Low Grade Chondrosarcoma: what is the best treatment? A review of literature and personal opinion

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Abstract

Introduction: chondroid lesions are very common bone tumours. Most of them are asymptomatic indolent chondromas and follow-up is the main approach. Just a minor percentage are malignant chondrosarcomas which need surgical intervention. If resection is considered the gold-standard for intermediate and high grade tumours, no consensus exists in literature about low-grade chondrosarcoma. Even if resection is recognized as the main treatment for low-grade chondrosarcoma located in the spine and pelvis to reduce the risk of local recurrence, most authors sustain curettage for low grade tumours located in the limbs, thus contradicting the general rule of obtaining a wide margin where needed for malignant tumours of the bone. Our aim is to perform a review of literature on evidence supporting this approach or not.

Methods: an electronic research of the medical archives was carried out in April 2014 seeking papers evaluating the results of curettage and resection in low-grade chondrosarcoma. The selected studies were analysed via evaluating demographic and clinical characteristics of patient populations, method of diagnosis, surgical approach and related recurrence and metastatic percentage.

Results: we selected nine studies corresponding to our criteria. Unfortunately, they were descriptive, non-randomized studies. We identified a population of 236 patients, 99 males and 137 females, for a total of 238 low-grade chondrosarcomas. 190 patients were treated with curettage and 48 with wide surgery (4 amputations included). Unfortunately, the two groups were not homogeneous for diagnosis and place of disease, so no comparison between resection and curettage was possible. The global weighted average percentage of local recurrence was 8.3% (16 cases) and 11.6% (5 cases) after curettage and after resection, respectively. No cases of metastasis were reported in the group treated with intralesionalsurgery, compared to two cases reported in the group treated with resection. Indications to surgery were given in most cases based on symptoms and imaging.

Discussion: the absence of a preoperative histological diagnosis and a scientific method to conduct the studies does not sufficiently support curettage for low-grade chondrosarcomas. In absence of this, resection must be considered a general rule for every malignancy. In our opinion, based on the low biological growth rate of low-grade chondrosarcoma, every chondromatous lesion can be followed-up. Biopsies must be performed based on clinical and radiological suspicion such as pain, scalloping or increase in size, rather than performing a PET scan to evidence more informative high metabolic areas.

KEY WORDS: chondrosarcoma, curettage, wide resection, recurrence, biopsy, PET.

Introduction

Background: chondrosarcomas (CSs) are a heterogeneous group of slow growing, malignant bone tumours that are characterized by the formation of cartilaginous neoplastic tissue. They are the third most common malignant bone tumour after myeloma and osteosarcoma, and are the most frequently occurring bone sarcomas in adulthood. The most frequent anatomic locations include: pelvis and proximal femur (approximately 50%), followed by proximal humerus and scapula; only 5% are located in the head and neck region. More than 80% are conventional, also called “classic” CS (1-3). Clear cell, mesenchymal and dedifferentiated variants constitute the remaining 20%; some of these rare variants can be found in younger patients or associated to higher malignancy. CSs can also be distinguished in central and peripheral tumours: central CSs originate intramedullary into the bone whereas the peripheral types onset from a preexisting osteochondroma (exostosis). Peripheral CSs are usually of low grade, nevertheless a dedifferentiation can occur.
Histology and behaviour: malignancy is subdivided into three stages (G1-3) based on criteria described by Evans et al. (4), considering cellularity, tumour matrix characteristics, nuclear features, and mitotic rate. The majority are low grade, locally aggressive, rarely-metastasizing tumours (G1) rather than intermediate and high grade (G2 and G3, respectively) (5). Histological evaluation of cartilaginous tumours poses a real challenge for the pathologist, regarding grading and distinguishing between benign and malignant lesions (5). Typical pathological findings of CS include: the hyaline cartilage matrix, the relative hypercellularity compared to enchondromas and the permeation between pre-existing trabecula (4). However, biopsies can assess the cartilaginous features of the lesion without relying on grading the tumour, since different areas can have different grades of malignancy and benign enchondroma may coexist with highly malignant tumours (1, 2). Moreover, central or peripheral CS may be secondary to pre-existing benign enchondroma or osteochondroma, respectively (1). Central CSs of the axial skeleton have more aggressive biologic behavior than appendicular tumours, presenting a high risk of local recurrence after surgical excision even in cases of low-grade lesions.

Diagnosis: clinical presentation and radiographs have a key role in differential diagnosis between benign cartilaginous lesions and low-grade CSs. Pain, interval enlargement, endosteal scalloping, disappearance or changes of pre-existing calcifications, cortical thinning, pathological fractures may suggest malignancy (2, 6). For this reason, clinical and imaging criteria must be considered in the decision-making process on which surgical approach to use in low-grade CS. Gadolinium contrast-enhanced MRI or FDG-PET reveal high-grade malignant areas, thus providing a useful guide to the most suitable site of biopsy (2, 6).

Treatment: for intermediate and high-grade CSs, wide surgery is the gold-standard treatment due to their chemoresistant and radio-resistance, albeit neoadjuvant chemotherapy can precede it in dedifferentiated form (7, 8). The treatment of G1 CS, however remains controversial. Given the slow biology and consequent favorable prognosis together with the goal of minimizing functional disability after surgery, several surgeons sustain that curettage is the main treatment for low grade CS based on clinical and radiological diagnosis (2, 3, 9). Instead, other authors suggest resection for histologically demonstrated G1 CS to decrease the risk of local recurrence and of undertreating higher grade tumours.

Aim: the aim of the study is to review the actual extent of evidence in literature and present the Authors’ approach.

Methods

Data sources and searches: a comprehensive electronic research was conducted in the databases of PubMed, Cochrane Library, Embase, Scopus, Trip and DARE in April 2014 using the keywords “low grade chondrosarcoma AND therapy” to include papers published in English without publication time restrictions, evaluating the results of curettage and resection in G1-CS.

Study selection: 295 papers were found and screened by two reviewers (CZ, BR) basing on title and abstract and, in case of doubt, on the entire article. Papers reporting a series of exclusive low-grade CS and its surgical approach were excluded in the study. Case reports and general CS series were excluded. Data extraction: papers with less than 2 years of follow-up or reporting fragmentary data were excluded as well. A further selection was carried out analysing the entire paper following the pre-established criteria. In case of doubt or disagreement a consensus was reached between the two reviewers. Relative references were than valued for further inclusion.

Demographic and clinical characteristics, diagnosis method, surgical approach and related recurrence and metastatic percentage were evaluated for each study.

Results

After the first round of electronic research 26 studies were identified, the following selection was based on the entire paper.

The study of Streitbürger et al. (10) and the study of Leerapunet al. (11), Schreuder et al. (12), Angelini et al. (13), Funovics et al. (14), Verdegal et al. (15) and Ma et al. (16) were excluded because the minimum follow-up reported was inferior to 24 months.

The paper of Andreou et al. was excluded because they report data concerning CS without differentiating the grade tumours (17). The study of Rizzo et al. was excluded because even though the authors assessed the local recurrence percentage rate, they suggested a resection with intralresional margin and not curettage ab initio (18).

The study of Mohler et al. (19) and the study of Bauer (20) were excluded because data were considered fragmentary and not replicable. Nine studies were selected and the characteristics of the population analysed assessing the specific treatment and success and recurrence percentage; studies and results are reported in Table 1. Unfortunately, all studies were observational, retrospective and not prospective.

Inclusion and exclusion criteria were not reported; the populations were not clearly identified and diagnosis was uncertain. Only two studies reported a preoperative histological diagnosis. Based on these factors and the resulting low power of related conclusions and poor levels of evidence, a meta-analysis was considered unsuitable and a critical review of literature was proposed.

No real comparison was found in the selected studies between patients who underwent curettage and patients who underwent resection. Just 4 out of 9 studies propose a group treated with curettage and another group treated with resection/amputation. Moreover, the respective groups were different in regards to site and stage of the pathologies; thus, no comparison could be carried out.
We selected a population of 236 patients, 99 males and 137 females, for a total of 238 low-grade CSs; the weighted average age of onset of the disease was 46.3 years. 190 patients were treated with curettage and 48 with wide surgery (4 amputations included). Indications for surgery were given in most of cases based on symptoms and imaging; only Souna et al. and Hanna et al. suggested to perform biopsies before undergoing therapy (25, 26).

Curettage with or without local adjuvant and cement was mainly reserved for stage IA (low-grade intra-compartmental) tumours located in long bones; stage IB (low-grade extra-compartmental) tumours and lesions located in pelvis were mainly treated with resections. The global weighted average percentage of local recurrence was 8.3% (16 cases) and 11.6% (5 cases) after curettage and after resection, respectively. No cases of metastasis were reported in the group treated with intralesional surgery, compared to two cases reported in the group treated with resection.

### Discussion

The main goal in oncological orthopedic surgery is to obtain a wide margin for malignant tumours as wide or radical surgical margins represent one of the most important prognostic factors (27-33). This rule could be applied to every histological type including osteosarcoma, Ewing’s sarcoma or CS (30-33). Even though today this type of treatment is recognized for high-grade CS, several authors propose intralesional treatment with or without local adjuvant treatment for low grade (G1) CS.

The present review shows this tendency but also highlights the total absence of scientific evidence supporting this approach. The first misunderstanding is diagnosis. From the histology of a benign chondroma to the histology of a G1 malignant CS a continuum of possible aspects is present. Differential diagnosis is difficult, sometimes impossible and is done based on imaging and symptoms (2, 6). Cartilaginous tumours are also...
characterized by an important heterogeneity and areas of chondroma can be simultaneously present with G1 or higher grade CS (1, 2). Moreover, central or peripheral CS may be secondary to pre-existing benign chondroma or osteochondroma, respectively (1). Based on this aspect most surgeons indicate surgery without undergoing a preoperative biopsy. The present review demonstrates that a preoperative histological diagnosis was reported in only two out of nine papers (25, 26). In one paper, the authors performed an intraoperative extemporaneous diagnosis (28), while in the other series just imaging and symptoms were considered sufficient to perform a curettage suspecting a low grade tumour.

The first study proposing curettage for low-grade CS is that of Bauer et al. in 1995 (20). They reported their experience about the treatment of 40 chondromas and 40 CSs. They also report to have carried out a biopsy in just two cases of CS and to have then followed up the patients. No progression of disease was evident in both cases even if one of them died for independent causes, assuming a behaviour more typical of chondroma (20).

Currently, the rates of local recurrence reported in literature are lower than those related to the curettage of aggressive benign bone tumours such as giant cell tumour or chondroblastoma, thus some of these may probably be indolent chondromas (34-36). Most authors sustain the uselessness of biopsy as they have low reliability in accurately predicting the specific grade in cartilaginous tumours. De Camargo et al. observed that the correspondence between the grade obtained in biopsy and the resected specimen was 60%. In their 19 cases of grade-I CS treated with curettage and electrocauterization, they had 5 recurrences (26.3%). They also reported 3 cases treated with resection as well as a case of local recurrence, but it is not possible to give related conclusions due to the limited group number and because the authors did not explain why a resection was performed in only three cases (24).

Etchebehere et al. reported a diagnosis rate of 96% of CS cases, but correct grade identification in only 46% of the times (29).

This management tendency can cause two possible errors: overtreating chondroid lesions which are in actual fact chondromas and undertreating chondroid lesions which are actually low-grade or also higher grades CS.

Meftah et al. have recently published the results of intrallesional curettage and cryosurgery for treatment of low-grade CS. Out of 43 cases 4 recurrences were reported in 42 patients, occurring when tumours had involved the surrounding soft tissue (Enneking stage-IB) (22). If this could support the surgical approach for those surgeons who perform curettage for stage-IA chondroid lesions and resection for stage-IB, otherwise underlines the possibility that stage-IB chondroid lesions could be real CS while a part of stage-IA chondroid lesions could be chondromas.

In pelvic and spine low-grade CSs, wide resection is sustained by most authors, as local recurrence is particularly dangerous in these anatomic sites. Boriani et al., in a recent review together with a multicenter cohort study indicated how achieving wide margins reduce local recurrence rate and mortality. They reported 26 local recurrences out of 53 cases of low-grade CS treated with intrallesional surgery and three local recurrences out of 41 cases treated with wide surgery. Nonetheless, no specific data reported on the average follow-up but just a minimum follow-up of 12 months, insufficient for low-grade tumours (37).

In our opinion, a preoperative histological diagnosis is highly recommended to improve the tumour grade determination and PET-TC and functional MRI could be used to identify the most active area where, with a better probability, a biopsy could provide more information. Nevertheless, much more evidence is necessary to support this strategy.

Another important limitation presented in this review is the absence of prospective studies in literature. The inclusion criteria consisted in a postoperative diagnosis of low-grade CS in every paper evaluated. This causes the loss of all those chondroid lesions preoperatively diagnosed as low-grade CS based on symptoms and imaging which were diagnosed chondromas at definitive histology. Moreover, the postoperative confirmation of a low grade CS could be also involuntarily misdiagnosed by pathologists who may be more predisposed to diagnose a low grade CS than a chondroma after surgical treatment. These confounding factors further decrease the power of the studies present in literature.

**Conclusion**

Until today, the total absence of scientific evidence supporting curettage for low-grade CSs still has to be confirmed. Researchers have to identify more reliable methods and criteria to make diagnosis of low-grade CS more accurate and reproducible. Subsequent, prospective randomized studies with a minimum follow-up major than two years are advocated to confront curettage and resection for low-grade CS. In absence of evidence, the general rule sustaining wide margin for malignant tumours could be applied.

Given its slow growing biology, if a chondromatous lesion is discovered, if it is asymptomatic and it does not meet radiological criteria of possible aggressiveness such as scalloping or reaching a size more than 5 cm, it can be maintained in follow-up. If there is a possible malignancy suspected radiologically and is present or a growth is evident, a PET should be executed to show where metabolism is higher and a biopsy can be performed.

Osteochondromas have to be followed-up as well taking the thickness of cartilaginous cup in to account. If they are located in the pelvis they can always be resected, nevertheless, lesions located around the acetabular area and in the spine have to be assessed carefully case by case before giving any surgical indication.

In our opinion, only CS that are histologically demonstrated should be treated.
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References


