Original papers

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The Influence of Adjuvants on Local Recurrence Rate in Giant Cell Tumour of the Bone

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Abstract. *Introduction :* Intralesional surgery of giant cell tumour of the bone (GCT) may result in a high rate of local recurrence. The introduction of local adjuvants, such as cementation, cryosurgery or phenolization, has proved to be successful in the reduction of recurrence rates. This study presents the results of a single institution in surgery of GCT with an evolution in treatment strategies.
Material & Methods : Forty primary and 25 recurrent surgical procedures in 46 patients with GCT of the bone with a median follow-up of 72 months were reviewed retrospectively. The mean age was 32.6 years (range 13.6-57.9 years). Forty-seven curettages and 18 resections were performed. For the curettages, a large bone window was cut followed by high speed burring and bone grafting or cementation. In 34 of 47 curettages and 7 of 18 resections, phenol was additionally applied.
Results : Two patients showed pulmonary metastasis, one died due to metastatic disease. In total, a third of the patients developed local recurrence (32.3%). This was evenly spread among primary and recurrent diesease (32.5% vs. 32%). Seven of 13 curettages without adjuvant recurred (53.9%), compared to 11 of 34 curettages with adjuvant phenol (32.4%). Three of 18 resections developed a recurrence (16.7%). No complications in respect to the use of phenol were seen.
Discussion : Phenolization is a safe local adjuvant therapy for GCT. Although the recurrence rate was lower with the use of phenol, this drop was not significant. The comparable high recurrence rate in our study, even if phenol was used, might be due to the fact that curettage was our favoured treatment, even in cases with an extensive juxta-articular tumour. We recommend adjuvant phenolization in the treatment of GCT of the bone after thorough curettage in applicable cases, including where cementation is used for defect filling.

Introduction

GCT of the bone is a true neoplasia originating from the undifferentiated mesenchymal cells of the bone marrow. It is one of the most common primary bone tumours in young adults (1, 2). Representing 5% of all primary bone tumours and 20% of all benign tumours it arises from the meta-epiphyseal junction generally around the knee but is also frequently found at the proximal humerus, distal radius and the axial skeleton (1).

The male : female ratio is 1:1.5, with 60-75% of the cases appearing from the second to fourth decade of life (2).

Histologically the tumour consists of multinucleated giant cells and mononuclear precursor cells. Both of them express CD68-antigen (3). Despite attempts to classify GCT histologically into a grading system, the prognostic impact of histological grading is very poor (4). Even in cases of a 'benign' histology, pulmonary metastases occur in 2-3% of the cases. DNA cytometry has not been proven to be helpful either (5).

The remarkable local aggressiveness of GCT as a benign bone tumour continues to be a surgical challenge. Until 1912, amputation was the preferred method of treatment, at which time intralesional resection and bone grafting was introduced (6). With no further treatment, local recurrence may develop in 80% of such cases (7). There is no doubt that wide resection reduces the risk of recurrence. Due to the typical meta-epiphyseal location, wide resection may result in a major functional deficiency. Hence, intralesional curettage is the most recommended treatment, with reported local recurrence rates ranging between 0% and 50% (1, 8, 9).

Despite reports showing a significant reduction in recurrence rates due to the introduction of local adjuvant therapy (10, 9, 4), recurrence rates differ considerably. Even if the same treatments are applied they vary between 20% and 50% (11, 12).

The aim of this study was to analyse the influence of introducing adjuvants in the treatment of GCT on local recurrence rates over a period of 26 years in a single institution.

Material and Methods

From September 1981 to January 2007, 65 consecutive operations on 46 patients were performed in our institution for GCT of the bone. The patients consisted of 20 (43%) men and 26 (57%) women with a mean age of 32.6 years (13.6-57.9 years) at the time of the first treatment (Fig. 1). Forty operations were done for newly diagnosed GCT, 25 procedures for disease recurrence. Thirteen patients experienced a disease recurrence after the initial treatment in our institution and were treated with a second operation in our hospital. Six of these 13 patients had a second recurrence. Four of these 6 patients were surgically treated in our hospital for the second recurrence, two in another hospital. Six patients presented in our clinic with a disease reccurence who had already had their initial treatment for GCT elsewhere. Two of our patients experienced disease recurrence three times. Follow-up for all patients included radiographical and clinical evaluations perfomed by a physician in our institution or in the patient's community. As MRI is much more sensitive for detecting typical radiographical findings of GCT, this method was preferentially used in addition to conventional radiographs. The median time to follow-up was 72 months (range : 1-289 months).

The "Recurrence free survival" was calculated using a Kaplan-Meier survival curve.

Results

Pain was in most cases the first clinical symptom of GCT (90%). The duration of complaints varied greatly, corresponding to the unpredictable course of the tumour. The average time interval between the onset of symptoms and surgical treatment was 6.8 months (SD : 9 ; range : 3 weeks to 42 months).

Five patients (10.7%) suffered from a pathological fracture caused by the tumour. In four of these patients the fracture was the initial presentation of the disease : one patient had a fracture due to local recurrence.

Initial diagnosis, based on radiographical findings, was confirmed by biopsy in all cases. Predominantly the lower extremities were affected (n = 37). The most frequent site was the proximal tibia with 14 manifestations, followed by the femur with n = 12, the foot n = 5, the distal tibia n = 5 and the fibula in one case. Eleven of the 12 manifestations on the femur affected the distal part, only one patient presenting with GCT of the greater trochanter. A pelvic manifestation of GCT was seen in only one case. The spine was affected in three patients and in one case a rib was involved in the process. In the upper extremity 5 manifestations were seen. Two GCT cases presented in the humeral head, one in the distal ulna and one in the proximal radius. One GCT was found in os metacarpal four (Fig. 2).

The primary surgical procedure performed was curettage with or without using an adjuvant (n = 47) : a tumour resection was done in 18 cases.

Resection

In 8 patients resection was the initial treatment. Except for one case no adjuvant was used when the tumour was resected. The remaining 10 patients were treated by resection after the first recurrence of the disease. The recurrence rate was 25% for primary lesions and 10% for treatment of recurrent lesions by resection. The total

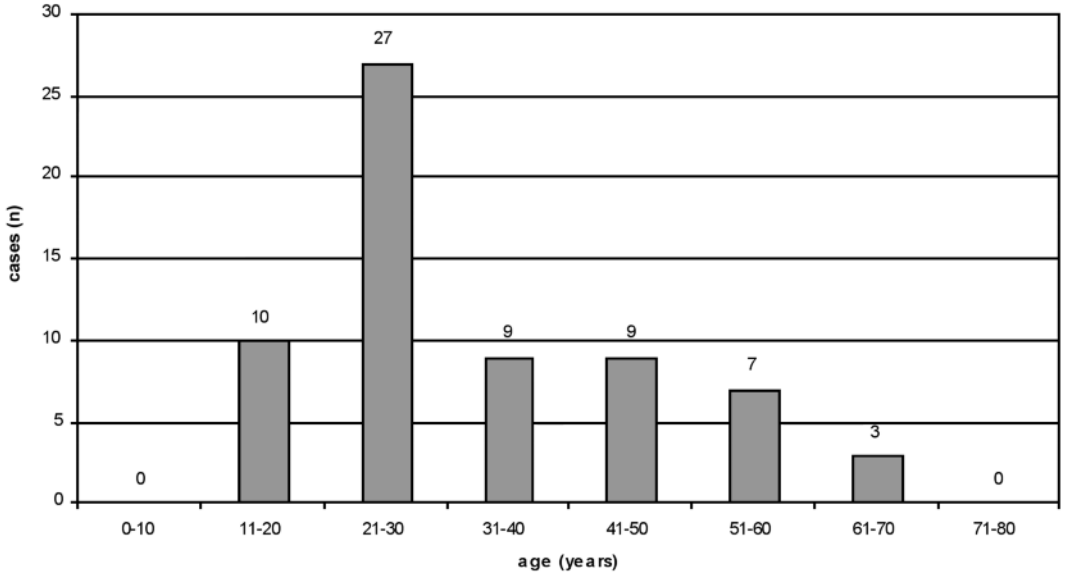

Fig. 1.
Distribution of age in patients with GCT at time of surgery (primary and recurrent lesions).

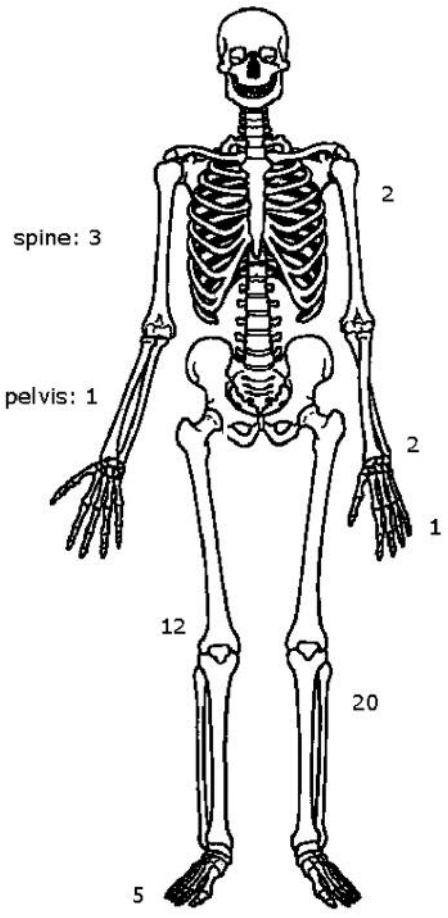

Fig. 2
Location of giant cell tumours of bone

recurrence rate was 16.7% (Table I and Fig. 3). In two out of 18 performed tumour resections the histological examination revealed an R1-situation.

Curettage only

Thirteen patients were treated by curettage without an adjuvant. For curettages, a large window was cut into the bone followed by high-speed burring. The defect was reconstructed by autologous (n = 6), homologous (n = 1) or both types (n = 4) bone grafting. In one patient the defect did not need bone grafting and another patient received a lumbar spine prosthesis. Ten of these patients had a primary tumour, three a first recurrence. As expected, the recurrence rate was quite high with 50% in the primary treatment group and 66.7% for groups with recurrent disease. The total recurrence rate was 53.9% (Table I and Fig. 3).

Curettage with adjuvant

The majority of patients (n = 34) received curettage with phenol as an adjuvant. Twenty-two patients as the initial treatment of the tumour and 12 for recurrent disease. A solution of 50% phenol in 75% alcohol was administered on swabs, put into the lesion for 1 min. followed by irrigation with sodium bicarbonate and Ringer's solution (10). The defect was then reconstructed by autologous (n = 11), homologous (n = 2) or both types (n = 7) bone grafting or palacos spacer implantation (n = 14). In primary lesions the recurrence rate was 27.3% and in recurrent lesions 41.7%. The total recurrence rate was 32.4%. With the increasing use of phenol as an adjuvant the local recurrence rate decreased from 70% in the early 1980s to almost 10% today (Fig. 4). The high number of recurrences in the period 1996-2000 (70%) is caused by two individuals, who suffered from three local recurrences each in a short period of time. No complications with regard to the use of phenol were seen (Table I and Fig. 3).

Table I
Recurrence rates in patients with GCT

	Recurrence (n)	Recurrence (%)
primary lesions (n =40)	13	32.5
recurrent lesions (n = 25)	8	32.0
Total (n = 65)	21	32.3
resection primary lesion (n = 8)	2	25.0
resection recurrent lesion (n = 10)	1	10.0
Total (n = 18)	3	16.7
curettage without adjuvant / primary lesion (n = 10)	5	50.0
curettage without adjuvant / recurrent lesion (n = 3)	2	66.7
Total (n = 13)	7	53.9
curettage with adjuvant / primary lesion (n = 22)	6	27.3
curettage with adjuvant / recurrent lesion (n = 12)	5	41.7
Total (n = 34)	11	32.4

Survival and metastatic disease

Three of the 46 patients treated in our institution died during follow-up (6.5%). In two cases the cause of death was not related to the giant cell tumour.

One patient suffered from progressive pulmonary metastases and died 12 months after surgery for a local recurrence, due to disseminated pulmonary disease while receiving chemotherapy. Another 26-year-old patient patient presenting with local recurrence had bilateral pulmonary metastases too. He underwent surgical resection of the tumour in both lungs, as well as

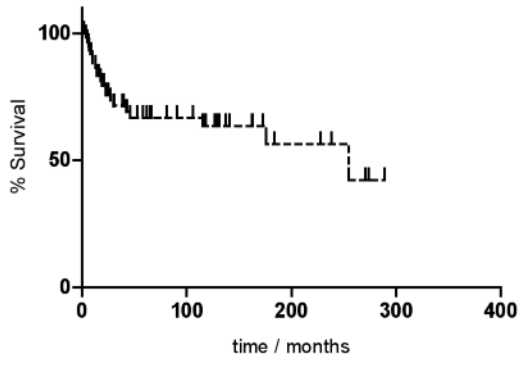

Fig. 3
Recurrence-free survival in 65 cases of surgically treated GCT of bone.

in the bone, and has been free of tumour for 162 months since surgery (Table I and Fig. 3).

Discussion

GCT of bone accounts for 4 to 9.5% of primary bone neoplasms in Western populations (13, 7), whereas in south-east Asian populations, it is more common, accounting for 20% of primary bone tumours (14). Females are more frequently affected than males, which was also seen in our series (15, 7). The tumour occurs most commonly in the distal femur, proximal tibia and distal radius of skeletally mature individuals (7, 15). The most frequent tumour site in our study (48%) was the lower end of the femur and the proximal tibia, corresponding to the results of other authors who have reported that approximately half of the tumours occur around the knee (16).

Although GCT is a benign tumour, pulmonary metastases are found in approximately 3-10% of cases (17-19). Even in the rare cases of metastatic pulmonary disease only about 10% of the patients die during follow-up, so long-term survival is not incompatible with persistent pulmonary lesions (18-20).

In the majority of cases the remarkable local aggressiveness of GCT as a benign tumour and its recurrence continues to be a surgical challenge.

There is no doubt that wide resection reduces the risk of recurrence, as also shown in our own patients, but salvage of the adjacent joint is often required by the patient, since GCT is most commen in the third decade of life, a period when individuals are in a productive phase in their lifes (1, 21). In our series the mean age was 32.6 yrs with 59% of all patients being in their third decade of life at time of initial treatment.

The appropriate surgical treatment strategy remains controversial. Resection should be performed when GCT is found in areas where reconstruction is not necessary, such as the proximal fibula, radius, or in the wing of the ilium. Historically, curettage has been associated with a high rate of recurrence of up to 56% (22, 7). In the past decades therefore different adjuvants have been introduced to further reduce the recurrence of GCT. They all aim to remove tumour cells that remain in situ after curettage because of their chemical (phenol, alcohol, hydrogen-peroxide) or thermal (liquid nitrogen, bone cement) effects. But even when the same treatment options are applied the recurrence rates vary considerably between 20-50% (11, 12). We try to preserve the joint even in cases with involvement of the subchondral bone plate, taking into account a higher rate of local recurrences. Our treatment of choice in most GCT's is curettage with local instillation of phenol and subsequent bone grafting. Our data suggest that there is a lower probability of recurrence when using phenol with curettage, though no signifcance could be shown in our series. Another widely used adjuvant is bone cement, which has some advantages such as immediate full weight bearing, being cost effective and allowing a better diagnosis of recurrence in plain X-ray or MRI (23). We do not use bone cement when the subchondral bone plate is affected, especially in the lower extremities. The difference in elasticity and stiffness of bone cement compared to subchondral bone may lead to early cartilage degeneration with subsequent osteoarthritis.

As in most rare diseases, it is very difficult to identify prognostic factors for GCT. There is a lack of large randomised, prospective studies. The existing differences in treatment philosphy and statistical analysis are making it almost impossible to compare the data of different patient series. There is no doubt that the histological grading by Jaffe *et al.* (24) and radiological grading by Campanacci *et al.* (1) have little prognostic value (7).

The most important factor in predicting recurrence is the adequacy of surgical procedure. In our study, curettage without adjuvant therapy showed the highest recurrence (53.9%) versus resection (16.7% recurrence). This observation has been confirmed by many authors (10, 25). McDonald *et al.* did not find a correlation between recurrence and the size, location and stage of the tumour or involvement of the subchondral bone in his patients (26). A pathological fracture does not seem to increase the risk of recurrence (27). In four of our patients who were newly diagnosed with GCT after suffering from a fracture, only one had a local recurrence.

Pulmonary metastases excision has been shown to provide good results (28, 19) but the role of chemotherapy in the course of treatment is still under debate. In our series, two patients suffered from lung metastases while experiencing a local recurrence at the same time. This might be an indication for a higher risk of getting lung metastasis with recurrent disease. Nevertheless,

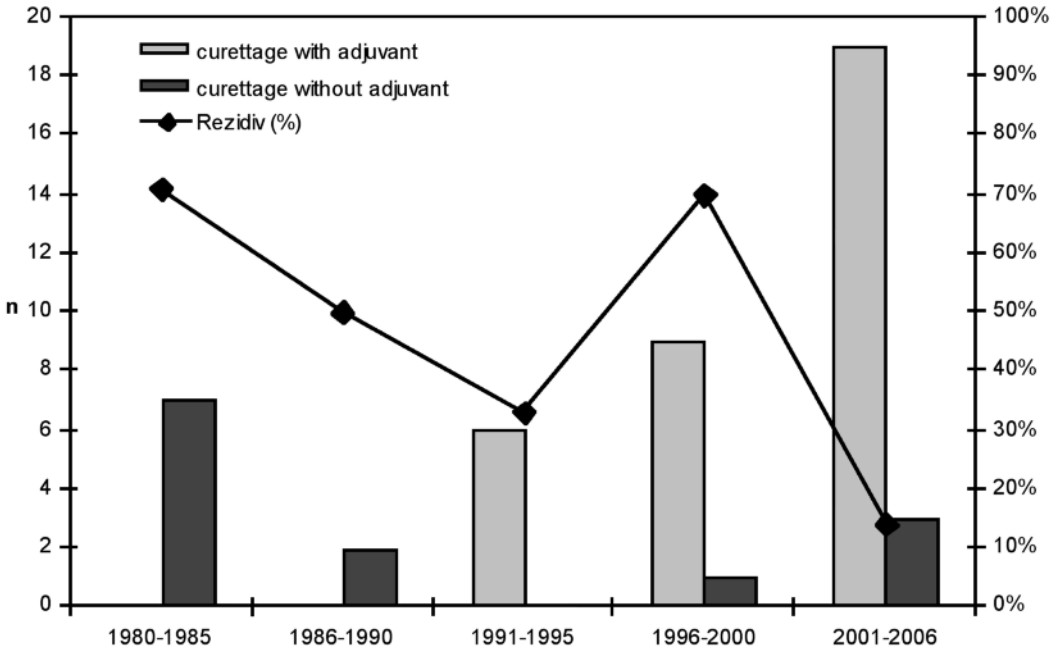

Fig. 4
Recurrence rate subject to use of phenol with curettage : 1981-2007

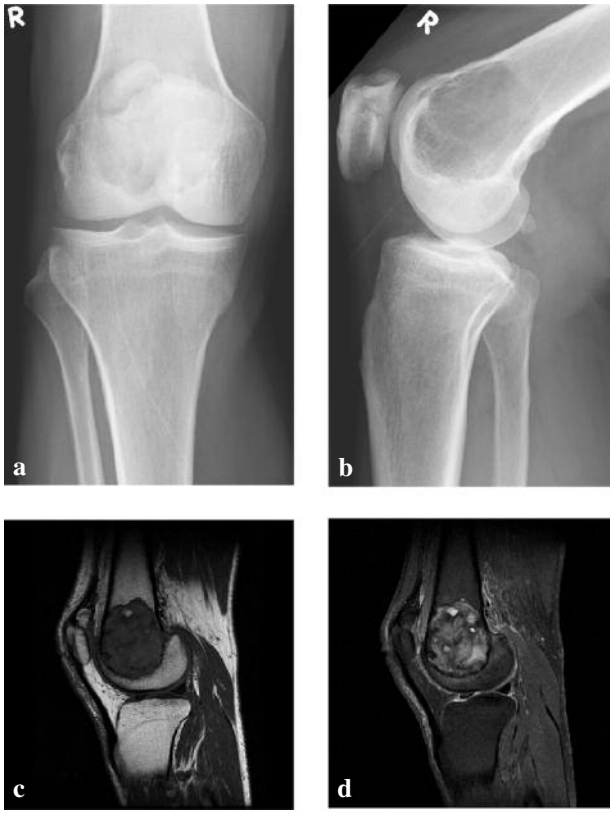

Fig. 5
Typical osteolytic lesion in the epi-/metaphysis of the distal femur (a and b).
On MRI scan the solid tumour is hypo-intense in T1-w SE (c) and demonstrating a heterogeneous hyperintense signal in STIR image (d).

metastatic disease has been reported as the first presentation of GCT (2). A computer tomography scan should therefore be done at the first presentation, followed by plain chest radiographs during follow-up. However, even in cases of metastatic lung disease an appropriate surgical approach may achieve a good clinical outcome with long-term survival, as seen in our series as well as in others (29).

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