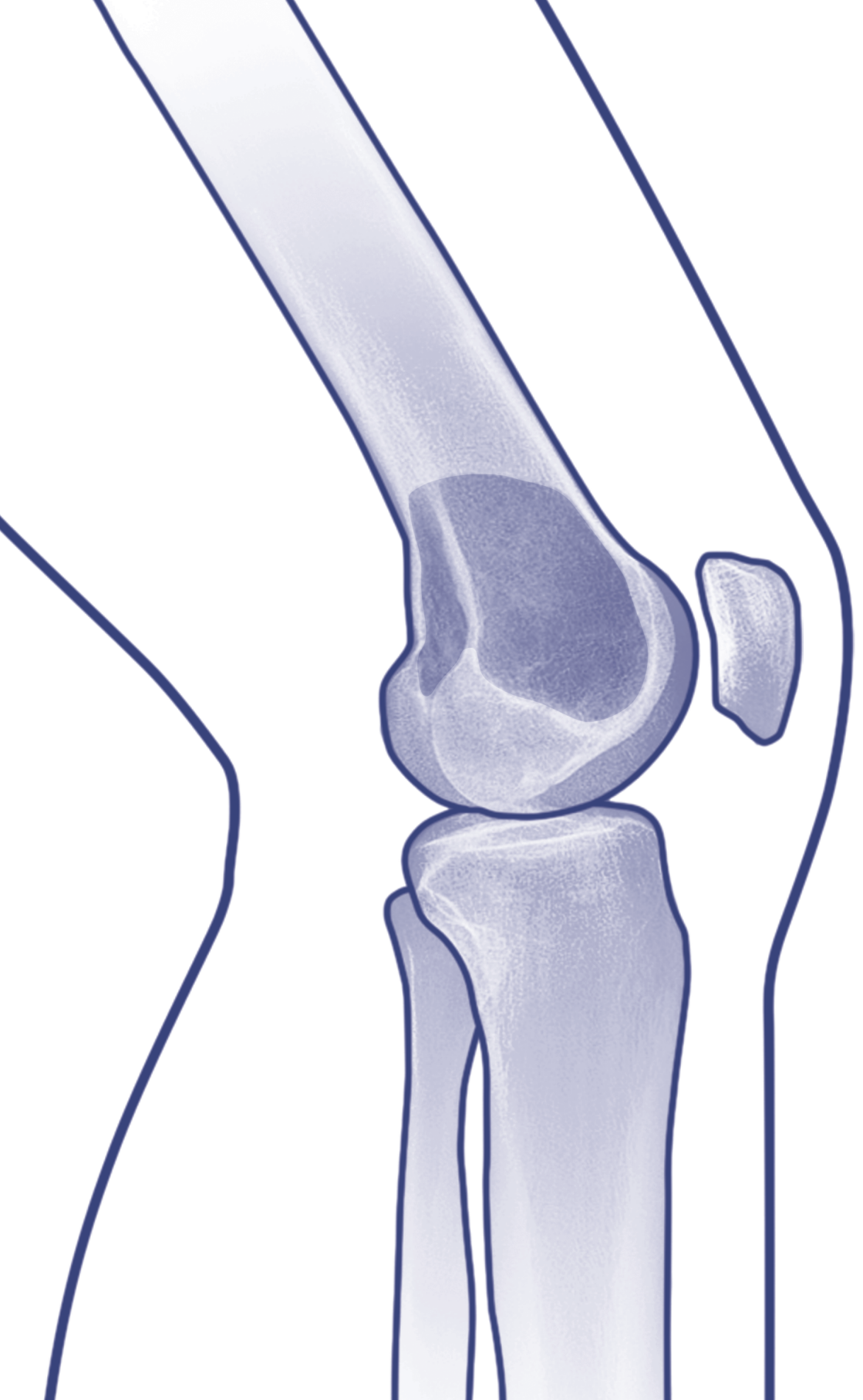

Chapter 5

Giant cell tumors of the small bones of the hands and feet – Long-term results of 30 patients and systematic literature review

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Abstract

Background Giant cell tumor of bone (GCTB) of the small bones of the hands and feet are rare. Small case series have been published but there is no consensus about ideal treatment.

Patients and methods We performed a systematic review, initially screening 775 titles, and included 12 papers comprising 91 patients with GCTB of the small bones. We then retrospectively analyzed 30 patients treated for GCTB of the small bones between 1987 and 2010 in five specialized centers. We evaluated the rate of complications and recurrence as well as the factors that influenced their functional outcome.

Results The rate of recurrence in literature was found to be 72% (18 of 25) after curettage, 13% (2 of 15) after curettage with adjuvants, 15% (6 of 41) after resection and 10% (1 of 10) after amputation. In this study, primary treatment was curettage in six, curettage with adjuvants (phenol or liquid nitrogen with or without polymethylmethacrylate (PMMA)) in 18 and resection in six. At a mean follow-up of 7.9 years (2 to 26) the rate of recurrence was 50% (n=3) after curettage, 22% (n=4) after curettage with adjuvants and 17% (n=1) after resection (p=0.404). The only complication was pain in one patient, which resolved after surgical removal of remnants of PMMA. We could not identify any individual factors associated with a higher rate of complications or recurrence. The mean postoperative Musculoskeletal Tumor Society scores were slightly higher after intralesional treatment including curettage and curettage with adjuvants (mean 29; range 20–30) compared with resection (mean 25; range 15–30) (p=0.091).

Conclusions Repeated curettage with adjuvants eventually resulted in the cure for all patients and is therefore a reasonable treatment for both primary and recurrent GCTB of the small bones of the hands and feet.

Introduction

Giant cell tumor of bone (GCTB) is a relatively common benign lytic lesion that accounts for 4% to 5% of primary bone tumors and almost 20% of benign bone tumors [1]. It occurs mainly between the ages of 30 and 50 years and is slightly more common in women [2, 3]. The most common sites are the meta-epiphyseal regions of the long bones (85%), with more than 50% located in the distal femur, proximal tibia and distal radius [4]. GCT of the axial skeleton accounts for a further 10% [2, 4]. It is rare in the small bones of the hands and feet (between 1.7% and 5% of all GCT) [5-11]. The differential diagnosis includes enchondroma, fibrous dysplasia, aneurysmal bone cyst, osteomyelitis and brown tumor from hyperparathyroidism.

The standard treatment of lesions in the long bones is curettage, often with local adjuvants such as phenol, liquid nitrogen (cryosurgery) and/or polymethylmethacrylate (PMMA) to reduce the recurrence rate, which has been reported from 12% to 34% [12-16]. More aggressive lesions of the long bones with soft tissue extension, pathologic fracture or involvement of joints may be treated by *en bloc* resection [14, 16].

Only a few studies of GCTB of the small bones have been published. As most are single case reports there is no consensus about the preferred treatment, which ranges from curettage (with or without adjuvants) to *en bloc* resection and even amputation. Local recurrence rates anywhere between 0% and 100% have been reported after surgical treatment [6-8, 17].

Most recurrences occur within two years of surgery, and *en bloc* resection has been shown to result in a lower rate of recurrence (0% to 50%) [6-8, 18, 19]. However, reconstruction after resection may be difficult in cases of multicentric GCTB of the small bones, which has been reported in 7% to 18% of cases [5, 20]. Curettage without adjuvants may not afford complete tumor removal, resulting in a higher rate of recurrence (0% to 100%) [6, 8, 17, 21, 22]. Radiation-induced sarcoma has been reported in 5% to 10% of patients receiving radiotherapy as adjuvant treatment, and it is therefore not recommended for primary lesions [4, 8].

The aims of this multicenter study were first to perform a systematic literature review of the surgical treatment of GCTB of the small bones. Secondly, we aimed to evaluate the rates of complication and recurrence and attempt to define any association between patient and tumor characteristics and functional outcome after different surgical approaches.

Patients and methods

We performed a systematic search of the literature on GCTB of the small bones published between 1 January 1990 and 17 January 2011. Search terms and MeSH headings used were 'giant cell tumors', 'GCT', 'small bones', 'hand bones', 'foot bones', and all the individual small bones separately. We identified 775 unique titles in PubMed, EMBASE, Web of Science and Academic Search Premier. All titles and abstracts were screened by two reviewers (VCO, LH). Inclusion criteria were case series only published after 1990 in English, Dutch, Portuguese, French, Italian or German; other languages were excluded. Furthermore, we excluded papers that focused purely on radiological and/or histopathological assessment of GCTB of the small bones, reviews without new clinical cases, and papers on GCTB of the long bones, giant cell tumor of soft tissue (GCT-ST), diffuse-type giant cell tumor (Dt-GCT) and giant cell tumor of the tendon sheath (GCT-TS). After review of the 775 titles, 42 abstracts were screened, of which 23 full-text articles were assessed. Full text assessment resulted in 11 further exclusions, leaving a total of 12 papers for systematic review (Figure 1) [6-9, 17-19, 21-25].

In addition we retrospectively reviewed 31 consecutive patients with primary GCTB of the small bones from a total of 570 consecutive patients with GCTB (5.4%) treated between 1987 and 2010 in the authors' five tertiary referral centers for orthopedic oncology. One patient with a malignant GCTB after local recurrence was excluded. The 30 remaining patients had a mean follow-up of 7.9 years (range 2–26; median 5.2). No patient was lost to follow-up. There were 17 men and 13 women with a mean age of 29.6 years (mean 13–68) (Table 1). As primary treatment, six patients underwent curettage, 18 curettage plus adjuvants (nine phenol, five liquid nitrogen, two phenol and PMMA, one liquid nitrogen and PMMA and one PMMA), and six resection (five *en bloc* and one marginal) (Table 2). Thorough curettage was followed by three cycles of phenolization and neutralization with ethanol, or by three cycles of liquid nitrogen, and subsequently by filling the cavity with either bone graft or PMMA. A high-speed burr was used in nine patients treated with curettage and adjuvants (Table 2). In the Leiden University Medical Center, Leiden, the Netherlands (center 1) and the Centro Hospitalar do Porto – Hospital Santo Antonio, Porto, Portugal (center 5) musculoskeletal pathologists graded the

GCTB histologically, but this did not influence the choice of surgical treatment. As extension of the tumor can be evaluated very accurately on MR imaging, the purely radiological grading system of Campanacci *et al.* [1] was not used. In practice, every GCTB is treated according to its tumor characteristics, such as site, the presence of a pathologic fracture and/or soft tissue extension, instead of according to a specific grading system.

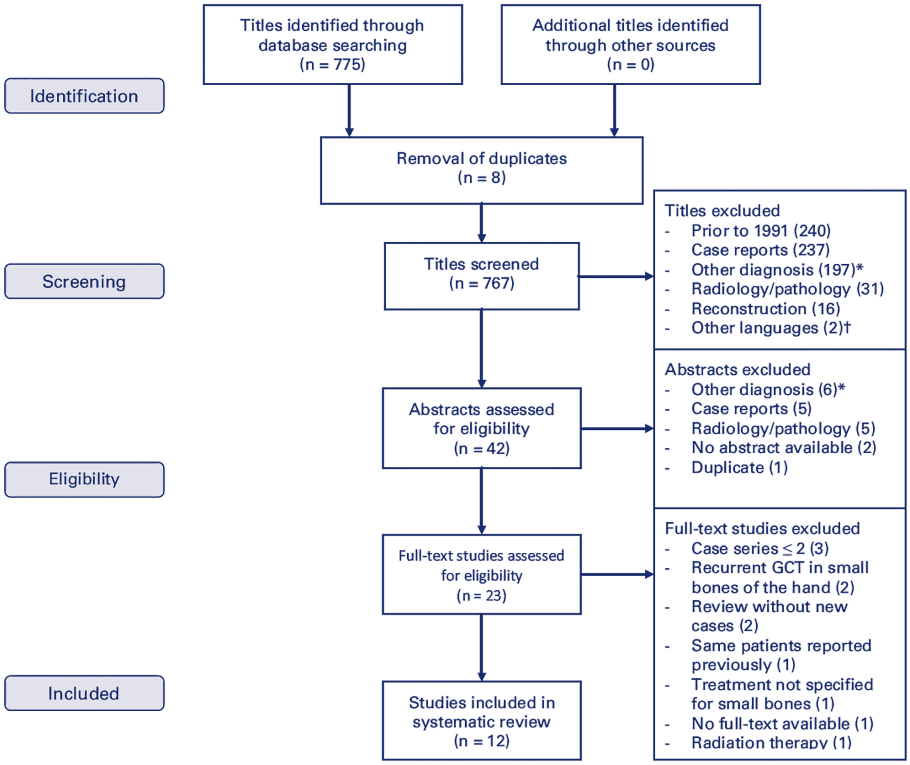

Figure 1 Flowchart of systematic literature search

*Including but not limited to: GCTB of the long bones (mainly distal radius), GCTB of the axial skeleton, multifocal GCTB, malignant GCTB, other bone and soft tissue tumors (e.g. Dt-GCT, GCT-TS, chondroblastoma, chondrosarcoma, osteosarcoma), GCTB in animals etc.
**Excluded languages were Chinese and Turkish.

Table 1 Descriptives

	n	%
Gender		
Male	17	57
Female	13	43
Site		
Foot	18	60
Hand	12	40
Treatment		
Curettage	6	20
Curettage with adjuvants	18	60
Wide or marginal resection	6	20
Tumor characteristics		
Soft tissue extension	7	23
Pathologic fracture	6	20
Complications	1	3
Local recurrence		
1st recurrence	8	27
2nd recurrence	2	
3rd recurrence	1	
4th recurrence	1	

Table 2 Individual patient characteristics, treatment and outcome

					Treatment[‡]		Local recurrence						
Patient/ Gender/ Age (years)	**Centre[*]**	**Site[†]**	**Soft-tissue extension**	**Pathologic fracture**	**Primary**	**Reconstruction**	**n**	**Time to recurrence (months)**	**Treatment[§]**	**Complications**	**Follow-up (months)**	**MSTS[¶]**	**Final outcome[**]**
1 / F / 31	1	MT5	-	Yes	Marginal resection	Non-vascularized fibular graft	1	9	Resection + bone graft	-	78	30	NED
2 / M / 34	1	Cuneiform	-	-	Curettage + phenol + PMMA	-	0	-	-	-	24	-	NED
3 / M / 35	1	MC1	-	-	Curettage	Bone graft	1	8	Curettage + PMMA	Surgical removal (PMMA remnants causing pain)	88	-	NED
4 / M / 20	1	MT1	Yes	Yes (intra-articular)	Curettage + phenol	Non-vascularized fibular graft + K-wires	2	6; 4	1) Curettage + phenol + PMMA; 2) Curettage + PMMA + non-vascularized fibular graft	-	94	30	NED
5 / F / 23	1	MC2	-	-	Curettage	Bone graft	4	20; 57; 127; 3	1) Curettage + PMMA; 2) Curettage + bone graft; 3) Curettage + bone graft; 4) Curettage + high-speed burr + phenol + bone graft	-	267	28	NED

6 / M / 40	1	MC2	Yes	-	Curettage	Bone graft + K-wires	0	-	-	-	46	-	NED
7 / M / 60	1	MC3	-	-	Curettage + phenol	Bone graft	0	-	-	-	120	-	DOOD
8 / F / 37	1	Talus	Yes	-	Curettage + phenol	Bone graft	1	31	Curettage + phenol + bone graft	-	102	28	NED
9 / M / 20	1	MC3	Yes	-	Curettage + PMMA	-	1	7	Curettage + PMMA	-	117	30	NED
10 / F / 15	1	Talus	-	-	Curettage	Bone graft	0	-	-	-	24	-	NED
11 / F / 13	1	MT1	-	-	Curettage + phenol + PMMA[††]	-	0	-	-	-	28	28	NED
12 / F / 22	1	MT3	-	-	Curettage + phenol	Bone graft	1	15	Curettage + phenol + bone graft	-	47	-	NED
13 / F / 46	1	Ph3	-	Yes	Curettage	-	1	14	Curettage + phenol + bone graft	-	24	29	NED
14 / M / 20	2	Cuboid	-	-	Curettage + high-speed burr + phenol	Bone graft	0	-	-	-	63	30	NED
15 / M / 24	2	Calcaneus	-	-	En bloc resection	Bone graft	0	-	-	-	68	15	NED
16 / F / 38	2	Scaphoid	-	-	En bloc resection	Bone graft + screw fixation	0	-	-	-	122	28	NED
17 / F / 68	2	Calcaneus	-	-	Curettage + phenol	Bone graft	0	-	-	-	128	30	NED
18 / F / 22	2	MT4	-	-	En bloc resection	Transposition of MT3	0	-	-	-	24	-	NED

Table 2 Continued

					Treatment‡		Local recurrence						
Patient/ Gender/ Age (years)	Centre*	Site†	Soft-tissue extension	Pathologic fracture	Primary	Reconstruction	n	Time to recurrence (months)	Treatment§	Complications	Follow-up (months)	MSTS¶	Final outcome**
19 / F / 15	3	MT2	-	-	En bloc resection	Non-vascularized fibular graft	0	-	-	-	105	29	NED
20 / M / 25	3	Ph2	Yes	-	Curettage	Bone graft	0	-	-	-	118	30	NED
21 / M / 22	3	Talus	Yes	Yes (intra-articular)	Curettage + high-speed burr + phenol	Bone graft	0	-	-	-	67	30	NED
22 / M / 40	3	Talus	-	Yes	Curettage + high-speed burr + phenol	Bone graft	0	-	-	-	24	20	NED
23 / F / 22	4	MC1	-	Yes (intra-articular)	Curettage + high-speed burr + liquid nitrogen	Bone graft	0	-	-	-	53	30	NED
24 M / 15	4	Talus	-	-	Curettage + high-speed burr + liquid nitrogen	Bone graft	0	-	-	-	24	30	NED
25 / M / 45	4	MC4	-	-	Curettage + high-speed burr + liquid nitrogen + PMMA	-	0	-	-	-	30	30	NED

26 / M / 15	4	Cuneiform	-	-	Curettage + high-speed burr + liquid nitrogen	Bone graft	0	-	-	-	61	30	NED
27 / M / 36	4	MC5	Yes	-	Curettage + high-speed burr + liquid nitrogen	Bone graft	0	-	-	-	49	28	NED
28 / F / 17	4	MT4	-	-	Curettage + high-speed burr + liquid nitrogen	Bone graft	0	-	-	-	58	30	NED
29 / M / 51	5	Scaphoid	-	-	En bloc resection	Bone graft + K-wires	0	-	-	-	61	-	DOOD
30 / M / 18	5	Calcaneus	-	-	Curettage + phenol	Bone graft	0	-	-	-	32	30	NED

* 1, Leiden University Medical Center, Leiden, the Netherlands; 2, Centro Traumatologico Ortopedico, AOU-Careggi, Florence, Italy; 3, Nuffield Orthopaedic Centre, Oxford University Hospitals, Oxford, United Kingdom; 4, Radboud University Medical Center, Nijmegen, the Netherlands; 5, Centro Hospitalar do Porto – Hospital Santo Antonio, Porto, Portugal
† MT, metatarsal; MC, metacarpal; Ph2/3, middle/distal phalanx
‡ PMMA, polymethylmethacrylate; K-wire, Kirschner wire
§ including reconstruction
¶ MSTS, Musculoskeletal Tumor Society score
** NED, no evidence of disease; DOOD, died from other disease
†† PMMA was replaced with a non-vascularized fibular graft five months after the index surgery, to allow for better function in the long term for this young patient

Data including age, gender, tumor site, soft tissue extension, pathologic fracture, surgical treatment, local adjuvants, local recurrence, complications and further surgical treatment were collected. All data were complete. Functional outcome was assessed at final follow-up using the Musculoskeletal Tumor Society (MSTS) scoring system [26] and was available for 22 patients (73%). The remaining patients were discharged from follow-up (n=1), relocated (n=5) or had died (n=2), and therefore could not be reached by telephone and/or post.

Statistical analysis

Recurrence-free survival was calculated for the three different treatment groups using Kaplan-Meier survival analysis with 95% confidence intervals (CI), and differences between the groups were analyzed using the log rank test. Associations between different patient and tumor characteristics and the resulting recurrence rates were calculated using Pearson's chi-squared test and Fisher's exact test. Unpaired t-tests were used to compare MSTS scores between different treatment groups. The results were analyzed statistically with SPSS 20.0 (IBM SPSS Statistics, Chicago, Illinois) and a p-value < 0.05 was used to denote statistical significance.

Results

Data including number of cases, tumor localization, treatment, reconstruction, local recurrences and complications from the studies included in our systematic review are listed in Table 3. Within the 12 included studies, a total of 25 patients were treated with curettage alone [6, 8, 17, 21, 22], 15 were treated with curettage and adjuvants [6, 8, 9, 25] and 41 were treated with resection [6-8, 18, 18, 22-24]. A further ten patients from the studies were treated with amputation [6-8, 17, 21, 22, 25]. Results from our systematic review showed that the highest mean rate of recurrence occurred after curettage alone (72%; range 0%–100%; n=18) followed by resection (15%; range 0%–50%; n=6) and curettage with adjuvants (13%; range 0%–50%; n=2). The lowest recurrence rates were reported after amputation (10%; range 0%–100%; n=1); however, this is associated with marked functional and aesthetic impairment and is only indicated rarely as a salvage procedure.

Table 3 Overview of literature on surgical treatment of GCTB of the small bones

							Local recurrence					
Authors	**Patients/ Lesions (n)**	**Mean age (years) (range)**	**Mean follow-up (years) (range)**	**Site***	**Primary treatment†**	**Reconstruction‡**	**n (%)**	**Mean time to recurrence (months) (range)**	**Treatment§**	**Complications¶**	**Functional outcome****	**Metastasis (n, %)**
Picci et al. [17]	52 (9)††	31.1 (SD 14.7)	2	MC (4), P (2), Cb (1), MT (1), Cc (1)	Amputation (2); Marginal resection (6); Curettage (1)		0	-	-	NR	NR	NR
Sanjay et al. [27]	7 (7)	24.6 (14 to 35)	10.9 (7 to 15)	MC (6), P (1)	Wide resection (7)	Internal fixation with K-wires (4); Bone graft (3); Index finger transposition (1)	1‡‡ (14)	3	Resection	NR	NR	1 (14)
Athanasian et al. [8]	14 (13)§§	32.7 (11 to 54)	5.8 (1 to 39)	MC (7), P (5), S (1)	Wide resection (2)	-	1 (50)	17	Pending (lung metastasis)	1 gross intralesional contamination after resection	NR	2 (15)
					Amputation (1)	-	0	-	-			
					Curettage (8)	Bone graft (5)	7 (88)	6 (3 to 10)	**First (6):** Curettage (3, 1 with phenol); Resection (4, 1 with EBRT). **Second (6):** Curettage with phenol (1); Resection (5, 1 with EBRT)			

Table 3 Continued

							Local recurrence					
Authors	**Patients/ Lesions (n)**	**Mean age (years) (range)**	**Mean follow-up (years) (range)**	**Site***	**Primary treatment†**	**Reconstruction‡**	**n (%)**	**Mean time to recurrence (months) (range)**	**Treatment§**	**Complications¶**	**Functional outcome****	**Metastasis (n, %)**
					Curettage with burr (1) + Curettage with phenol (1)	Bone graft (2)	1 (50)	7	Resection			
Biscaglia et al. [6]	29 (26)¶¶	27.4 (26 to 59)	6.75 (1 to 28)	T (9), MC (8), Cb (3), Cn (3), MT (3), N (2), Cc (1)	Resection (6)	-	1 (17)	5	Amputation	NR	NR	0
					MC disarticulation (1)	Arthrodesis (1)	0	-	-			
					Curettage (11)	Bone graft (14)	7 (64)	15	Resection (3); Curettage with phenol (2); Curettage (1); Amputation (1)			
					Curettage with phenol (8)	-	0	-	-			
Patradul et al. [20]	3 (3)	23 (18 to 31)	3	MC (2), P (1)	Resection (3)	Bone graft and osteosynthesis (K-wires) (3)	1 (33)	12	Marginal resection	NR	Satisfactory§§	NR

Wittig et al. [9]	3 (3)	23.7 (16 to 33)	4.5 (4 to 5)	P (2), MC (1)	Curettage with liquid nitrogen and PMMA (3)	Osteosynthesis (K-wires) (3)	0	-	-	1 minor wound necrosis	ROM and grip strength within normal limits	0
Kamath et al. [26]	8 (3)[§§]	28.8 (13 to 47)	3 (3 to 15)	Cc (1), T (1), Cn (1)	2 curettage with burr and H_2O_2	Bone graft (2)	1 (50)	24	Curettage with PMMA	NR	NR	NR
					1 amputation	-	0	-	-			
Ozalp et al. [24]	5 (5)	41.6 (27 to 74)	7.8 (4 to 17)	MC (2), P (3)	4 curettage	Bone graft (2); Arthrodesis (1)	3 (75)	8 (2 to 18)	**First (3):** Wide resection (1); Marginal resection (1); Ray amputation (1). **Second (1):** Ray amputation	NR	NR	0
					1 ray amputation	-	1 (100)	6	**First:** Soft-tissue resection. **Second:** Advanced amputation[***]			
Ropars et al. [25]	4 (4)	40.5 (25 to 72)	3 (2 to 8)	P (3), MC (1)	3 amputation	-	0	-	-	NR	NR	NR
					1 curettage	Bone graft (1)	1 (100)	4	**First:** Resection. **Second:** Resection		Limited ROM	
Minhas et al. [7]	19 (7)[§§]	24.3 (SD 5.7)	4.5	MC (4), P (3)	6 wide resection; 1 ray resection	Bone graft (6)	0	-	-	0	NR	NR

Table 3 Continued

							Local recurrence					
Authors	**Patients/ Lesions (n)**	**Mean age (years) (range)**	**Mean follow-up (years) (range)**	**Site***	**Primary treatment†**	**Reconstruction‡**	**n (%)**	**Mean time to recurrence (months) (range)**	**Treatment§**	**Complications¶**	**Functional outcome****	**Metastasis (n, %)**
Vergara et al. [22]	3 (3)	27 (18 to 38)	NR	P (1), Carpal bone††† (1), MC (1)	3 resection	Bone graft (1); Bone elongation (2); MCP joint arthroplasty (1)	0	-	-	NR	Limited ROM	NR
Ge et al. [18]	8 (8)	28.5	3.8	MC (3), MT (4), P (1)	Wide resection (8)	Bone graft and osteosynthesis (8)	2 (25)	12 (11 to 14)	Wide resection (2)	NR	Excellent§§§	0
Current study	30 (30)	29.6 (13 to 68)	7.9 (2 to 26)	MC (8), MT (7), T (5), Cc (3), S (2), P (2), Cn (2), Cb (1)	Curettage (6)	Bone graft (5)	3 (50)	14 (8 to 20)	**First (3):** Curettage with phenol (1); Curettage with PMMA (2). **Second (1):** Curettage. **Third (1):** Curettage. **Fourth (1):** Curettage with phenol	Pain due to cement remnants after treatment of a recurrence (1)	MSTS: mean 29 (20 to 30)	0

	Curettage with adjuvants (18: 9 phenol, 2 phenol and PMMA, 1 PMMA, 5 liquid nitrogen, 1 liquid nitrogen and PMMA)	Bone graft (13); Non-vascularised fibula with K-wires (1)	4 (22)	15 (6 to 31)	**First (4):** Curettage with phenol (2), Curettage with PMMA (2). **Second (1):** Curettage with PMMA	See above
	Resection (6)	Bone graft (3: 1 with K-wires); Non-vascularised fibula (2); Transposition MT3 (1)	1 (16)	9	Resection	MSTS: mean 25 (15 to 30)

* MC, metacarpal; P, phalanx; Cb, cuboid; MT, metatarsal; Cc, calcaneus; S, scaphoid; T, talus, Cn, cuneiform; N, navicular
† PMMA, polymethylmethacrylate; H_2O_2, hydrogen peroxide
‡ K-wire, Kirschner wire; MCP, metacarpophalangeal; MT3, third metatarsal
§ EBRT, external beam radiation therapy
¶ NR, not reported
** ROM, range of movement; MSTS, Musculoskeletal Tumor Society score
†† the other patients had non-GCT lesions of the small bones of the hands and feet. Two of the nine GCTs were referred with local recurrence
‡‡ soft-tissue recurrence only
§§ the other patients had GCT in sites other than the small bones of the hands and feet
¶¶ only 26 patients underwent surgical treatment; the remaining three were under observation
*** forearm amputation because of soft-tissue extension
††† not further specified
§§§ not specified which method was used to assess functional outcome

In our 30 patients the anatomical distribution of the 12 cases of GCTB in the bones of the hand was first, second and third metacarpal bones (two each), fourth and fifth metacarpal bones (one each), scaphoid (two), and middle and distal phalanges (one each). The anatomical distribution of the 18 GCTB in the bones of the foot was: talus (five), calcaneus (three), cuneiform (two), cuboid (one), first and fourth metatarsal bones (two each), and second, third and fifth metatarsal bones (one each). No patient had a multicentric GCTB. There was soft tissue involvement in seven patients (four in small bones of the hand and three in the foot) and a pathologic fracture in six (four in small bones of the foot and two in the hand; two patients had both soft tissue extension and a pathologic fracture): only one of these underwent resection. None of the patients had any intra-articular involvement and none had distant or pulmonary metastases. Two patients died respectively five and ten years after their index surgery, both from conditions unrelated to the GCTB.

Overall, eight patients had a first local recurrence (three in metatarsal bones, three in metacarpal bones, one in a phalange and one in the talus), with a mean time to recurrence of 14 months (range 6–31) (Figure 2). The rate of recurrence was 50% (three of six) in patients treated with isolated curettage, 22% (four of 18) after curettage in conjunction with local adjuvants and 17% (one of six) after resection (Table 2). The Kaplan-Meier five-year estimated recurrence-free survival was 50% (95% confidence interval (CI) 1.6–2.4) for curettage, 76% (95% CI 1.7–2.2) for curettage with adjuvants and 80% (95% CI 1.6–2.3) for resection ($p=0.404$; log rank test) (Figure 3). The five-year estimated recurrence-free survival was 69% (95% CI 1.8–2.2) for all intralesional treatments and 80% (95% CI 1.6–2.3) for resection ($p=0.661$; log rank test). Surgical treatment of the first local recurrence consisted of repeated curettage with adjuvants (three with phenol and four with PMMA) and repeated resection (one). One patient, who had a total of four local recurrences, is currently free of disease at 26 years after repeated curettage procedures with variations of phenol, bone grafting and PMMA (Table 2).

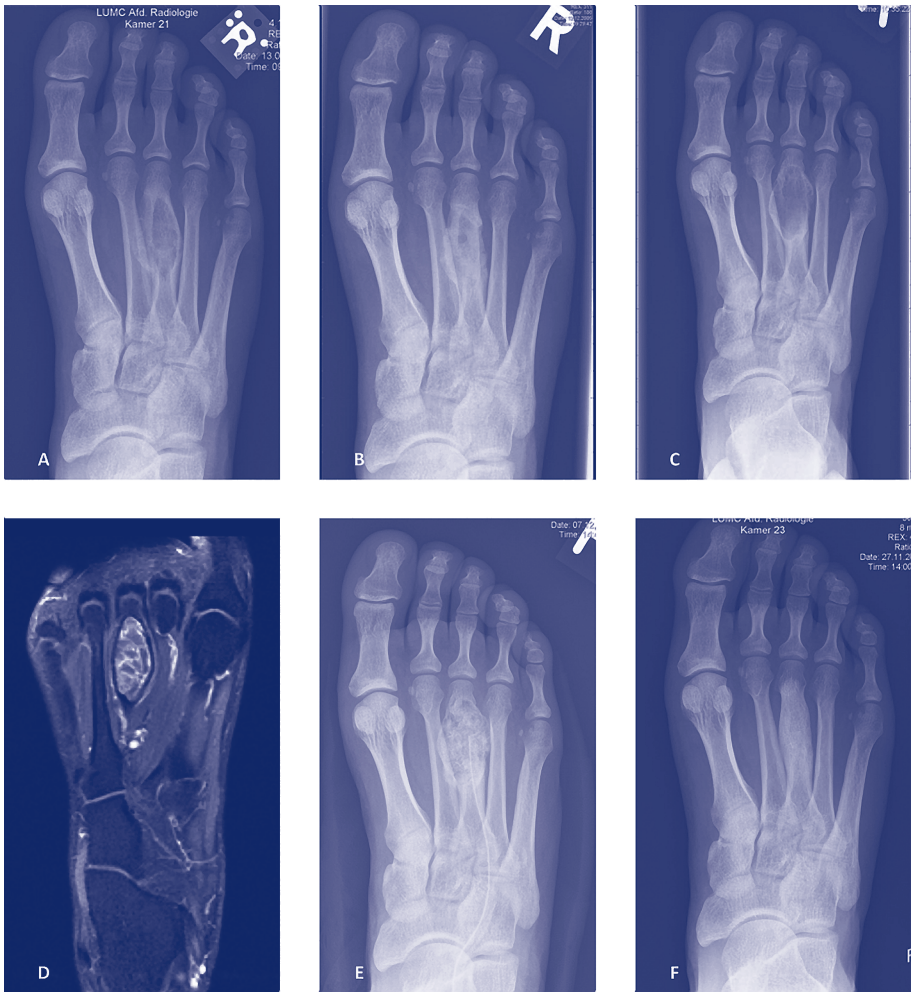

Figure 2 GCTB of the 3rd metatarsal bone of the right foot in a 22-year old female patient. (A) Preoperative conventional AP radiograph demonstrating an expansive lytic lesion without cortical disruption in the metaphysis of the 3rd metatarsal bone of the right foot. (B) Conventional AP radiograph taken 3 months postoperatively, after primary curettage, phenol and bone grafting. (C, D) Conventional AP radiograph and T2-weighted MR imaging taken 1 year postoperatively, revealing signs of a local recurrence with secondary aneurysmal bone cysts. (E) Conventional AP radiograph 3 months after repeat curettage, phenol and bone grafting for local recurrence. (F) Conventional AP radiograph 1 year after treatment for local recurrence (curettage, phenol and bone grafting), demonstrating complete incorporation of the bone graft. At a final follow-up of 4 years, there are no signs of further recurrences or pulmonary metastasis.

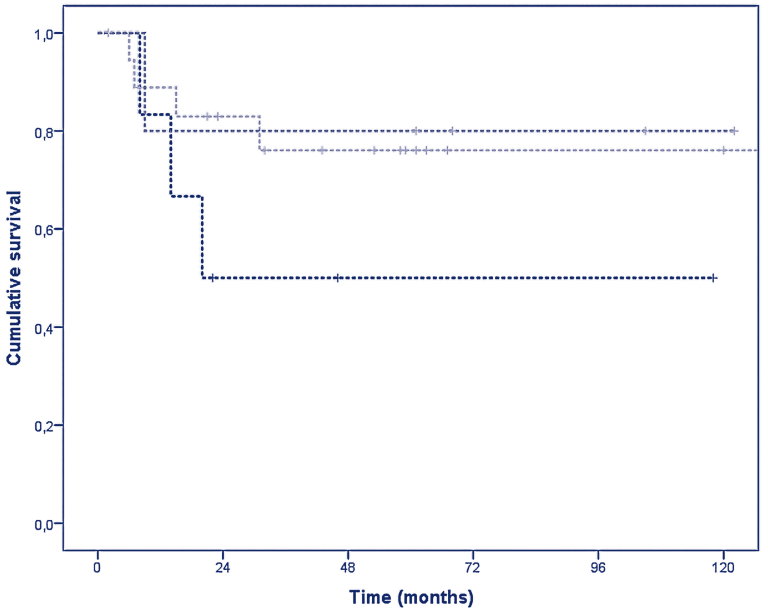

Figure 3 Kaplan Meier survival curve showing the estimated 5-years recurrence free survival after curettage (0.50; black line), curettage with adjuvants (0.75; light gray line) and resection (1.0; dark gray line) for GCTB of the small bones (p=0.160).

There was no statistical association between the use of different local adjuvants and the respective recurrence rate (p=0.28; chi-squared test) or the number of recurrences (p=0.40; chi-squared test). The same held true for recurrence rate and type of intervention (p=0.12; chi-squared test), pathologic fracture (p=0.62; Fisher's exact test) and soft tissue extension (p=0.31 Fisher's exact test).

The only minor complication reported was pain caused by remnants of PMMA in one patient that resolved completely after surgical removal of the PMMA fragment. No other complications were reported in this series.

The mean MSTS for functional outcome at final follow-up was 25 (range 15–30) for the four patients who underwent resection and 29 (range 20–30) for the 18 treated by curettage with or without adjuvants (p=0.091; unpaired *t*-test) (Table 2).

Discussion

GCTB of the small bones are believed to behave more aggressively than GCTB of the long bones [27-29]; high recurrence rates have been described after different types of surgery [6, 8, 17, 21].

Local recurrence rates from this study were comparable to those described in the literature: 50% versus 72% for curettage, 22% versus 13% for curettage with adjuvants and 17% versus 15% for resection. The rate of recurrence of GCTB of the small bones in the literature and in our group were at the higher end of the ranges reported in the literature for GCTB of the long bones, which are 27% to 65% after curettage [1, 12], 12% to 34% after curettage with adjuvants [12, 13, 16] and 0% to 12% after resection [12, 14]. Risk factors for recurrence such as soft tissue extension were not more common (23%) than in those reported for long bones (22% to 25%) [15, 30]. Complete removal of GCTB of the small bones can be difficult for both intralesional and wide resections, which may be explained by the technically challenging anatomical locations, the difficulty of applying adequate local adjuvants due to anatomical restrictions, their very rare incidence, which is likely to result in the surgeon's relative lack of experience. The differences between the rates of recurrence with the various treatment options in our study were not statistically significant and our sample size was too small to detect differences after the use of various local adjuvants. The mean time to local recurrence in our series was also consistent with the literature about GCTB of both long and small bones: only one patient had a first recurrence more than two years after surgery (Tables 2 and 3).

En bloc resection and ray amputation have been advocated in technically challenging cases, as they are believed to minimize the risk of recurrence [6, 8, 17, 21, 22, 25, 27]. However, similar recurrence rates have been reported for both resection (15%) and curettage with adjuvants (13%), indicating that resection is not necessarily better [18, 23]. Wide resection may also be associated with reduced function of the affected hand or foot. Reconstruction of a defect is often required such as bone grafting, osteosynthesis or joint replacement, thereby increasing the duration of rehabilitation and the risk of late complications [18, 23, 24, 31].

In this multicenter series the recurrence rate after curettage with adjuvants (22%) was somewhat higher than the mean rate of recurrence reported in the literature (13%) [6, 8, 9, 25] for GCTB of the small bones but remained within

the range reported after curettage with adjuvants for GCTB of the long bones (12% to 34%) [12-16]. Furthermore, in our study all first recurrences except one were successfully treated with repeated curettage and local adjuvants, thereby avoiding a more aggressive surgical approach. Finally, all patients were free of disease. This suggests that curettage with adjuvants can be a feasible treatment option for both primary and recurrent GCTB of the small bones.

Neither the type of local adjuvant or surgical treatment nor the presence of a pathologic fracture or soft tissue extension was associated with a higher risk of recurrence. To our knowledge, such associations for GCTB of the small bones have not previously been studied. In the literature, authors often referred to the potentially more aggressive behavior of GCTB of the small bones, which reflect the higher rates of multicentricity (7% to 18%) [5, 20] compared with the rate of multicentricity in GCTB of the long bones (approximately 1%) [28]. Of all multicentric GCTB, up to 61% have been reported in the small bones of the hands and feet [28, 29]. Interestingly, our study does not describe any patient with multicentric GCTB and are unable to corroborate previous reports.

Only a few studies reported post-operative complications, which included a reduced range of movement and wound necrosis after curettage with adjuvants [8, 9, 31]. We encountered only one minor complication of pain after curettage with PMMA due to cement remnants.

The role of different local adjuvants should be considered, considering the complications they may cause. Phenol in high concentrations is toxic to soft tissues and some studies have questioned its efficacy [15, 16], whereas others reported no difference between phenol and other adjuvants [32, 33]. The use of a high-speed burr allows the removal of tumor cells from the walls of the tumor cavity but also destroys healthy cancellous bone and carries the risk of dissemination of tumor [34]. Cryosurgery may result in thermal injury to surrounding healthy soft tissues, bone or cartilage [35]. PMMA is used both as a local adjuvant and as filling material, which is believed to substantially reduce the risk of recurrence due to thermal necrosis and its direct toxic effect on tumor cells but without producing major complications [36]. However, it is not always necessary to fill the defect in a small bone. Nevertheless, to reduce the risk of recurrence we recommend the use of local adjuvants after curettage.

Few authors have described functional outcome after surgery for GCTB of the small bones [9, 18, 23, 24]. In two studies it was described as satisfactory or excellent but the method of assessment was not reported [18, 23]. Three

other studies reported a limited or normal range of movement after resection or curettage for GCTB of the bones of the hand [9, 17, 24]. In this study we assessed functional outcome using the MSTS scoring system with the results being slightly better after intralesional surgery than after resection.

Our study has several limitations. First, it was retrospective and even recruiting from several centers, to obtain a larger group of patients, the sample size remained too small to comment with confidence on differences in the rates of recurrence after the use of various adjuvants. Second, the multicenter design implies that multiple treatment strategies have been applied, which may have resulted in selection and treatment bias.

In conclusion, we found the lowest rate of recurrence for resection, followed by curettage with adjuvants. Curettage alone was consistently associated with the highest rate of recurrence. We were unable to identify any factors that were associated with a higher risk of complication or recurrence. From the literature *en bloc* resection and ray amputation are associated with functional and aesthetic disability and are rarely indicated as a salvage procedure. Repeated curettage with adjuvants eventually resulted in the cure of all patients in our series. Therefore, curettage with adjuvants is a feasible treatment option for both primary and recurrent GCTB of the small bones of the hands and feet (Figure 4).

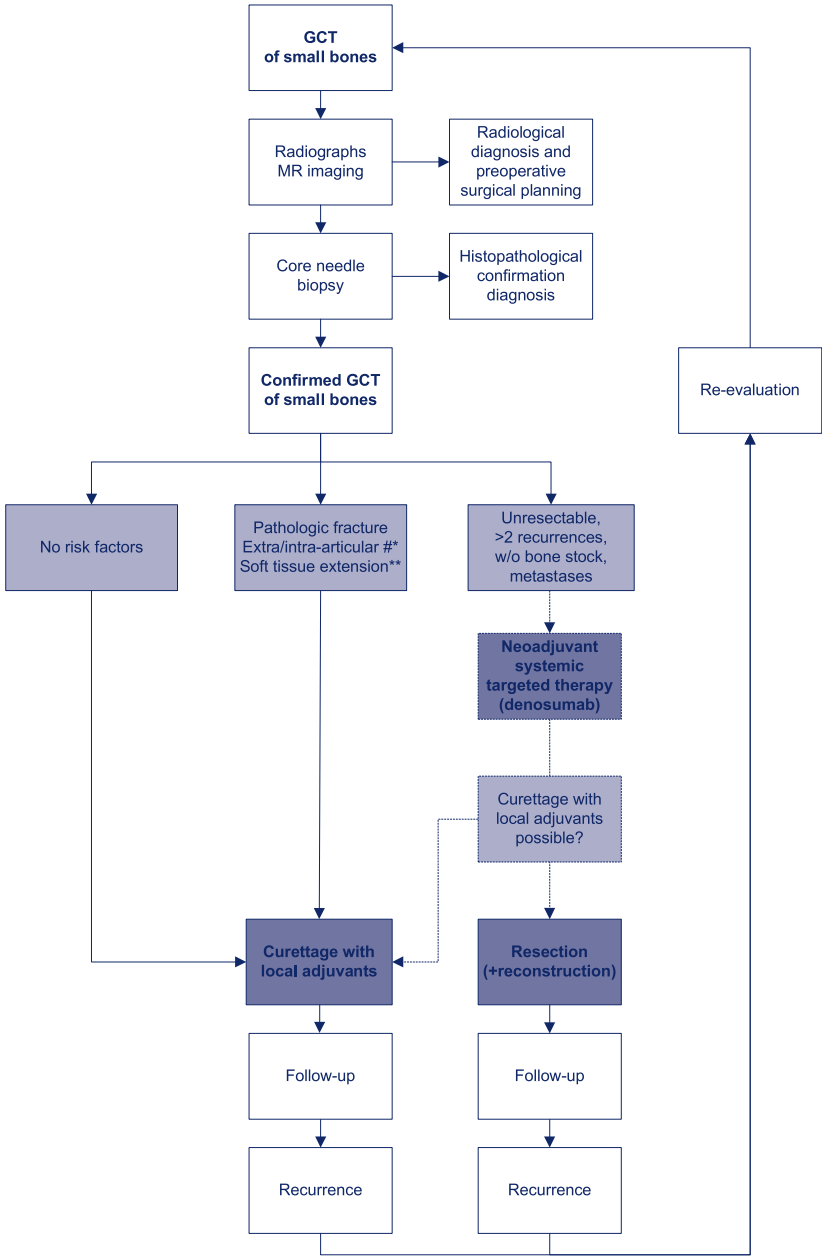

Figure 4 Flowchart of evaluation and treatment of GCTB of the small bones of the hands and feet. *With extra-articular pathologic fractures, preoperative fracture healing may be awaited before curettage with adjuvants, while immediate surgery is required with intra-articular pathologic fractures. **Attention should be paid to the application of local adjuvants such as phenol, alcohol and liquid nitrogen in the vicinity of soft tissues, because it may induce (severe) soft tissue necrosis.

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Addendum to Chapter 5

At the time of publication of this Chapter, the 2013 WHO Classification of Tumors of Soft Tissue and Bone was published, with updated nomenclature following rapidly increasing knowledge on cytogenetic and molecular data on bone and soft tissue sarcoma [1]. In this classification, osteoclastic giant cell-rich tumors were subdivided in giant cell tumor of bone (GCTB) [2] and giant cell lesion of the small bones (GCLSB) [3].

Chapter 5 of this thesis describes GCTB in its very rare location in the small tubular bones of the hands and feet (1.7-5%) [4-6]. Patients with a tumor that was histopathologically identified as giant cell reparative granuloma at the time of diagnosis, nowadays described as giant cell lesion of the small bones, were not included in the study of Chapter 5. Furthermore, studies included in the systematic review in Chapter 5 included only GCTB of the small bones of the hands and feet; studies on giant cell reparative granuloma and other giant cell-rich tumors were not included.

A limitation of Chapter 5 and previously published articles on GCTB of the small bones of the hands and feet is that retrospective data were used and histopathology was not revised with respect to recent criteria for diagnosis of bone and soft tissue tumors. In the future, especially for multicenter and international studies, revision of histopathological diagnoses is recommended, to have a methodological sound (i.e. uniform) classification of the histopathological diagnosis.

However, in the presented study of Chapter 5, the authors found no implications for treatment and prognosis, even though GCTB had an intermediate, locally aggressive behavior with an increased tendency of developing multicentricity and metastases in the small bones compared to the long bones. Namely, both giant cell-rich tumors were best treated with curettage with local adjuvants resulting in similar recurrence rates and with the possibility of repeating curettage in case of recurrent disease.

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