Joint Diseases and Related Surgery

Jt Dis Relat Surg
2022;33(2):440-448

ORIGINAL ARTICLE

Evaluation of prognostic factors affecting survival in chondrosarcoma treatment and comparison with literature

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Chondrosarcoma (CS) arising from chondrocytes producing cartilage tissue is one of the most common primary malignant bone tumors, with an estimated incidence of 200,000 per year.[1] Chondrosarcomas can be found in a wide range from low-grade tumors to aggressive and high-grade forms in terms of clinical presentation and prognosis. Although these types of tumors can occur sporadically, they may develop secondary to pathologies such as hereditary multiple exostosis, Ollier disease and Maffucci syndrome, based on pre-existing osteochondromas or multiple enchondromas.[2] In modern clinical practice, tumor grade, surgical stage, tumor size, and local recurrence are associated with the prognosis of CS. It is known that patients with metastasis at presentation usually have a poor prognosis.

Chondrosarcomas are relatively resistant to chemotherapy and radiotherapy (RT), and surgical excision is the definitive treatment method. It has

Received: June 04, 2022
Accepted: June 14, 2022
Published online: July 06, 2022

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Doi: 10.52312/jdrs.2022.526

Citation: Coşkun HS, Erdoğan F, Büyükceran İ, Dabak N. Evaluation of prognostic factors affecting survival in chondrosarcoma treatment and comparison with literature. Jt Dis Relat Surg 2022;33(2):440-448.

ABSTRACT

Objectives: The aim of this study was to identify the demographic characteristics of chondrosarcoma (CS) and prognostic factors affecting survival.

Patients and methods: A total of 87 patients (45 males, 42 females; median age: 51.3 years; range, 19 to 77 years) with CS treated in our clinic between January 2007 and June 2020 were retrospectively analyzed. Demographic characteristics, whether it was primary/secondary, tumor location, histopathological features, tumor grade and stage, clinical follow-up period, surgical treatment methods, use of radiotherapy and chemotherapy, and the presence of local recurrence and metastasis in the postoperative period were recorded. The relationship of these factors with prognosis was analyzed and survival rates were compared.

Results: Histological subtype, tumor grade, pathological stage and presence of metastasis were defined as independent predictors in both overall survival and disease-free survival analysis of CS. Overall and disease-free five-year and 10-year survival rates were found to be the highest in the clear cell chondrosarcoma group. While mortality increased in the first five years in the patient groups with histological Grade 2 and 3, all groups were followed in a balanced manner over time. The mortality rate in the group with metastatic disease (M2) was approximately four times higher than the other groups at 10-year follow-up. According to the surgical margins, we found that the five-year survival rates of the R1 (marginal resection) and R2 (residual tumor) groups were similar, with the highest rate being in the R0 (wide resection) group with 78.3%. In multivariate analysis, only grade and stage had a significant association with disease-specific survival. Surgical resection combined with adjuvant radiotherapy was found to increase survival in both overall and disease-free survival of patients with dedifferentiated chondrosarcoma compared to other treatments.

Conclusion: Histological subtype, grade, stage and presence of metastasis were the independent prognostic factors for survival in CS. However, marginal resection was a risk factor for local recurrence (LR), but there was no significant difference in overall survival in patients with or without LR. Although it is not significant, radiotherapy could increase survival in dedifferentiated CS variants.

Keywords: Chondrosarcoma, prognostic factors, survival, tumor.

been shown that the addition of adjuvant RT to surgery provides increased survival and better local control in cases localized in such critical locations, high-grade cases or cases with local recurrence.[3,4] Although chemotherapy has been proven to be largely ineffective on CS survival, the role of adjuvant chemotherapy remains unclear. There are reports that adjuvant chemotherapy can be used palliative in cases of unresectable or metastatic disease.[5]

In the present study, we aimed to identify the demographic characteristics of CS and prognostic factors affecting survival.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ondokuz Mayıs University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2007 and June 2020. A total of 87 patients (45 males, 42 females; median age: 51.3 years; range, 19 to 77 years) who were treated for CS were included. Using the hospital database, demographic characteristics, histopathological features of the tumor, tumor localization, clinical follow-up period, surgical and other treatment methods, and postoperative complications were recorded. The relationship of these factors with prognosis was analyzed and survival rates were compared.

Tumor location was divided into two categories: *(i)* axial (pelvis, spine, rib, scapula) and *(ii)* appendicular skeletal system. Low-grade tumors contain well-differentiated and moderately differentiated lesions (ICD-O-3 Class 1 and 2), while high-grade tumors include poorly differentiated, undifferentiated lesions (Class 3 and 4).[6] The staging was determined using the American Cancer Joint Committee (AJCC) staging system for bone sarcomas, and tumors were classified as a local, regional or distant disease (named M0, M1, and M2, respectively).[7] The margin was defined as R0 (wide resection) if there was healthy tissue around the lesion, R1 (marginal resection) if the surgical margin was microscopically contaminated but the tumor capsule remained closed, and R2 if residual tumor tissue remained.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median (min-max) or number and frequency. Demographic, clinical, tumor pathology and treatment variables were analyzed for their effects on survival using the log-rank test. Correlations between these categorical variables were made using the chi-square test. The Kaplan-Meier method was used to analyze the overall and disease-specific survival rates of five and

TABLE I
Demographic data of the patients

			Survival rate at 5 years	Overall survival	Disease free survival rate at 5 years	Disease free survival
Categories	n	%	%	*p*	%	*p*
Age (mean on year)				0.88		0.63
<50	49	56.3	73.4		78.0	
>50	38	43.6	76.3		77.1	
Sex (no. of patients)				0.92		0.65
Male	45	51.7	73.3		78.6	
Female	42	48.3	76.1		81.4	
Location (no. of patients)				0.24		0.41
Appendicular	63	72.4	76.2		83.3	
Axial	24	27.5	70.8		72.2	
Admission complaints				0.78		0.96
Pain	43	49.4	74.4		79.5	
Swelling with pain	38	43.6	79.8		82.3	
Pathological fracture	6	6.8	66.6		71.2	
Presentation type of cases				0.51		0.27
Primer CS	79	90.8	72.1		75.6	
Secondary CS	8	9.1	62.5		55.3	

CS: Chondrosarcoma.

10 years after the first diagnosis. A p value of <0.05 was considered statistically significant.

RESULTS

The median follow-up was 81.6 (range, 24 to 156) months. The patients followed for at least two years after diagnosis had 2, 5, and 10-year overall survival rates of 82.7%, 74.7%, and 71.2%, respectively, and disease-free survival rates of 93.1%, 82.7%, and 76.6%, respectively. The complaints of the patients were pain in 43 (49.4%) patients, pain and swelling in 38 (43.6%) patients, pathological fractures in six (7%) patients. The demographic data of the patients are given in Table I.

Since CSs typically occur in the adult age group and 40 to 70 years of age, the patients were divided into age groups under 50 years of age and over to investigate the prognostic significance of age. Sex and age did not significantly affect the survival prognosis (p>0.05).

The tumor was localized in the appendicular skeleton in 63 (72.4%) patients and in the axial skeletal system in the remaining 24 (27.5%) patients. The upper extremity was involved in 18 cases (humerus 9, ulna 1, hand 8), and the lower extremity in 45 cases (femur 32, tibia 8, fibula 2, foot 3). Eighteen patients had the lesion in the trunk (vertebrae 9, scapula 6, ribs 3), and six in the pelvis. The patients with axial

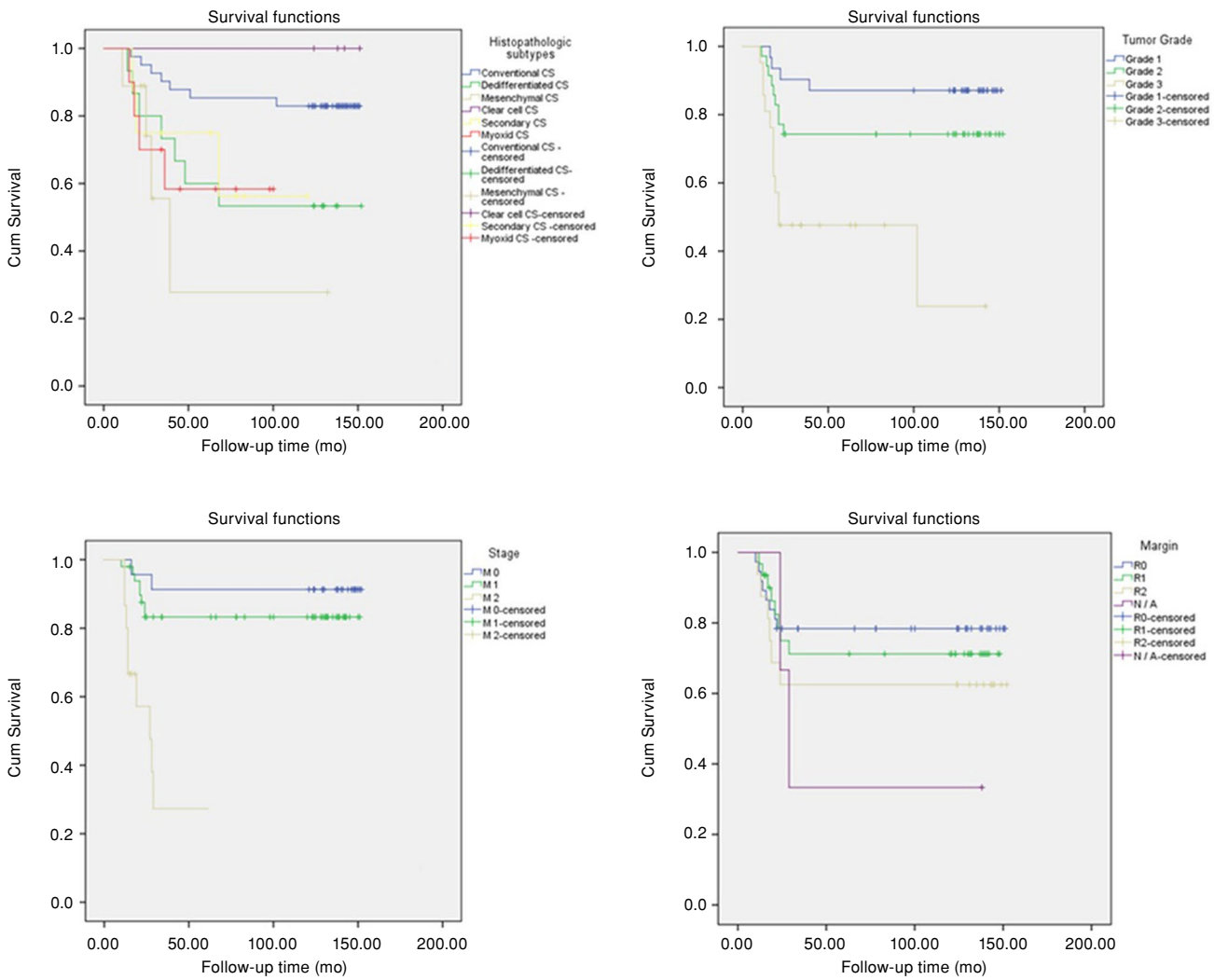

FIGURE 1. (a) Overall survival rates of patients with chondrosarcoma according to histological subtypes. **(b)** Overall survival rates of patients with chondrosarcoma according to tumor grade. **(c)** Overall survival rates according to the AJCC staging system. **(d)** Overall survival rates according to margin status.
AJCC: American Cancer Joint Committee.

skeletal localization had a lower survival rate than the appendicular-localized group, while there was no significant difference in survival between the two groups in terms of tumor localization (p>0.05).

When classified according to histopathological subtypes, 41 conventional, 15 dedifferentiated, 10 myxoid, nine mesenchymal, and four patients had clear cell CS. Secondary CS was defined in eight patients, five of which developed on the basis of solitary osteochondroma and three of them inherited multiple exostosis.

During follow-up, the highest overall survival rates were determined in conventional and clear cell CS groups (82.9% and 100%, respectively), and dedifferentiated and mesenchymal CS were associated with a worse survival rate (53.3% and 55%, respectively) (Figure 1a) (p>0.05). When the cases were analyzed for the presence of primary or secondary CS, the overall survival rates of five and 10 years were 74.6% and 72.1% in the group with primary disease, while it was 75% and 62.5% in the group with secondary disease, respectively. Therefore, no significant difference was observed between the survival rates (p<0.05).

Grade 1 and 2 tumors (n=31 and n=35) were grouped as low-grade lesions and Grade 3 tumors (n=21) were grouped as high-grade CSs. According to the AJCC staging system, 23 patients were classified as M0, 49 patients as M1, and 15 patients as M2. Data regarding histological subtype, stage, and grade are given in Table II. High tumor grade had a statistically significant negative effect on both overall and disease-free survival (p<0.05).

Overall survival rates were 87% and 71.4% in the Grade 1 and 2 groups, respectively, while this rate was only 47.6% in the Grade 3 group. Overall survival rates by tumor grade are shown in Figure 1b.

Overall survival rates of patients with localized disease (M0) and regional disease (M1) according to the AJCC staging system were similar (80.9% and 67.3%, respectively). In the group with metastatic disease (M2), a significant decrease in survival was detected with a rate of 26.6% (p<0.05) (Figure 1c).

TABLE II
Histological subtype, stage and grade of the patients

			Survival rate at 5 years	Overall survival	Disease free survival rate at 5 years	Disease free survival
Categories	n	%	%	*p*	%	*p*
Histological subtypes of primary chondrosarcomas*				0.08		0.35
Conventional	41	47.1	85.3		83.9	
Dedifferentiated	15	17.2	60.0		63.4	
Myxoid	10	11.4	60.0		65.0	
Mesenchymal	9	10.3	55.5		59.6	
Clear cell	4	4.5	100		75.0	
Grade				0.03		0.35
Grade 1	31	35.6	90.3		93.1	
Grade 2	35	40.2	74.2		78.2	
Grade 3	21	24.1	52.3		56.7	
Stage (AJCC)				0.01		0.04
M0	23	26.4	91.3		93.7	
M1	49	56.3	79.5		81.4	
M2	15	17.2	33.3		36.3	
Metastasis				0.01		0.03
Yes	8	9.1	25.0		31.2	
No	79	90.8	79.7		84.9	
Local recurrence				0.56		0.67
Yes	17	19.5	70.5		73.8	
No	70	80.5	74.2		78.6	

AJCC: American Cancer Joint Committee; * Histologic subtypes of secondary chondrosarcomas were not given in the table.

TABLE III
Treatment management

Categories	n	%	Survival rate at 5 years %	Overall survival p	Disease free survival rate at 5 years %	Disease free survival p
Surgery				0.01		0.03
Performed	84	96.5				
Not performed	3	3.4				
Margin status				0.08		0.26
R0	37	42.5	78.3		81.5	
R1	31	35.6	77.4		79.1	
R2	16	18.3	68.7		72.8	
N/A	3	3.4	66.6		33.3	
Radiation treatment				0.01		0.31
Yes	17	19.5	64.1		67.2	
No	70	80.4	80.0		83.6	
Chemotherapy				0.74		0.65
Performed	3	3.4	66.6		70.2	
Not performed	84	96.5	76.1		81.5	

N/A: Patients followed-up without surgical intervention.

After the diagnosis, 76 (87.3%) patients underwent limb salvage surgery and eight (9.1%) patients received amputation. In the limb salvage surgery group, prosthetic reconstruction was performed after tumor resection or the cavity was filled with cement after curettage + cryotherapy. A reconstruction with modular endoprostheses was performed after resection in 30 (34.4%) patients. Palliative treatment in the form of adjuvant chemotherapy and RT was applied to three (3.4%) patients with unresectable disease.

Resection margins were R0 in 37 (42.5%), R1 in 31 (35.6%) and R2 in 16 (18.3%) patients. Surgical margin status did not significantly affect overall or disease-free survival regardless of tumor grade or location (p>0.05). Although we found a high survival rate in the R0 group, our results were very close to being statistically significant (p=0.08). Survival rates by surgical margin are shown in Figure 1d. During follow-up, isolated lung metastasis in five patients, lung + brain metastasis in two patients, and lung + liver metastasis in one patient developed metastasis in eight patients and local recurrence in 17 (19.5%) patients. A total of 25 patients, seven with metastases and 12 with local recurrence, died during follow-up due to thromboembolic events, multiple organ failure, sepsis, and ileus.

TABLE IV
Multivariate analysis

Categories	n	Hazard ratio	95% Confidence interval	p value
Grade				
Low grade	66	Reference group	Reference group	Reference group
High grade	21	3.4	2.8 to 4.1	<0.05
Stage				
M0	23	Reference group	Reference group	Reference group
M1	49	1.9	1.6 to 2.4	<0.05
M2	15	5.8	4.5 to 7.5	
Metastasis				
No	8	Reference group	Reference group	Reference group
Yes	79	0.9	0.7 to 1.5	0.13

Adjuvant chemotherapy was applied in three cases with mesenchymal CS with pelvis and vertebral involvement with an unresectable mass. All patients received doxorubicin in combination with cisplatin. High-dose (75 Gy) radiation therapy was given to three patients who received chemotherapy and 14 patients with positive margins after resection to ensure local control. Treatment data are given in Table III.

Although 70.6% of the patients with local recurrence died during the follow-up, the effect of local recurrence on overall survival was not significant ($p>0.05$). We found that the possibility of mortality and recurrence was higher in the first two years in the group with positive surgical margins, but there was no significant change in recurrence rates in the following follow-up periods ($p>0.05$). While 10-year overall survival rate was 77.2% in patients with no metastasis development, this rate was 12.5% in patients with metastasis. This dramatic decrease was statistically significant ($p<0.05$).

All patients with unresectable tumors in the pelvis and vertebral region who were given adjuvant chemotherapy for palliation died during the follow-up. Although chemotherapy given for palliation had no significant effect on survival ($p>0.05$), we could not evaluate the effect on survival in these patients, as it was not given to patients who underwent surgery.

To achieve local control, 14 patients with positive margins after resection and three patients with unresectable tumors were given RT for palliation. The survival rates of patients who were diagnosed histopathologically with dedifferentiated CS after resection decreased (16% vs. 77%) in the group that received RT compared to the group not given RT, regardless of tumor size or localization ($p>0.05$). On the contrary, no effect of RT was found in mesenchymal CS. However, the survival rate of all patients who received RT was three times lower than the group that did not receive RT, and there was no effect of RT on survival ($p<0.05$). Among the parameters evaluated, histological subtype and grade, surgical stage and metastasis were found to be independent determinants of survival ($p<0.05$) (Table IV).

DISCUSSION

Chondrosarcoma is the second most common primary malignant tumor of bone.[8] Investigation of demographic variables and prognostic factors of this rare tumor has been often limited to small institutional experiences.[1,9-11]

In a study based on the Surveillance, Epidemiology, and End Results (SEER) data, higher survival was found in the appendicular skeletal localization compared to the axial.[1] Nota et al.[12] also reported that survival rate was lower in axial + pelvis involvement compared to other groups. In our study, we could not find that tumor location clearly had a prognostic effect.

It is well known that most cases of secondary CS are low to moderate, distant metastasis is rare, and the prognosis is good for most patients. Overall survival at five years has been reported in the literature to be approximately 76 to 90%.[9,13] Tsuda et al.[14] found a 10-year disease-free survival rate of 89.4% in their study, which included a small case series. However, it is noteworthy that approximately 40% of local recurrence cases are localized in the pelvis. Although we found no significant difference in terms of survival compared to primary CS in our study, our survival rates are consistent with this result.

In our study, 10-year survival rates in dedifferentiated and mesenchymal CS cases were 53.3% and 55%, respectively. This may be due to the fact that these two tumor variants, which have a worse survival rate, are associated with a high-grade tumor percentage (73% for dedifferentiated CS and 70% for mesenchymal CS; $p<0.05$). Amer et al.[11] found a five-year survival rate of 37.6% and 11.3% for mesenchymal and dedifferentiated CSs, respectively. Giuffrida et al.[1] reported in their large case series study that the relative five-year survival rates for traditional and mesenchymal CS were 93% and 48%, respectively. The results of our study are similar to the literature. However, despite the 100% survival rate in the clear cell CS group ($n=4$), it can be considered that it would not be considered sufficient for comparison. In the literature, although there are differences in the survival rates of clear cell CS, which is rare, it has been shown in many studies that it has the highest survival rates (Amer et al. 62.3%; Guiffrida et al. 100%).[1,11,15]

When the groups with localized disease (M0) and regional disease (M1) were evaluated together according to the AJCC staging system, we found that the mortality rates were approximately five times lower in the 10-year follow-up than the group with metastatic disease (M2). Giuffrida et al.[1] found that patients with localized disease (M0) had twice the 30-year survival rate of those with regional disease (M1) (43% *vs.* 22.30%). In patients with metastatic disease (M2), this rate was reported to be less than 10%, and local surgical stage was found to be associated with a significant disease-specific survival benefit.[1] These findings in our study are similar to those of other studies in the literature.[16,17]

In our study, accelerated mortality was observed in the first five years in patient groups with histological Grade 2 and 3, but the survival rate remained constant in subsequent follow-up. In Grade 1 group, there was a more gradual decrease in the survival rate over time. Although this is a predictable result, in the meta-analysis study of Nota et al.[12] reported five-year survival for Grade 1 CS ranged from 82% to 99%, and 10-year survival ranged from 89 to 95%. In Grade 2 CS, five-year survival was between 63% and 92%, and 10-year survival was between 58% and 86%. In Grade 3 CS, five-year survival was between 0% and 77%, and 10-year survival was reported between 0 and 55%. In this respect, our results are similar to the literature.[11,18]

When the relationship between surgical margin conditions and tumor grade is examined, the surgical margin of most Grade 1 cases was R0 and it was usually distributed as R1 and R2 in Stage 2-3 cases. Therefore, although the survival rate of the R0 group was higher than the others, no statistically significant difference was found ($p=0.08$). There are reports in the literature containing contrasting results in terms of the effect of surgical margin on survival.[16,17,19,20] Laitinen et al.[20] found that the local recurrence-free survival rate was significantly reduced in patients who underwent wide excision compared to intralesional margins. Andreou et al.[17] reported that the surgical margin did not reach statistical significance in terms of local recurrence and survival. The R2 surgical margin increased the risk in terms of local recurrence and was an independent risk factor ($p<0.05$). Similarly, it was found to have a slight effect on metastasis ($p>0.05$). Therefore, it can be thought that paying attention to the surgical margin during surgery would be important to reduce mortality and morbidity in high-grade cases.

In our study, RT was found to be a risk factor for CSS. We revealed that patients treated with RT had shorter survival times. The reason for this result can be attributed to the high-grade disease and axial skeletal localization, as they tended to have larger tumor extensions compared to the non-RT group. However, the therapeutic effect of RT was controversial in previous studies. Amer et al.[11] reported that, although radiation therapy was associated with reduced survival rates, there was no statistically significant difference between subtypes. Söderström et al.[21] found that patients who received RT were high-grade cases with wide extension to soft tissues, with a decrease in survival rates. Krochak et al.[22] found that RT had limited efficacy.

A diagnosis of dedifferentiated or myxoid CS was present in all patients who received RT, most of whom had high grade tumors. Regardless of the surgical margin status or localization, the overall survival rate was 77% in the group that received RT in patients with a diagnosis of dedifferentiated CS, and only 16.6% in the group that was not given. On the other hand, the overall survival rates in myxoid CS were found to be approximately the same (40%), and it was observed that there was no effect. Although not statistically significant, this may suggest that combining adjuvant RT with surgery may be a good option in dedifferentiated CS. Similar to our findings in the literature, Gao et al.[3] showed that RT was an independent protective factor and that adjuvant RT combined with surgery could improve both overall survival and cancer-specific survival of patients with high-grade myxoid and undifferentiated CS.

Although there are reports in the literature that it can be used in some variants of CS,[15,23] the role of chemotherapy in the treatment of local or advanced CS remains unclear. Italiano et al.[23] reported that conventional chemotherapy had very limited efficacy in patients with advanced CS and that it is in mesenchymal and dedifferentiated CS that sees the greatest benefit. Gelderblom et al.[15] considered that it was probably effective only in mesenchymal CS and that its therapeutic value in dedifferentiated CS was uncertain. Although we applied chemotherapy + RT for palliation in our three patients with unresectable tumors, we found that it did not affect the survival rates. In our study, statistical power could not be provided for this variable. Since chemotherapy is not routinely used in patients with metastatic or non-metastatic CS and is considered an adjuvant therapy for advanced CS, its therapeutic effect seems to need to be confirmed by clinical trials.[8]

In our study, metastatic disease and development of metastases were found to be independent risk factors. Tumor localization did not differ in terms of distant metastasis development and survival. In addition, we found that metastasis development was more common after resection of relatively large tumors that did not provide sufficient statistical power. Although metastatic disease has been reported as a prognostic factor by many authors in the literature,[24,25] there is no evaluation in terms of tumor size and its threshold value. Although we consider the small scale of our study as a limiting factor, we predict that minimizing the possibility of metastasis and local recurrence would have an effect on long-term survival.

Many studies on CS have revealed inconsistent data. We believe that there may be many reasons for this. The first is that these studies were usually done in single-center and small groups. Second, due to the subjectivity of the existing grading system, pathologists may have different reports during the histopathological evaluation of CS. This may lead to individual and institutional differences in the determination of histological degrees, and there are studies on this subject.[26] Third, there may be variability in the results of CS, which may show histopathological heterogeneity, depending on whether the biopsy samples were taken while making the diagnosis are taken properly.[27] The fourth and last is that it can be confused with benign lesions in the diagnosis of some low-grade CS, such as enchondroma. This may lead to a misdiagnosis of the patient and then a difference in treatment management.[28] Although the distinction between low-grade CS and benign chondroid tumors has been extensively investigated, there is low reliability in clinical or radiological distinction, as well as low reliability in such histological grading, even among experienced bone tumor clinicians and pathologists.[29] In addition, a standard management guide has not been published yet. It is important to differentiate low-grade CS in his diagnosis due to its similarity with benign lesions, and the multidisciplinary approach of radiologist, surgeon, and pathologist is important in diagnosis and treatment.[30]

There are several limitations to our study. First, this is a retrospective study. Second, although many variables are included, we have a relatively small sample size and, therefore, statistical power cannot be provided for some variables.

In conclusion, we attempted to focus on the changes that may affect survival in patients with CS. As we mentioned earlier, we found that the factors affecting prognosis in the surgery of CS were histological type, grade, surgical stage and metastasis. The mean survival time of patients in the differentiated CS groups was significantly lower compared to other groups. Local recurrence is associated with a marginal resection. The presence or absence of local recurrence does not affect the overall survival rate. Based on these findings, our study shows that adjuvant RT combined surgery can improve the survival of patients with dedifferentiated CS. Currently, the primary treatment method of CS is surgery, and despite all the advances in RT and chemotherapy, no significant evidence has been provided in the treatment. However, there is a universal consensus that a new treatment management is required.

Acknowledgements: The authors thank them for the support of our department secretary and our ethics committee, who assisted in collecting data from the hospital database and official authorization for the study.

Ethics Committee Approval: This study was found ethically appropriate by the Ondokuz Mayıs University Clinical Research Ethics Committee (date: 17.07.2020, no: 2020/413). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: N.D., H.S.C.; Design: N.D., H.S.C., F.E.; Control/supervision: N.D.; Data collection and/or processing: F.E., H.S.C.; Analysis and/or interpretation: F.E., H.S.C., İ.B.; Literature review: İ.B., F.E.; Writing the article: F.E., H.S.C.; Critical review: N.D.; References and fundings: İ.B.; Materials: İ.B., F.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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