group in 1986.

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