Low-grade chondrosarcoma of bone: experiences from the Vienna Bone and Soft Tissue Tumour Registry

Philipp T. Funovics · Joannis Panotopoulos · Manuel Sabeti-Aschraf ·
Farshid Abdolvahab · Josef M. Funovics · Susanna Lang · Rainer I. Kotz ·
Martin Dominkus

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Abstract In a retrospective single-centre study, 70 low-grade chondrosarcoma (LCS) (31 female/39 male patients with a mean age of 40 years) were reviewed to evaluate surgical management. The mean overall follow-up was 81 months (median: 73 months, range: 6–317 months). Seventeen lesions (24.3%) in the trunk and 53 (75.7%) in the extremities were treated by curettage (48.6%) or resection (51.5%). Local recurrence occurred in eight patients (11.4%) 18 months postoperatively (median: 18 months, range: 0–41 months). Recurrence-free survival was significantly better for patients with extremity lesions compared to truncal lesions, but was not affected by resection margin. The anatomical site “trunk” and an “intralesional” resection margin had a significant independent prognostic influence in multivariate analysis. Curettage with local adjuvants is a viable treatment option for most extremity LCS. In truncal LCS wide resection is recommended despite a potentially higher complication rate.

Introduction

Chondrosarcoma is the second most common primary bone tumour in the general population and the most common one in patients over the age of 25 years [1, 2]. Treatment of chondrosarcoma mainly consists of surgical resection as adjuvant modalities only show limited effects [3, 4]. The

extent of resection is dependent on tumour grade. The importance of adequate resection margins is well established in most high-grade sarcomas and consequently accepted in high-grade chondrosarcoma. However, in low-grade chondrosarcoma (LCS), the influence of wide resection on morbidity, local recurrence and outcome possibly should be newly defined with increasing scientific reports emerging from retrospective clinical series in the absence of controlled trials. In spite of on going controversial surgical attitudes, the basic behaviour of LCS is described as being associated with a less aggressive clinical course, lower recurrence and higher survival rates [3, 5–8]. Among the most important prognostic factors, tumour location, nuclear DNA ploidy, high proliferation index and tumour grading have been described [3, 8–10]. Therefore, the evaluation of LCS as an aggressive benign tumour rather than a low-grade malignancy by some authors together with its low metastatic potential [3, 5, 11] have favoured a less invasive treatment at least in the long bones, i.e. intralesional curettage including the use of local adjuvants such as polymethylmethacrylate (PMMA), pasteurisation or cryosurgery [12–15]. More recent reports about extremity LCS were able to confirm that intralesional surgery was not associated with higher rates of local recurrence. Additionally, functional results were better and complication rates were lower [7, 16–19]. The majority of these reports were limited to long bone lesions and did not reflect data concerning truncal LCS. Since local recurrence in a truncal location is more related to the adequacy of surgical margins than to grading, the literature reflects the acceptance of this principle as the only treatment factor that potentially can be controlled or influenced by the surgeon [10, 20–22]. Moreover, in contrast to extremity lesions, where local recurrence can be treated by wide excision after intralesional treatment [23], local recurrence in the trunk is

P. T. Funovics (✉) · J. Panotopoulos · M. Sabeti-Aschraf ·
F. Abdolvahab · J. M. Funovics · S. Lang · R. I. Kotz ·
M. Dominkus
Medical University of Vienna Department of Orthopaedic
Surgery, Vienna General Hospital,
Währinger Gürtel 18–20,
1090 Vienna, Austria
e-mail: philipp.funovics@meduniwien.ac.at

technically difficult to treat and is associated with a higher complication rate [7]. Accordingly, most reports on pelvic or sacral LCS advocate wide resection whenever possible [10, 20, 22], but do not compare the results with regard to tumour location.

We therefore investigated whether our experience with the surgical management of LCS was able to identify a difference in outcome in terms of local recurrence and complications depending on surgical margins and location in the trunk or extremities in order to define the best possible extension and method of surgery.

Materials and methods

From 1968 to 2006 the prospective database of the Vienna Bone and Soft Tissue Tumour Registry contained 248 chondrosarcomas available for retrospective follow-up. There were 178 high-grade lesions (71.8%) and 70 LCS (28.2%). All database files and medical records of patients with LCS were retrospectively reviewed in this single-centre analysis. Institutional Review Board approval was obtained prior to the investigation. The group included 31 female and 39 male patients with a mean age of 40 years (median: 37 years, range: 10–72 years). The fourth decade of life was the most predominant (24 patients, 34.3%). The mean overall follow-up was 81 months (median: 73 months, range: 6–317 months). Eighteen patients (25.7%) underwent their first surgical treatment outside our institution including open biopsy in eight, intralesional curettage in six, resection in three and arthroscopy in one. This retrieved 17 histological specimens (in all cases but arthroscopy, 94.4%) that were assessed as LCS in 13 cases (76.5%) and as chondroma or chondromatosis in two cases each (11.8% each). All other patients had their index surgery at our institution.

Establishing the diagnosis of LCS included clinical exploration, radiography and histological evaluation by the same institution and specialised musculoskeletal pathologists over the whole study period. Histopathological differentiation between LCS and proliferative chondroma was based on cellularity of the specimen, the identification of double- or multinucleated cells, increased size of nuclei, permeative growth into bony trabeculae and a high proliferative index confirmed by MIB-1 staining (Ki-67). DNA ploidy was not routinely assessed for clinical routine purposes. In doubtful lesions, clinical (pain) and radiological (extent of endosteal scalloping, cortical erosion, extracortical tumour) aspects were included into the interpretation of the lesion throughout multidisciplinary evaluation.

Seventeen lesions (24.3%) occurred in the trunk and 53 (75.7%) in the extremities (Fig. 1) including 68 central LCS (97.1%) and two secondary peripheral tumours (2.9%). Thirty-four patients underwent intralesional treatment (48.6%, one in the trunk/33 in the extremities) by curettage, high-speed burring and PMMA packing. Additional plating was used if required for biomechanical stability. Resection was performed in 36 patients (51.5%, 16 trunk/20 extremities); 13 patients (18.6%, three trunk/ten extremities) required further reconstruction of the resulting defect which consisted of a Kotz-type modular tumour prosthesis in ten (14.3%, two trunk/eight extremities) and an allograft in three (4.3%, one trunk/two extremities). The postoperative events of infection, fracture, dislocation, pseudarthrosis and nerve palsy were regarded as major complications potentially requiring further surgery. Resection margins were defined according to Enneking's classification as intralesional, marginal and wide [24]. Our standard follow-up protocol for patients with LCS foresees clinical and radiographic examination three, six, 12, 18 and 24 months postoperatively and yearly thereafter. Advanced imaging only applied when there was the suspicion of recurrent tumour on standard radiographs. Local recurrence was defined as recurrence of a tumour throughout this protocol at least three months after surgery. In cases of intralesional treatment a possible residual tumour on follow-up examination was considered a local recurrence for statistical data analysis purposes.

Statistical analysis

Statistical analysis of the data focused on local recurrence. Descriptive data (mean, median, range, proportions) are reported for the entire patient cohort. Differences between means and proportions were tested with the χ^2 test for categorical variables and the unpaired *t* test for continuous variables. Actuarial survival was estimated using the Kaplan-Meier method. The investigated endpoints were local recurrence as defined above and death from disease. Significances between survival functions were identified by the log-rank test. A multivariate model was calculated by Cox regression, where age was regarded as a continuous variable, and all other covariates (sex, previous surgery, site and type of resection) were modelled as categorical variables. All statistical tests were two-sided. A *p* value of <0.05 was considered significant. All calculations were made with the SPSS® (version 13.0, 2004, SPSS Inc., Chicago, IL, USA) and GraphPad Prism® (version 4.00, 2003, GraphPad Software Inc., La Jolla, CA, USA) software packages; graphical visualisation was performed using GraphPad Prism®.

Fig. 1 Anatomical distribution in 70 patients with LCS

Results

Tables 1 and 2 outline treatment results with respect to anatomical site and resection margins. Resection margins were rated as intralesional in 39 patients (55.7%, five trunk/34 extremities), marginal in seven (10.0%, three trunk/four extremities) and wide in 24 (34.3%, nine trunk/15 extremities); no radical operation was performed. In general, resection was mostly indicated in truncal lesions, while

curettage was performed in the majority of extremities ($p < 0.001$); consequently, there were significantly more intralesional procedures in the extremities compared to the trunk ($p = 0.012$). As intralesional treatment was planned in 34 patients and resection in 36, this means that clear margins were not achieved in five patients (four trunk/one extremity), despite aiming at resection of the lesion. Three of these patients (all trunk) have subsequently developed a local recurrence. Surgical complications were encountered in nine

Table 1 Main patient and treatment characteristics of 70 patients with LCS according to anatomical site

Variable	Trunk	Extremity	Total	<i>p</i>
Total	17 (24.3%)	53 (75.7%)	70 (100%)	–
Mean age in years	39 (35, 17–62)	40 (38, 10–72)	40 (37, 10–72)	NS
Sex				
Male	13 (76.5%)	18 (34.0%)	31 (44.3%)	0.002
Female	4 (23.5%)	35 (66.0%)	39 (55.7%)	
Mean follow-up in months	58 (42, 6–205)	88 (76, 6–317)	81 (73, 6–317)	NS
Previous surgery	4 (23.5%)	6 (11.3%)	10 (14.3%)	NS
Resection	16 (94.1%)	20 (37.7%)	36 (51.5%)	<0.001
KMFTR	2 (11.8%)	8 (15.1%)	10 (14.3%)	NS
Allograft	1 (5.9%)	2 (3.8%)	3 (4.3%)	NS
Intralesional surgery	1 (5.9%)	33 (62.3%)	34 (48.5%)	<0.001
Margin				
Intralesional	5 (29.4%)	34 (64.2%)	39 (55.7%)	0.012
Marginal ^a	3 (17.6%)	4 (7.5%)	7 (10.0%)	
Wide ^a	9 (52.9%)	15 (28.3%)	24 (34.3%)	
Complications	2 (11.8%)	7 (13.2%)	9 (12.9%)	NS
Local recurrence	4 (23.5%)	4 (7.5%)	8 (11.4%)	NS
Multiple recurrence	2 (11.8%)	1 (1.9%)	3 (4.3%)	NS
Metastasis	1 (5.9%)	0	1 (1.4%)	NS
Death from disease	1 (5.9%)	0	1 (1.4%)	NS

KMFTR Kotz Module for Tibia and Femur Reconstruction

^a Numbers for marginal and wide resections were added and compared to intralesional resection for statistical analysis purposes

Table 2 Main treatment characteristics of 70 patients with LCS according to resection margin

Variable	Intralesional	Marginal ^a	Wide ^a	<i>p</i>
Total	39 (55.7%)	7 (10.0%)	24 (34.3%)	–
Complications	2 (5.1%)	0	7 (29.2%)	0.030
Local recurrence	7 (17.9%)	1 (14.3%)	0	NS
Multiple recurrence	2 (5.1%)	1 (14.3%)	0	NS
Metastasis	1 (2.6%)	0	0	NS
Death from disease	1 (2.6%)	0	0	NS

^a Numbers for marginal and wide resections were added and compared to intralesional resection for statistical analysis purposes

patients (12.9%). The postoperative complications were independent from the anatomical site of the lesion (trunk 11.8%, extremities 13.2%), but were significantly different in frequency with respect to surgical extent (intralesional 5.1%, marginal 0%, wide 29.2%, $p=0.030$). There were significantly more male patients with truncal lesions ($p=0.002$).

Local recurrence occurred in eight patients (11.4%), all in the intralesional (17.9%) or marginal (14.3%) and none in the wide resection group. Different recurrence rates were observed in trunk (23.5%) and in extremities (7.5%); however, this was not statistically significant. All recurrences occurred within a mean of 18 months postoperatively (median: 18 months, range: 0–41 months). Overall recurrence-free survival was 90.6% at 24 months and 86.9% at 48 months, respectively, and remained constant thereafter (Fig. 2). There was no significant difference in recurrence-free survival according to resection margins at 24 months (83.4% for intralesional resections versus 100% for marginal resections) or at 48 months (80.1% for intralesional resections versus 83.3% for marginal resections, Fig. 3). Recurrence-free survival was significantly better for patients with extremity lesions compared to truncal lesions at 24 months (94.0% for extremities versus 78.7% for trunk) and at 48 months (91.5% for extremities versus 69.9% for trunk, $p=0.026$, Fig. 4). This difference remained evident after the exclusion of LCS of the hand

and foot, but was no longer significant ($p=0.066$). The respective survival rates for extremity tumours without lesions to the hand and foot at 24 and 48 months were 93.8 and 90.5% (Fig. 5). Table 3 shows a detailed description of the eight patients with local recurrence. Six recurrences were treated surgically; one patient with pelvic chondrosarcoma declined the indicated pelvic resection and is still alive with disease 13 months after index surgery. Three patients underwent resection of their recurrence; three patients had further curettage. There were three second recurrences (two trunk/one extremities) within nine, ten and 18 months after the last operation, respectively, two in patients with resection and one in a patient after curettage. Further surgery consisted of resection in two and a third curettage in one and culminated in all patients without evidence of disease. The remaining patient with an LCS of the cervical spine that initially had been resected outside our institution developed a single skeletal metastasis in his left tibia 13 months postoperatively that was resected. Histology confirmed an LCS without evidence of dedifferentiation. However, the patient also developed a retroauricular local recurrence 18 months after surgery and concomitant stenosis of the basilar artery and finally died 42 months after index surgery due to cerebral complications before further treatment. Six further patients died over the study period for reasons not related to LCS. Therefore the disease-specific survival was 98.0% at 48 months and thereafter (Fig. 2). Even with only one case of disease-related death, this caused a significant difference in survival between patients with extremity lesions (100% at 48 months) versus patients with truncal tumours (88.9% at 48 months, $p=0.031$; graph not shown). There was no such difference regarding resection margins. A multivariate Cox regression model was calculated with local recurrence as endpoint. There was no significant influence of the covariates sex, age or previous surgery outside our institution. The anatomical site “trunk” (versus “extremity”, $p=0.017$) and an “intralesional” resection margin (versus “marginal” and “wide”, $p=0.022$) had a significant independent prognostic influence: hazard ratio for “trunk”: 8.2, 95% confidence interval: 1.5–46.2; hazard ratio for “intralesional”: 14.2, 95% confidence interval: 1.5–138.9. These two covariates even remained statistically significant after

Fig. 2 Kaplan-Meier graph of recurrence-free and disease-specific survival of all 70 patients with LCS (see text for details)

Fig. 3 Kaplan-Meier graph of recurrence-free survival of all 70 patients with LCS according to surgical margin. There was no significant difference between the survival functions, $p=0.109$ (see text for details)

exclusion of LCS of the hand and foot: hazard ratio for “trunk”: 8.1, 95% confidence interval: 1.2–55.9; hazard ratio for “intralesional”: 21.7, 95% confidence interval: 1.9–243.5.

Discussion

This study reflects a single-centre clinical experience with the surgical treatment of LCS in the trunk and extremities by different extents of resection. We have been able to show that the recurrence-free survival not only was dependent on resection margins, but also on primary anatomical site.

There are certainly limitations to this study, which mainly consist of its retrospective design and a relatively small number of patients, especially in subgroup analyses. However, to the best of our knowledge there are no

Fig. 4 Kaplan-Meier graph of recurrence-free survival of all 70 patients with LCS according to anatomical site including lesions of the hand and foot. There was a significantly better survival for patients with extremity tumours, $p=0.026$ (see text for details)

Fig. 5 Kaplan-Meier graph of recurrence-free survival of all 70 patients with LCS according to anatomical site excluding lesions of the hand and foot. There was no significant difference between the survival functions, $p=0.066$ (see text for details)

prospective trials available to date and only a few retrospective studies have reviewed larger series of LCS, mainly due to its rarity [7, 23]. Secondly, the patient cohort is not homogeneous in terms of tumour site and distribution, as it included both truncal and extremity tumours, which was the natural consequence of comparing these two groups. Interestingly there was a male preponderance in the group with truncal LCS. We do not have a conclusive explanation for that, but as we are not aware of any gender-related impact on outcome in LCS described in the literature, we might conclude that this is of no consequence. Finally, we decided to include lesions of the hand and foot in the extremity group, which is unusual with regard to previous reports, as these lesions have been characterised by a benign clinical course [12]. But we felt that the impact of anatomical sites could be even better evaluated by both inclusion and exclusion of these lesions, as other reports [15].

Today the surgical procedure for the treatment of chondrosarcoma is predominantly defined by tumour grade. While high-grade lesions stipulate adequate surgical margins, the management of LCS remains controversial. Since the five year survival rates including all types of LCS surgery exceed 90–96% [3, 6–8], there are two competing principles in selecting the appropriate procedure: avoidance of local recurrence and preservation of function. The vast majority of all 70 LCS in this series were located peripherally and only 24% in the trunk; intralesional and marginal excision (together >65%) constituted the group where preservation of function was the guiding principle rather than resection margin. Most reports of extremity LCS found low rates of local recurrence even when intralesional curettage was performed ranging from 0 to 18% [7, 12, 15–19], but rates were always higher when compared to wide resection of the tumour [7, 16, 18, 19].

Table 3 Main treatment characteristics and outcome of eight patients with recurrent LCS

Patient	Age (years)	Sex	Site	Previous surgery	Surgery	Margin	LR (months)	Surgery	2nd LR (months)	Surgery	Met	Outcome, FU in months
1	26	F	Fibula	–	Curettage	I	22	Resection	–	–	–	Alive, 219
2	32	M	Humerus	–	Curettage	I	5	Curettage	–	–	–	Alive, 84
3	33	M	Pubis	–	Resection	M	30	Resection	10	Resection	–	Alive, 41
4	62	M	Pubis	–	Resection	I	0	Declined	–	–	–	Alive, 13
5	70	M	Tibia	–	Curettage	I	41	Curettage	–	–	–	Alive, 130
6	28	F	Ilium	Curettage	Resection	I	9	Resection	18	Resection	–	Alive, 58
7	33	M	Cervical spine	Resection	Resection	I	19	None	–	–	Tibia	DFD, 42
8	58	M	Hand	–	Curettage	I	18	Curettage	9	Curettage	–	Alive, 137

LR local recurrence, Met metastasis, FU follow-up, I intralesional, M marginal, W wide, DFD death from disease

Considerations that further strengthen the rationale for limited surgery were a better functional outcome and the fact that, given appropriate approaches, subsequent treatment in extremities is not necessarily compromised by curettage [16, 18]. The role of local recurrence and its impact on survival, however, is critical, because local recurrence might be interpreted as an aggressive phenotype of LCS [23] and therefore can dedifferentiate into higher grade lesions with metastatic potential [7]. In pelvic and spinal chondrosarcoma, the effects of inadequate margins and local recurrence on overall survival have been described as significant predictors of worse overall outcome besides age and tumour grade [22]. However, when considering LCS of the pelvis alone, these influences diminish substantially and should be considered when mutilating resection is the only alternative [20].

The majority of extremity LCS in our series were treated by curettage, while the majority of truncal lesions were resected. Nevertheless, the local recurrence rate was lower in extremities, and intralesional surgery as such had no significant effect on overall survival. Nor were we able to identify a significant impact of the resection margin on the local recurrence rate, even if there was a noticeable difference. Nevertheless, it remains obvious that there were no recurrences in patients treated by wide resection. With only one patient developing metastasis and finally dying from local recurrent disease, it remains very difficult to deduct any conclusions about the influence of local recurrence on overall outcome.

The fact that four of five patients with failed wide resection had trunk tumours suggests that wide resection in this site might be technically much harder to achieve than in extremities [7]. However, we have observed a higher complication rate with wide resections compared to curettage, but complications were equally distributed between trunk and extremities. This could imply that complications are less related to the anatomical site, but rather to more extensive surgery, which was also evident in patients with lesions confined to the long bones [16, 18].

The higher incidence of local recurrence in the trunk, however, cannot only be explained by surgical issues or resection margins, as we have seen that intralesional resection should not worsen the recurrence rate. Tumour-related histological features also seem to play an important role. We have observed a significantly lower recurrence-free survival of truncal compared to extremity lesions. This difference remained almost unchanged in terms of survival functions when lesions of the hand and foot were excluded, but no longer carried significance. Although the respective *p* value of 0.066 was above the accepted standard, we still feel that the magnitude of this finding could have clinical relevance (Fig. 5), emphasising the need for a more aggressive surgical treatment in the trunk than in extrem-

ities. Multivariate analysis has also identified anatomical site as a significant prognostic factor with a notable hazard ratio of 8.2 for the trunk. This remained unaffected by the exclusion of hand and foot tumours.

It is difficult to interpret the finding that intralesional resection was of no significant influence in a monovariate analysis and turned into a significant factor in the multivariate model. We might postulate that the negative impact of intralesional surgery was outweighed by the better prognosis of extremity tumours, again underlining the reason surgical treatment of LCS should differ according to anatomical site.

An additional potential reason for low recurrence rates might be the use of bone cement in all our patients with intralesional curettage. These findings were confirmed by nearly all reports on LCS [7, 13–19, 23]. For anatomical reasons such adjuvants are rarely applicable in the spine or pelvis, thus making intralesional resection in these locations less effective than in long bones [7].

We did not identify a significant influence of previous surgery outside our institution on local recurrence rates in the multivariate analysis, which reflected other experiences [23]. However, the 24% rate of misdiagnosed specimens (4/17) clearly represents the clinical and pathological difficulties in diagnosing LCS and favours a centre-based treatment [22].

The treatment of recurrences in our series included both resection and repetitive curettage. As two of eight recurrences had not been treated surgically, this means that we had a 50% further recurrence rate. With similar findings, other authors have already emphasised the need for a more aggressive treatment of recurrences even in the long bones [19, 23] in order to avoid dedifferentiation and this is clearly underlined by our findings.

Tumour conversion to a higher grade was not observed in our series, as with several other authors [16–18]. Only one patient with a cervical LCS developed a single bone metastasis and also finally died from local recurrence. Statistically this led to a significantly worse overall prognosis of truncal LCS compared to extremity tumours. However, again we feel that the numbers are too small to deduct viable conclusions concerning the impact on overall survival, but might lead to the conclusion that truncal LCS cannot be regarded as a benign lesion.

Conclusion

Intralesional resection of LCS does not necessarily affect overall survival but can lead to higher recurrence rates, albeit with fewer complications and possibly a better functional outcome. Our results warrant the approach of applying less surgical aggression—i.e. intralesional curettage and use of local adjuvants—in most extremity LCS

with the primary intention of preserving function. Recurrences, however, should be resected with wide margins. In truncal LCS wide resection is recommended despite a potentially higher complication rate because (a) this anatomical site seems to be linked to a higher recurrence rate, (b) local adjuvants are rarely usable and (c) local recurrences are more difficult to treat.

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