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SYSTEMATIC REVIEW

Surgical challenges, novel techniques, and systemic treatment of giant cell tumour of bone of the distal radius

CLINICAL OUTCOMES AND SYSTEMATIC REVIEW OF THE LITERATURE

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Aims

Giant cell tumour of bone (GCTB) treatment changed since the introduction of denosumab from purely surgical towards a multidisciplinary approach, with recent concerns of higher recurrence rates after denosumab. We evaluated oncological, surgical, and functional outcomes for distal radius GCTB, with a critically appraised systematic literature review.

Methods

We included 76 patients with distal radius GCTB in three sarcoma centres (1990 to 2019). Median follow-up was 8.8 years (2 to 23). Seven patients underwent curettage, 38 curettage with adjuvants, and 31 resection; 20 had denosumab.

Results

Recurrence rate was 71% (5/7) after curettage, 32% (12/38) after curettage with adjuvants, and 6% (2/31) after resection. Median time to recurrence was 17 months (4 to 77). Recurrences were treated with curettage with adjuvants (11), resection (six), or curettage (two). Overall, 84% (38/45) was cured after one to thee intralesional procedures. Seven patients had 12 months neoadjuvant denosumab (5 to 15) and sixmonths adjuvant denosumab; two recurred (29%). Twelve patients had six months neoadjuvant denosumab (4 to 10); five recurred (42%). Two had pulmonary metastases (2.6%), both stable after denosumab. Complication rate was 18% (14/76, with 11 requiring surgery). At follow-up, median Musculo-Skeletal Tumour Society score was 28 (18 to 30), median Short Form-36 Health Survey was 86 (41 to 95), and median Disability of Arm, Shoulder, and Hand was 7.8 (0 to 58).

Conclusion

Distal radius GCTB treatment might deviate from general GCTB treatment because of complexity of wrist anatomy and function. Novel insights on surgical treatment are presented in this multicentre study and systematic review. Intralesional surgery resulted in high recurrence-rate for distal radius GCTB, also with additional denosumab. The large majority of patients however, were cured after repeated curettage.

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Keywords: giant cell tumor of bone, distal radius, wrist, denosumab, curettage, resection

Introduction

Giant cell tumour of bone (GCTB) is a rare intermediate and locally aggressive primary bone tumour, primarily affecting epimetaphyses of long bones after skeletal maturity. GCTB consists of receptor activator of nuclear factor kappa-B (RANK) expressing reactive osteoclast-like giant cells, RANK ligand (RANK-L) expressing neoplastic spindle-shaped cells and mononuclear osteoclast precursor cells.[1] Incidence of GCTB is estimated at 1.7 per million individuals per year, with the third most common localization in the distal radius (10%).[2] Patients

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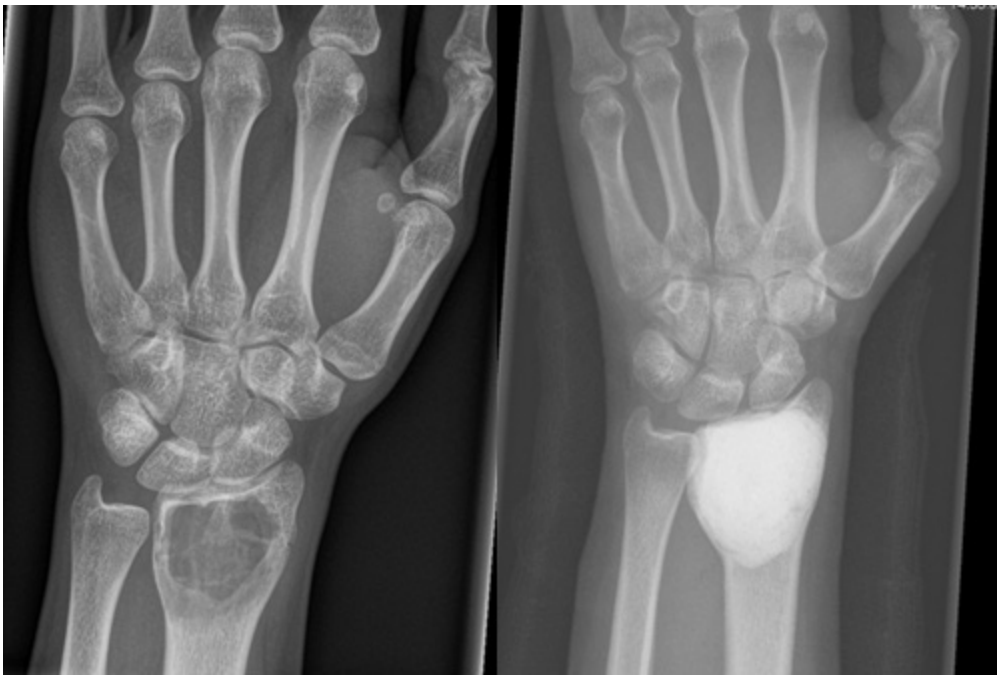

Fig. 1

35-year-old patient with conventional giant cell tumour of the distal radius, without cortical breakthrough nor soft-tissue extension. Treatment consisted of extended curettage with high-speed burring, phenol and filling of the remaining cavity with bone cement. There were no recurrences nor complications during follow-up.

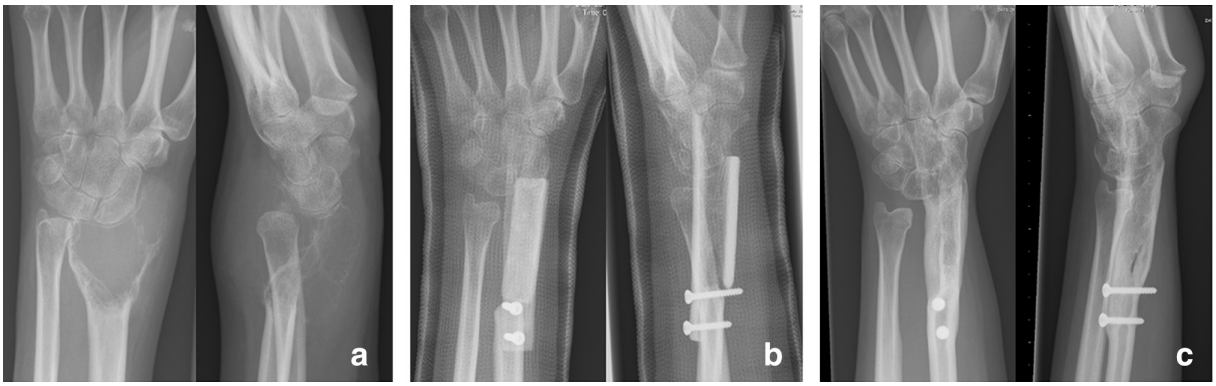

Fig. 2

a) 32-year-old patient with high-risk giant cell tumour of of the distal radius with cortical thinning, soft-tissue extension, and disturbed radiocarpal alignment. b) En bloc resection was performed with arthrodesis with a tibia strut autograft and screw fixation. c) Radiographs at five-year follow-up show complete fusion of both radiocarpal arthrodesis and proximal bone junction, with remodelling of the graft.

report pain, swelling, and often decreased joint mobility. Pathological fracture and soft-tissue extension are seen frequently. Rarely, lung metastases occur (3%), but only few develop progressive metastases with poor outcome.[3] From all GCTB patients with lung metastases, 31% to 38% was localized in distal radius, suggesting an association with increased incidence of lung metastases.[4,5]

Historically, treatment of distal radius GCTB consisted of surgery, including curettage with or without adjuvants, resection with joint reconstruction or wrist arthrodesis (Figures 1 to 4). Several reconstruction options exist, namely arthroplasty or arthrodesis with structural bone graft (non-vascularized or free vascularized fibula autograft (FVFG) or massive allograft), centralization of distal ulna, and endoprosthetic arthroplasty. Reconstructions are technically challenging, and functional outcome may be unsatisfactory due to impaired range of motion compared with joint-sparing approaches and probability of multiple revisions over time. Therefore, intralesional surgery with joint salvage is preferred in relatively young and active (working) patients. Resection is preferred over intralesional surgery when joint salvage is impossible

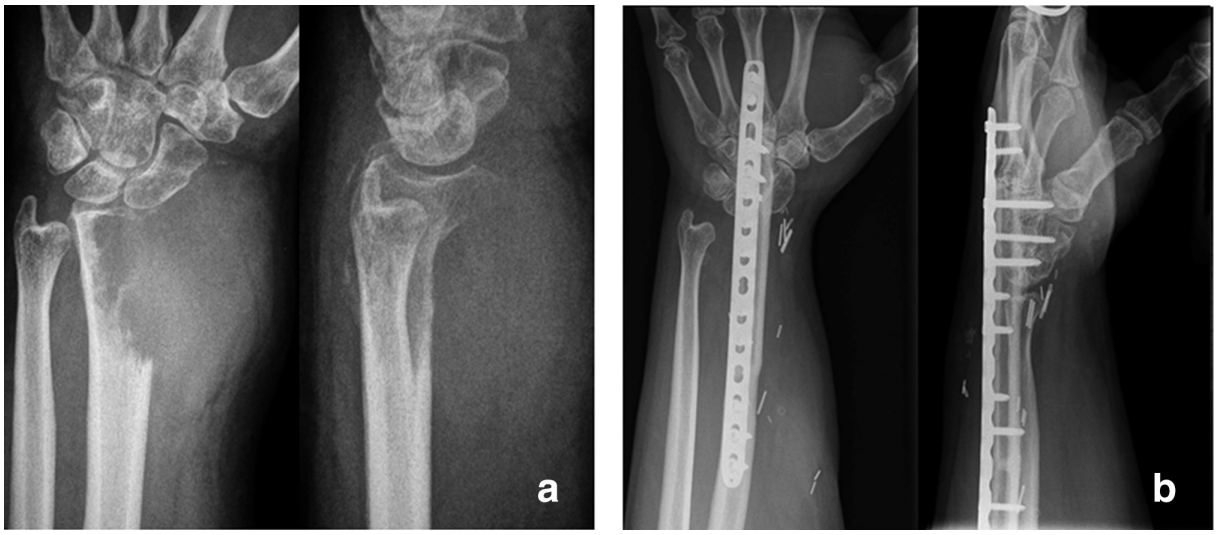

Fig. 3

a) 36-year-old patient with high-risk giant cell tumour of of the distal radius with cortical thinning and soft-tissue extension. b) En bloc resection was performed with wrist arthrodesis with osteoarticular allograft and plate fixation. There were no recurrences nor complications during 15-year follow-up.

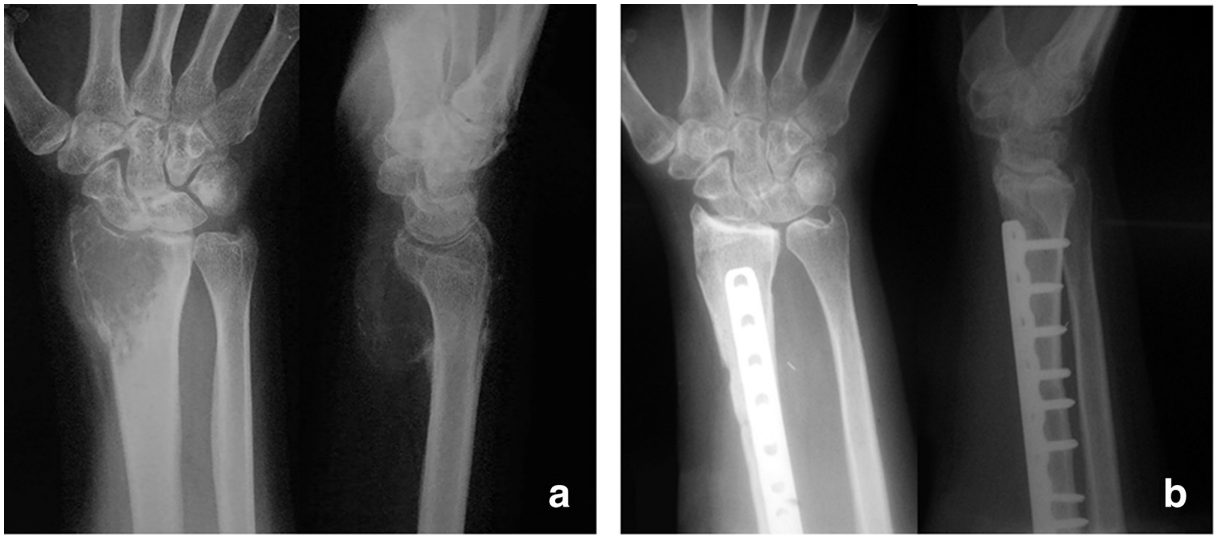

Fig. 4

a) 36-year-old patient with high-risk giant cell tumour of the distal radius with cortical thinning and very large soft-tissue component. b) En bloc resection was performed with wrist arthrodesis with a free vascularized fibula autograft and plate fixation. This patient developed pulmonary metastases, treated with continuous denosumab. Otherwise, there were no recurrences nor complications during ten-year follow-up.

due to intra-articular fracture or large soft-tissue components. Recurrence rates are after isolated curettage 12% to 65%, curettage with adjuvants 12% to 27%, and en bloc resection 0% to 12%.[6] Several studies mentioned higher recurrence-rates after curettage for distal radius GCTB compared with other long bones (27% to 35%).[7-10]

Denosumab can be used as neoadjuvant therapy, creating newly formed bone at the lesion's periphery, offering a mechanical scaffold against which curettage can be performed.[11] Unfortunately, this scaffold withholds neoplastic cells, which reactivate and result in recurrence. Also, typical GCTB tissue is replaced with gritty layered fibro-osseous tissue, hindering removal of all tumorous tissue. These effects may be more abundant when denosumab is given for longer durations. Thus, instead of an expected recurrence-risk reduction, this may actually be increased with longer use, and shorter denosumab regimens were given as a consequence.[11,12]

Since the introduction of denosumab, GCTB treatment changed from purely surgical towards multidisciplinary. To date, it remains unknown what best treatment combination for advanced distal radius GCTB should be in terms of oncological and functional outcome (i.e. if curettage is impossible). This might deviate from general GCTB

Table I. Patient and treatment demographics.

Variable	Data		
Sex, n			
Male	41		
Female	35		
Centre 1	26		
Centre 2	31		
Centre 3	19		
Median age at diagnosis, yrs (IQR)	34 (15 to 79)		
Median follow-up, mnths (IQR)	106 (24 to 271)		
Surgical treatment, n	**Isolated curettage, n = 7**	**Curettage with adjuvants, n = 38**	**En bloc resection, n = 31**
Phenol		2	
PMMA		15	
Phenol + PMMA		19	
LN + PMMA		2*	
Soft-tissue extension	0	10	8
Pathological fracture	0	4	4

*One with zoledronic acid-loaded cement.
LN, liquid nitrogen; PMMA, polymethylmethacrylate.

treatment because of complexity of wrist joint anatomy and function. In this retrospective, multicentre study, we evaluated oncological, surgical, and functional outcomes for distal radius GCTB, with different surgical approaches and reconstructions and different denosumab regimens. In addition, a critically appraised systematic literature review gives novel insights on current techniques for distal radius GCTB.

Methods

All consecutive patients with distal radius GCTB treated in three sarcoma centres (1990 to 2019) were retrospectively reviewed and a pseudo-anonymized dataset was used. No patients were recalled specifically for this study; all data were obtained from medical records; therefore informed consent was not needed under Dutch law. The study was approved by the institutional review board (N 20.020). Gathered data included age, sex, histological diagnosis, tumour characteristics (soft-tissue extension, pathological fracture), surgical treatment (local adjuvants, reconstruction technique), and systemic therapy (doses, durations, side-effects, and complications). Imaging surveillance protocols consisted of local conventional radiographs after six weeks, three, six, 12, 18, and 24 months, and yearly thereafter until five years postoperatively, with additional MRI with intravenous Gadolinium on indication. Local recurrences and complications were evaluated with their further treatment. Minimum follow-up was two years. Functional outcome and quality of life were evaluated at follow-up using MusculoSkeletal Tumour Society (MSTS),[13] Disability of Arm, Shoulder, and Hand (DASH),[14] and Short Form-36 Health Survey (SF-36).[15]

From 82 eligible patients, 76 patients were included (Table I), and six were excluded (four with missing data, and two with follow-up < 24 months). Soft-tissue extension and pathological fracture at diagnosis were recorded (Table I). Different reconstructions were used in 31 patients with resection: (17 (55%) osteoarticular allograft reconstructions, nine (29%) primary arthrodeses (six wrist arthrodesis with FVFG, two wrist arthrodesis with allograft, and one radiocarpal arthrodesis with autologous tibia struts); and two fibula-pro-radius with FVFG.

Statistical analysis and systematic review. Descriptive analyses were performed in this study. Continuous data were described by medians and ranges and categorical data by number and percentages. Because of risk of confounding by indication with different indications for treatments, comparative statistical analyses were not performed.

A systematic literature search (2000 to date of search) was performed in search engines PubMed, Embase, Web of Science, COCHRANE library, and Emcare on 3 October 2021 and resulted in 389 references (Figure 5; Supplementary figure a). Relevance of titles and abstracts was determined by two independent reviewers. Methodological quality was assessed using the Newcastle-Ottawa Scale for quality assessment of cohort studies (Table II).

Results

Recurrences. Risk factors for recurrence, such as soft-tissue extension and pathological fracture, at diagnosis were equally distributed in the curettage with adjuvants and resection groups; isolated curettage was not performed in any case of soft-tissue extension, nor with pathological fracture (Table I). In all, 19 patients had local recurrences (Table III). Median time to recurrence was 17 months (4 to 77). First recurrences were treated with curettage with adjuvants in 11 patients (58%), resection

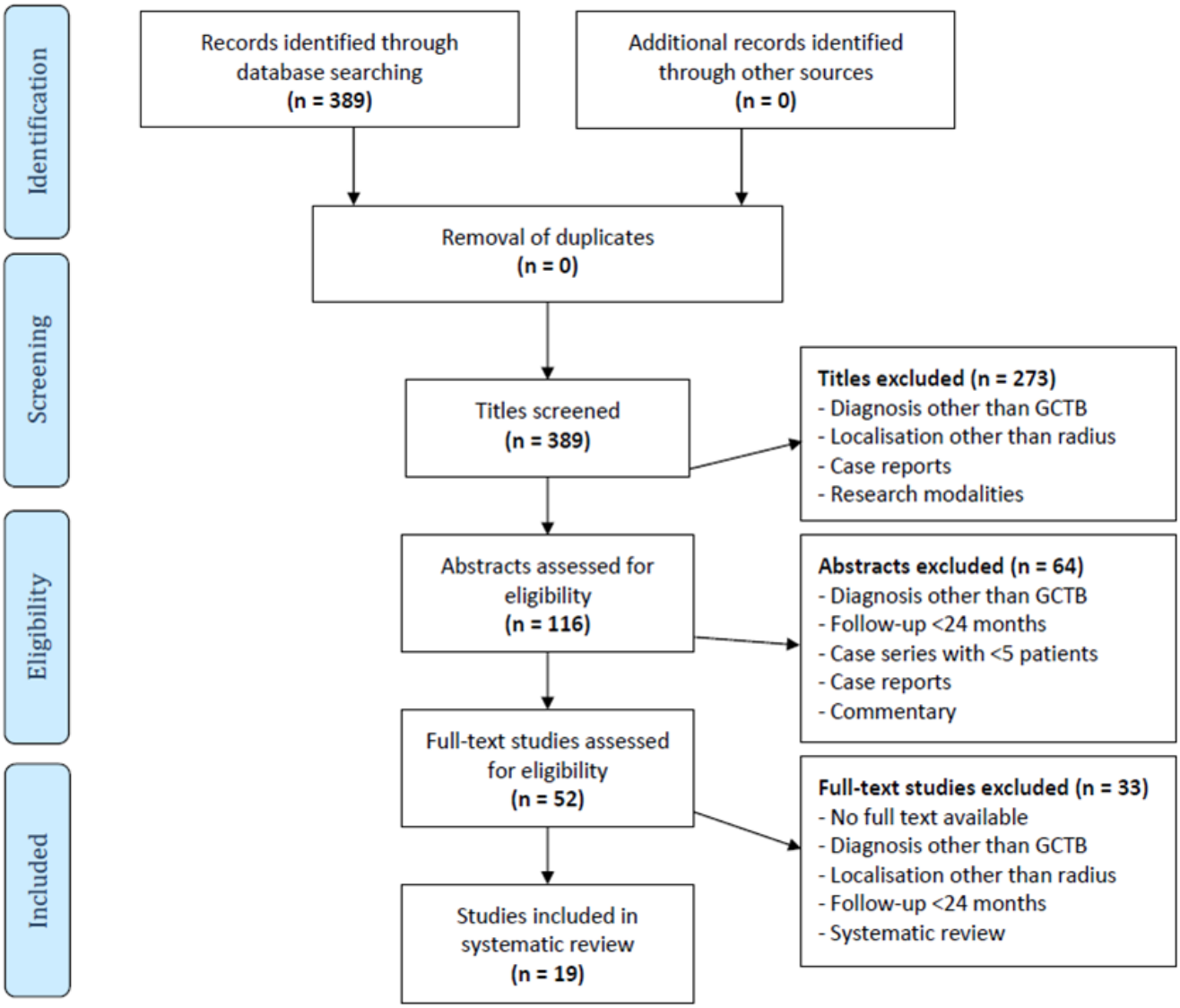

Fig. 5

Flowchart of systematic literature review following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

in six (32%), and curettage in two (10%) (Figure 6). Four patients had multiple recurrences (five, three, two, and two, respectively). From six patients with final resection, four had radiocarpal arthrodesis with autologous tibia struts, one had fibula-pro-radius FVFG, and one had wrist arthrodesis. Two had soft-tissue recurrence excision. In total, 38/45 of patients (84%) undergoing primary intralesional surgery was cured after one to three intralesional procedures. Overall recurrence rate was 32% for patients aged < 40 years, and 12% of patients aged > 40 years. However, the majority of patients aged < 40 years was treated with intralesional surgery (64%), and only a smaller group with resection (36%), whereas patients aged > 40 years were more likely to undergo resection (50%).

Denosumab. Overall, 20 patients had denosumab, followed by curettage in 17, and resection in three. Seven had median 12 months neoadjuvant denosumab,[5–12,16,42,43] and six months adjuvant denosumab; two recurred (29%). In all, 13 had median six months neoadjuvant denosumab;[4-10] five recurred (42%). Two developed pulmonary metastases (2.6%); one remained stable on adjuvant denosumab monthly (108 months) without metastasectomy; and one recurred and had 12 months neoadjuvant denosumab and surgery, without metastasectomy. At follow-up, 72 had no evidence of disease, two were alive with disease, and two died of unknown cause.

Complications. A total of 14 patients had complications (Table III). Three graft fractures occurred, treated with

Table II. Critical appraisal of all included studies by means of Newcastle-Ottawa Quality Assessment Scale (NOS); one point could be obtained for each item of the NOS.

Variable	n (%)
Selection	
Representativeness	19 (100)
Selection non-exposed	2 (11)
Ascertainment exposure*	19 (100)
Outcome not present at start study†	0 (N/A)
Comparability	
Controls for most important factor‡	3 (16)
Controls for any factor	0 (N/A)
Outcome	
Assessment of outcome§	17 (89)
Follow-up long enough (2 years)	19 (100)
Adequacy of follow-up (> 90%)	19 (100)
Scores, points	
7	2 (11)
6	0 (0)
5	16 (84)
4	1 (5)
3	0 (0)
2	0 (0)

*Through secure records (e.g. medical records, radiological, pathological, and surgical reports), or structured interviews.
†Explicit demonstration that all included patients were treated for primary giant cell tumour of bone (GCTB) and not for local recurrence, as this might induce bias.
‡Advanced GCTB.
§Through independent blind assessment (e.g. by independent surgeons, radiologists, or pathologists), or record linkage.
N/A, not applicable.

Functional outcome and quality of life. Hand and wrist function were assessed with MSTS and DASH, and quality of life with SF-36 (Table III). Overall, there was no clinically relevant nor statistically significant difference in either score. However, per SF-36 subdomain, median outcomes were better after resection and wrist or radiocarpal arthrodesis compared with intralesional surgery, especially regarding subdomain pain (100 vs 79.6).

Systematic review. A systematic literature review resulted in 19 relevant articles (Tables III–IV). Included studies had minimum two years' follow-up and were small series with median 12 patients (9 to 27). There were two comparative cohort studies with curettage and resection. All other studies evaluated results after resection and various reconstructions, including osteoarticular allografts, (non-)vascularized fibula grafts with wrist arthrodesis, fibula-pro-radius with FVFG, ulna centralization and (custom-made) wrist arthroplasty. Median MSTS was 27 (25 to 29) after resection (eight studies), median DASH was 9.1 (7 to 15) (four studies), and median SF-36 was 71 (two studies).

Discussion

In this retrospective, multicentre study, we aimed at evaluating oncological, surgical, and functional outcomes for distal radius GCTB, with different surgical approaches, reconstructions and denosumab regimens. Additionally, a critically appraised literature review provides novel insights on reconstructive techniques in advanced distal radius GCTB.

Table III. Postoperative results.

Variable	Isolated curettage (n = 7)	Curettage with adjuvants (n = 38)	En bloc resection (n = 31)
One recurrence, n (%)	5 (71)	12 (32)	2 (6)
Multiple recurrences, n (%)	0 (0)	4 (17)	0 (0)
Complications, n (%)	1 (14)	4 (11)	9 (29)
Functional outcome	**Curettage ± adjuvants**		**En bloc resection**
Median SF-36 (range)	90 (43 to 95) (n = 4)		86 (41 to 93) (n = 14)
Median MSTS (range)	28 (19 to 30) (n = 17)		29 (18 to 30) (n = 25)
Median DASH (range)	8.5 (0 to 30) (n = 12)		5.0 (0 to 58) (n = 15)

DASH, Disability of Arm, Shoulder, and Hand; MSTS, MusculoSkeletal Tumour Society; SF-36, Short Form-36 Health Survey.

revision allograft, revision FVFG, or plate osteosynthesis with original FVFG maintenance. Three nonunions occurred, treated with iliac crest bone grafting. Three were treated for persistent pain (one with carpal instability with subluxation had capsular tightening, one tenolysis of extensor compartments, and one plate removal). Two had tendon ruptures (one had EIP-pro-EPL transposition and one EPL/ECRB repair). Two had extensile physiotherapy for ROM improvement. One had prolonged tendonitis of second to third extensor compartments, treated with non-steroidal anti-inflammatory drugs/bracing.

Surgical techniques. In our study, reported recurrence-rate was lowest after resection, but more complications were reported when compared with curettage. It was previously suggested that recurrence-rate after curettage in distal radius GCTB would be higher compared with other sites.[42] In our systematic review, only two other studies evaluated outcome of intralesional surgery for distal radius GCTB in a limited number of patients (six each). This suggests a wide preference for

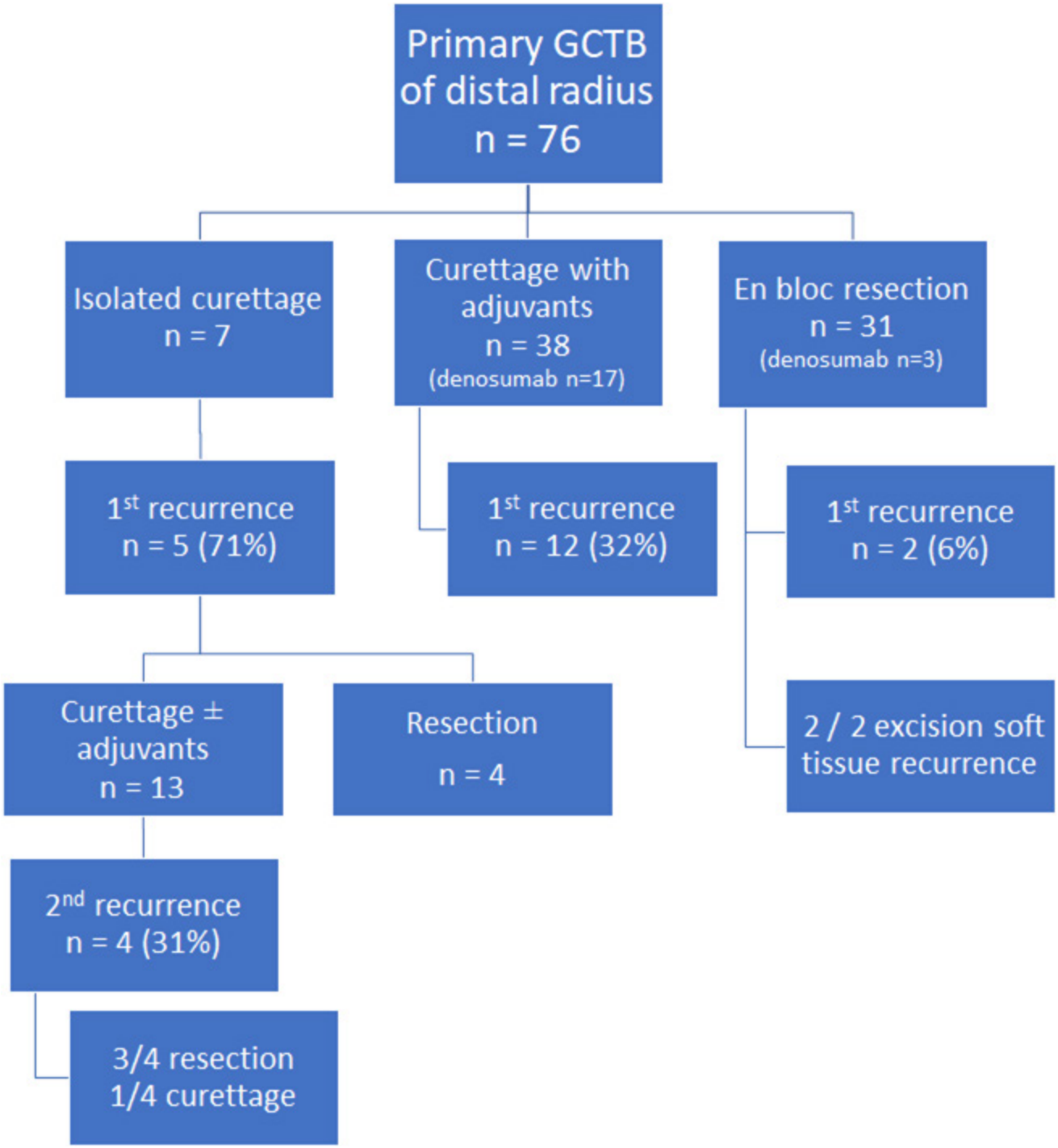

Fig. 6

Flowchart of treatment for primary distal radius giant cell tumour of bone and their recurrences.

resection in this specific site (41% in our series), not in accordance with ratio between surgical treatments in all GCTB. Possible explanations for the high recurrence rate are small size of the bone resulting in earlier expansile growth (e.g. compared with distal femur) and pathological fracture, paucity of musculature surrounding the bone, complexity of radiocarpal and distal radioulnar joints and proximity of neurovascular structures. After resection, our systematic literature review shows mean recurrence-rate of 5% (0 to 15), consistent with all GCTB. In our study, recurrence rate after curettage with adjuvants was moderately high but 84% of patients initially treated with curettage were cured after one to three intralesional surgeries, indicating that

Table IV. Systematic literature review on surgical treatment of giant cell tumour of the distal radius.

Study	NOS	M/F, n	Mean age, yrs (range)	Treatment	Complications (treatment)	Mean functional outcome and QoL (range)	Recurrences, n (%)	Time to recurrence, yrs	Metastasis, n	Mean final outcome and follow-up, yrs (range)
Cheng et al, 2001[16]	7	n = 12; 4/8	35 (16 to 72)	Curettage + phenol 6 Resection 6 (osteoarticular allograft 4, fibula autograft 2) (Grade 3)	Curettage: none Resection: 3 radiocarpal osteoarthritis (N/R) 2 DRUJ osteoarthritis (N/R) 2 DRUJ diastasis (N/R) 2 ulnar translation carpals (N/R)	MSTS 10 excellent to 2 good*	0 (0)	N/A	0	NR FU 6 (3 to 16)
Szabo et al, 2006[17]	4	n = 9; 2/7	42 (34 to 83)	Resection + osteoarticular allograft (Grade 3)	1 infection (antibiotics) 1 fixation failure (re-do ORIF) 1 FCR tendonitis (conservative) 1 stress fracture allograft (casting) 2 ulnar synostoses (resection; 1 after RTx)	DASH 15 (2 to 41) SF-36 72 (59 to 90) Mayo wrist 73 (50 to 90)	0 (0)	N/A	0	9 NED FU 8.3 (3 to 18)
Bassiony et al, 2009[18]	5	n = 10; 3/7	33 (25 to 45)	Resection + non-vascularized fibula autograft (Grade 2 + 3)	1 nonunion (iliac bone graft) 1 graft resorption (wrist arthrodesis)	MSTS 93% (83 to 96)	1 soft-tissue (10)	NR	0	10 NED FU 3.9 (2.5 to 5)
Chadha et al, 2010[19]	5	n = 9; 8/1	40 (21 to 59)	Resection+ non-vascularized fibula autograft (Grade 2)	2 graft fracture (plate revision, bonegraft) 1 tourniquet palsy+ resorption of fibular autograft (arthrodesis) 1 subluxation (orthotics) 1 iatrogenic radial artery injury (ligation)	N/R	1 (11)	NR	NR	NR FU 4.7 (3.2 to 5.8)
Saikia et al, 2010[20]	5	n = 24; 14/1	32 (17 to 56)	Resection + non-vascularized fibula autograft (Grade 3[21] + Grade 2[5])	1 infection (antibiotics) 1 graft fracture (cast 10 wks) 10 subluxation: 6 no functional deficit, 2 fibulocarpal diastasis (all orthotics) 2 osteoarthritis (none) 2 transient peroneal nerve palsy (none)	N/R	1 soft-tissue (4.2)	NR	0	24 NED FU 6.6 (2 to 11)

Continued

Table IV. Continued

Study	NOS	M/F, n	Mean age, yrs (range)	Treatment	Complications (treatment)	Mean functional outcome and QoL (range)	Recurrences, n (%)	Time to recurrence, yrs	Metastasis, n	Mean final outcome and follow-up, yrs (range)
Saini et al, 2011[22]	5	n = 12; 7/5	35 (21 to 43)	Resection + non-vascularized fibula autograft (Grade 2 + 3)	1 infection (antibiotics) 3 subluxation with functional deficit (NR) 2 nonunion (iliac bone graft) 9 EPL weakness (none)	MSTS 91% (77 to 93)	1 (8.3)	2	0	12 NED FU 5.8 (8.2 to 3.7)
Chung et al, 2013[21]	5	n = 12; 4/8	33 (17 to 62)	Resection + FVFG fibula-pro-radius arthroplasty (Grade 2)	5 instability and osteoarthritis (NR) 7 mild osteoarthritis (N/R) 1 median nerve palsy (median nerve decompression)	MSTS 26[23–29]	1 (8.3)	1.5	0	12 NED FU 6.3 (3.6 to 11.5)
Duan et al, 2013[30]	5	n = 15; 8/7	35 (17 to 56)	Resection+ osteoarticular allograft (Grade 3)	1 pain due to osteoarthritis (none)	Mayo wrist 70 (50 to 90) SF-36 71 (55 to 90)	1 soft-tissue (6.7)	3	0	15 NED FU 5.2 (3 to 11.6)
Flouzat-Lachaniette et al, 2013[31]	5	n = 13; 7/6	37 (31 to 48)	Resection + corticocancellous tibial autograft (arthrodesis) (Grade 3)	1 pain distal ulna (distal ulna resection) 2 nonunion (ORIF and bone graft) 1 fracture distal graft-host bone junction (ORIF)	MSTS 86% (80 to 97)	2 soft-tissue (15)	NR	0	13 NED FU 6 (2 to 14)
Taraz-Jamshidi et al, 2014[32]	5	n = 15; 4/11	29 (19 to 48)	Resection + non-vascularized fibula autograft (Grade 2 + 3)	4 mild pain (NR) 3 moderate pain (NR)	Mayo wrist 64	4 (1 fibula, 1 carpals, 2 soft-tissue)	1.5 to 2	0	15 NED FU 7.2 (4 to 11)
Sujai et al, 2015[33]	5	n = 10; 6/4	33 (25 to 41)	Resection + non-vascularized fibula autograft (Grade 3^6 + Grade 2^4)	1 nonunion (iliac bone graft) 2 subluxation (none)	MSTS used but results N/R	0 (0)	NA	NR	10 NED FU 3.6 (3 to 5)
Zhang et al, 2015[23]	5	n = 11	34 (26 to 42)	Resection+ custom made prosthetic arthroplasty (Grade 2^2 + Grade 3^9)	1 infection (antibiotics) 1 pain (none)	MSTS 83% (63 to 93)	1 soft-tissue (9.1)	1.3	0	11 NED FU 4.6 (2 to 6.9)
Meena et al. 2016[34]	5	n = 10; 3/7	31 (25 to 40)	Resection + ulna centralization arthrodesis (Grade 1^6 + Grade 2^4)	4 extensor lag thumb (NR) 4 painful subluxation (wrist arthrodesis)	MSTS used but results N/R	N/R	N/R	0	NR FU 3.8 (2.5 to 5)
Wang et al, 2016[24]	5	n = 10; 7/3	39 (20 to 59)	Resection + custom made unipolar wrist hemiarthroplasty (Grade 3)	2 pain (NSAID) 1 aseptic loosening (asymptomatic) 2 wrist subluxation (N/R) 3 osteoarthritis (none)	Mayo wrist 68 (45 to 90)	0 (0)	N/A	0	10 NED FU 4.3 (2 to 7.5)

Continued

Table IV. Continued

Study	NOS	M/F, n	Mean age, yrs (range)	Treatment	Complications (treatment)	Mean functional outcome and QoL (range)	Recurrences, n (%)	Time to recurrence, yrs	Metastasis, n	Mean final outcome and follow-up, yrs (range)
Wang et al, 2017[35]	5	n = 27; 11/16	29 (15 to 42)	Resection + wrist arthrodesis (Grade 3)	4 hardware failure (3 revision, 1 declined Tx) 1 symptomatic loose hardware (removal) 2 nonunion (bone graft) 1 fracture (revision)	MSTS 29[26–29,36] DASH 9 (0 to 24)	3 (1 soft-tissue, 2 bone)	1.2	3	24 NED, 2 AWD, 1 DOD FU 3.8 (2 to 8.6)
Mozaffarian et al, 2018[37]	5	n = 13; 6/7	35 (28 to 44)	Curettage + cement 6 Resection+ proximal fibula autograft 7 (Grade 3)	Curettage: none Resection: 1 transient peroneal nerve palsy	N/R	Curettage: 4 (67) Resection: None	0.9 (0.3 to 1.3)	0	NR FU 6 (2.3 to 12.3)
Liu et al, 2019[38]	5	n = 26; 4/22	37 (19 to 60)	Resection + fibula autograft (Grade 3[39] + Grade 2[8])	3 DRUJ subluxation (none) 5 radiocarpal osteoarthritis (none)	MSTS 28[26–29] DASH 9.1 (3 to 18) VAS pain 0.7 ± 0.7	1 soft-tissue (3.8)	1.2	0	26 NED FU 5.6 (2.3 to 9.4)
Qu et al, 2019[40]	7	n = 21; 10/11	36 (17 to 72)	Resection + fibula autograft (arthroplasty 13 or arthrodesis 8) (Grade 3)	Arthroplasty: 4 subluxation (1 DRUJ K-wire fixation; 3 none) 1 malunion (NR) 1 flap necrosis (debridement) 1 transient peroneal nerve paralysis Arthrodesis: 1 fracture (ORIF+ iliac bone graft)	Arthroplasty: MSTS 83% DASH 17 Arthrodesis: MSTS 93% DASH 7	1 (4.8)	0.8	0	21 NED FU 6.7 (2.4 to 16.5)
Barik et al, 2020[41]	5	n = 11; 0/11	37 (24 to 57)	Resection + non-vascularized fibular arthroplasty (Grade 3)	1 subluxation (orthotics) 1 transient peroneal nerve palsy 1 delayed wound healing (dressings 2 wks)	Mayo wrist 66 (55 to 80) MSTS 21[21,23,24,34,37,39,40] VAS pain 1.1 (0 to 2)	1 fibula, no soft-tissue (9)	1.6	0	NR FU 3.4 (2.3 to 3.4)

Continued

Table IV. Continued

Study	NOS	M/F, n	Mean age, yrs (range)	Treatment	Complications (treatment)	Mean functional outcome and QoL (range)	Recurrences, n (%)	Time to recurrence, yrs	Metastasis, n	Mean final outcome and follow-up, yrs (range)
Van der Heijden et al, (current study)	7	n = 76; 41/35	34 (15 to 79)	Curettage 7 Curettage+ adjuvants 38 Resection + 31 (17 osteoarticular allografts, 8 wrist arthrodesis, 2 fibula-pro-radius, 1 radiocarpal arthrodesis)	Curettage: 1 pain (plate removal) Curettage+ adjuvants: 1 tendonitis (NSAIDs and orthotics) 2 decreased ROM (physiotherapy) 2 tendon rupture (repair or transposition) 1 pain (carpal instability, capsule tightening) Resection: 3 nonunion (iliac crest autograft) 3 graft fracture (2 revision, 1 osteosynthesis) 1 pain (extensor tenolysis)	Curettage ± adjuvants: MSTS 28[21,23–29,34,36,37,40] DASH 8.5 (0 to 30) SF-36 90 (43 to 95) Resection: MSTS 29[21,23–29,34,36,37,39,40] DASH 5.0 (0 to 58) SF-36 86 (41 to 93)	Curettage: 5 (71) Curettage + adjuvants: 12 (32) Resection: 2 (6)	1.4 (0.3 to 6.4)	2	74 NED, 2 AWD, 2 UCD FU 8.8 (2 to 23)

*Not further specified.

AWD, alive with disease; DASH, Disabilities of the Arm, Shoulder and Hand; DOD, death of disease; DRUJ, distal radio-ulnar join; EPL, extensor pollicis longus; FCR, flexor carpi radialis; LFU, lost to follow-up; MSTS, MusculoSkeletal Tumor Society score; N/A, not applicable; NED, no evidence of disease; NOS, Newcastle-Ottawa Quality Assessment Scale; N/R, not reported; N/S, not specified; NSAID, non-steroidal anti-inflammatory drug; ORIF, open reduction and internal fixation; QoL, quality of life; RTx, radiotherapy NOS Newcastle-Ottawa Scale for quality assessment of cohort studies; SF-36, Short Form 36-item health survey; TESS, Toronto Extremity Salvage Score; UCD, unknown cause of death; VAS, visual analogue scale.

most recurrences after curettage can be treated with repeated curettage.[43] High-speed burr and local adjuvants should always be used, as recurrence rate increases tremendously without chemical adjuvants; isolated curettage is not recommended for GCTB in the distal radius given the high recurrence risk. There was a wide variety in ages in our series, with higher recurrence rate for younger patients, probably due to confounding by indication as the younger patients (aged < 40 years) more likely underwent joint sparing surgery (64%), and older patients were more likely to undergo resection and joint reconstruction including arthrodesis (50%).

Reconstructive options. After resection, in our study and in literature, various reconstructive techniques were used, depending on local experience and graft or custom-made prosthesis availability.

Some centres have experience with osteoarticular allografts (centre 2; Figure 3).[16,17,30,39] This possibility is dependent on availability via national tissue donation programs and bone banks. Sometimes, non-vascularized fibular autografts are used. Due to morphological mismatch between articular sides of graft and host bone, radiocarpal or DRUJ osteoarthritis may develop, but reported functional results were moderate to good at mid-term follow-up in literature (mean 5 to 8 years).

Most experience exists with non-vascularized or FVFG, which can be used for several reconstructions, including wrist arthrodesis (Figure 4) or radiocarpal arthrodesis (Figure 2) or fibula-pro-radius arthroplasty (centre 2).[21,37] Using proximal fibular heads as substitute for resected distal radius is reasonable because of similarity in shapes and availability of autografts.[8,40] However, comparable to osteoarticular allografts, using proximal fibular heads to form new articulations may result in instability and carpal translation, often resulting in radiocarpal osteoarthritis. Yet, moderate to good functional results are reported at short- to mid-term follow-up (mean 3 to 6 years). Also, donor site morbidity needs to be considered when using (proximal) fibula or tibia strut autografts, with accompanying risks (e.g. peroneal nerve damage). One study from our review compared results for fibula autograft arthroplasty versus arthrodesis, and authors reported better function and grip strength and less complications after wrist arthrodesis. Shared decision-making, including patients' daily activities and profession, has an important role, as wrist arthrodesis is more suitable in patients with heavy labour and arthroplasty may be preferred in patients needing a mobile wrist.

One study reported outcomes of ulnar centralization arthrodesis in ten patients with recurrent GCTB after resection or curettage, with short-term follow-up (2.5 to 5 years).[34] After resection, articular cartilage of distal ulna was removed, an insertion site made in the lunate and the reconstruction stabilized with two Kirschner wires; half of patients also had cancellous bone grafting. During rehabilitation, above-elbow casts were given for three months, followed by elbow splints until wrist union. Apart from loss of wrist mobility, this technique also results in smaller wrist circumference and more extensor lag of EPB, APL, and EPL tendons compared with other reconstructions. Nonetheless, the technique can be a viable treatment option in recurrent cases where contra- or ipsilateral proximal fibula was already used.

Two studies reported outcomes of custom-made prosthetic (hemi)arthroplasty.[23,24] At short- to mid-term follow-up (2 to 7.5 years), one study reported high complication rate of 8/10, with progressive osteoarthritis due to unipolar wrist arthroplasty as the most important reason for complaints. The authors therefore rightly concluded that alternative reconstruction methods including autologous fibula graft should be explored first. Also, this is probably the most expensive reconstructive option, and may not be worldwide available. Both studies reported satisfactory to good functional outcomes. In conclusion, this option should be chosen only for recurrent GCTB or after failure of other techniques.

Denosumab. In distal radius GCTB, soft-tissue extension is often present and most advanced tumours are treated with resection and various reconstructions. From the literature, the ratio between intralesional surgery and wide excision is different for distal radius GCTB compared to other sites. With vicinity of neurovascular structures, flexor and extensor tendons and complex radiocarpal joint anatomy, it is useful to create a clear demarcation between tumorous and healthy tissues, facilitating either intralesional surgery or resection. Therefore, especially in distal radius GCTB, neoadjuvant denosumab may be effective in facilitating planned resection with preservation of native joint function in advanced lesions or pathological fracture.[37] In our study, 20 patients had neoadjuvant denosumab. Half of patients with neoadjuvant denosumab (median eight months) and extended curettage developed recurrence. In the literature, recurrence rates of 60% were reported after six to 12 months denosumab,[25] and 43% after three months (1 to 6) denosumab.[26] Denosumab regimens > three months result in sclerosis and extensive perilesional new bone formation; the longer the denosumab administration, the thicker this layer becomes.[27] Therefore, several studies evaluated shorter denosumab regimens of two to three months, while maintaining effectiveness but without increased recurrence-risk and difficulties with surgery.[28,29,36] Especially when considering curettage or planned resection in advanced distal radius GCTB, including pathological fracture, a short-course neoadjuvant denosumab can be considered. With curettage, cauterization of the sclerotic rim even after using a high-speed burr has been suggested to attempt to eliminate embedded neoplastic cells while maintaining the structural scaffold.

Metastasis. It has been suggested that distal radius GCTB is associated with a higher rate of pulmonary metastases. In our study, two patients developed metastases (2.6%), both stable with denosumab. Wang et al[44] was the only other group reporting pulmonary metastases (11%; 3/27), typically latent or slowly progressive and seldomly resulted in symptoms. One of their patients demonstrated uncontrolled growth of fatal metastases. The authors stated that recurrences and tumour bearing time can be risk factors for developing lung metastases, and that some metastases shrink and/or fade after operating the primary tumour.[44]

Limitations. There are several limitations to our study. First, the retrospective, multicentre study design implies different treatment strategies and local preferences, making it impossible to draw firm conclusions or strong recommendations on optimal treatment, but this is also reflects current reality of GCTB treatment in Europe. Second, different patient and tumour characteristics influence choices for intralesional surgery or resection to a certain extent, resulting in confounding by indication. Third, different denosumab regimens were given during the study period, including both neoadjuvant and adjuvant courses resulting in variable tumour responses, the latter making it difficult to compare results. Finally, even in this relatively large series, numbers of individual treatments and reconstructive options remain too small to perform adequate risk analysis, and no hard recommendations on preferred treatment can be given.

In conclusion, recurrence rate was lowest but complication rate highest for resection compared with curettage with adjuvants. Intralesional surgery resulted in cure in 84% after one to three intralesional procedures. In advanced GCTB, when considering curettage with adjuvants or planned resection, short-course neoadjuvant denosumab can be considered. Various reconstruction methods exist, and most experience was gained with (vascularized) proximal fibular autografting as wrist or radiocarpal arthrodesis or fibula-pro-radius arthroplasty. Shared decision-making should be applied when considering wrist arthrodesis or wrist arthroplasty. Limited experience was gained with custom-made unipolar endoprosthetic arthroplasty or ulnar centralization; this should be reserved for recurrent GCTB or after failure of previous reconstruction.

Take home message

- In distal radius giant cell tumour of bone (GCTB), recurrence rate was lowest, but complication rate highest, for resection compared with curettage with adjuvants.
- In advanced distal radius GCTB, when considering curettage with adjuvants or planned resection, short-course neoadjuvant denosumab can be considered.
- In advanced distal radius GCTB, shared decision-making should be applied when considering wrist arthrodesis or wrist arthroplasty.

Supplementary material

Details of the PubMed search.

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