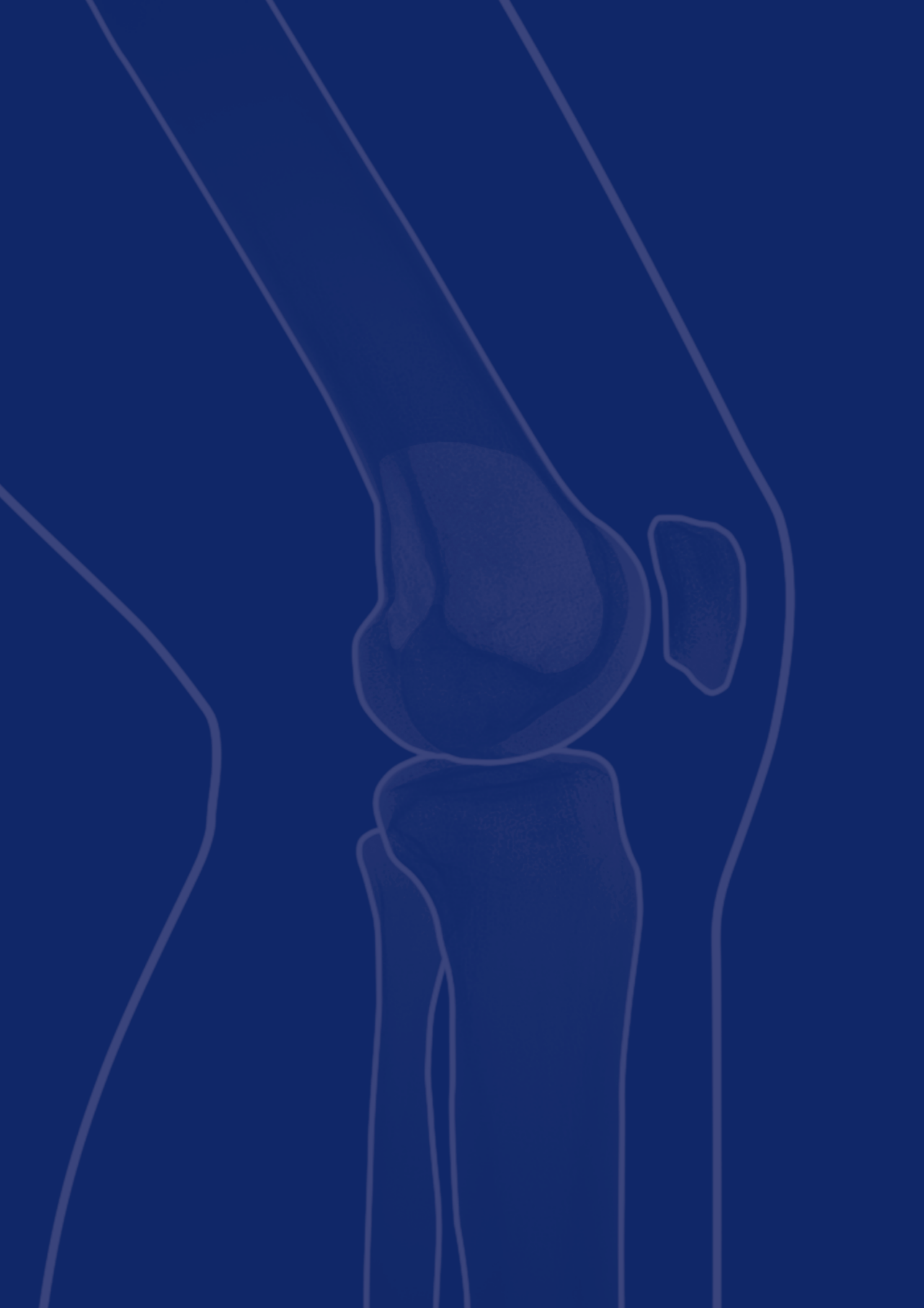
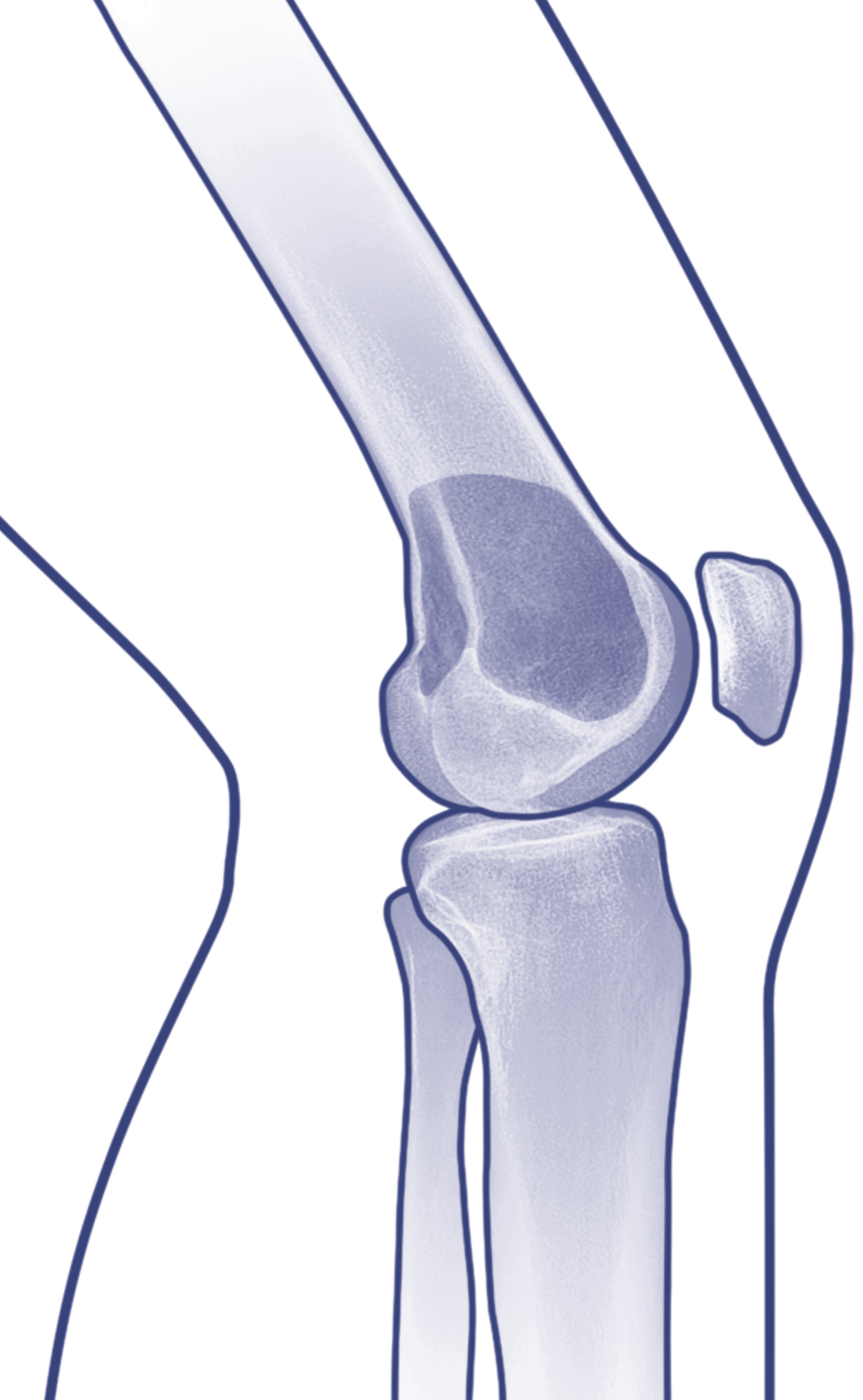


Part I

Giant cell tumor of bone



Chapter 2

The clinical approach towards giant cell tumor of bone

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Abstract

We provide an overview of imaging, histopathology, genetics and multidisciplinary treatment of giant cell tumor of bone (GCTB), an intermediate, locally aggressive but rarely metastasizing tumor. Overexpression of receptor activator of nuclear factor kappa-B ligand (RANKL) by mononuclear neoplastic stromal cells promotes recruitment of numerous reactive multinucleated giant cells. Conventional radiographs show a typical eccentric lytic lesion, mostly located in meta-epiphyseal area of long bones. GCTB may also arise in axial skeleton and very occasionally in small bones of the hands and feet. Magnetic resonance imaging is necessary to evaluate the extent of GCTB within bone and surrounding soft tissues to plan a surgical approach. Curettage with local adjuvants is the preferred treatment. Recurrence rates after curettage with phenol and polymethylmethacrylate (PMMA; 8-27%) or cryosurgery and PMMA (0-20%) are comparable. Resection is indicated when joint salvage is not feasible (e.g. intra-articular fracture with soft tissue component). Denosumab (RANKL-inhibitor) blocks and bisphosphonates inhibit GCTB-derived osteoclast resorption. With bisphosphonates, stabilization of local and metastatic disease has been reported, although level of evidence was low. Denosumab has been studied to a larger extent and seems to be effective in facilitating intralesional surgery after therapy. Denosumab was recently registered for unresectable disease. Moderate dose radiotherapy (40-55Gy) is restricted to rare cases in which surgery would lead to unacceptable morbidity and RANKL-inhibitors are contraindicated or unavailable.

Introduction

Giant cell tumor of bone (GCTB) is an intermediate, locally aggressive but rarely metastasizing tumor (International Classification of Diseases for Oncology (ICD-O) code 9250/1), representing 5% of primary bone tumors and 20% of benign bone tumors [1]. It occurs mostly between the ages of 30-50 years and rarely arises in the immature skeleton. There is a slight predominance for female patients [1,2]. At presentation, 15-20% of patients have a pathologic fracture due to substantial cortical destruction followed by relatively minor trauma. GCTB is typically seen solitary, mostly located in the metaepiphyseal region of long bones (85%), but may also occur in the axial skeleton (10%) or occasionally in the small bones of hands and feet (5%) [2,3]. At the latter location, so-called giant cell lesion of the small bones—a different entity—should be considered [4]. Approximately 1-4% of otherwise conventional patients develop pulmonary metastases [3,5-9]. These metastases often have a relatively indolent behavior. Multifocal GCTB is rare, appearing either simultaneously or metachronously. In these presentations, so-called brown tumor associated with hyperparathyroidism should be ruled out by blood biochemistry as they are histologically barely distinguishable from GCTB. Malignant transformation has been described in less than 1% of all GCTB and may be either primary (i.e. sarcomatous progression) or more commonly secondary (mostly radiation-induced) [1].

The main problem in the management of GCTB is local recurrence after surgical treatment: 27-65% after isolated curettage [2,3]; 12-27% after curettage with adjuvants such as high-speed burr, phenol, liquid nitrogen or polymethylmethacrylate (PMMA) [2,10-12]; and 0-12% after en bloc resection [2,13]. In clinical practice, the choice of surgical treatment depends mostly on the feasibility of curettage and local adjuvants versus resection, but also in part on the expected risk for local recurrence in each individual patient. Soft tissue extension, for example, is commonly present and increases the risk for local recurrence [14,15]. Pathologic fractures are also common, and although this does not in itself increase recurrence risk, it may render curettage technically more difficult. In general, the aim for joint preservation is justified, considering the benign but locally aggressive nature, young patient population and significant complications including need for revision surgery after resection and reconstruction with tumor prostheses [16-19].

The clinical challenge in GCTB treatment is to improve local control and broaden indications for intralesional surgery, providing optimal functional and oncological results. This may be aided by the promising results of systemic targeted therapy with receptor activator of nuclear factor kappa-B ligand (RANKL)-inhibitors or bisphosphonates [20-23]. Consequently, a multidisciplinary evaluating system including radiological, histopathological and clinical features is required as basis of an optimal treatment protocol. This review addresses most relevant issues concerning diagnosis and multidisciplinary treatment of GCTB and future perspectives.

Imaging

Conventional radiographs and contrast-enhanced magnetic resonance imaging (MRI) are the most important imaging modalities in diagnosing GCTB, local staging, evaluating response to systemic treatment and detecting local recurrence [24,25].

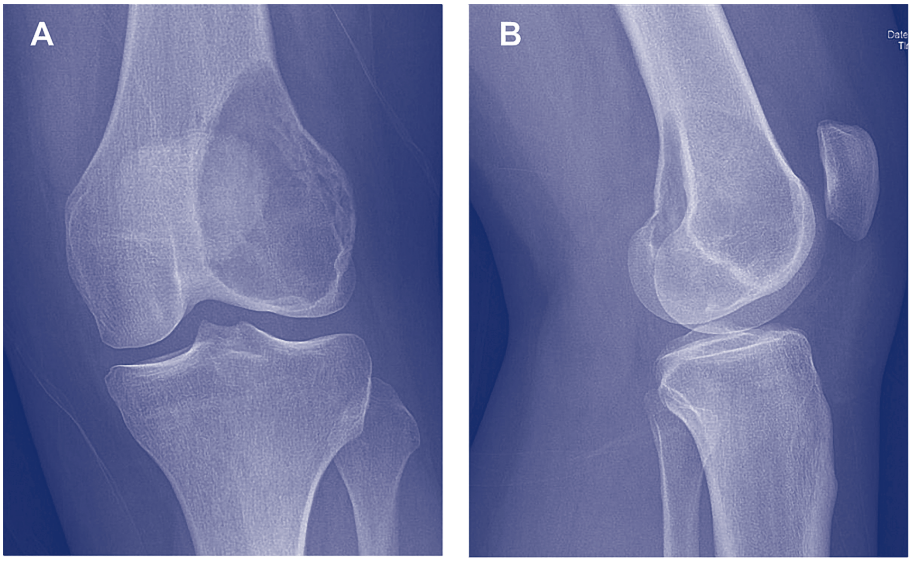

Figure 1 (A, B) Radiographs demonstrating an eccentric, sharply demarcated lytic lesion in the distal femur metaphysis extending to the epiphysis without tumor mineralization. Radiographic features are consistent with giant cell tumor of bone.

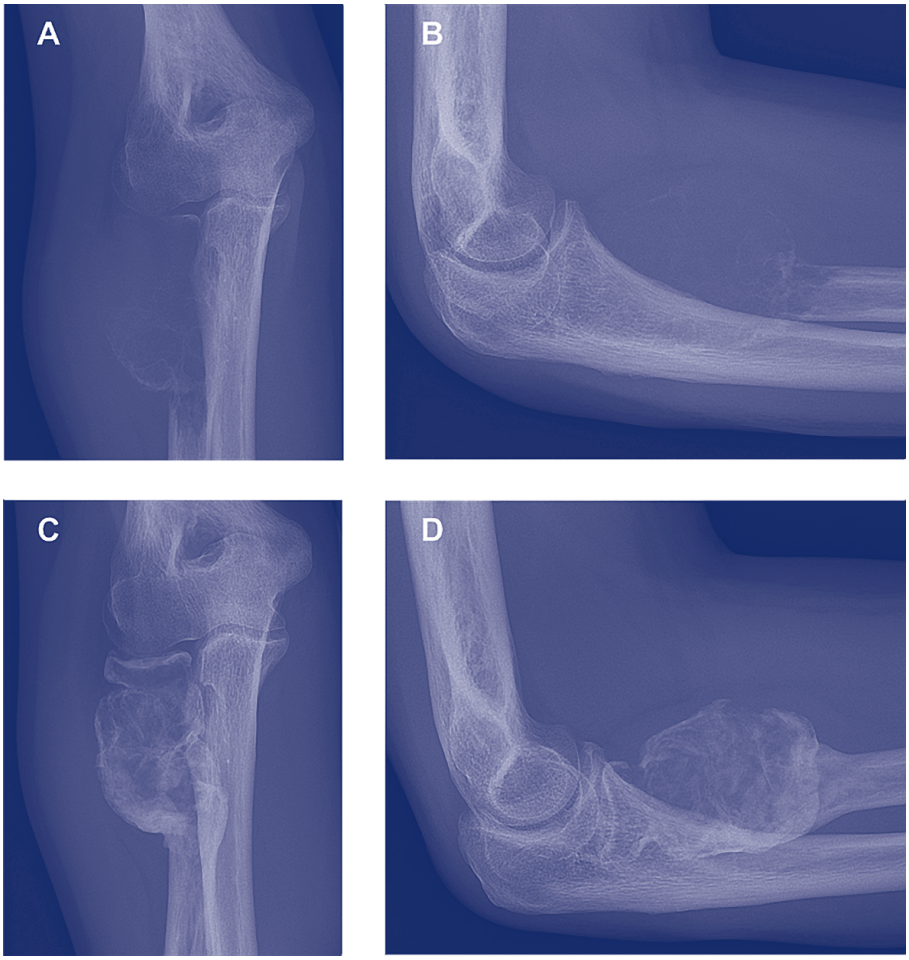

Figure 2 (A, B) Radiographs of a large expansile completely osteolytic lesion in the proximal radius demonstrating a permeative destruction pattern with cortical destruction, consistent with giant cell tumor of bone. (C, D) Radiographs demonstrate new bone formation with reconstitution of cortical bone after five months of treatment with denosumab.

The radiographic appearance of GCTB is rather characteristic. GCTB appears as an eccentric, lytic lesion with a non-sclerotic and sharply defined geographic border (narrow zone of transition), located in the metaphysis of long bones and extending to the epiphysis in subarticular region [26,27]. The periosteum may be elevated with expansion of the cortex (Figure 1). In more aggressive lesions, however, the zone of transition can be wide, with cortical breakthrough and extension into surrounding soft tissues (Figure 2). Matrix mineralization is absent. In short tubular bones of the hands and feet, radiographic features

are similar to those in long bones and indistinguishable from the so-called giant cell lesion of the small bones, which is considered another entity [4]. In addition, giant cell tumor of tendon sheath (GCT-TS) may mimic osseous lesions on radiographs as they are capable of invading bone [28]. The sacrum is the most frequently affected bone within the axial skeleton, but GCTB may also appear in vertebral bodies with extension to pedicles and possibly compression fractures [29].

GCTB was generally categorized radiologically following the system of Campanacci et al. [3] or Enneking et al. [30]; both were purely based on radiographs and are now considered less useful. MRI is more useful for staging and predicting clinical behavior of GCTB [26,31]. Computed tomography (CT) can be used to assess cortical thinning, pathologic fractures and to monitor fracture consolidation. On MRI, GCTB typically shows low to intermediate signal intensity on T1-weighted sequences and intermediate to high signal intensity on T2-weighted sequences. Areas of low signal intensity can be seen due to haemosiderin deposition, causing local changes in susceptibility especially on gradient echo sequences (Figure 3) [32]. A cystic appearance with fluid-fluid levels from secondary cyst formation or aneurysmal bone cyst-like changes is present in 10-14% of GCTB [1,26,27]. Dynamic contrast-enhanced MRI with intravenous gadolinium administration shows early and rapidly progressive enhancement followed by contrast washout (Figure 4) [24,25,33].

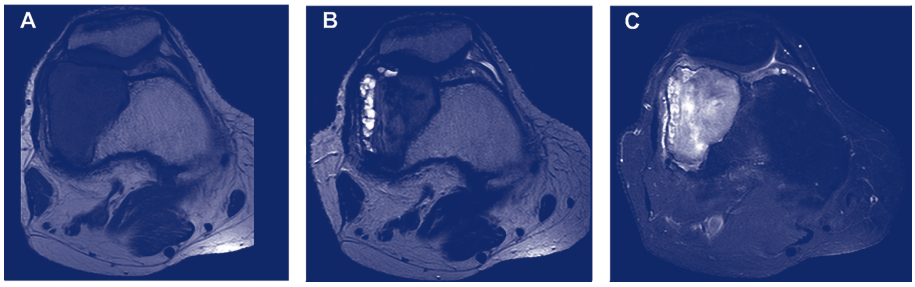

Figure 3 (A) T1-weighted MRI demonstrates an eccentric lesion with mild expansion with intermediate signal intensity. (B) T2-weighted MRI shows low signal intensity through haemosiderin depositions and high signal intensity through secondary cystic changes. (C) T1-weighted MRI with fat suppression after intravenous Gadolinium administration demonstrates marked relatively homogeneous enhancement.

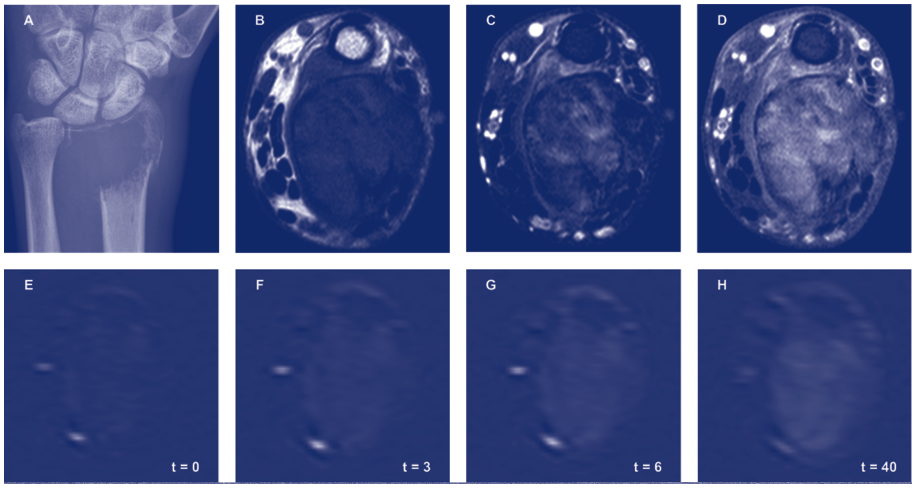

Figure 4 (A) Plain radiograph shows a lytic lesion with extensive cortical destruction and a pathologic fracture in the distal radius. (B-D) T1- and T2-weighted MRI shows inhomogeneous low to high signal intensity and marked enhancement after Gadolinium administration. (E-H) Dynamic contrast-enhanced MRI (DCE-MRI) shows homogeneous enhancement within 6 seconds after Gadolinium administration. DCE-MRI can provide functional information on tumor angiogenesis and permeability but will not be part of standard imaging protocols in many centers.

Clinical and radiographic characteristics usually allow a correct diagnosis. The differential diagnosis includes chondroblastoma, intraosseous ganglion or subchondral cyst. Chondroblastoma typically occurs in the immature skeleton and may contain calcifications. Brown tumor of hyperparathyroidism, plasmacytoma, osteolytic metastasis, aneurysmal bone cyst, giant cell lesion of the small bones and teleangiectatic osteosarcoma are included in the differential diagnosis and are sometimes less easy to rule out.

Detection of local recurrence can be difficult because of granulation tissue at the site of curettage followed by bone grafting or reconstruction with PMMA. Increased focal osteolysis around the area of treatment on serial conventional radiographs with high signal intensity on T2-weighted MR images with early dynamic enhancement followed by wash-out are highly suggestive for local recurrence.

Histopathology

With appropriate radiographic findings, the diagnosis GCTB can often be made before surgery. However, core needle biopsy or intra-operative frozen section is advised to establish the final diagnosis before or during surgery, given the aggressive nature of the tumor and its rare tendency to malignant transformation [34,35]. Macroscopically, GCTB is well vascularized and contains broad bands of cellular or collagenous fibrous tissue. Areas of hemorrhage, haemosiderin deposition and foamy macrophages can be noted and necrosis and hemorrhage are especially common in large sized GCTBs. In addition, primary GCTB associated with lung nodules commonly shows large areas of hemorrhage and thrombus formation, that is not seen in primary GCTB without local or distant recurrence [36]. Reactive bone formation is common after pathologic fracture or open biopsy. Secondary aneurysmatic bone cysts are seen in 10-14% of GCTB [1,26,27].

Microscopically, GCTB is composed of neoplastic and reactive cell populations (Figure 5). The neoplastic cell population includes rounded mononuclear histiocytic or marcophage-like osteoclast precursor cells and spindle-shaped mononuclear neoplastic "stromal" cells [1,37]. The stromal cells have poorly defined cytoplasm and spindle-shaped nuclei and show variable degrees of mitotic activity (up to 20 per 10 high power fields). Mononuclear stromal cells also express smooth muscle actin, which may be useful in the differential diagnosis of giant cell-rich lesions of bone, as its expression differs between several primary bone tumors [38].

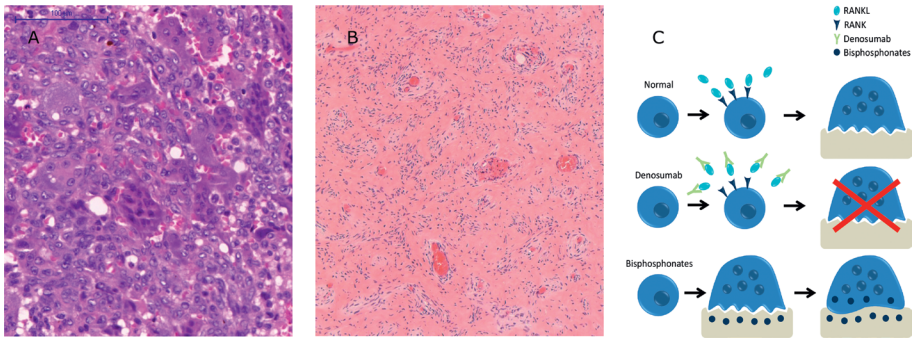

Figure 5 (A) Biopsy with numerous uniformly spaced multinucleated giant cells and mononuclear stromal cells. (B) Surgical specimen after denosumab shows stromal cells, scattered mononuclear spindle cells without evident atypia and diffuse foamy macrophages; no multinucleated giant cells are seen. (C) Mechanism of action of RANKL-inhibitors and bisphosphonates.

The reactive cell population includes numerous large reactive multinucleated osteoclast-like giant cells causing lacunar bone resorption [1,37]. Osteoclast-like giant cells have eosinophilic cytoplasm and vesicular nuclei (up to 20 to 50) with prominent nucleoli, and are often larger than normal osteoclasts.

Regarding the functional molecular biology of GCTB, RANKL is highly expressed by neoplastic mononuclear stromal cells [39-41]. RANK-RANKL interaction and macrophage colony-stimulating factor (M-CSF) play important roles in osteoclastogenesis by stimulating recruitment of osteoclastic cells from blood-born mononuclear osteoclast precursor cells that differentiate into multinucleated osteoclast-like giant cells [37,42-45]. This is supported by the fact that giant cells in GCTB have an osteoclast-like phenotype (CD45+, CD68+, CD33+, CD14-, CD51+, CD163-, HLA-DR-) [44,45]. CD33+, which is characteristic for GCTB, may constitute a novel therapeutic target, analogous to the treatment of acute myeloid leukemia with gemtuzumab, an anti-CD33 antibody [44]. Epidermal growth factor receptor signaling (EGFR), a tyrosine kinase expressed by neoplastic mononuclear stromal cells, supports stromal cell proliferation and promotes osteoclastogenesis in the presence of M-CSF [46]. EGFR expression was more frequent in recurrent and metastatic disease, suggesting that it may be related with disease progression [46].

There are also several RANKL-independent mechanisms of osteoclastogenesis expressed by GCTB; known RANKL-substitutes are tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and tumor growth factor-β (TGF-β) [37]. Recently, other cytokines and growth factors including a proliferation-inducing ligand, B cell-activating factor, nerve growth factor, insulin-like growth factors (IGF)-I and IGF-II, demonstrated osteoclastogenesis and formation of multinucleated giant cells capable of lacunar bone resorption [37]. Although less potent than RANKL, these substitutes may form alternative therapeutic targets for GCTB.

Cathepsin K is the principal protease exclusively expressed in osteoclast-like giant cells that actively absorb bone, resulting in the osteolysis associated with GCTB [47]. This could be triggered by overexpression of transcription factor CCAAT/enhancer binding protein beta, but exact etiology remains unclear [48]. Recently, an *in vivo* model for growing GCTB cell lines on chick chorio-allantoic membranes was developed, which may offer new perspectives to test therapeutical agents and monitor their effects [49].

Cytogenetically, telomeric associations—a chromosomal end-to-end fusion seen in 50-70% of GCTBs—are the most common chromosomal aberrations

[50,51]. Telomere length maintenance is an important key factor in the pathogenesis of GCTB, probably through a structural telomere protective-capping mechanism [52]. GCTB expresses telomerase maintenance markers (human telomerase reverse transcriptase and promyelocytic leukemia body-related antigens) in mononuclear rounded osteoclast precursor cells and spindle-shaped mononuclear neoplastic stromal cells [52]. There is a moderate reduction in telomere length [52,53]; however, telomere dysfunction is not the only factor responsible for genetic instability [53,54]. Recently, a driver mutation has been identified in H3F3A in 92% of GCTB; these alterations were seen exclusively found in stromal cells and not in precursor or mature osteoclasts [55]. In addition, it has been hypothesized that chromosomal instability may be caused by centrosome abnormalities, through erroneous mitotic segregation during cell-cycle progression [56]. Centrosome amplification and aneuploidy were reportedly higher in recurrent and metastatic GCTB, suggesting a relation with clinical behavior [57,58]. Allelic losses of 1p, 9q and 19q are common in primary, recurrent and metastatic GCTB [50]. Mutations of TP53 and HRAS are seen in secondary malignant GCTB and may thus play a role in malignant progression [59,60]. However, even if nuclear TP53 expression may indicate potential suppressor gene damage, there might be TP53 abnormalities that do not result in tumor formation, implicating other causes of genomic instability [57].

Primary malignancy in GCTB is seen at initial diagnosis as an area of high-grade sarcoma within an otherwise conventional GCTB. In secondary malignant GCTB, a high-grade sarcoma arises subsequent to previous radiation or surgical treatment, and the pre-existing GCTB is not always evident anymore. Atypical mitotic figures are suggestive of malignancy.

In view of the current treatment modalities, histopathological features of GCTB have not yet been clearly predictive for clinical behaviour, including risk for recurrent or metastatic disease [61]; however, the abovementioned novelties may offer new approaches for predicting clinical behavior based on histopathological, genetic and functional findings.

Surgery

The most important challenge in surgical management of GCTB of the long and small bones is the relatively high recurrence rate after curettage, mostly diagnosed within two years after index surgery [11]. Although recurrence rates are lowest after en bloc resection (0-16%), curettage with local adjuvants is preferred as it presents less morbidity and functional impairment [2,10,11,13,14,62-66]. When local adjuvants are not utilized, the mean recurrence rate is ~42% (21-65%) [2,10,11,14,67-70]. The most established standard treatment with acceptable recurrence rates is curettage with local adjuvant application of phenol and PMMA (3-33%) [2,10,13-15,63-65,67,71,72] or PMMA alone (0-29%) [2,10,11,14,15,62-65,67,70,71,73]. Centers specialized in cryosurgery apply liquid nitrogen with bone grafts or PMMA resulting in recurrence rates of 8-42% [62,64,67,74-78] and 0-20% [62,79-81] respectively (Table 1).

With extensive curettage, a large oval window is made in the cortex, creating sufficient exposure of the tumor cavity and taking the fracture risk into account. GCTB is then carefully curetted with curettes of different sizes, followed by high-speed burring of cavity walls. When using phenol, cavity walls are phenolized with protection of surrounding soft tissues, followed by rinsing with alcohol and neutralizing with repeated (high-speed pulse) lavage. This is repeated two to three times. Although phenol is effective on GCTB *in vitro*, infiltration depth *in vivo* is unknown [82], and beneficial effects of phenol when used combined with PMMA are currently under debate [11,14,15]. Complications resulting from phenol use include chemical burns, and caution is warranted in vicinity of neurovascular structures and soft tissues [83,84]. With cryosurgery, a liquid nitrogen spray is used, allowing for more equal freezing of cavity walls and better penetration in bone compared with pouring liquid nitrogen directly into the cavity. Thermocouples placed in the tumor cavity and surrounding soft tissues are advisable to monitor freezing [85]. Soft tissues should be irrigated with warm fluids to protect from thermal injury. Three cycles of rapid freezing (-50°C) and slow thawing (20°C) are performed to increase margins up to 2cm, comparable with marginal resection [77,86]. Complication rates of 12-50% have been reported after use of liquid nitrogen, including postoperative fracture, skin necrosis, (transient) nerve palsy and infection [74,78,86]. Whereas

postoperative fractures were the most important concern after cryosurgery in the past, adequate monitoring of freezing temperatures and prophylactic osteosynthesis in selected cases have decreased fracture rates dramatically (from 25-50% [77,78] to 0-7% [62,74]). Several options exist for filling the cavity, which can be left empty awaiting new bone formation during partial immobilization [70,87,88], or may be filled with cancellous bone grafts [64,83,89].

However, reported recurrence rates are high after both options, and this may only be adequate after use of a potent local adjuvant such as cryosurgery. The most commonly used technique is filling with PMMA, which hypothetically lowers recurrence risk through its hyperthermic properties. Furthermore, it provides immediate mechanical support and facilitates early detection of local recurrences [2,10,11]. Complication rates of 13-25% have been reported after use of PMMA, including cement leakage into joints or surrounding soft tissues and osteoarthritic changes. PMMA is recommended as a filling and local adjuvant [2,10,11,13,14,90,91].
Local recurrence risk is strongly increased by soft tissue extension (20-25% of all GCTBs) [14,15]. Curettage with adjuvants is reasonable depending on the extent of the soft tissue component. If initially inoperable, neoadjuvant systemic targeted therapy may facilitate intralesional surgery at a later stage, avoiding more invasive surgery. Pathologic fractures are also common (15-20%) but do not appear to increase local recurrence risk [15], contrary to previous suggestions [71]. Recent studies confirmed both resection and curettage as viable treatment options for GCTB with a pathologic fracture [92]. If joint salvage is feasible, GCTB with a pathologic fracture can safely be curetted. With extra-articular fractures, consolidation may be awaited before surgery; with intra-articular fractures, immediate curettage should be performed. Resection should be considered for dislocated intra-articular fractures, fractures with soft tissue extension or when structural integrity cannot be regained [92-95]. Young age has also been suggested to increase risk for recurrence [11,14], but was not confirmed by others [15].

Table 1 Recurrence rates after different types of surgical treatment for giant cell tumor of bone

Study	Year	Follow-up	Total	Resection			Curettage without local adjuvants			Curettage with phenol			Curettage with phenol and PMMA			Curettage with PMMA			Curettage with liquid nitrogen			Curettage with liquid nitrogen and PMMA		
		months (range)	n	n	rec	%	n	rec	%	n	rec	%	n	rec	%	n	rec	%	n	rec	%	n	rec	%
Marcove et al.[a] [75]	1978	43 (3-120)	52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	52	12	23	-	-	-
Jacobs et al. [76]	1985	(26-132)	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12	2	17	-	-	-
Capanna et al. [65]	1990	NR	667	-	-	-	280	126	45	147	28	19	33	1	3	187	36	19	20	4	19	-	-	-
Marcove et al.[b] [73]	1994	147 (24-170)	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	2	29	-	-	-
O'Donnell et al. [69]	1994	48 (24-120)	60	-	-	-	-	-	-	-	-	-	17	3	18	43	12	28	-	-	-	-	-	-
Alkalay et al. [77]	1996	(24-48)	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	0	0
Dürr et al. [66]	1999	61 (6-178)	26	-	-	-	7	3	43	11	1	9	-	-	-	-	-	-	-	-	-	-	-	-
Malawer et al. [72]	1999	78 (48-180)	102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	86	8	8	-	-	-
Schreuder et al. [74]	1999	34 (18-79)	13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13	4	31	-	-	-
Trieb et al. [67]	2001	121 (48-516)	47	-	-	-	14	3	21	12	3	25	-	-	-	-	-	-	-	-	-	-	-	-
Wittig et al.[c] [79]	2001	54 (49-62)	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	0	0
Boons et al. [60]	2002	84 (24-372)	36	11	0	0	-	-	-	-	-	-	-	-	-	4	1	25	12	5	42	5	1	20
Ghert et al. [61]	2002	62 (24-224)	75	24	3	12	-	-	-	-	-	-	9	3	33	38	6	16	-	-	-	-	-	-
Turcotte et al.[d] [62]	2002	57 (24-192)	186	38	6	16	-	-	-	37	NR	18	U	U	18	62	NR	18	10	0	0	-	-	-
Wada et al. [71]	2002	46 (24-188)	15	-	-	-	-	-	-	-	-	-	-	-	-	15	1	7	-	-	-	-	-	-
Ward et al.[e] [63]	2002	59 (12-115)	31	7	0	0	-	-	-	9	1	11	14	1	7	1	0	0	-	-	-	-	-	-
Saiz et al. [70]	2004	76 (28-175)	40	-	-	-	-	-	-	-	-	-	40	5	13	-	-	-	-	-	-	-	-	-
Su et al. [64]	2004	62 (28-138)	87	31	1	3	-	-	-	56	10	18	-	-	-	-	-	-	-	-	-	-	-	-
Abdelrahman et al. [78]	2008	34 (24-40)	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	28	1	4
Balke et al.[e] [2]	2008	60 (8-281)	214	18	0	0	55	32	65	-	-	-	42	5	12	91	26	29	-	-	-	-	-	-
Becker et al. [10]	2008	64 (1-440)	256	48	1	2	65	32	49	-	-	-	50	13	27	69	15	22	-	-	-	-	-	-
Kivioja et al. [11]	2008	60 (3-216)	294	92	11	12	47	24	51	-	-	-	-	-	-	147	32	22	-	-	-	-	-	-

Errani et al. [13]	2010	91 (36-204)	349	149	18	12	-	-	-	136	24	18	64	8	13	-	-	-	-	-	-	-	-	-
Gaston et al. [68]	2011	77 (2-319)	330	-	-	-	246	73	30	-	-	-	-	-	-	84	12	14	-	-	-	-	-	-
Klenke et al. [14]	2011	108 (36-233)	118	22	1	5	22	7	32	32	11	34	40	6	15	1	0	0	-	-	-	-	-	-
Lin et al. [129]	2011	58 (36-156)	26	-	-	-	-	-	-	26	3	12	-	-	-	-	-	-	-	-	-	-	-	-
Benevenia et al. [130]	2012	55 (10-184)	93	-	-	-	-	-	-	18	4	22	-	-	-	-	-	-	-	-	-	-	-	-
van der Heijden et al. [15]	2012	96 (24-288)	93	-	-	-	-	-	-	-	-	-	75	20	27	18	5	28	-	-	-	-	-	-
Recurrence rates mean (range)				6 (0-16)			42 (21-65)			19 (9-34)			17 (3-33)			17 (0-29)			21 (8-42)			6 (0-20)		

PMMA = polymethylmethacrylate, rec = recurrence, NR = not reported, U = unknown

[a]Only in later cases PMMA was used instead of bone grafts, but it is not stated in how many patients

[b]In this study only GCTB of the sacrum were reported

[c]In this study only GCTB of the small bones of the hand were reported

[d]In this study only the overall recurrence rate was given after curettage with different adjuvants (18%) including phenol, PMMA, liquid nitrogen and combinations thereof. Only for the use of liquid nitrogen, the recurrence rate was further specified (0%).

[e]H_2O_2 was used as alternative to phenol as local adjuvant

Secondary osteoarthritis may result from curettage with PMMA in large subchondral GCTB [70,89,96]. This relatively low risk would be increased after repeated curettage for recurrence, with close proximity to articular cartilage [89,97], and with large subchondral defects [96,97].

Generally, curettage with PMMA can be repeated for recurrence as it presents acceptable re-recurrence rates of 14-22% [93,94]. Although 1-4% of patients have pulmonary metastases at primary presentation, a higher incidence was noted after multiple recurrences (10-15%), but this seemed independent from surgical treatment [93,94]. Location in distal radius was thought to have an increased risk for metastases [6], but this was not generally confirmed [7].

Considering the above-mentioned points, en bloc resection should be considered in case of multiple recurrent or unresectable GCTB, impossible joint salvage, extensive cortex destruction (i.e. insufficient cortex left to curette) and extensive soft tissue involvement. Defects can be reconstructed with endoprosthetic replacement, structural allografts, or a combination [98]. The most important disadvantages are higher complication risk, subsequent need for revision surgery and decreased function [16,19,99]. En bloc resection can also be performed in expendable bones (e.g. proximal fibula, distal ulna, iliac wing), in which a bony reconstruction is not required and functional outcome is not likely to be affected.

Postoperative treatment after curettage consists of functional mobilization and immediate full weight bearing for most patients. With reduced bone integrity (i.e. pathologic fracture, large oval window or close relation to the joint), only partial weight bearing is allowed during the first 6-12 weeks. After resection and endoprosthetic reconstruction, immediate full weight bearing is allowed. Follow-up protocol, based on the National Comprehensive Cancer Network guidelines for GCTB and on the European Society for Medical Oncology guidelines for low grade sarcoma, consists of physical examination and radiographs, MRI and/or CT of the surgical site as clinically indicated to detect local recurrences and complications and chest imaging to detect pulmonary metastases every six months during the first two postoperative years and annually thereafter for at least ten years [34,35].

Surgical management of GCTB in axial skeleton and sacrum (2-8% of all GCTBs) is more challenging because of often late discovery, large size, spinal or pelvic instability and involvement of nerve roots [100-102]. Preoperative arterial embolization can be performed as primary treatment [100,103-105], or as

preoperative treatment reducing intraoperative hemorrhage [100,106,107]. Total spondylectomy for vertebral GCTB or en bloc resection for sacral GCTB may result in severe morbidity with bleeding, infection and neurological deficits, and total spondylectomy for sacral GCTB may result in bladder, rectal and sexual dysfunction; therefore, the procedure should not be considered as primary treatment [108-110]. Marginal resection is less mutilating and can be performed in small vertebral lesions and sacral GCTB distal from S3 [100]. Curettage is less invasive and advantages are salvage of nerve roots and visceral structures and maintenance of intrinsic spinal or pelvic support; however, it results in relatively high recurrence rates of 10-37%, because complete removal is difficult and adequate local adjuvants are absent [102,111,112]. Caution is warranted with application of local adjuvants such as phenol or liquid nitrogen in vicinity of neurovascular structures [75,113]. After curettage, spinal or pelvic stability should be assessed and stabilization performed if needed. If at least S1 is preserved after intralesional resection, reconstruction is generally unnecessary. If S1 is partially or completely resected, stabilization with ilio-lumbar screw fixation is preferred.

Systemic therapy

In light of the current understanding of molecular biology of GCTB, systemic targeted therapy has been introduced, in addition to existing surgical treatment options with the aim of facilitating intralesional surgery at a later stage instead of performing more mutilating surgery for the most complex cases.

Bisphosphonates bind to bone mineral and are assumed to inhibit GCTB-derived osteoclast formation, migration and osteolytic activity at sites of bone resorption and to promote apoptosis of osteoclasts (Figure 5). Over the past decade, there has been some experience with bisphosphonate zoledronic acid as systemic therapy for GCTB [22,114,115]. In most reported inoperable tumors, stabilization of local and metastatic disease was achieved. These were, however, small retrospective series with different other treatments; therefore, the level of evidence is low. Currently, a phase II randomized study with zoledronic acid is ongoing in high-risk GCTB patients after surgery (www.clinicaltrials.gov, NCT00889590).

Recently, denosumab has become a new treatment option for locally advanced GCTB. Denosumab is a RANKL-inhibitor that blocks osteoclast maturation and

therewith its osteolytic properties (Figure 5) [21,116]. Denosumab is a fully human monoclonal antibody [117] that is approved for osteoporosis treatment in postmenopausal women at risk for fracturing; to increase bone mass in patients with prostate or breast cancer at risk for fracture due to androgen deprivation therapy or aromatase inhibitor therapy, respectively; and for the prevention of skeletal-related events in patients with bone metastases from solid tumors. In addition, denosumab has been approved by the U.S. Food and Drug Administration for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or when surgical resection is likely to result in severe morbidity [23]; it is currently pending approval by the European Medicines Agency. A first open-label phase II study has shown clear clinical benefits in the treatment of GCTB [20]. In 86% of patients (30 of 35), there was an objective response to denosumab therapy, defined as ≥90% elimination of giant cells on histological evaluation or no radiographic progression of the lesion. Only a small minority of these patients underwent intralesional surgery after denosumab, and to date, it remains unknown whether local recurrence rate will be affected by denosumab treatment. Data with longer follow-up will follow and will provide more information on a possible lowering effect of denosumab on the recurrence rate. The interim analysis of a second and larger study (n=282) was recently published and confirmed the high efficacy of denosumab in GCTB [23]. Ninety-six percent of surgically unsalvageable patients had no disease progression after a median follow-up of 13 months. Seventy-four of 100 patients with tumors needing morbid surgery at study entry had no surgery and 16 of 26 patients underwent less morbid surgery after a median follow-up of 9.2 months. Long-term treatment may be required for long-term local tumor control. Most important side effects are headache and bone pain (1-10%), osteonecrosis of the jaw (1-2%), hypocalcaemia and hypophosphatemia (<0.01%) [20,23,118,119].

In response to denosumab treatment, sclerosis and reconstitution of cortical bone is seen on conventional radiographs and CT (Figure 2) [27]. On dynamic contrast-enhanced MRI, later enhancement followed by slower washout compared to index MRI may indicate response to treatment. Furthermore, reduced uptake is seen on fluorodeoxyglucose-positron emission tomography (FDG-PET) after denosumab treatment, suggesting that FDG-PET may be a sensitive monitor for the response to denosumab [20]. Histopathologically, a strong decrease of reactive osteoclast-like giant cells (≥90%) and a reduced

number of neoplastic stromal cells was seen after denosumab treatment, in addition to new formation of non-proliferative dense fibrous tissue and woven bone [21].
Denosumab is clearly an active drug in GCTB treatment and has an acceptable toxicity profile. Consequently, It should be standard for unresectable disease to facilitate intralesional surgery at a later stage, avoiding more invasive surgery. Data on the use of denosumab for metastatic GCTB are scarce; it is hoped that final data of the open-label phase II trial will provide more knowledge about this matter.

Radiation therapy

Curettage with local adjuvants is the mainstay of treatment for GCTB. With the advent of neoadjuvant systemic targeted therapy using RANKL-inhibitors, promising short-term phase II results with regard to local control have been obtained. However, even after neoadjuvant systemic treatment, extensive soft tissue involvement and axial localization (e.g. sacral lesions) can offer challenges for a satisfactory surgical approach.
In the past, moderate-dose radiotherapy (40-55Gy) has shown to be effective as primary treatment in unresectable GCTB or in cases of residual or recurrent disease when surgery would result in unacceptable morbidity. Most studies were retrospective and included only limited numbers of patients over a considerable time span. In this setting, reported 5-year local control was approximately 80% and ranged between 62-90% [120-131]. Risk factors for local recurrence or residual disease after radiotherapy are large size (>8.5cm) and recurrent disease [128].
Radiotherapy may induce (secondary) malignant transformation, which is of concern especially because most patients are relative young (presenting between 30-50 years of age). The reported risk of malignant transformation varies between 0% and 5% [120,123,125,127,129].
In the era of RANKL-inhibitors, the role of radiotherapy in the treatment of GCTB needs to be redefined. Currently, there is no data on the use of radiotherapy in combination with RANKL-inhibitors for the treatment of primary unresectable or recurrent GCTB. However, given the promising short-term results of phase II studies with RANKL-inhibitors so far, use of radiotherapy should be restricted to those rare cases of unresectable, residual or recurrent GCTB in which treatment

with RANKL-inhibitors is not possible or has been proven to be ineffective, and when surgery would lead to unacceptable morbidity (often in axial location).

Conclusion

GCTB is an intermediate, locally aggressive but rarely metastasizing tumor [1]. Treatment decisions should be made by a multidisciplinary team consisting of dedicated experts in the field of musculoskeletal oncology and should include radiography, dedicated MRI, histopathological assessment and planned surgery, supplemented with systemic targeted therapy if indicated (Figure 6).

Ideally, all patients should be treated with intralesional excision with local adjuvant treatment (e.g. phenol, liquid nitrogen, PMMA), achieving joint salvage and optimal functional outcome. Concurrently, recurrence risk should be minimized to rates similar to those reported after en bloc resection. In this regard, curettage with local adjuvants is safe in patients with GCTB confined to bone or with a pathologic fracture in which joint salvage is feasible. For soft tissue extension, the feasibility of intralesional surgery depends on the extent of the soft tissue component. For GCTB in the axial skeleton, feasibility of intralesional surgery depends on the involvement of neurovascular structures and soft tissue extension.
In patients with high-risk GCTB (e.g. large cortical defects; large soft tissue components; localization in vertebrae, sacrum or pelvis; and multiple recurrent GCTB), acceptable recurrence rates are not achievable with intralesional surgery alone, and these patients are ideally suited for systemic targeted therapy with RANKL-inhibitors or bisphosphonates. Denosumab was associated with tumor responses and reduced the need for morbid surgery; further data on possible delay or avoidance of recurrent disease and further investigation on the duration and dose of denosumab as a therapy for GCTB is warranted. Consequently, neoadjuvant therapy with denosumab should be standard treatment for unresectable disease to facilitate intralesional surgery at a later stage, avoiding more invasive surgery. Long-term effects as well as optimal therapy duration still warrant further study. For patients who require immediate surgery due to intra-articular pathologic fracture or spinal cord compression, adjuvant systemic targeted therapy might reduce recurrence risk, but this is still unknown and is currently under study.

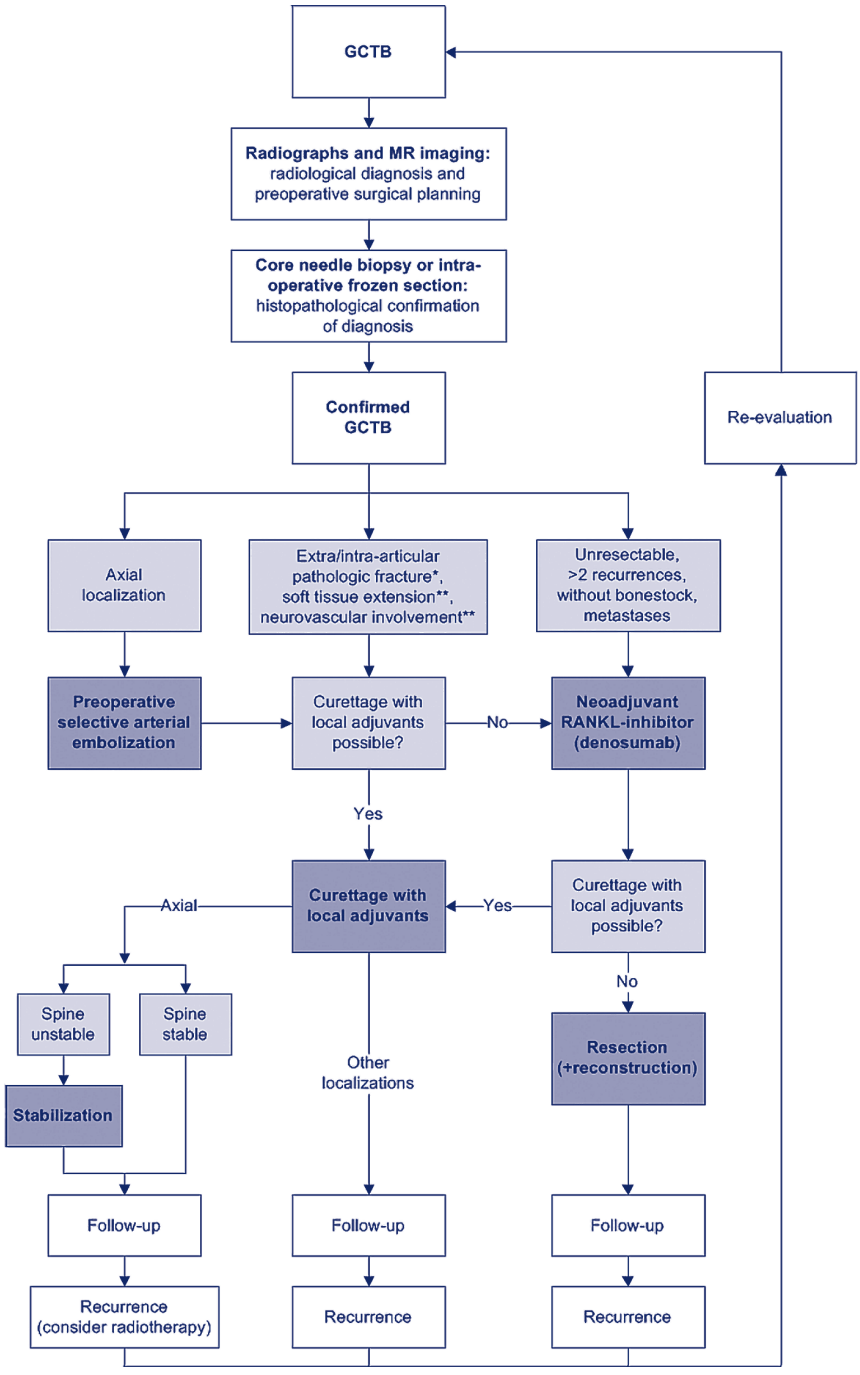

Figure 6 Multidisciplinary treatment recommendations for GCTB *With extra-articular pathologic fractures, preoperative fracture healing may be awaited, while immediate surgery is required with intra-articular pathologic fractures. **Caution is warranted with local adjuvants (e.g. phenol, alcohol, liquid nitrogen) in case of involvement of soft tissues or neurovascular structures as it may induce (severe) necrosis.

Use of moderate-dose radiotherapy (40-55Gy) should be limited to rare cases of unresectable, residual or recurrent GCTB in which denosumab is not available, is contraindicated or is not effective and when surgery would lead to unacceptable morbidity.

In conclusion, we propose multidisciplinary integrated recommendations for the management of GCTB, including radiological, histopathological and surgical aspects. Especially for patients with high-risk GCTB, multidisciplinary treatment should be optimized with respect to immediate local control and optimal functional outcome. The role for systemic targeted therapy needs to be further explored.

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