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ORIGINAL PAPER

Giant cell tumor of bone: treatment and outcome of 214 cases

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Abstract
Background Two hundred and fourteen patients with benign giant cell tumor of bone (GCTB), treated from 1980 to 2007 at the Department of Orthopedics of the University of Muenster (Germany), were analyzed in a retrospective study.
Patients and methods The mean age was 33.3 years with a female-to-male ratio of 1.2 : 1. The mean follow up was 59.8 months. The recurrence rate of patients who received first treatment at our institution was 16.6%. The most common primary treatment was curettage (188 patients) usually followed by adjuvant local therapy. The effects of bone cement (PMMA), burring and hydrogen peroxide (H_2O_2) were statistically analyzed and the influence of a subchondral bone graft on the recurrence rate was evaluated.
Results PMMA alone ($n = 52$) reduces the likelihood of recurrence by the factor 8.2, additional high-speed burring ($n = 39$) by the factor 3.9 (compared to PMMA only). H_2O_2 ($n = 42$) seems to have an additional effect comparable to that of phenol although it did not reach statistical significance.
Conclusion The combination of all adjuncts (PMMA, burring, H_2O_2 – $n = 42$) reduces the likelihood of recurrence by the factor 28.2 compared to curettage only and therefore should be recommended as a standard treatment. If the tumor reaches close to the articulating surface a subchondral bone graft ($n = 42$) can be performed without risking a higher recurrence rate. We add seven cases of pulmonary metastases and two cases of multicentricity to the literature. Bisphosphonates and interferon alpha may have a beneficial effect.

Keywords Giant cell tumor of bone · Bone neoplasm · Local recurrence · Hydrogen peroxide · Bone cement · Curettage · Pulmonary metastases

Ethical Board Review statement: Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Giant cell tumor of bone (GCTB) usually is a benign primary skeletal lesion that accounts for about 5% of all primary bone tumors in adults. It is typically located in the meta-epiphyseal region of long bones, preferably in distal femur and proximal tibia, but occasionally also arises in the vertebrae, pelvis and sacrum (Campanacci et al. 1987; Freyschmidt et al. 1998). Giant cell tumors occur predominantly after skeletal maturity, exhibit a slight female predilection and have their peak incidence in the third and fourth decade of life (Campanacci 1990; Carrasco and Murray 1989; Freyschmidt et al. 1998; Larsson et al. 1975; Salzer-Kuntschik 1998; Schwartz 1998).

The histogenesis remains unclear (Freyschmidt et al. 1998). Histologically giant cell tumors consist of mainly three cell types: multinucleated giant cells resembling osteoclasts (hence the old name osteoclastoma), secondarily recruited mononuclear histiocytic cells, and neoplastic stromal cells which are the main proliferating cell population (Werner 2006). All attempts to classify the histological findings into a grading system (Campanacci 1994; Jaffe

et al. 1940) have not been able to provide any reliable prognostic significance in terms of recurrence rates or occurrence of metastases (Lausten et al. 1996; Masui et al. 1998; Turcotte et al. 2002).

On radiographs GCTB typically present as a lucent lesion without matrix calcifications eccentrically located within the bone (Fig. 1) (Freyschmidt et al. 1998). At first diagnosis the behavior of giant cell tumors is unpredictable. They may vary from indolent and static tumors to locally aggressive lesions with extensive bony destruction, cortical breakthrough, and soft-tissue expansion (Enneking 1986). Campanacci (1990) and Campanacci et al. (1987) inaugurated a three-stage classification system mainly based on radiological findings, which is in accordance to the surgical staging system of Enneking (1983).

The usual treatment of GCTB is intralesional curettage followed by bone grafting and/or bone cement packing [polymethyl methacrylate (PMMA)], with or without a local adjunct (Fig. 1). When close to the articulating surface, a subchondral bone graft may be performed. With this procedures the local recurrence rate ranges from 10 to 40% (Blackley et al. 1999; Campanacci et al. 1987; Goldenberg et al. 1970; Lausten et al. 1996; Malek et al. 2006), but exact statistical data on the individual effects of the different adjuncts and of the subchondral bone graft is lacking.

Local recurrence is accompanied by an increased risk of so called 'benign' pulmonary metastases (Bertoni et al. 1985; Bertoni et al. 1988; Campanacci et al. 1987; Cheng and Johnston 1997; Dominkus et al. 2006; Goldenberg et al. 1970; Kay et al. 1994; Maloney et al. 1989; McDonald et al. 1986; Osaka et al. 1997; Rock et al. 1984; Sanjay and Kadhi 1998; Siebenrock et al. 1998; Tubbs et al. 1992). Patients may also present with incompletely resectable or surgically inaccessible lesions (e.g. spine and pelvis). In rare cases patients may suffer from multicentric giant cell tumors either synchronous or metachronous during disease progression. Even with multidisciplinary approaches, the treatment results of these cases are still unsatisfying.

Aims of this study

The aim of this study is to summarize the experiences with giant cell tumors of bone treated at the University Hospital of Muenster, Germany from 1980 to 2007. Besides that we aim to evaluate the individual effects of bone cement, high-speed burring and hydrogen peroxide (H_2O_2) on local recurrence and to answer the question if a subchondral bone graft negatively influences the local recurrence rate.

Patients and methods

This is a retrospective comparative study based on revision of surgical protocols and patient records. The follow up was done via personal contact or phone call.

Two hundred and fourteen patients who have been treated on GCTB at the Department of Orthopedics of the University of Muenster, Germany from 1980 to 2007 were included in this study. All tumors were histologically certified as benign GCTB. Tumors that turned out to be osteosarcoma, fibrosarcoma, malignant fibrous histiozytosis or other malignant neoplasia were excluded. In cases of pulmonary metastases only patients were included who underwent a surgical procedure followed by histological confirmation of the diagnosis. The

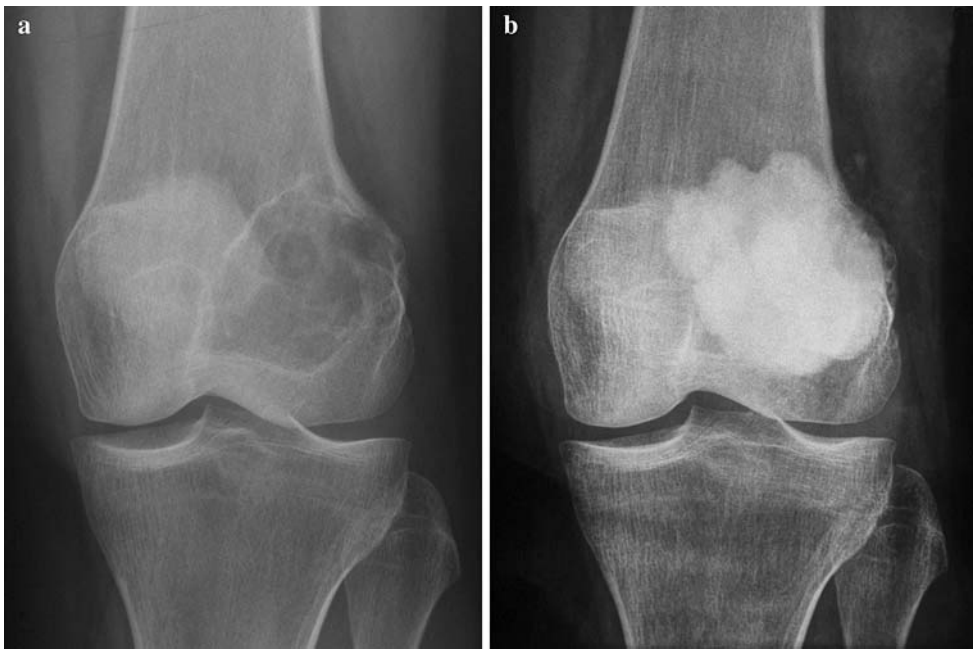

Fig. 1 Typical radiograph of GCTB of the distal femur Anteroposterior radiograph of an expansive stage II GCTB in typical meta-diaphyseal localization in the distal femur pre-operatively (**a**) and after curettage and bone cement packing (**b**)

term "multifocal" was used if two or more bones were involved at different anatomical locations, either synchronous (one case) or metachronous (one case).

One hundred and thirty nine patients received their first surgical treatment on GCTB at our hospital, while 75 were referred from other hospitals due to local recurrence or special surgical difficulties. One hundred and seventeen patients were female, 97 male, a relation of 1.2:1 (Fig. 2). One hundred and thirteen patients had a tumor of the left and 91 patients of the right half of the body (1.2:1), in five patients the tumor was located in the spine or sacrum without side-preference. The mean age at first diagnosis of the female patients was 33.0 (14.5–66.9) years, of the male patients 33.6 (14.7–73.9) years, both together 33.3 (14.5–73.9) years (Fig. 2). The mean follow-up was 59.8 (8.2–280.8) months.

The vast majority of tumors were sited in the meta-epiphyseal region of the long bones (Fig. 3). 48.6% of GCTB were localized around the knee joint (58 × distal femur, 42 × proximal tibia, 10 × proximal fibula), followed by pelvis (9.4%, $n = 20$), proximal femur (6.5%, $n = 14$), spine/sacrum (6.5%, $n = 14$), distal tibia and proximal humerus (5,1 %, $n = 11$ each). The rest ($n = 34$) was distributed in other localizations (Table 1; Fig. 3).

The diagnostics before treatment included plain X-rays of the involved region, local magnetic resonance imaging (MRI), nuclear scintigraphy and chest X-ray and/or chest CT.

Ninety-nine patients (71.2%) presented with a stage III, 39 patients (28.1%) with a stage II and 1 patient (0.7%) with a stage I lesion according to Campanacci and Enneking (Campanacci et al. 1987; Enneking 1983). In 75 patients the radiological findings were no longer available.

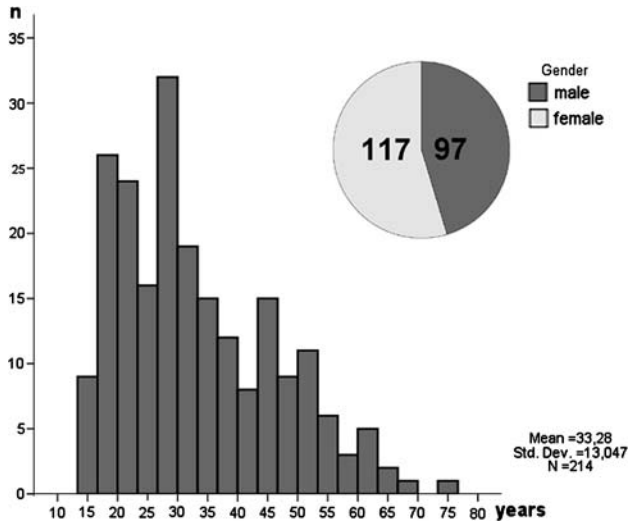

Fig. 2 Age and gender distribution of GCTB Typical age and gender distribution of GCTB. The mean age at first diagnosis of the female patients was 33.0, of the male patients 33.6 years. The youngest patient was 14.5 years and the oldest 73.9 years. The female-to-male ratio was 1.2:1

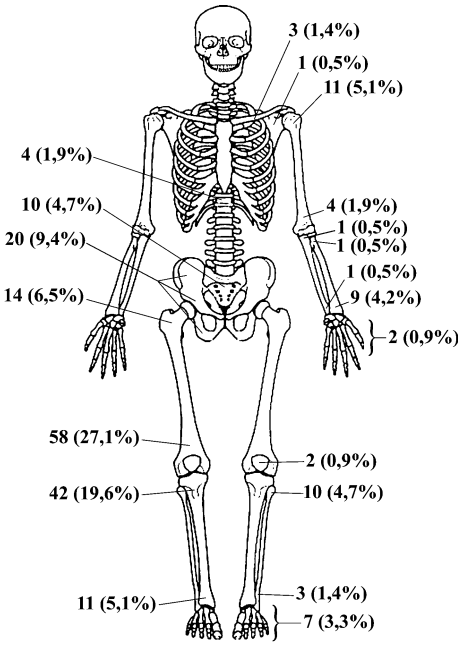

Fig. 3 Anatomical localizations of giant cell tumors of bone Anatomical distribution of giant cell tumors of bone. The percentage is indicated in parentheses with a total of 214 patients. The vast majority of tumors affected the meta-epiphyseal region of the long bones especially around the knee joint

Table 1 Local recurrence rate in relation to anatomical site

All patients			Localization	First treatment in Muenster		
N	Rec. n	Rec. %		*n*	Rec. n	Rec. %
11	1	9.1	Humerus prox.	7	0	0.0
9	8	88.9	Radius dist.	5	4	80.0
14	5	35.7	Femur prox.	13	3	23.1
58	20	34.5	Femur dist.	38	6	15.8
42	10	23.8	Tibia prox.	26	1	3.9
11	5	45.5	Tibia dist.	6	2	33.3
10	2	20.0	Fibula prox.	8	1	12.5
20	0	0.0	Pelvis	15	0	0.0
14	5	35.7	Spine/sacrum	6	1	16.7
25	10	40.0	Other	15	4	26.7
214	66	30.8		139	23	16.6

The left part of the table represents the whole patient collective (overall recurrence rate of 30.8%), the right part represents the patients who received first treatment at our institution (recurrence rate of 16.6%). Tumors of the distal radius had the highest recurrence rates followed by tumors of the distal tibia. No local recurrence occurred in the pelvis

Rec. n patient count with recurrence, *Rec %* recurrence rate, *prox.* proximal, *dist.* distal

To evaluate the effects of bone cement [polymethyl methacrylate (PMMA) abbreviated as "P"], high-speed burring (abbreviated as "B") and hydrogen peroxide (H_2O_2,abbreviated as "H") as well as of subchondral bone graft (abbreviated as "S") on local recurrence, the

Table 2 Overview of the different treatment regimen of curetted GCTB and their relation to local recurrence

Group	Surgical procedure	*n*	Rec. n	Rec. %
C	Curettage without adjunct	46	30	65.2
CB	Curettage + burring	9	2	22.2
CP	Curettage + PMMA	45	16	35.6
CPB	Curettage + PMMA + burring	21	5	23.8
CPBH	Curettage + PMMA + burring + H_2O_2	25	4	16.0
CPS	Curettage + PMMA + sponge-bone	7	3	42.9
CPSB	Curettage + PMMA + sponge-bone + burring	18	2	11.1
CPSBH	Curettage + PMMA + sponge-bone + burring + H_2O_2	17	1	5.9
		188	63	33.5
Subchondral bone graft				
CP + CPB + CPBH	Curettage + PMMA ± adjunct	91	25	27.5
CPS + CPSB + CPSBH	Curettage + PMMA ± adjunct + sponge-bone	42	6	14.3
High-speed burring and hydrogen peroxide				
CP + CPS	Curettage + PMMA ± sponge-bone	52	19	36.5
CPB + CPSB	Curettage + PMMA ± sponge-bone + burring	39	7	18.0
CPBH + CPSBH	Curettage + PMMA ± sponge-bone + burring + H_2O_2	42	5	11.9

Groups of different treatment regimen of curetted giant cell tumors of bone. Note the extraordinary high recurrence rate without using adjuncts (C) compared to using all possible adjuncts (CPBH + CPSBH)

Rec. n patient count with recurrence, *Rec. %* recurrence rate

different treatment regimen were grouped and compared with each other. The grouping was performed as followed (Table 2):

- Curettage with or without sponge-bone without any adjunct (group C, $n = 46$)
- Curettage followed by burring (group CB, $n = 9$)
- Curettage followed by PMMA packing without any other adjunct (group CP, $n = 45$)
- Curettage followed by burring and PMMA packing (group CBP, $n = 21$)
- Curettage followed by burring, H_2O_2-lavage and PMMA packing (group CBHP, $n = 25$)
- Curettage followed by PMMA packing in combination with a subchondral bone graft (group CPS, $n = 7$) either after burring only (group CPSB, $n = 18$) or after burring and H_2O_2 (group CPSBH, $n = 17$)

To find out if burring plus H_2O_2 is better than burring only, three new groups were formed and compared to each other (CP + CPS, $n = 52$; CPB + CPSB, $n = 39$ and CPBH + CPSBH, $n = 42$). Then two groups were formed to compare curettage plus PMMA (CP + CPB + CPBH, $n = 91$) with curettage plus PMMA and an additional subchondral bone graft (CPS + CPSB + CPSBH, $n = 42$) regardless of other adjuncts.

To evaluate the sole effects of the adjuncts the different treatment regimen were re-grouped neglecting the use of a subchondral bone graft (Tables 2, 3). Curettage with PMMA packing (group CP + CPS) was defined as standard treatment and the additional use of burring and H_2O_2 was evaluated.

Table 3 Statistical analysis of the different treatment regimen of curetted GCTB

Group	Group	*P*	Likelihood ratio
C vs.	CB	0.006	5.782
	CP	0.001	8.128
	CPB	0.000	10.254
	CPBH	0.000	16.876
	CPS	0.193	1.251
	CPSB	0.000	16.725
	CPSBH	0.000	20.274
	CPBH + CPSBH	0.000	28.184
	CP + CPS	0.004	8.145
CP + CPS vs.	CPB + CPSB	0.038	3.906
	CPBH + CPSBH	0.005	7.870
CPB + CPSB vs.	CPBH + CPSBH	0.519	0.586
CP + CPB + CPBH vs.	CPS + CPSB + CPSBH	0.098	2.983

Statistical analysis of variance of the different treatment regimen in relation to local recurrence. Every adjunct on its own is able to significantly reduce the local recurrence rate. The combined use of all possible adjuncts leads to a reduction of the likelihood of recurrence by the factor 28.2 (CPBH + CPSBH) compared to curettage only. The additional use of hydrogen peroxide decreases the likelihood of recurrence but does not reach statistical significance. The p-value was determined using ANOVA with post hoc tests (LSD), the likelihood ratio using Chi-square tests

Statistical analysis was done with SPSS 15 (significance level $P < 0.05$). The statistical significance was determined using ANOVA with post hoc tests (LSD) and the likelihood ratio using chi-square tests.

Results

The most common primary treatment was curettage [188 patients (87.9%)] with filling of the defect either with sponge-bone [38 patients (20.2%)], bone cement only [91 patients (51.1%)] or bone cement in combination with a subchondral bone graft [42 patients (22.3%)]. In 17 patients (9.6%) curettage without filling of the defect was performed. Ten of these patients were operated in other hospitals (no tumor centers), in two patients very small bones (toe and metatarsus) were affected, and in five patients the margins after intralesional resection were additionally curetted (prox. fibula, ischium, pubic bone, sacrum, prox. humerus with fibula-reconstruction).

Wide resection was done in 18 patients (8.4%). In three of these patients dispensable bones (two clavicles, one proximal fibula) were afflicted. In one case the Os ischium and in four cases the Os ilium was resected (one case with implantation of a pelvic prosthesis). The size of the tumor or pathologic fracture necessitated amputations in two cases (distal femur and distal tibia) and reconstructions with tumor prostheses in eight cases (3 × proximal humerus, 1 × distal tibia, 1 × proximal tibia, 3 × distal femur). Resection without adequate margins was performed in four cases (2 × proximal fibula, 2 × thoracic spine)

four patients were inoperable due to tumor localization (3 × sacrum, 1 × acetabulum) and received irradiation.

Local recurrence

Sixty-six out of 214 patients developed local recurrence (30.8%) after a median time period of 12.4 (1.6–172.2) months. The recurrence rate varied depending on the tumor site. The highest recurrence rate of 88.9% (8 out of 9) was in distal radius followed by 45.5% (5 out of 11) in distal tibia (Table 1). No local recurrence occurred in the pelvis.

Twenty percent (8 out of 40 patients) with a grade II and 31.3% (31 out of 99 patients) with a grade III lesion developed local recurrence. The difference was not statistically significant ($P = 0.337$).

The recurrence rate without a soft-tissue component was 16.2% (11 out of 68). When a soft-tissue component was present (either documented in the radiographic finding or in the surgical protocols) the recurrence rate was 29.7% (27 out of 91). In Chi-square tests the difference was statistically significant ($P = 0.045$; likelihood ratio 4.0). On 55 patients information on soft-tissue component was missing.

None of the patients treated with wide resection developed local recurrence (mean follow-up of 66.8 months).

Intralesional curettage

The overall recurrence rate after intralesional curettage was 33.5% (63 out of 188). Between the different groups the recurrence rates varied from 65.2% (30 out of 46) if only curettage without any adjunct was performed (group C) to 11.9% (5 out of 42) if all adjuncts (PMMA, burring, H_2O_2) were combined (group CPBH + CPSBH).

A statistical analysis of variance revealed a significant difference of the between-subject factor group ($P = 0.000$, $F = 6.369$). To further analyze these findings post hoc tests (LSD) were performed.

If compared to curettage only, every adjunct is able to significantly reduce the local recurrence rate on its own. The best results were achieved with a combination of all adjuncts ($P = 0.000$, Table 2).

A subchondral bone graft does not have a negative effect on local recurrence ($P = 0.098$).

Performing the worst treatment regimen (group C, curettage without adjunct) leads to a likelihood of recurrence which is 28.2 times higher ($P = 0.000$) compared to the best treatment (group CPBH + CPSBH, combination of all adjuncts). Bone cement without any other adjunct is able to reduce the likelihood of recurrence by the factor 8.2 ($P = 0.004$). The additional use of high-speed burring (group CPB + CPSB) reduces the likelihood of recurrence by the factor 3.9 ($P = 0.038$) increasing even to factor 7.9 ($P = 0.005$) if combined with H_2O_2 (group CPBH + CPSBH). Although H_2O_2 is able to increase the effect of the other adjuncts, its solely influence is not statistically significant (group CPB + CPSB vs. CPBH + CPSBH, $P = 0.519$).

Pulmonary metastases

The rate of pulmonary metastases was 3.3% (7 out of 214 patients, 5 male, 2 female). No patient developed pulmonary metastases without showing local recurrence. The median time period until diagnosis of pulmonary metastases (time-point of histological confirmation) was 22.3 (5.2–106.3) months. The anatomical localizations of the primary tumor were distal femur, distal tibia, proximal femur, proximal tibia, thoracic spine and proximal radius/ulna. One of the patients suffered from multifocal GCTB of the proximal and distal femur and the proximal tibia. In all patients the first treatment of the primary tumor was intralesional curettage/resection.

The treatment of the pulmonary metastases was surgical removal in four cases, neoadjuvant chemotherapy (combination of ifosfamide, cisplatin and adriablastin) followed by surgical resection in one case, application of interferon alpha and bisphosphonates in three cases, and interferon alpha and bisphosphonates added by chemotherapy in one

case. Two patients were inoperable of which one was treated with chemotherapy plus irradiation and the other with interferon alpha plus bisphosphonates.

At final follow-up (mean 54.9; minimum 19.8; maximum 129.7 months) one patient was cured of disease, five had stable disease and one died of disease. Despite high dose chemotherapy the latter developed metastases in the lung, soft tissue of the upper arm, chest, tongue, brain and small intestine and finally died due to intestinal perforation.

Multifocal GCTB

The rate of multifocal GCTB was 0.9% (2 out of 214 patients). One patient was male (16 years at first diagnoses), another female (17 years at first diagnosis). The first presented with synchronous affliction of the proximal and distal femur and the proximal tibia followed by pulmonary metastasis, the latter developed a metachronous involvement of the distal tibia/fibula and proximal femur during the course of disease.

The treatment in both cases was surgery of the involved localizations followed by medication with interferon alpha and bisphosphonates. At final follow-up the female (after 41.1 months) was free of disease and the male (after 211.2 months) presented with stable disease.

Discussion

The age and gender distribution, the typical localizations as well as the recurrence rates of our patient collective are in accordance with the literature (Campanacci 1990; Campanacci et al. 1987; Carrasco and Murray 1989; Freyschmidt et al. 1998; Goldenberg et al. 1970; Larsson et al. 1975; Ritschl et al. 1989; Salzer-Kuntschik 1998; Schwartz 1998).

The recurrence rate varied significantly depending on tumor site. The extraordinary high recurrence in the distal radius (88.9%; 8 out of 9) is in contrast to previous reports (Ozalp et al. 2006). It may be explained by insufficient primary treatment. Despite the aggressiveness of the tumors (all grade III, 6 with a soft tissue component) the initial procedure was intralesional curettage in all cases, bone cement packing was performed in five cases only. Contrary to this no recurrence occurred when the tumor was located in the pelvis. This may be partially explained by the chosen treatment. In 14 out of 20 patients the usual intralesional procedure was performed (ten curettage and packing with bone cement and four intralesional resection followed by additional curettage of the margins). Five out of 20 patients underwent wide resection, which might have influenced the low recurrence rate (one patient was only irradiated). The data in the literature on GCTB of the pelvis is controversial with approximately 50% local recurrence after surgery with intralesional margins and 0% after wide resection (Leggon et al. 2004; Sanjay et al. 1993).

The amount of active and aggressive lesions (99.3% stage II and III) according to the classification of Campanacci et al. (1987) and Enneking (1983) is slightly higher than indicated in the literature (Campanacci 1990; Campanacci et al. 1987; Ritschl et al. 1989; Turcotte et al. 2002). This is most likely due to the fact that our institution is a center of excellence for bone tumors and especially patients with progressed disease are referred from other hospitals. As expected the recurrence rate of stage III tumors was higher than of stage II (Oda et al. 1998; Prosser et al. 2005) but the difference was not statistically significant ($P = 0.337$). Soft-tissue extension has been proven to be a prognostic marker concerning local recurrence which could be reproduced by our data with a likelihood four times higher when a soft-tissue component was present ($P = 0.045$) (Prosser et al. 2005).

There is a vast number of surgical procedures on GCTB ranging from intralesional curettage to wide resection (Harle and Wuisman 1989; Lausten et al. 1996; Persson et al. 1984; Ward and Li 2002; Wuisman et al. 1989). Although wide resection leads to the lowest local recurrence rates it can not be recommended as standard treatment (Liu and Wang 1998). The usually benign behavior of GCTB and the satisfying local control with intralesional procedures in most cases does not legitimate mutilating surgeries (Vult von Steyern et al. 2006).

The high local recurrence rate in curettage without adjunct was already described in previous studies (Goldenberg et al. 1970; Lausten et al. 1996; Masui et al. 1998; Persson et al. 1984; Tunn and Schlag 2003; Wuisman et al. 1989). This is most likely due to the incomplete tumor removal. Therefore the standard procedure is accurate intralesional curettage with additional adjuncts for eradication of remaining tumor cells. This can be accomplished by physical adjuncts such as cryotherapy, hyperthermia or high-speed burring (Blackley et al. 1999; Demichev 1994; Fan et al. 1996; Malawer et al. 1999; Malek et al. 2006) or chemical substances with cytotoxic effects such as phenol, alcohol, H_2O_2 or methotrexate (Blackley et al. 1999; Durr et al. 1999; Goldenberg et al. 1970; Jones et al. 2006; Kirchen et al. 1996; Lausten et al. 1996; Masui et al. 1998; Nicholson et al. 1998; Ritschl et al. 1989; Rooney et al. 1993; Schiller et al. 1989; Schwartz 1998; Szendroi 1992; Trieb et al. 2001; Wuisman et al. 1989). Bone cement reveals both effects: physical via thermal necrosis (Leeson and Lippitt 1993; Mjoberg et al. 1984) and cytotoxic via free radicals (Nelson et al. 1997).

This study was focused on the effects of bone cement, high-speed burring and H_2O_2 and is supposed to answer the question if a subchondral bone graft negatively influences the local recurrence rate.

Bone cement

The use of bone cement is reported as a safe and effective procedure that provides local adjuvant therapy and immediate stability (Bini et al. 1995; Blackley et al. 1999; Malek et al. 2006; Rooney et al. 1993; Szendroi 1992). Apart from that it presents ideal radiological features to easily identify local recurrences (Becker 1989; Wada et al. 2002). Although reconstruction with bone cement is accepted by most experts as the standard treatment of GCTB, exact data on its efficacy is lacking. This is most likely because the use of cement is usually combined with other adjuncts such as burring or phenol (Saiz et al. 2004; Szendroi 1992). In these cases it is not possible to determine the cement-associated effect. Due to our high count of patients we were able to statistically analyze the solely effect of bone cement (without any other adjunct) after curettage and show that it reduces the local recurrence rate by the factor 8.2 ($P = 0.004$) compared to curettage only.

Removal of the bone cement after a few recurrence-free months and filling of the defect with a bone graft as it was recommended by some authors in the past (Becker 1989; Harle and Wuisman 1989), is no longer a routine procedure since no specific complications according to cementation occurred in practice (Turcotte 2006; Turcotte et al. 2002; Wada et al. 2002; Ward and Li 2002). Removal of the bone cement necessitates a preventable surgery and hospitalization of a mostly painless patient, with the risk of infection and temporary reduced weight bearing. An accelerated rate of arthritis due to bone cement compared to packing with sponge-bone has not been documented so far (Szalay et al. 2006). There is no significant difference in the functional outcome of the two procedures (Turcotte et al. 2002) but a significant reduction of local recurrence with the use of bone cement, without any donor-site morbidity.

Subchondral bone graft

If the tumor reaches close to the articulating cartilage bone cement packing can be combined with a subchondral bone graft. Although this is a widely accepted procedure there is no data in the literature regarding its effect on local recurrence. To prevent cartilage destruction burring may not be performed as aggressive as needed and the bone cement is unable to reveal its effect in the subchondral area. Therefore the recurrence rate might be higher in these cases (Suzuki et al. 2007).

We were able to show that there is no significant difference in local recurrence compared to bone cement only. A subchondral bone graft can be performed safely. If it is of any benefit regarding the incidence of arthritis is not answered yet (Frassica et al. 1990; Suzuki et al. 2007; Szalay et al. 2006).

High-speed burring

The additional burring of the cavity with a high-speed burr after intralesional curettage is reported to decrease the recurrence rate (Blackley et al. 1999; Malek et al. 2006; Schiller et al. 1989; Turcotte et al. 2002). This is most likely due to the thermal effect and the additional millimeter of resection. In our study burring turned out to be the most relevant factor for reducing local recurrence. The likelihood of recurrence after curettage and bone cement packing was almost 4 times higher ($P = 0.038$) than after the same procedure with additional burring. Therefore additional burring with a high-speed air drill should be recommended as a standard procedure.

Lavage with hydrogen peroxide

Although the most prevalent chemical adjunct in treatment of GCTB is phenol (Durr et al. 1999; Ritschl et al. 1989; Saiz et al. 2004; Schiller et al. 1989; Trieb et al. 2001; Turcotte et al. 2002) we regularly perform the lavage with H_2O_2 in our institution. There are only a few reports about its effect on recurrence in GCTB (Ward and Li 2002). Nicholson et al. examined the effects of hydrogen peroxide on giant cell tumor cells and osteoblasts grown in culture. Cell lysis and death occurred when exposed to a minimal concentration of H_2O_2 as it is commonly used in clinical practice (Nicholson et al. 1998).

With curettage and bone cement packing as the standard basic treatment, the likelihood of recurrence can be reduced by the factor 7.9 with additional burring and H_2O_2 lavage. Additional burring without H_2O_2 leads to a reduction by the factor 3.9. But comparing the recurrence rates after curettage, bone cement and burring to curettage, bone cement, burring plus H_2O_2 the solely effect of H_2O_2 is not statistically significant ($P = 0.519$).

These data show that the results with H_2O_2-lavage are comparable to that obtained with phenol (Durr et al. 1999; Ritschl et al. 1989; Saiz et al. 2004; Schiller et al. 1989; Trieb et al. 2001; Turcotte et al. 2002). Both chemicals are able to reduce the recurrence rate, but clear statistical evidence is lacking. Compared to phenol, that can cause serious chemical burn and systemically toxicity, H_2O_2 has no major side effects so that it can be used as an alternative.

Pulmonary metastases

The rate of pulmonary metastasis in our collective counts 3.3% and is in accordance with previous reports (Bertoni et al. 1985, 1988; Cheng and Johnston 1997; Goldenberg et al. 1970; Kay et al. 1994; Masui et al. 1998; Osaka et al. 1997; Rock et al. 1984; Sanjay and Kadhi 1998; Siebenrock et al. 1998; Tubbs et al. 1992). Interestingly the gender

distribution is contrary to non-metastasizing tumors. Although there is usually a female-preponderance, metastases occurred predominantly in male (5:2), which might be an incidental finding due to the small number of patients ($n = 7$) in this group.

The literature indicates that local recurrence is accompanied by an increased risk of pulmonary metastases (Bertoni et al. 1985; Cheng and Johnston 1997; Kay et al. 1994; Lausten et al. 1996; Masui et al. 1998; Rock et al. 1984; Sanjay and Kadhi 1998; Tubbs et al. 1992). This can be supported by our data because all cases of metastases appeared after local recurrence. Like the prior study of Dominkus et al. (2006) we were not able to confirm the high incidence of metastases in tumors of the distal radius indicated in the literature (Tubbs et al. 1992). Eight out of nine patients with tumors of the distal radius developed local recurrence (88.9%) but none of them developed metastases.

Although the prognosis after surgical removal of the metastases is usually good (Sanjay and Kadhi 1998; Siebenrock et al. 1998; Tubbs et al. 1992) the individual course remains unpredictable. In some cases patients may die due to metastasizing GCTB (Leichtle et al. 2006; Siebenrock et al. 1998) as it happened to one of our patients. Cases of multiple metastases besides involvement of the lung, as in one patient of our series, are rare and may be associated with a fatal outcome (Leichtle et al. 2006). There are also reports about spontaneous regression or permanence of metastases without specific therapy (Bertoni et al. 1988; Dominkus et al. 2006; Kay et al. 1994; Siebenrock et al. 1998).

Some centers simply observe metastases (Sanjay and Kadhi 1998; Sanjay and Younge 1996) but most centers perform surgical removal (Kay et al. 1994; Maloney et al. 1989; Rock et al. 1984; Siebenrock et al. 1998). In that case early detection is essential (Kay et al. 1994). Patients should be regularly examined with a chest-CT, especially after local recurrence has occurred (Osaka et al. 1997). In cases of suspicious findings, histological verification should be aspired (Maloney et al. 1989).

After surgery or if removal of the lesions is not possible, some experts advocate systemic chemotherapy (e.g. ifosfamide, cyclophosphamide, cisplatin, adriblastin). If this is an effective therapy or simply an over-treatment, is still discussed controversially (Bertoni et al. 1985; Cheng and Johnston 1997; Kay et al. 1994; Maloney et al. 1989; Osaka et al. 1997; Sanjay and Kadhi 1998; Stewart et al. 1995). In our patients we routinely administered bisphosphonates in combination with interferon alpha as adjuvant therapy. Bisphosphonates are described to reveal zytotoxic activity against osteoclasts and giant cell tumor cells (Chang et al. 2004; Cheng et al. 2004; Fujimoto et al. 2001; Punyaratabandhu et al. 2007). Interferon alpha is known to have anti-angiogenic effects (Dickerman 1999; Kaban et al. 1999; Kaban et al. 2002; Kaiser et al. 1993). Whether these substances are of any clinical importance in treatment of GCTB has to be imvestigated in future studies.

Multifocal GCTB

In our series as well as in the former literature approximately 1% of GCTB present as multiple synchronous or metachronous lesions (Haskell et al. 2003; Hindman et al. 1994; Hoch et al. 2006; Leggon et al. 2004; Taraporvala et al. 1997; Taylor et al. 2003). As reported by several authors, patients with multicentric GCTB are likely to be younger than those with a solitary lesion (Hindman et al. 1994; Hoch et al. 2006). According to Hoch et al. (2006) 59% of the patients are younger than 20 years of age. These findings are supported by our study. The male was 16 years, the female 17 years of age at first diagnosis. The first presented with synchronous affection and developed pulmonary metastases after 5 months. The treatment is usually the same as for solitary lesions.

Conclusion

Every tested adjunct was proven to significantly reduce the rate of local recurrence. Bone cement alone reduces the likelihood of recurrence by the factor 8.2, additional high-speed burring by the factor 3.9 (compared to bone cement only). H_2O_2 seems to have an additional effect comparable to that of phenol although it did not reach statistical significance.

The combination of all adjuncts (bone cement, burring, H_2O_2) reduces the likelihood of recurrence by the factor 28.2 compared to curettage only and therefore should be recommended as a standard treatment.

If the tumor reaches close to the articulating surface a subchondral bone graft can be performed without risking a higher recurrence rate.

We add seven cases of pulmonary metastases (one with additional extrapulmonal metastases and dismal course) and two cases of multicentricity to the literature. Bisphosphonates and interferon alpha may have a beneficial effect.

Conflict of interest statement Each author certifies that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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