■ ONCOLOGY

Grade 2 central chondrosarcoma treated by intralesional curettage: observation or surgery?

A MULTICENTRE RETROSPECTIVE STUDY

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Aims

The most appropriate management of patients who have undergone curettage for a suspected low-grade chondrosarcoma (CS), which has subsequently been found to be of grade 2, remains unknown. We aimed to assess whether these patients have an increased risk of local recurrence and distant metastasis if followed up over time, compared to those who undergo further treatment soon after the diagnosis has been established.

Methods

A retrospective study was undertaken which included 71 patients treated between January 2010 and December 2022 by intralesional curettage for a supposed low-grade CS, but who subsequently proved to have a histological grade 2 CS. Thereafter, patients either underwent further surgery (resection group) or follow-up (follow-up group).

Results

The estimated local recurrence rate was 36.8% at five (95% CI 35.6 to 38.0) and 48.1% at ten years (95% CI 46.4 to 49.8), and was significantly higher in the follow-up group (48.4%, 95% CI 45.4 to 51.4) than in the resection group (9.6%, 95% CI 8.1 to 11.1) at five years ($p = 0.005$). Locally recurrent CS, considered as a time-dependent covariate, had an increased risk of metastasis (36.8% vs 2.5% at five years; $p < 0.001$) and a worse disease-specific survival (81.3% vs 100% at five years; $p = 0.007$).

Conclusion

The optimal treatment strategy should be individualized based on the histological features of the tumour, tumour location, morbidity of resection, and patient-specific factors. We recommend that patients who have undergone unplanned surgery be treated in the standard manner. Observation may be appropriate in specific cases with a properly informed patient.

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Introduction

Central chondrosarcoma (CS) is a malignant matrix-producing cartilage tumour.[1] It can vary in behaviour from a low-grade, slowly growing lesion with negligible metastatic potential to a highly aggressive, invasive, and metastasizing tumour. The WHO 2020 classification distinguishes between low-grade conventional CS (grade 1/atypical cartilaginous tumour) and high-grade (grades 2 and 3) CS.[2–5] Notably, there is consensus that the histological grade is one of the major determining factors for outcome.[6]

CS is essentially resistant to radiotherapy and chemotherapeutic regimens: surgical resection remains the mainstay of treatment.[7] For low-grade CS, intralesional curettage with or without various adjuvants is usually sufficient, whereas wide resection is recommended for higher-grade lesions.[8] Consequently, preoperative differentiation between low-grade and high-grade CS is of the utmost importance, as it informs the choice of the most appropriate treatment.

Preoperative assessment depends on the histology, imaging features, and location of the

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Table I. Patient characteristics.

Characteristic	Overall	Follow-up	Resection	p-value
Patients, n	71	49	22	
Median age, yrs (IQR)	45 (35 to 57)	49 (37 to 59)	42 (34 to 53)	0.098*
Sex, n (%)				0.148†
Male	37 (52.1)	23 (46.9)	14 (63.6)	
Female	34 (47.9)	26 (53.1)	8 (36.4)	
Localization, n (%)				0.189†
Digital (hand and foot)	10 (14.1)	6 (12.2)	4 (18.2)	
Diaphysis	9 (12.7)	7 (14.3)	2 (9.1)	
Meta-epiphysis	48 (67.6)	32 (65.3)	16 (72.7)	
Girdles	4 (5.6)	4 (8.2)	0	
Median length, mm (IQR)	50 (34 to 78)	54 (36 to 86)	45 (33 to 64)	0.066*

*Mann-Whitney U test.
†Chi-squared test.

Table II. Treatment characteristics.

Characteristic	Overall	Follow-up	Resection	p-value
Patients, n	71	49	22	
Median follow-up, mths (IQR)	70 (46 to 120)	74 (49 to 121)	67 (46 to 122)	0.441*
LR, n (%)				0.002†
Yes	28 (43.5)	25 (51.0)	3 (13.6)	
No	43 (56.5)	24 (49.0)	19 (86.4)	
Surgical treatment of LR, n (%)				0.764†
Curettage	4 (14.3)	4 (16.0)	0	
Amputation	4 (14.3)	4 (16.0)	0	
Resection	18 (64.3)	15 (60.0)	3 (100)	
None	2 (7.1)	2 (8.0)	0	
Distant metastasis, n (%)				0.082†
Yes	11 (15.5)	10 (20.4)	2 (9.1)	
No	60 (84.5)	39 (79.6)	20 (90.9)	
Status at follow-up, n (%)				
DOC	1 (1.4)	1 (2.1)	0	0.206†
DOD	10 (14.1)	8 (16.3)	2 (9.1)	
NED	60 (84.5)	40 (81.6)	20 (90.9)	

*Mann-Whitney U test.
†Chi-squared test.
DOC, died of other causes; DOD, died of the disease; LR, local recurrence; NED, no evidence of the disease.

tumour. However, even with diligent clinical practice and advanced radiological and histological techniques, the diagnosis can be difficult.[9,10] Imaging may help to differentiate a low-grade from a high-grade CS by identifying particular imaging characteristics, such as endosteal scalloping and erosion, soft-tissue components, and myxoid component among others.[11-14] Biopsy suffers from sampling errors and discrepancies in tumour grading even between specialized bone tumour pathologists.[15,16] The morphological heterogeneity of cartilaginous tumours can be broad and high-grade areas can be focally present. The correct diagnosis of the grade of a chondroid lesion from needle biopsy material can only be made in between 36% and 86% of cases, compared with the diagnosis after resection of the lesion.[17-19] Consequently, there is a considerable risk of undergrading these tumours,[18,20,21] thereby potentially resulting in the unplanned curettage of grade 2 CS.[22,23] The most appropriate management of these patients remains unknown.[24]

This multicentre retrospective study aimed to assess whether patients who had undergone an unplanned curettage of what proved to be a grade 2 CS had an increased risk of local recurrence (LR) and distant metastasis (DM) if followed up over time, compared to those who were treated further soon after the diagnosis.

Methods

Participants. All members of the European Musculoskeletal Oncology Society (EMSOS) were invited to participate in this study. The inclusion criteria for the study were patients treated between January 2010 and December 2022 who had undergone an intralesional curettage for a supposed low-grade CS. Only patients who had a definitive histological diagnosis of grade 2 CS with a follow-up ≥12 months were included. Patients with CS localized to the spine (n = 4) were excluded due to the inability to perform a wide resection. All consecutive patients meeting the inclusion criteria were included. Institutional Review Board approval was obtained at each participating centre before the start of the study.

Patient characteristics. A total of 71 cases were collected from 15 referral centres. The median age of the patients at the time of surgery was 46 years (IQR 35 to 57). Most tumours were in

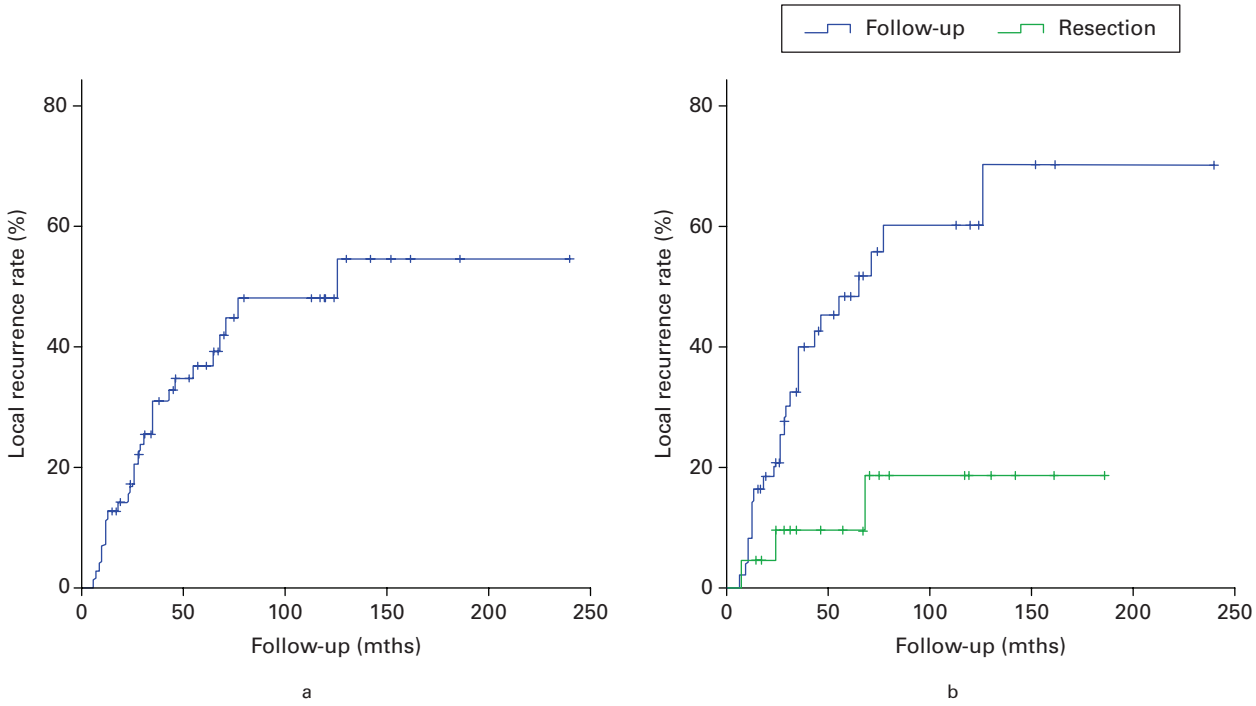

Fig. 1

a) Kaplan-Meier local recurrence (LR) curve. b) Kaplan-Meier LR curve according to the type of second treatment.

the femur (n = 27; 38.0%), tibia (n = 12; 16.9%), and humerus (n = 15; 21.1%), with no significant differences between the follow-up and resection groups (p = 0.589, chi-squared test). The two groups were homogeneous at baseline (Table I). However, patients in the follow-up group tended to be older with larger tumours at the time of diagnosis. Tumours in the limb girdles and bony diaphyses were more common in the follow-up group.

Diagnosis and radiography. At each centre, the suspicion of a low-grade CS was determined by a multidisciplinary team (MDT), taking into account MRI assessment, which included tumour growth, cortical destruction, endosteal scalloping, periosteal reaction, relation to the cortex, and perilesional bone marrow oedema.[25] In nine cases, the suspicion was based on both MRI and preoperative biopsy. Eight patients reported pain at the time of diagnosis. Size was measured as the greatest diameter of the tumour on radiographs, CT, or MRI carried out before intralesional surgery.

Resection specimens were examined by specialized bone sarcoma pathologists at each participating centre for grade assessment. The highest grade seen on histology was the grade recorded, even when this higher grade consisted of a small number of cells. After receiving the diagnosis of a grade 2 CS on the surgical specimen, patients either underwent further surgery ('resection group') or follow-up ('follow-up group'). A case-by-case decision was made, taking into account the site and size of primary tumours, preoperative imaging, and possible morbidity of further surgery.[26] In the resection group, all secondary procedures were carried out within four months of intralesional surgery.

Statistical analysis. Quantitative data are summarized by frequencies and percentages for categorical variables; continuous variables are reported as median and IQR. The chi-squared test was used to compare variables between groups, and the Mann-Whitney U test for medians between groups.

The Kaplan-Meier method was used to estimate LR, DM, and disease-specific survival (DSS) rates. LR rate was defined as the time between the first surgery (curettage) and the first LR or the last follow-up available, whichever came first. DM rate was defined as the time between the first surgery (curettage) and the first DM or the last follow-up available, whichever came first. Similarly, DSS interval was defined as the time between surgery and death because of the disease or the last follow-up available, whichever came first. Patients who died from other causes were censored. Differences in survival rates were assessed using the log-rank test. Significance was set with p-values < 0.05 in all statistical analyses, which were completed using SPSS Statistics v. 22.0 for Windows (IBM, USA).

Results

Prophylactic plate osteosynthesis was undertaken in nine cases during index curettage; eight of these were in the follow-up group. Prophylactic osteosynthesis was more frequent with larger tumours.

In the resection group, the median time to second surgery was 2.0 months (IQR 1.0 to 3.5). Overall, the median follow-up was 70 months (IQR 46 to 120). LR was observed in 28 patients (39.4%) of the whole cohort after a median 27 months (IQR 12 to 45). Most of the local recurrences were seen in the follow-up group (p = 0.002, chi-squared test) (Table II).

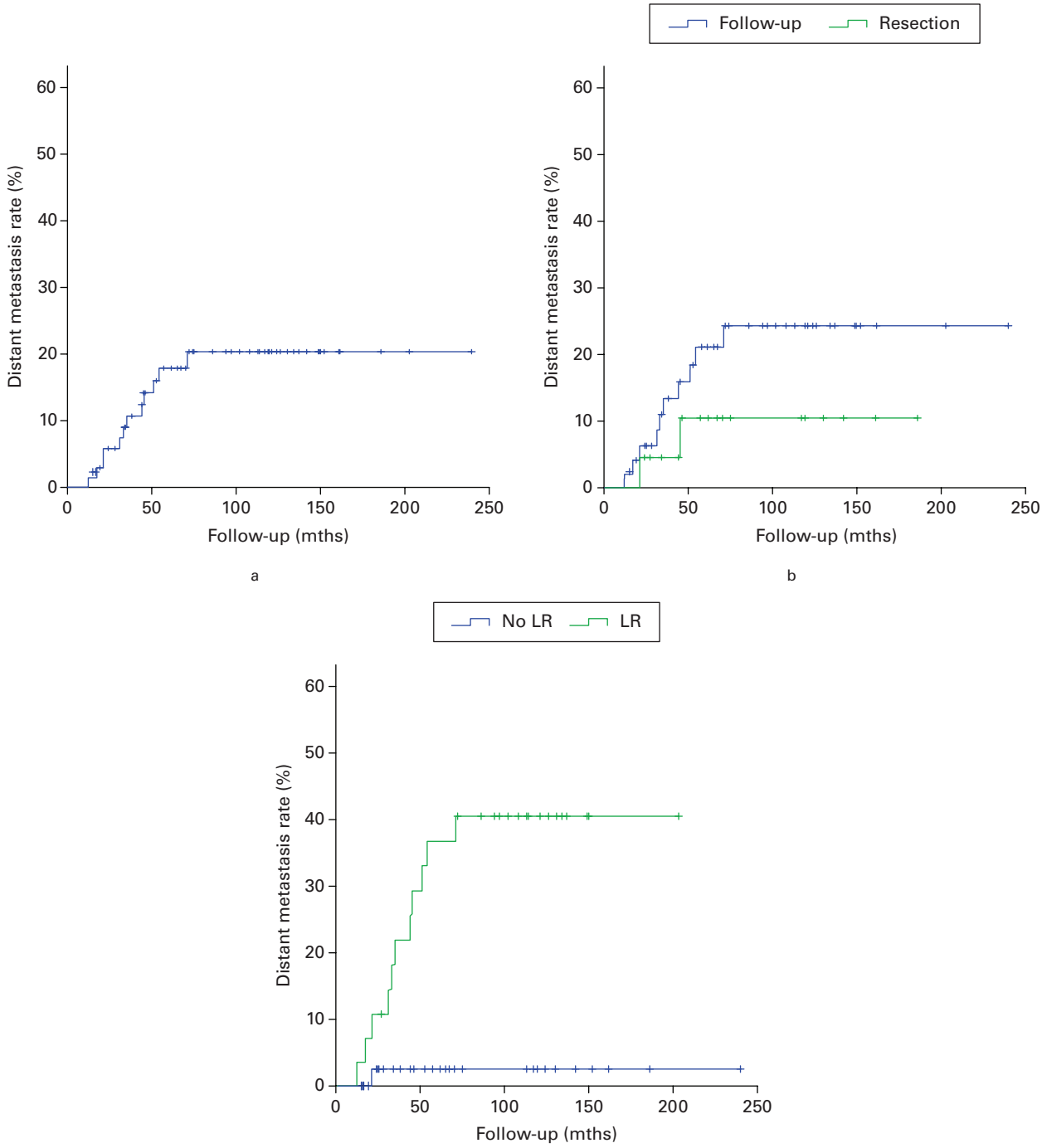

Fig. 2

a) Kaplan-Meier distant metastasis (DM) curve. Kaplan-Meier DM curve according to b) the type of second treatment and c) local recurrence.

Kaplan-Meier analysis with LR as a primary endpoint showed an estimated LR rate of 36.8% at five (95% CI 35.6 to 38.0) and 48.1% at ten years (95% CI 46.4 to 49.8) (Figure 1a).

A significantly higher risk of LR was seen in the follow-up group (48.4%, 95% CI 45.4 to 51.4) compared to the resection group (9.6%, 95% CI 8.1 to 11.1) at five years ($p = 0.005$, Kaplan-Meier analysis) (Figure 1b). This was confirmed by excluding digits and girdles from the survival analysis (LR rate at five years 44.4% in the follow-up group, compared to 11.9% in the resection group; $p = 0.024$, Kaplan-Meier analysis).

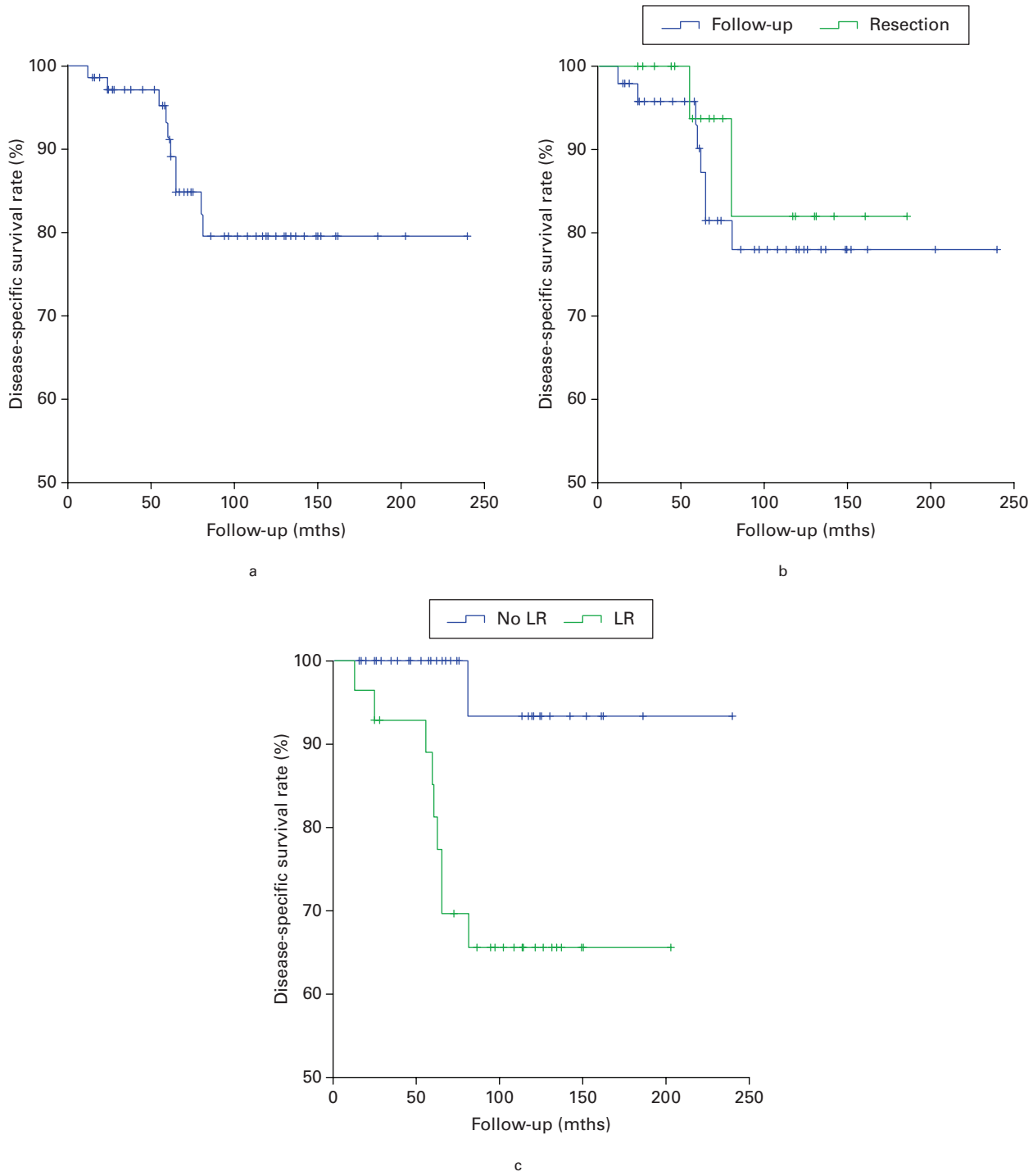

Fig. 3

a) Kaplan-Meier disease-specific survival (DSS) curve. b) and c) Kaplan-Meier DSS curve according to b) the type of second treatment and c) local recurrence.

Patients who underwent plating at the same time as the initial operation did not show an increased risk of LR (p = 0.876, Kaplan-Meier analysis).

Surgical treatment of recurrences included curettage in four patients (14.3%), amputation in four (14.3%), and resection in 18 (64.3%). Two patients had no local treatment of their LR because of metastatic disease and only received palliation chemotherapy. The histology of the LR was available in 23 out of 28 patients (82.1%). In all of them, the grade was the same as seen in the initial curetted specimen. Further recurrences were

seen in all four curetted patients and in four of the 18 resections (22.2%).

Overall, DM rate was 17.9% (95% CI 16.9 to 18.9) at five years and 20.4% (95% CI 19.3 to 21.5) at ten years. This was higher in the follow-up group than in the resection group (21.2% (95% CI 19.0 to 23.4) and 10.5% (95% CI 8.5 to 12.5)), although not statistical significance (p = 0.170, Kaplan-Meier analysis) (Figures 2a and 2b). A comparable DM rate was found by removing digits and girdles from analysis (14.1% in the follow-up group compared to 12.8% in the resection group at five years; p = 0.661, Kaplan-Meier analysis).

Kaplan-Meier analysis with DSS as a primary endpoint showed an estimated survival rate of 91.2% (95% CI 90.3 to 92.1) at five years and 79.5% (95% CI 78.3 to 80.7) at ten years. DSS was similar between the follow-up and the resection groups (90.1% (95% CI 88.0 to 92.2) and 93.8% (95% CI 91.3 to 96.3) at five years, respectively; p = 0.448, Kaplan-Meier analysis) (Figures 3a and 3b). Comparable DSS were also found by limiting survival analysis to diaphyseal and metaphyseal tumours (7.7% (95% CI 6.8 to 8.6) in the resection group, 9.1% (95% CI 8.0 to 10.2) in the follow-up group at five years; p = 0.659, Kaplan-Meier analysis).

Locally recurrent CS, considered as a time-dependent covariate, had an increased risk of DM (36.8% (95% CI 35.2 to 38.4) vs 2.5% (95% CI 1.8 to 3.2) at five years; p < 0.001) and a worse DSS (81.3% vs 100% at five years; p = 0.007, Kaplan-Meier analysis) (Figures 2c and 3c).

Discussion

Surgical resection remains the mainstay of the treatment of central CS, as these tumours do not respond to chemotherapy and radiotherapy.[27] With low-grade central CS, the risk of LR and metastasis is low; consequently, marginal or intralesional surgical margins are deemed to be acceptable.[6,7,28] On the other hand, it is generally accepted that wide margins are needed in high-grade CS. Nevertheless, due to the difficulties in the preoperative grading of CS, it may be that a curetted lesion preoperatively assessed as grade 1 CS eventually proves to be of histological grade 2.[22,23] In such cases, whether the surgeon should immediately reoperate to achieve clear margins or observe the patient and intervene if isolated LR occurs is controversial.[24]

The main finding of the present study was significantly better local control in patients who underwent resection soon after the definitive diagnosis of grade 2 CS.[29,30] The benefit of further resection may have been enhanced by the very short interval between intralesional curettage and second surgery, as all initial operations had been carried out at the same referral centres. An increased risk of LR in grade 2 CS with a previous intervention had been suggested by Puri et al.[31] In their series, which included 14 CS patients (tumour grade was not specified) with a previous intervention, either in the form of an open biopsy or a curettage/unplanned excision at a non-specialist centre, they reported a LR rate of 36%. Recently, Stevenson et al[32] reported a LR rate of 60% in grade 2 CS treated with a surgical margin < 1 mm, compared to 20% if margins were > 2 mm, thereby highlighting an increased risk of recurrence if a grade 2 CS is removed inappropriately. The LR risk in the resection group of this series highlights that, even if previously inadvertently curetted, a subsequent resection can give excellent local control, comparable to that in patients initially treated by primary wide resection.

The real risk of extensive curettage is that it may spread tumour cells locally and facilitate local tumour recurrence. Therefore, while an intralesional margin in a true grade 1 CS is acceptable, it remains critical to observe oncological orthopaedic principles so as not to compromise any subsequent surgery if a lesion is subsequently found to be of higher grade. Moreover, whenever plating is deemed necessary, it should be done in a way to minimize contamination: furthermore, it may require a wide resection of the entire plate to truly achieve an uncontaminated field at the time of second surgery. Also, a careful grading of definitive specimens is mandatory, to identify patients who may require further treatment. The grade of CS should be defined by the highest grade seen in the specimen regardless of how small the area of involvement.[33]

The survival rate in this series was comparable to the highest DSS rates reported in the literature for grade 2 CS.[6,34] It is likely that the grade 2 CS for which a curettage was attempted had very few aggressive features. Recently, it has been reported that in a series of patients with an intraosseous CS, none developed metastatic disease.[34,35] Nevertheless, we confirm that local failure might be a prelude to distant disease and a risk factor for survival.[31,36,37] Minimizing LR by achieving wide surgical margins is the only surgically modifiable prognostic factor.[38] In patients without metastases at the time of detection of LR, further radical surgical treatment gives a good chance of long-term cure.

This study has certain limitations. A retrospective review introduces several forms of bias by its inherent heterogeneity and lack of control or randomization. In particular, such a multicentre series might have introduced some heterogeneity in terms of the absence of central pathological and radiological review. Histological grading can be difficult due to the heterogeneity of chondroid material within individual tumours, leading to discrepancies as a result of sampling errors within tumours, and disagreement between pathologists. Despite extensive experience in CSs, histopathological grading remains difficult with the possibility of misdiagnosis. Moreover, the rationale behind the initial treatment decision could not always be retrieved from the patient records. Also, the lack of a standardized curettage technique (with or without burring and local adjuvants) as well as the choice of resection/follow-up can introduce potential bias.

However, this is the first series with a long median follow-up which has directly investigated the outcome of unplanned curetted grade 2 CS. Since the risk of LR is nearly 50%, it is appropriate to ask whether immediate surgery represents overtreatment, or if the effect on survival is so substantial that it should be undertaken regardless.[32] Despite increased local control, large resections and reconstructions in the primary operation are more costly and may reduce the possibility of further limb salvage surgery. The management of high-grade CS with inadvertent intralesional margins is challenging due to the aggressiveness of the tumour and the need to achieve local control.

In conclusion, this series shows a significantly higher risk of LR in patients without resection at the time of definitive grade 2 CS diagnosis. Despite DM, the survival rate seems not to be influenced by the treatment chosen; LR may play a role in determining survival. Thus, prevention of LR might ultimately improve survival.

The optimal treatment strategy should be individualized based on the histological features of the tumour, tumour location, morbidity of resection, and patient-specific factors. Even if it is difficult to make any definitive recommendations about management, as the number of cases is small, we recommend that patients who have undergone unplanned surgery be treated in the standard manner (wide resection). Observation may be used in specific cases with a properly informed patient.

Take home message

- Inadvertent curettage of grade 2 central chondrosarcoma carries a high risk of local recurrence, which significantly increases the likelihood of distant metastasis and negatively impacts disease-specific survival.
- Early resection following unexpected grade 2 diagnosis after curettage results in improved local control and may reduce systemic progression.
- Treatment decisions should be individualized, but standard oncological resection should be strongly considered in most cases to optimize outcomes.

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