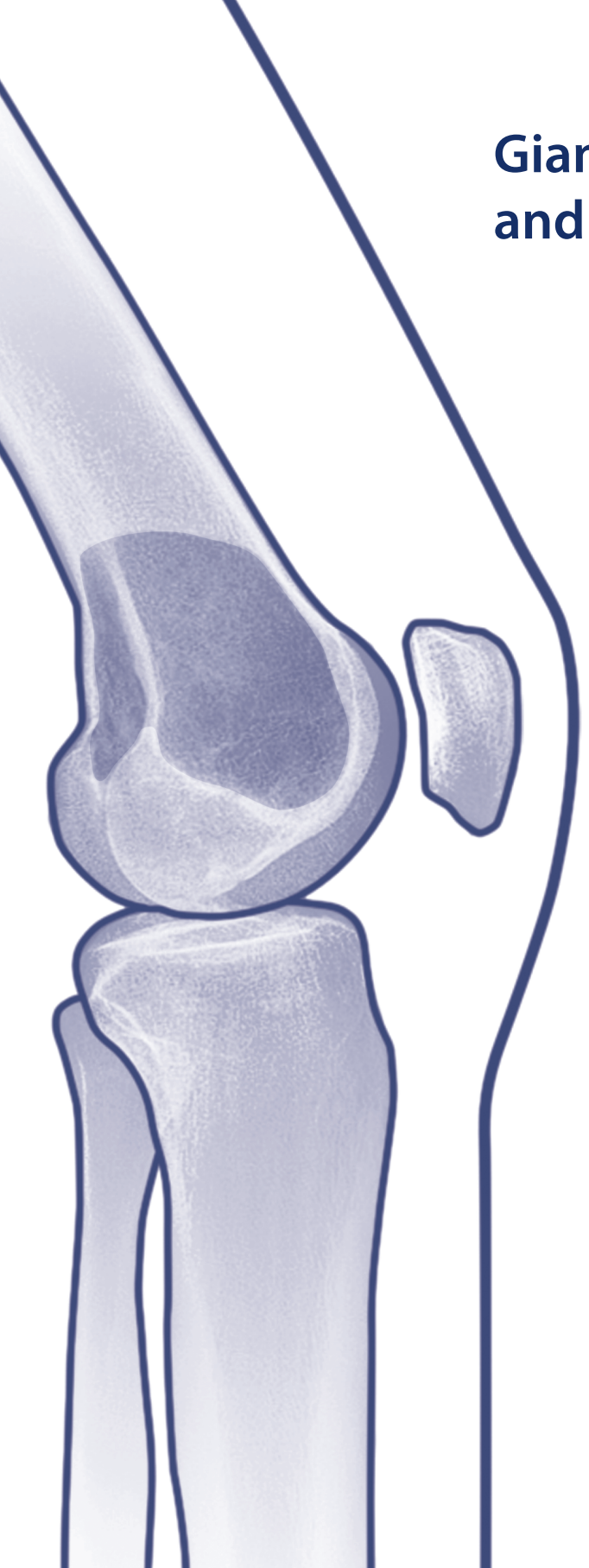

Giant cell tumor of bone and tenosynovial tissue

Surgical outcome

Lizz van der Heijden

Giant cell tumor of bone and tenosynovial tissue
Surgical outcome

Giant cell tumor of bone and tenosynovial tissue – Surgical outcome
PhD thesis, Leiden University, Leiden, the Netherlands

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PROEFSCHRIFT

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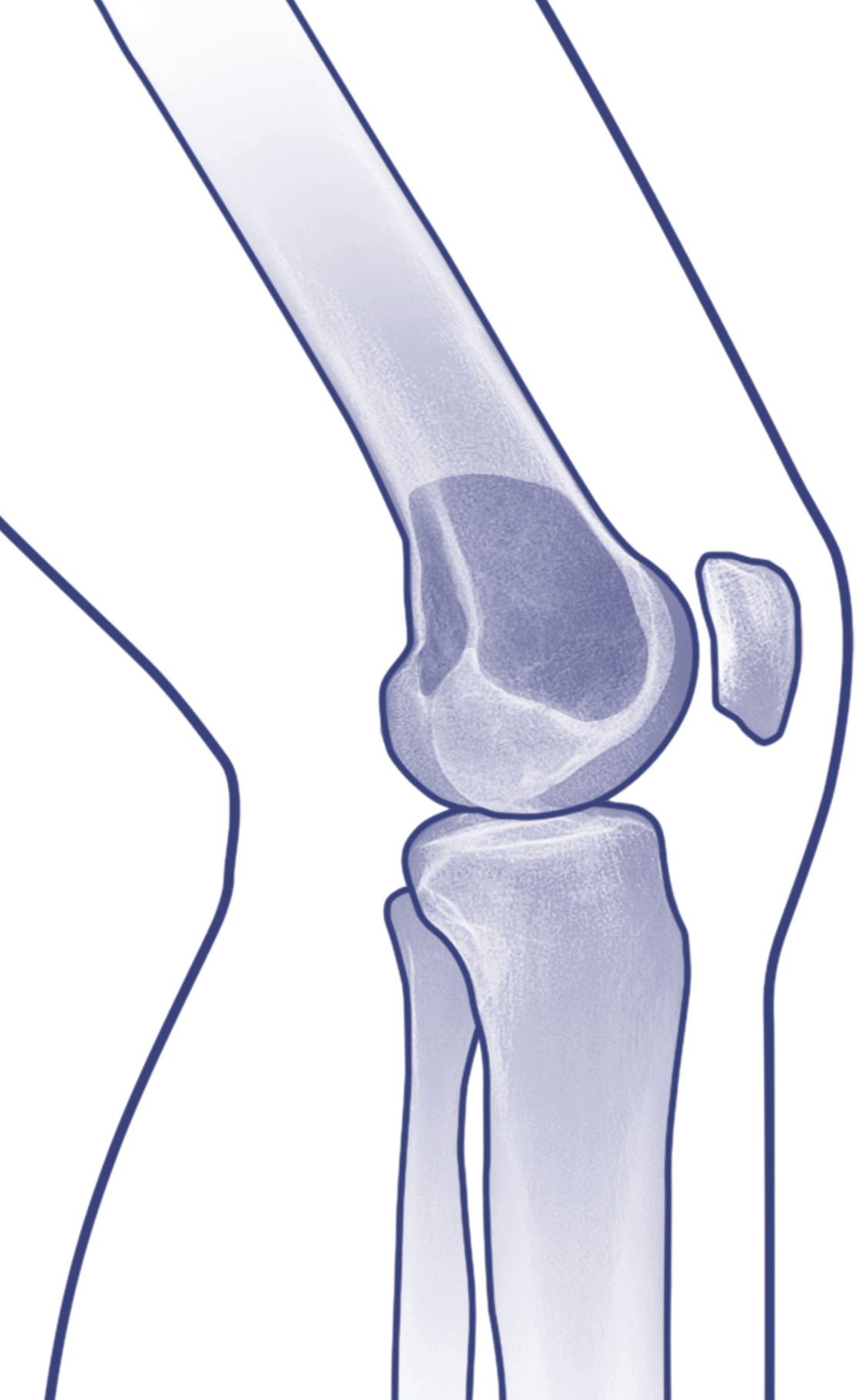
Standing on the shoulders of giants
Isaac Newton

Contents



Chapter 1

General introduction

Background of thesis

Various types of giant cell-rich tumors exist, which are all distinct clinico-pathological and genetic entities (Table 1). This thesis focusses exclusively on giant cell tumor of bone and tenosynovial tissue.

Table 1 WHO classification of primary giant cell-rich tumors of bone and soft tissue

Tumor	Synonym	Site	Epidemiology
Osteoclastic giant cell-rich tumors			
Giant cell tumor of bone (GCTB*)	Osteoclastoma	85% distal femur, proximal tibia, distal radius; 5-10% sacrum; <5% small bones of hands and feet	Age 20-45, slight female predominance
Giant cell lesion of the small bones (GCLSB)	Giant cell reparative granuloma	Phalangeal, metacarpal and metatarsal bones	Age <30, no difference in gender
So-called fibrohistiocytic tumors			
Tenosynovial giant cell tumor, localized type	Giant cell tumor of tendon sheath (GCT-TS*), nodular tenosynovitis	85% fingers; 15% wrist, ankle/ foot, knee (intra-articular)	Age 30-50, female predominance 2:1
Tenosynovial giant cell tumor, diffuse type	Diffuse-type giant cell tumor (Dt-GCT*), pigmented villonodular synovitis (PVNS*)	75% knee; 15% hip; 10% ankle, elbow, shoulder	Age <40, slight female predominance
Giant cell tumor of soft tissue (GCT-ST)	Osteoclastoma of soft tissue, giant cell tumor of low malignant potential	70% extremities; 20% trunk; 7% head and neck	Age 40-50, no difference in gender

*Abbreviations as used in this thesis
MRI = magnetic resonance imaging
CT = computed tomography

Diagnostics	Histopathology	Behavior	Treatment
Radiography: expansile, eccentric, osteolytic lesion CT: cortical thinning, pathologic fracture MRI: intra-osseous spread, soft tissue and joint involvement, Dynamic MRI: fast uptake, slow wash-out of contrast	Mononuclear cells, macrophages, large osteoclast-like giant cells. Malignancy (<1%): primary or secondary after radiotherapy or previous surgery.	Intermediate, locally aggressive, rarely metastasizing (2%)	Curettage with local adjuvants. Re-curettage in recurrent disease (15-50%).
Radiography: expansile, osteolytic lesion.	Fibrous stromal tissue, spindle-shaped fibroblasts, osteoclast-like giant cells.	Benign, tumor-like lesion	Curettage with local adjuvants. Re-curettage in recurrent disease (15-50%).
Radiography MRI	Mononuclear cells, multinucleated giant cells, foamy macrophages, siderophages, stroma.	Benign	Local excision. Re-excision in recurrent disease (4-30%).
Radiography: cystic lesions, degenerative joint disease MRI: haemosiderin artefacts	Few or absent osteoclastic giant cells. Mononuclear cells: small histiocyte-like cells, rounded cells with haemosiderin granules. Malignancy (very rare): increased mitotic rate, necrosis.	Locally aggressive, non-metastasizing	Open complete synovectomy. Re-excision in recurrent intra-articular tumors (18-46%) and extra-articular tumors (33-50%).
MRI	Multinodular (85%), haemosiderin-laden macrophages, round to oval mononuclear cells, multinucleated osteoclast-like giant cells.	Intermediate, locally aggressive, rarely metastasizing	Local excision. Re-excision in recurrent disease (12%).

Giant cell tumor of bone

Giant cell tumor of bone (GCTB) is described histopathologically as an admixture of rounded mononuclear histiocytic or macrophage-like osteoclast precursor cells and spindle-shaped mononuclear neoplastic stromal cells and large reactive multinucleated osteoclast-like giant cells [1]. Overexpression of receptor activator factor kappa-B ligand (RANKL) by mononuclear neoplastic stromal cells promotes recruitment of reactive multinucleated giant cells, capable of lacunar bone resorption [1].

Radiologically, GCTB is an eccentric, lytic lesion with a non-sclerotic and sharply defined geographic border, located in the metaphysis of long bones and extending to the epiphysis of the subarticular region [2,3]. MR imaging typically shows low to intermediate intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images.

Clinically, GCTB behaves as a benign but often aggressive lesion with a typical tendency towards recurrence [4]. GCTB accounts for around 5% of all primary bone tumors and around 20% of all benign bone tumors, the incidence is higher in Asian populations compared to Caucasians. GCTB occurs mostly between the ages of 30-50 years, with a slight predominance for female patients.

GCTB was first described in 1818 by Cooper and Travers and was known as *giant-cell sarcoma* or *osteoclastoma*; it was considered malignant until the beginning of the 20th century [5,6]. In 1912, Bloodgood was the first to introduce the term *giant-cell tumor*; he emphasized the probably benign nature and recognized the importance of radiographs in the diagnosis [7]. By 1925, the benign nature of GCTB was confirmed and the term *giant-cell sarcoma* was officially abandoned [6]. In 1940, Jaffe et al. were the first to identify GCTB as distinct clinical, radiological and pathological entity, separate from other giant cell containing lesions including brown tumor of hyperparathyroidism, giant cell reparative granuloma, chondroblastoma, non-ossifying granuloma and osteoblastoma [8]. This definition of GCTB as one separate entity was based on only fourteen cases, and the histological grading was later proven of little clinical predictive value [6,9]. From the second half of the 20th century, publication of larger series of GCTB increased knowledge on its pathology and clinical behavior [10-12].

Already in 1912, Bloodgood had proposed a surgical approach for GCTB that is in part still valid today [7]. At the time, amputation was common, but Bloodgood advocated curettage, application of carbolic acid (i.e. phenol),

alcohol and bone grafting as first choice treatment for all GCTB, instead of primary resection [7,13]. From the 1950s, the use of local chemical adjuvants other than phenol also became widespread. In 1965, cryosurgery was introduced, consisting of curettage followed by the use of liquid nitrogen [14]. From the 1970s, polymethylmethacrylate (PMMA) was increasingly used to fill the cavity after curettage and it soon started replacing bone grafting [15]. Over the past four decades, surgical treatment options for GCTB remained rather static and there is still no consensus on standard treatment for more extended cases of GCTB [16].

The clinical challenge in the treatment of giant cell tumor of bone is to extend indications for intralesional surgery, while providing optimal oncological, functional and quality of life results. This may be aided by promising results of systemic therapy such as receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors and bisphosphonates, which may enable less invasive forms of surgery [17-20].

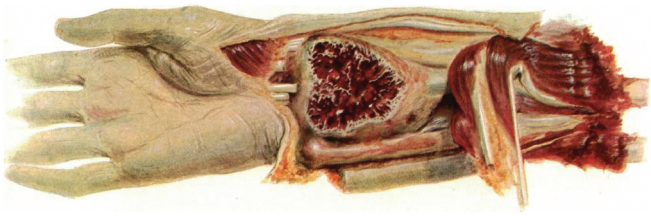


Figure 1 Painting of a giant cell tumor of bone located in the distal radius by Dr. Harvey Cushing. (In: Bloodgood JC. *Ann Surg* 1912; 56:210-239. Reprinted with permission of the Annals of Surgery and Yale University, Harvey Cushin/John Hay Whitney Medical Library.

Giant cell tumor of tenosynovial tissue

Giant cell tumors arising from synovium and tendon sheath are histopathologically described as an admixture of synovial lining cells containing hemosiderin, extracellular hemosiderin deposits, siderophages, lipid-laden foamy macrophages and multinucleated osteoclast-like giant cells [21,22]. Overexpression of macrophage colony-stimulating factor 1 (M-CSF) and its receptor (M-CSFR) by synovial fibroblasts promotes formation of a tumor-like mass [23].

On MR images, hemosiderin depositions cause local changes in susceptibility, resulting in the characteristic low signal intensity appearance of tenosynovial giant cell tumors on T1- and T2-weighted spin echo sequences [24].
Clinically, a distinction is made between localized and diffuse types of tenosynovial giant cell tumor, with the latter being more aggressive and with a higher risk for recurrence. The incidence is approximated at two per million people per year, mostly under the age of 40 and with an equal distribution between the sexes.
The first cases of localized type tenosynovial giant cell tumor were described in 1852 by Chassaignac and the first cases of diffuse type tenosynovial giant cell tumor early in the 20th century [25-27]. At the time, it was considered a malignant condition, but nomenclature was confusing including *fibrous xanthoma*, *myeloxanthoma*, *villous arthritis* and *benign synovioma* [26]. In 1912, Dowd was the first to question the malignant character of the lesion [27]. In 1941, *pigmented villonodular synovitis* (PVNS) or *nodular synovitis* was recognized as a distinct clinical, radiological and pathological entity by Jaffe et al. [28]. As the authors observed similar histological features in local and diffuse lesions and a benign course of disease, they concluded that it must have been a reactive or inflammatory condition instead of a malignancy. This definition of PVNS as one separate entity was based on only twenty cases. In 1984, the lesions were again suggested to be neoplastic rather than reactive or inflammatory [29]. This was confirmed by chromosomal aberrations found in both local and diffuse forms [30-32]. Nowadays, the localized subtype characterized by solitary pedunculated lesions in synovium or tendon sheath is called giant cell tumor of tendon sheath (GCT-TS), also described as *tenosynovial giant cell tumor, localized type* [21]. The diffuse subtype involving the entire synovium of predominantly large joints is called diffuse-type giant cell tumor (Dt-GCT), also described as *tenosynovial giant cell tumor, diffuse type* [22]. Nevertheless, to date the disease remains best known under the term PVNS among most treating physicians.
From the 1940s, surgical treatment for localized and diffuse disease consisted of partial or complete open synovectomy, respectively. From the 1950s, radiation therapy was introduced in order to address the high recurrence rates after synovectomy. However, as high rates of joint stiffness were feared and satisfactory results were obtained even after irradical removal, the role of radiation therapy soon became questioned [26]. With the development

of arthroscopy in the 1980s, this was introduced in the surgical treatment of tenosynovial giant cell tumor. However, recurrence rates were generally higher after arthroscopy when compared to open synovectomy and consensus on standard treatment currently remains under debate.
The clinical challenge in the treatment of tenosynovial giant cell tumor is to improve oncological results and maintain a functional joint and quality of life. To that aim, adjuvant radioactive colloids and external beam radiation therapy and neoadjuvant systemic targeted therapy with M-CSFR-targeted tyrosine kinase inhibitors have been introduced, but not yet validated.

Aim of thesis

Given the above, enhanced and up-to-date decision making is required to optimize treatment for giant cell tumors of bone and tenosynovial tissue. Therefore, the aims of this thesis are to improve patient selection for different types of surgery by identifying risk factors for recurrences and complications, to define indications for systemic targeted therapy and to evaluate clinical outcome after treatment for both types of disease by providing for a clinical decision analysis based on outcome data. More specifically, surgical management of different clinical presentations is evaluated and integrated in multidisciplinary treatment recommendations for both giant cell tumors of bone and tenosynovial tissue.

Thesis outline

Giant cell tumor of bone

A multidisciplinary evaluating system of giant cell tumor of bone including radiological, histopathological and clinical features is required as basis of an optimal treatment protocol [16].
Chapter 2 addresses most relevant issues concerning diagnosis and multidisciplinary treatment of GCTB. Local adjuvants phenol, liquid nitrogen and PMMA decrease recurrence rates after curettage, but relative effectiveness of these local adjuvants has never been compared. **Chapter 3** presents a

retrospective cohort study on relative effectiveness of different standard treatments in two tertiary referral centers; the aim is to determine recurrences, complications and functional outcome after curettage with phenol and PMMA; liquid nitrogen and PMMA; or liquid nitrogen and bone grafts.Approximately one in five patients with GCTB presents with a pathologic fracture, which may impede adequate intralesional surgery [33-35]. Recurrence rates after *en bloc* or intralesional resection differ substantially and it is unclear when curettage is reasonable after a pathologic fracture. **Chapter 4** addresses recurrence rates, complications and functional outcome after curettage with adjuvants or *en bloc* resection for GCTB with a pathologic fracture in a multicenter retrospective cohort study.

GCTB in the small bones of hands and feet accounts for only 2-5% of all GCTB [36-41]. **Chapter 5** contains a systematic literature review and a retrospective multicenter study evaluating recurrence rates, complications and functional outcome after different surgical approaches for GCTB of the small bones of the hands and feet.

The sacrum is the most affected bone within the axial skeleton, representing about 2-8% of all GCTB [42-44]. Surgical management of sacral GCTB is challenging because of its often large size due to late discovery, involvement of sacral nerve roots and spinal instability.

Figure 2 Resection specimen of a benign giant cell tumor of bone originating from the distal femur. Photograph from the collection of the Anatomical Museum of the Leiden University Medical Center, Leiden, the Netherlands (estimated date between 1770 and 1818).

Figure 3 Resection specimen of a giant cell tumor of bone located in the distal femur of a 36-year old male. Photograph from the collection of the Anatomical Museum of the Leiden University Medical Center, Leiden, the Netherlands (1966).

Chapter 6 evaluates oncological, surgical and functional results after intralesional excision with different adjuvant treatments for sacral GCTB in a retrospective nationwide study.In clinical practice, the choice for type of surgery depends on the feasibility of curettage with local adjuvants versus *en bloc* resection, and on the expected risk of local recurrence in individual patients. Cortex destruction, soft tissue extension, pathologic fracture, young age and localization in distal radius have been proposed as risk factors for recurrence [45-51], but this was not confirmed in other studies [52-54]. **Chapter 7** aims at identifying individual risk factors for recurrence exclusively after curettage with adjuvants in a retrospective single center study.

Hyperthermic reaction from PMMA polymerization in combination with **su**bchondral bone involvement by GCTB in close relation with articular cartilage may result in secondary osteoarthritis [55-60]. **Chapter 8** is a radiological study to determine prevalence, risk factors and clinical relevance of radiological osteoarthritis after curettage and PMMA for GCTB around the knee.

Giant cell tumor of tenosynovial tissue

A multidisciplinary evaluating system of tenosynovial giant cell tumor including radiological, histopathological and clinical features is required for optimal surgical and systemic treatment decisions. **Chapter 9** addresses most relevant issues concerning diagnosis and multidisciplinary treatment of tenosynovial giant cell tumor.

Chapter 10 outlines a framework for diagnosis and management of localized and diffuse types of tenosynovial giant cell tumor. Results from a systematic review including all cases available from the literature treated with arthroscopic or open synovectomy, radiation therapy or synoviorthesis are combined with experience from two tertiary referral centers and integrated in multidisciplinary treatment recommendations for Dt-GCT and GCT-TS.

The majority of studies on treatment of Dt-GCT about the knee only reported oncological outcomes after arthroscopic or open synovectomy. Only few studies described functional results, and quality of life results have never been published. **Chapter 11** describes functional outcome and quality of life after multiple surgical interventions including arthroscopic and open synovectomy for Dt-GCT in the knee.

Finally, a summary of this thesis is provided in **Chapter 12** and conclusions, clinical implications and future perspectives for the subjects of this thesis are discussed in **Chapter 13.**

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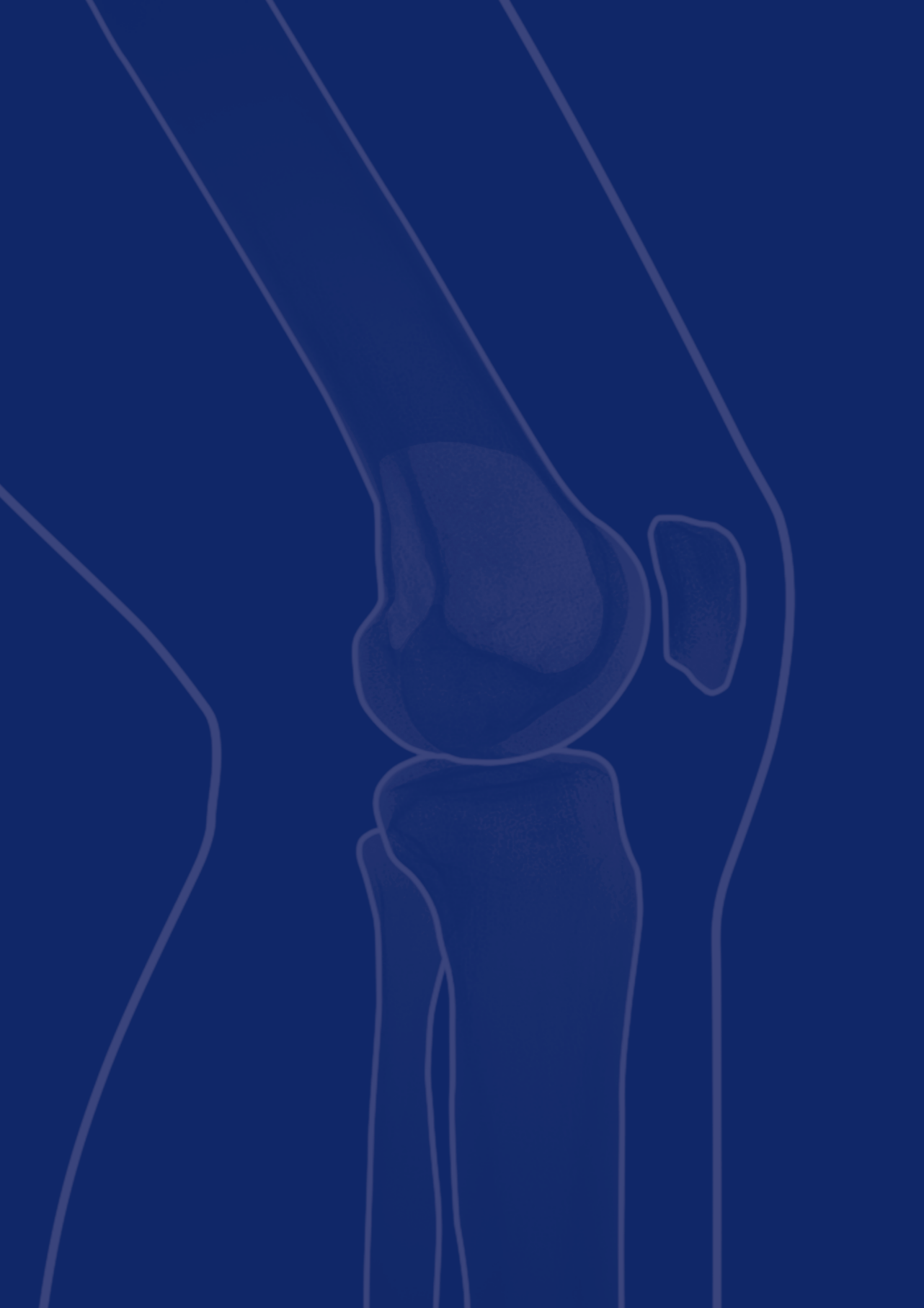
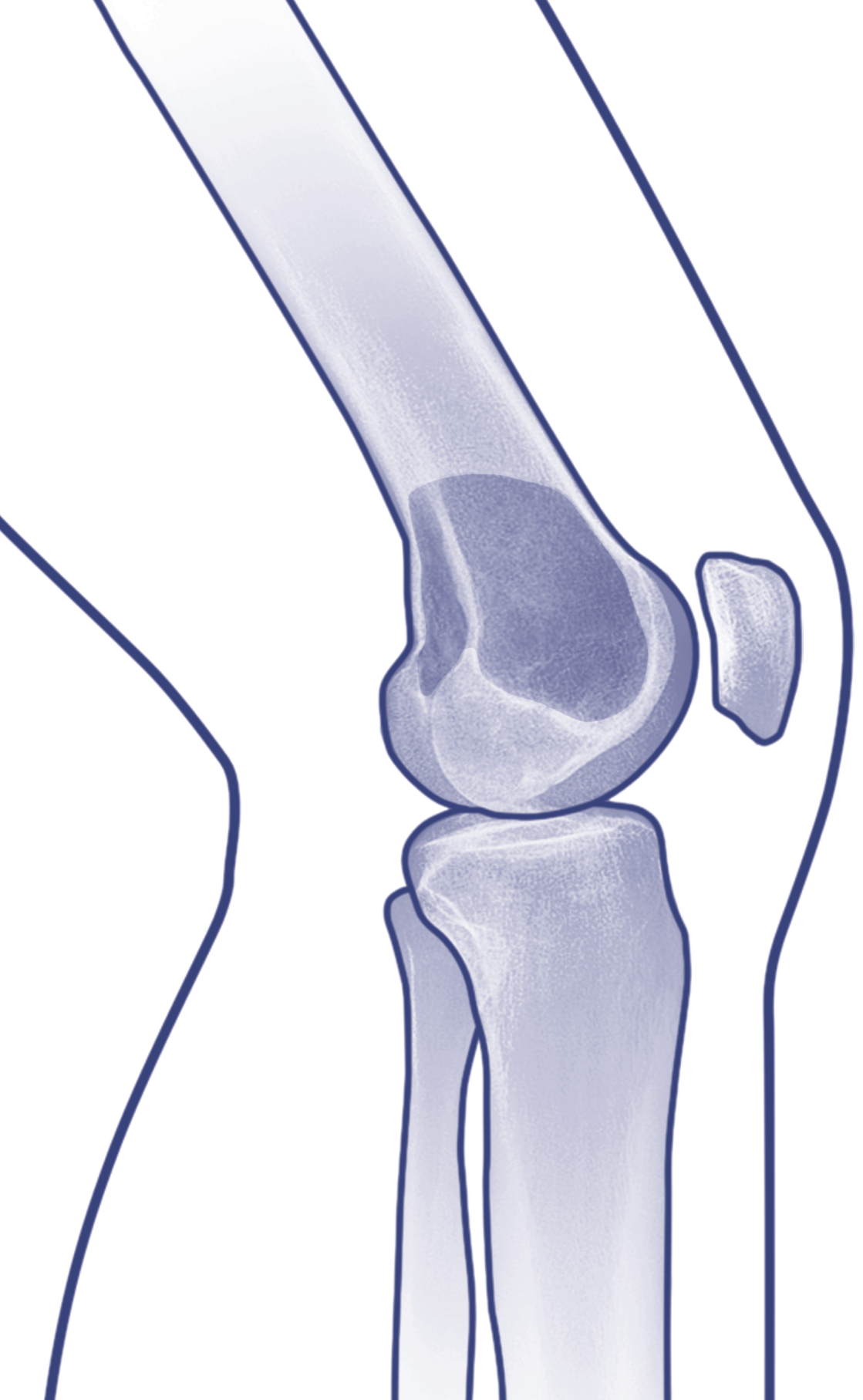


Part I

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].

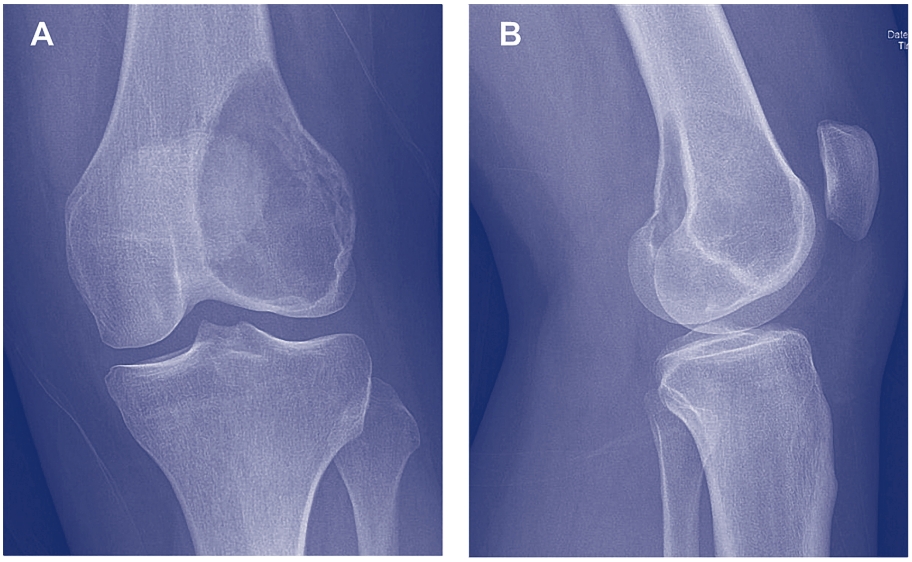

Figure 1 (A, B) Radiographs demonstrating an eccentric, sharply demarcated lytic lesion in the distal femur metaphysis extending to the epiphysis without tumor mineralization. Radiographic features are consistent with giant cell tumor of bone.

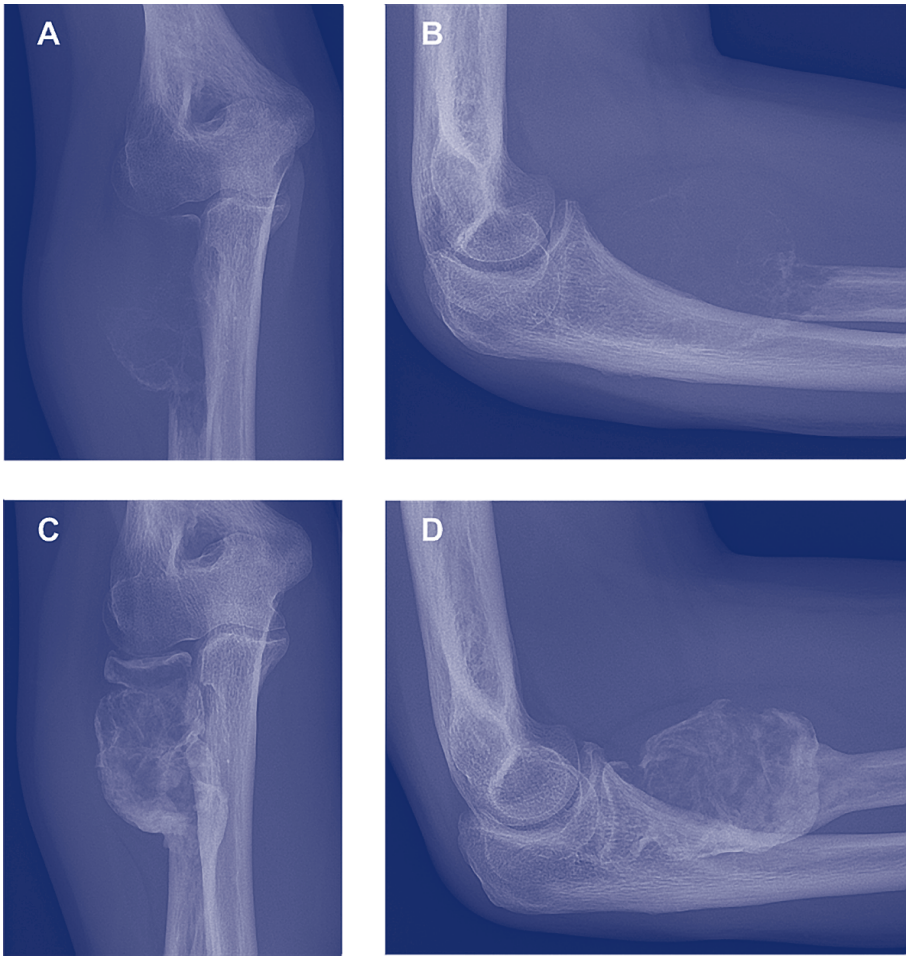

Figure 2 (A, B) Radiographs of a large expansile completely osteolytic lesion in the proximal radius demonstrating a permeative destruction pattern with cortical destruction, consistent with giant cell tumor of bone. (C, D) Radiographs demonstrate new bone formation with reconstitution of cortical bone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

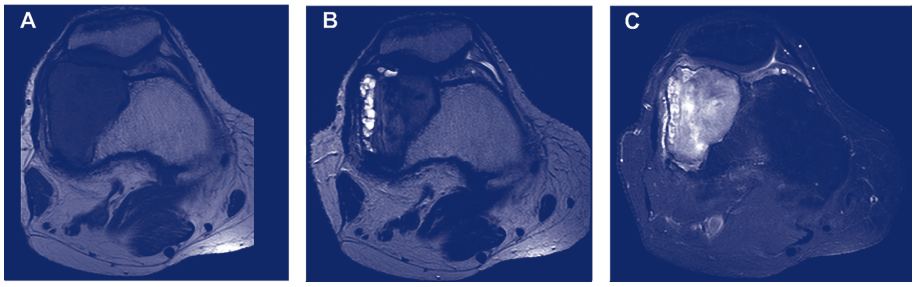

Figure 3 (A) T1-weighted MRI demonstrates an eccentric lesion with mild expansion with intermediate signal intensity. (B) T2-weighted MRI shows low signal intensity through haemosiderin depositions and high signal intensity through secondary cystic changes. (C) T1-weighted MRI with fat suppression after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

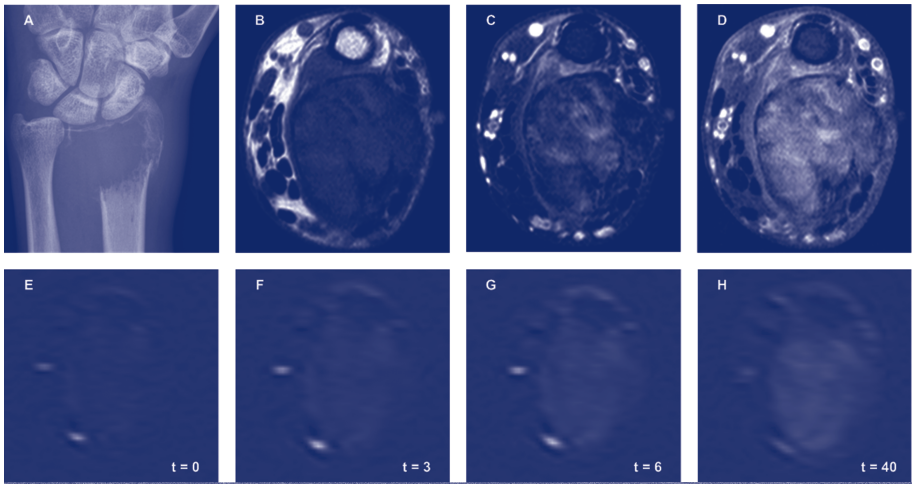

Figure 4 (A) Plain radiograph shows a lytic lesion with extensive cortical destruction and a pathologic fracture in the distal radius. (B-D) T1- and T2-weighted MRI shows inhomogeneous low to high signal intensity and marked enhancement after Gadolinium administration. (E-H) Dynamic contrast-enhanced 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].

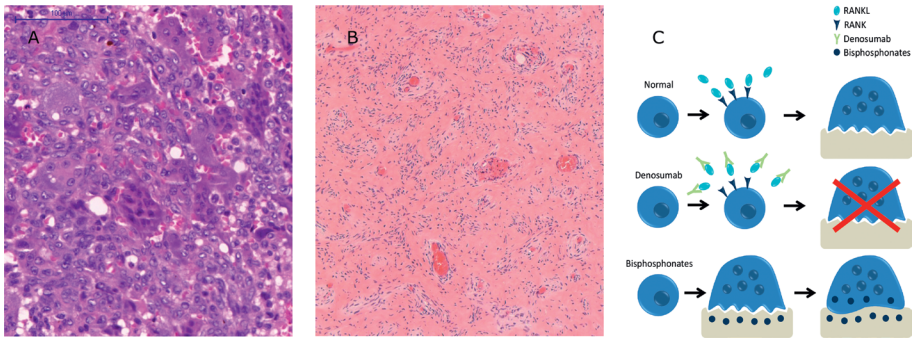

Figure 5 (A) Biopsy with numerous uniformly spaced multinucleated giant cells and mononuclear stromal cells. (B) Surgical specimen after denosumab shows stromal cells, scattered mononuclear spindle cells without evident atypia and diffuse foamy macrophages; no multinucleated giant cells are seen. (C)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

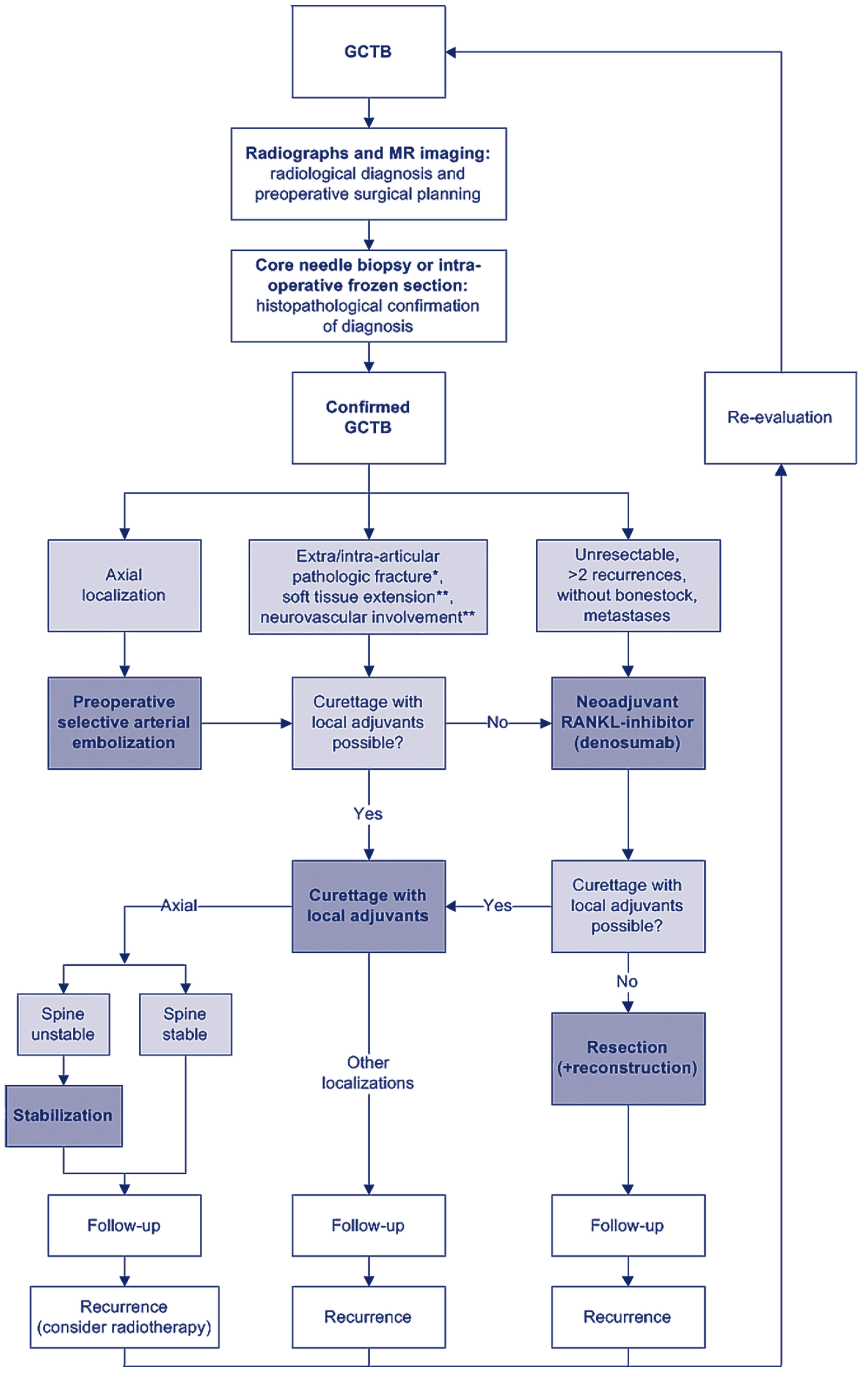

Figure 6 Multidisciplinary treatment recommendations for GCTB *With extra-articular pathologic fractures, preoperative fracture healing may be awaited, while immediate surgery is required with intra-articular pathologic fractures. **Caution is warranted with local adjuvants (e.g. phenol, alcohol, liquid 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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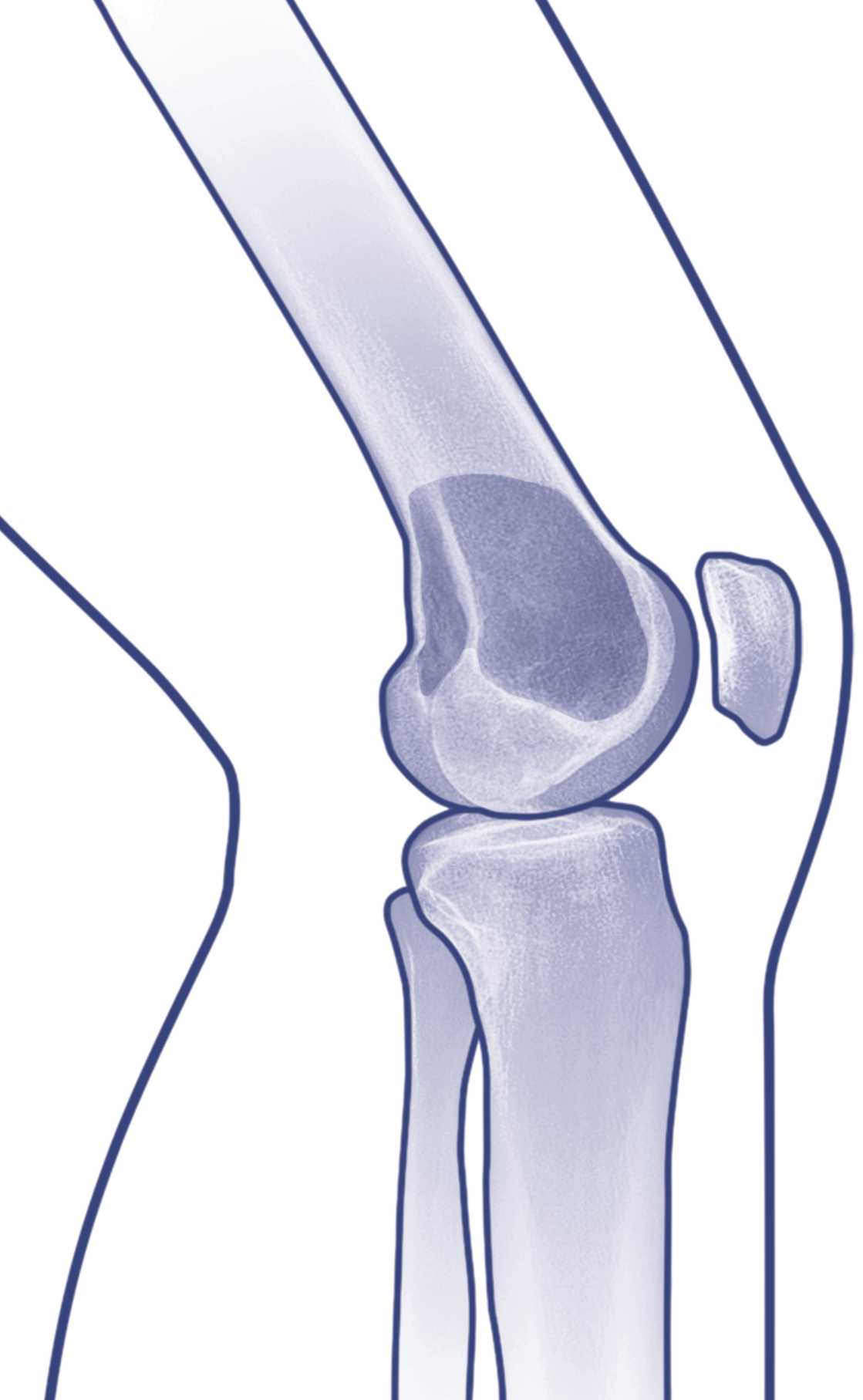

Chapter 3

Liquid nitrogen or phenolization for giant cell tumor of bone? A comparative cohort study of various standard treatments at two tertiary referral centers

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Abstract

Background The rate of recurrence of giant cell tumor of bone (GCTB) is decreased by use of adjuvant treatments such as phenol, liquid nitrogen, or polymethylmethacrylate (PMMA) during curettage. We assessed recurrence and complication rates and functional outcome after curettage with use of phenol and PMMA, liquid nitrogen and PMMA, and liquid nitrogen and bone grafts.

Methods We retrospectively compared the relative effectiveness of treatment of GCTB at two tertiary centers with a regional function from 1990 to 2010. The 132 (of 201) patients who met the inclusion criteria had a mean age of 33 years (range 11-69 years). Treatment assignment depended purely on the center, with primary treatment consisting of curettage with use of phenol and PMMA (n=82) at one center and with use of either liquid nitrogen and PMMA (n=26) or liquid nitrogen and bone grafts (n=24) at the other center. Recurrence and complication rates were determined, and functional outcome was assessed on the basis of the Musculoskeletal Tumor Society (MSTS) score.

Results The mean duration of follow-up was 8 years (range 2-22 years). Recurrence rates were comparable among the groups (28% for phenol and PMMA, 31% for liquid nitrogen and PMMA, and 38% for liquid nitrogen and bone grafts; p=0.52). Soft-tissue extension increased the recurrence risk (hazard ratio [HR]=2.1, 95% confidence interval [CI]=1.1-4.0, p=0.024). The complication rate was 33% after use of liquid nitrogen and bone grafts, 27% after liquid nitrogen and PMMA, and 11% after phenol and PMMA (p=0.019); complications included osteoarthritis, infection, postoperative fracture, nonunion, transient nerve palsy, and PMMA leakage. The complication risk was increased by the presence of a pathologic fracture (HR=4.1, 95%CI=1.7-9.5, p=0.001) and use of liquid nitrogen (HR=3.9, 95%CI=1.5-10, p=0.006 for liquid nitrogen and bone grafts; HR=3.1, 95%CI=1.1-8.6, p=0.028 for liquid nitrogen and PMMA). The mean MSTS score was 26 (range 8-30) and was comparable among all three cohorts (p=0.52).

Conclusions Recurrence rates were comparable for treatment with phenol and PMMA, liquid nitrogen and PMMA, and liquid nitrogen and bone grafts. Complications rates were higher after use of liquid nitrogen. The functional outcome was excellent in all three cohorts.

Introduction

The main difficulty in management of giant cell tumors of bone (GCTB) is the relatively high recurrence rate after curettage, with most recurrences occurring within the first two postoperative years [1]. Although recurrence rates are lower (0 to 12%) after *en bloc* resection, curettage with local adjuvants is preferable as it results in less morbidity and superior functional outcome [2-5]. Without any local adjuvant, reported recurrence rates range from 21% to 65% [6,7]. The most widely accepted treatment today is curettage combined with phenolization and use of polymethylmethacrylate (PMMA) [7-11].

Phenol is a chemical agent that induces tumor necrosis and coagulation of proteins at the borders of the cavity [12,13]. The cytotoxic effect of phenol has been studied *in vitro* on monolayer cultures of cells from GCTB, and the infiltration-depth has been estimated at 0.2 mm [14]; the *in vivo* infiltration-depth in bone remains unknown [15]. Reported recurrence rates range from 9% to 34% after curettage with phenol [5,10,16,17] and 8% to 27% after curettage with phenol and PMMA [7-11]; the additional effect of phenol during curettage with use of PMMA remains unclear [1,10,11]. Complications resulting from phenol use include chemical burns, and caution is warranted in vicinity of neurovascular structures and soft tissues [18,19].

Cryosurgery is used at some centers for aggressive benign bone tumors (e.g. GCTB, aneurysmal bone cyst, chondroblastoma) and low-grade malignant bone tumors (e.g. chondrosarcoma grade I) [20,21]. Liquid nitrogen induces tissue necrosis by causing the formation of intracellular ice crystals and membrane disruption [22]. Repetitive cycles of rapid freezing and slow thawing increase surgical margins by up to 2 cm, comparable with marginal resection [21,23]. Use of liquid nitrogen after curettage has been reported to result in recurrence rates of 8% to 42% when used with bone grafts [13,24-26] or 0% to 20% when used with PMMA [13,27,28]. Complication rates of 12% to 50% have been reported, with the complications including postoperative fracture, skin necrosis, (transient) nerve palsy, and infection [23,24,29].

PMMA is a thermal adjuvant that increases surgical margins by up to 1.5 to 2 mm in cancellous and 0.5 mm in cortical bone [30,31]. When applied after curettage, PMMA has been reported to lower the recurrence risk to 7% to 29%, hypothetically through its hyperthermic reaction [1,7,9,11,32-35]. PMMA provides immediate mechanical support and facilitates early radiographic

detection of recurrences. Complication rates of 13% to 25% have been reported, with the complications including cement leakage into joints or surrounding soft tissues and osteoarthritic changes. The latter may occur after curettage with PMMA if a large giant cell tumor is close to the articular cartilage [36-39]. Various combinations of local adjuvants have been used in the past, but the effectiveness of phenol has never been compared with that of liquid nitrogen in a comparative cohort study involving various standard treatments. We therefore assessed recurrences, non-oncological complications, and functional outcome after curettage with use of phenol and PMMA, liquid nitrogen and PMMA, and liquid nitrogen and bone grafts.

Patients and methods

After approval by the local ethics committee, we retrospectively evaluated 201 consecutive patients treated for giant cell tumor of a long bone at two tertiary centers from 1990 to 2010. Sixty-nine patients did not meet the inclusion criteria (Figure 1). Sixty of these patients underwent a primary treatment other than the standard treatment because of soft-tissue extension, an intra-articular pathologic fracture, or a difficult anatomic location. (Thirty-two underwent resection, sixteen underwent isolated curettage, eight underwent curettage with use of PMMA, and four underwent curettage with phenol.) Two patients had giant cell tumors at multiple sites. Seven patients were lost to follow-up within two years (4-17 months) after the primary surgery; two of these had had a recurrence (after two and 11 months).

The remaining 132 patients (63 female) were included in the analysis. These patients had a mean follow-up of 93 months (range 24-266 months) and a mean age of 33 years (range 11-69 years). All included patients had a histologically verified GCTB. Two patients developed pulmonary metastases (after 11 and 12 months). Four patients died of a cause unrelated to the tumor after four to nine years; no recurrent or metastatic disease was noted at the time of death. No patients were recalled specifically for this study; all data were obtained from medical records and imaging studies used in the follow-up.

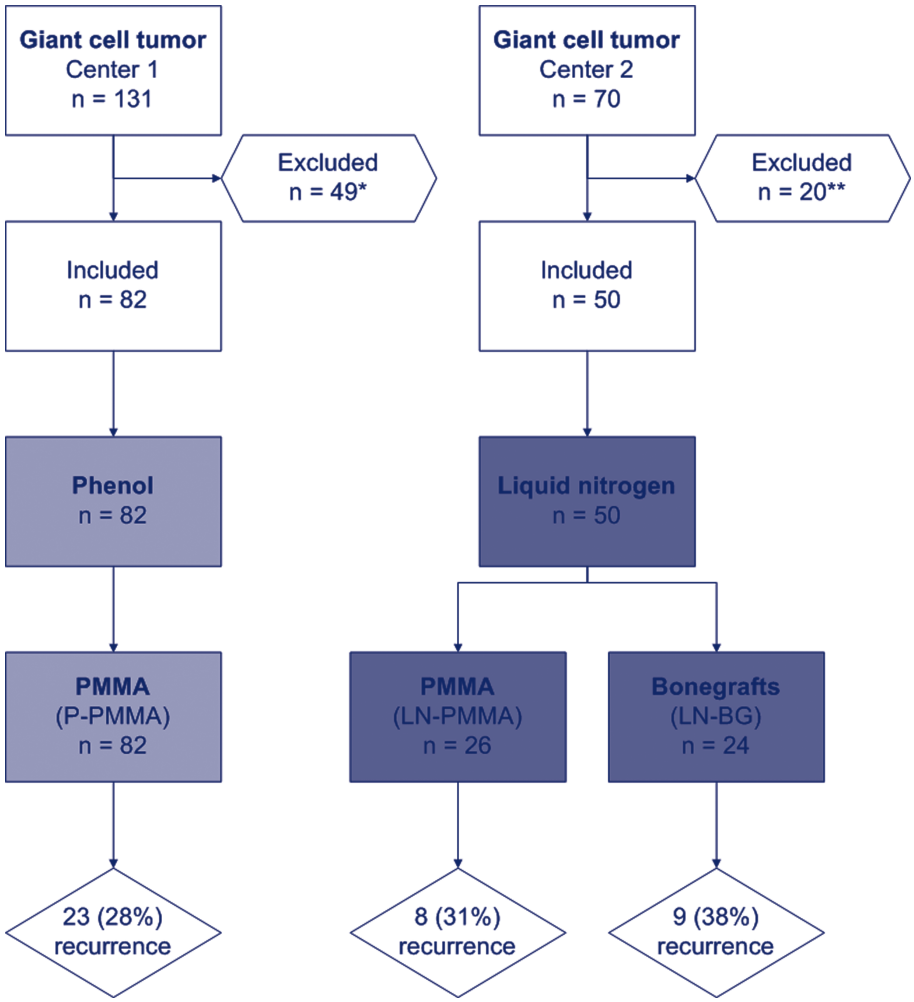

Figure 1 Surgical treatment for giant cell tumor of bone at two tertiary referral centers for orthopaedic oncology with different standard treatment protocols approximating randomization for phenol and liquid nitrogen use, and resulted in three cohorts for this retrospective comparative cohort study. *The primary treatment in forty-three patients was not the typical method described, and six were lost to follow-up. **The primary treatment in 17 patients was not the typical method described, two had giant cell tumors in multiple locations, and one was lost to follow-up. P-PMMA = phenol and PMMA, LN-PMMA = liquid nitrogen and PMMA, LN-BG = liquid nitrogen and bone grafts.

Patients were treated at two tertiary referral centers for musculoskeletal oncology. All surgeons were fellowship-trained orthopaedic oncologists; surgical expertise was comparable at the two centers, and each center specialized in its standard technique. Confounding by indication was minimal

as both centers apply similar indications for curettage, with both including patients with a pathologic fracture or soft-tissue extension—primary *en bloc* resection was rarely considered. Center 1 is situated in a more densely populated area, resulting in a greater number of patients. However, both centers have a regional function, as patients are referred on the basis of their residence, and this minimized the differences between the study populations at the two centers. All patient and tumor characteristics except anatomic location were similar among the three treatment cohorts (Table 1).

Table 1 Patient demographics

	Total (n=132)	Phenol and PMMA (n=82)	Liquid nitrogen and PMMA (n=26)	Liquid nitrogen and bone grafts (n=24)	p-value
Age at diagnosis (yr)	33 (11-69)	32 (13-61)	37 (16-69)	32 (11-63)	0.29
Time to recurrence (mo)	29 (4-156)	32 (4-156)	18 (7-29)	31 (8-72)	0.71
Time to complication (mo)	45 (1-203)	40 (6-115)	35 (1-85)	59 (3-203)	0.87
Follow-up (mo)	93 (24-266)	100 (24-266)	72 (28-151)	92 (24-228)	0.21
Sex					0.27
Male	69 52%	46 56%	14 54%	9 38%	-
Female	63 48%	36 44%	12 46%	15 62%	-
Age <30 years	64 48%	44 54%	10 38%	10 42%	0.31
Location					0.004
Distal femur	63 48%	47 57%	9 34.5%	7 29%	-
Proximal tibia	25 20%	14 17%	9 34.5%	2 8%	-
Distal radius	15 11%	9 11%	2 8%	4 17%	-
Distal tibia	8 6%	5 6%	2 8%	1 4%	-
Proximal humerus	7 5%	3 4%	1 4%	3 13%	-
Proximal femur	7 5%	2 2.5%	3 11%	2 8%	-
Fibula	5 4%	2 2.5%	- -	3 13%	-
Distal ulna	2 1%	- -	- -	2 8%	-
Tumor characteristics					
Soft-tissue extension	34 27%	22 27%	6 23%	6 25%	0.90
Pathologic fracture	28 22%	17 21%	7 27%	4 17%	0.68
Intra-articular	9 -	6 -	2 -	1 -	-
Complex	8 -	4 -	1 -	3 -	-

Reconstruction with bone grafts was sometimes preferred in non-weight-bearing bones, whereas PMMA was used more often in weight-bearing bones to facilitate immediate weight-bearing.

The standard primary treatment at Center 1 consisted of curettage with use of phenol and PMMA (n=82). Three cycles of phenolization of the cavity walls were performed, followed by application of 70% ethanol. Surrounding soft tissues were carefully protected. After treatment, the cavity was rinsed extensively by means of high-speed pulsatile lavage with saline solution. When <10 mm of subchondral bone remained after curettage, bone grafts were used to increase the health of the articular cartilage (n=42). The cavity was filled with PMMA in all 82 patients. One patient also underwent osteosynthesis.

The standard treatment at Center 2 consisted of curettage and high-speed burring followed by cryosurgery involving a liquid nitrogen spray. Thermocouples were used to monitor freezing of the cavity walls [40], and surrounding soft tissues were continuously irrigated with warm fluids to protect against thermal injury. Three cycles of rapid freezing (to ≤-50 °C) and slow thawing (to 20 °C) were performed. In 26 patients, PMMA was used to fill the cavity. As at Center 1, subchondral bone grafts were used when <10 mm of subchondral bone remained (n=17). In 24 patients, the cavity was entirely filled with bone grafts, with no PMMA used. Prophylactic osteosynthesis was used to prevent postoperative fracture in 17 patients treated with liquid nitrogen and PMMA and in eight patients treated with liquid nitrogen and bone grafts. The choices regarding cavity filling with either bone grafts or PMMA and regarding prophylactic osteosynthesis were made intraoperatively and depended on tumor location, cortical stability, and anticipated fracture risk. PMMA was used as often as bone grafts after cryosurgery, and both types of filling material are still used at Center 2.

Postoperative treatment after use of phenol and PMMA consisted of functional mobilization with immediate full weight-bearing. Postoperative treatment after use of liquid nitrogen and either bone grafts or PMMA consisted of functional mobilization with partial weight-bearing for at least six weeks. Weight-bearing was increased when radiographs indicated sufficient incorporation and excluded postoperative fracture. High-impact activities were avoided during the first six months, with no subsequent activity restrictions.

Follow-up protocols were similar at the two centers. Potential bias resulting from patient-requested visits between the administratively scheduled regular follow-up appointments would have been similar for both centers and unlikely to influence the outcomes of this study. Follow-up consisted of radiographs at 1.5, 3, 6, 12, 18, and 24 months postoperatively followed by yearly radiographs for the next 10 years. Magnetic resonance (MR) imaging was performed at two and five years postoperatively and if recurrence was suspected. Thoracic computed tomography (CT) scans or chest radiographs were made at presentation and with every proven recurrence to detect pulmonary metastases.

Medical records were reviewed to determine age, sex, tumor location, presence of soft-tissue extension, presence of a pathologic fracture, type of surgery and reconstruction, development of local recurrences, development of non-oncological complications, functional outcome, and duration of follow-up (Table 1).

The local recurrences were confirmed by imaging studies and histopathology during the follow-up, and the recurrence rate in each of the three treatment cohorts was confirmed by review of the medical records. Non-oncological complications were recorded and were evaluated in each treatment cohort and according to the use of PMMA or bone grafts for reconstruction. In all patients in whom the location of the tumor was about the knee, preoperative and postoperative radiographs (if available) were reviewed to assess knee osteoarthritis with use of the Kellgren-Lawrence scale [41]. Complete radiographic data were available for 77 (88%) of these 88 patients, and the presence of osteoarthritis of the knee on radiographs was defined as a Kellgren-Lawrence grade 3 or 4 [41]. The functional outcome was evaluated in each treatment cohort and according to the use of PMMA or bone grafts for reconstruction with use of the Musculoskeletal Tumor Society (MSTS) score. Functional results were available for 113 (86%) of the patients at the time of the latest follow-up (mean 8 years [range 2-22 years]); the remaining 19 patients could not be reached.

Statistical analysis

Baseline differences among the cohorts were assessed with use of chi-square and Mann-Whitney U tests. Recurrence-free survival was assessed with use of Kaplan-Meier survival analysis and compared among cohorts with use of log-

rank tests. Univariate and multivariate Cox regression analyses were performed to determine risk factors for recurrence and complications. MSTS scores were compared with use of Mann-Whitney U tests.

Results

The recurrence rate after curettage was 28% (23 of 82) in the patients treated with phenol and PMMA, 31% (8 of 26) in those treated with liquid nitrogen and PMMA, and 38% in those treated with liquid nitrogen and bone grafts (Figure 2).

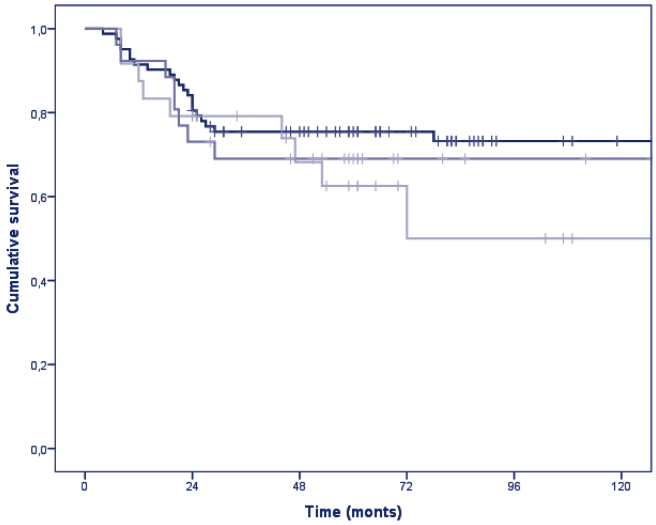

Figure 2 Kaplan-Meier recurrence-free survival for giant cell tumor of bone treated with curettage with use of phenol and PMMA (black line), liquid nitrogen and PMMA (dark grey line), and liquid nitrogen and bone grafts (light grey line) (p = 0.52).

Recurrence-free survival at five years was estimated to be 0.76 after use of phenol and PMMA, 0.69 after use of liquid nitrogen and PMMA, and 0.63 after use of liquid nitrogen and bone grafts (p=0.52). In the 40 patients with recurrence, the median time to recurrence was 20 months (range 4-156 months). Seven recurrences occurred later than three years postoperatively.

Recurrences were confined to bone in 27 patients and had soft-tissue extension in 13. In the multivariate Cox regression analysis, soft-tissue extension at initial presentation increased the risk for recurrence (hazard ratio [HR]=2.3, 95% confidence interval [CI]=1.2-4.5, p=0.0012). Fifteen (44%) of the 34 patients with soft-tissue extension at presentation developed recurrence. An age of less than 30 years, sex, the presence of a pathologic fracture, and the choice of local adjuvant treatment did not influence the risk for recurrence (Table 2). In the patients treated with phenol and PMMA, the recurrence rate did not differ between those who underwent reconstruction with and without subchondral bone grafting (31% [13 of 42] compared with 25% [10 of 40], p=0.36). Likewise, in the patients treated with liquid nitrogen, it did not differ between the patients who did and did not receive bone grafts (18% [4 of 22] compared with 7% [2 of 28], p = 0.23). Local control was achieved with use of one or multiple intralesional procedures in 119 (89%) of the 132 patients. Thirty of the 40 first recurrences were treated with curettage with use of phenol and PMMA (n=17), liquid nitrogen and PMMA (n=7), liquid nitrogen and bone grafts (n=4), PMMA (n=1), or phenol (n=1); seven were treated with resection; and the remaining three were still awaiting surgery. Ten patients developed a second recurrence; five were treated with curettage with use of phenol and PMMA (n=1), PMMA (n=2), or liquid nitrogen and bone grafting (n=2); four were treated with resection; and the remaining patient was still awaiting surgery. Two patients developed a third recurrence; one was treated with curettage with use of liquid nitrogen and PMMA, and the other was treated with excision of the soft-tissue recurrence.

Non-oncological complication rates were significantly higher (p=0.019) after curettage with use of liquid nitrogen and bone grafts (33%; 8 of 24) or liquid nitrogen and PMMA (27%; 7 of 26) compared with phenol and PMMA (11%; 9 of 82) (Table 3).

The rate of complications was also significantly higher (p=0.038) after reconstruction with bone grafts (33%; 8 of 24) compared with PMMA (15%; 16 of 108). The median time to development of a complication was 31 months (range 1-203 months). Non-oncological complications included osteoarthritis, infection, postoperative fracture or femoral condyle collapse, nonunion, nerve palsy, and PMMA leakage (Table 3). In the multivariate Cox regression analysis, the complication risk was increased by the presence of a preoperative

pathologic fracture (HR=4.1, 95%CI=1.7-9.5, p=0.001) and by use of liquid nitrogen (HR=3.9, 95%CI=1.5-10, p=0.006 for use of liquid nitrogen and bone grafts; HR=3.1, 95%CI=1.1-8.6, p=0.028 for use of liquid nitrogen and PMMA).

Table 2 Cox regression analysis of risk factors for recurrence and complications after curettage with adjuvants for giant cell tumor of bone

	n	Recurrences	Hazard ratio	95% confidence interval	p-value
Univariate analysis					
Soft-tissue extension	34	15 44%	2.1	1.1-4.0	0.024
Age <30 years	64	22 34%	1.5	0.78-2.7	0.24
Pathologic fracture	28	6 21%	0.64	0.27-1.5	0.31
Sex (female)	63	18 29%	0.80	0.43-1.5	0.48
Local adjuvants					
Phenol and PMMA	82	23 28%	-	-	0.52
Liquid nitrogen and PMMA	26	8 31%	1.3	0.56-2.8	0.58
Liquid nitrogen and bone grafts	24	9 38%	1.6	0.56-3.4	0.27
Multivariate analysis					
Soft-tissue extension	34	15 44%	2.3	1.2-4.5	0.012
Age <30 years	64	22 34%	1.6	0.81-3.0	0.18
Local adjuvants					
Phenol and PMMA	82	23 28%	-	-	0.32
Liquid nitrogen and PMMA	26	8 31%	1.4	0.62-3.2	0.41
Liquid nitrogen and bone grafts	24	9 38%	1.8	0.82-4.0	0.14
	n	Complications	Hazard ratio	95% confidence interval	p-value
Univariate analysis					
Pathologic fracture	28	11 39%	3.6	1.6-8.2	0.002
Soft-tissue extension	34	7 21%	1.1	0.45-2.6	0.87
Sex (female)	63	10 16%	0.94	0.42-2.1	0.87
Age <30 years	64	6 9%	0.42	0.17-1.0	0.054
Local adjuvants					
Phenol and PMMA	82	9 11%	-	-	0.016
Liquid nitrogen and PMMA	26	9 35%	3.3	1.2-9.1	0.019
Liquid nitrogen and bone grafts	24	6 25%	3.4	1.3-8.9	0.011
Multivariate analysis					
Pathologic fracture	28	11 39%	4.1	1.7-9.5	0.001
Soft-tissue extension	34	7 21%	1.4	0.55-3.4	0.49
Local adjuvants					
Phenol and PMMA	82	9 11%	-	-	0.012
Liquid nitrogen and PMMA	26	9 35%	3.1	1.1-8.6	0.028
Liquid nitrogen and bone grafts	24	6 25%	3.9	1.5-10	0.006

Eleven (39%) of the 88 patients with a pathologic fracture developed complications (osteoarthritis in six, infection in two, postoperative fracture in two, and nonunion in one). An age of less than 30 years, sex, and soft-tissue extension did not influence the complication risk (Table 2). Knee osteoarthritis (a Kellgren-Lawrence grade of 3 or 4) was found on radiographs made at a median of 34 months (range 3-116 months) postoperatively in 12% (6 of 50) patients treated with phenol and PMMA, 17% (3 of 18) treated with liquid nitrogen and PMMA, and 22% (2 of 9) treated with liquid nitrogen and bone grafts. None of these patients had had Kellgren-Lawrence grade 3 or 4 knee osteoarthritis preoperatively. In addition, two patients treated with liquid nitrogen developed carporadial osteoarthritis. Among the patients treated with phenol and PMMA, 24% (4 of 17) who received subchondral bone grafts and 44% (4 of 9) treated without bone grafts developed osteoarthritis (p=0.26) Among the patients treated with liquid nitrogen and PMMA, one of eleven who received subchondral bone grafts and two of five patients treated without bone grafts developed osteoarthritis (p=0.21). The osteoarthritis in ten of the patients did not require surgery, two underwent total knee arthroplasty, and one underwent wrist arthrodesis.

Other complications included osteomyelitis (n = 2) and wound infection (n = 2), which resolved after intravenous antibiotics. One of these patients also underwent PMMA replacement with cancellous bone grafts. Two patients had femoral condyle collapse (after 3 and 35 months); the first had Kellgren-Lawrence grade 4 osteoarthritis and underwent total knee arthroplasty, and the second was not treated because of palliative care for a comorbidity. One patient had a postoperative fracture that healed after PMMA replacement. Nonunion occurred in two patients; both underwent PMMA replacement with cancellous bone grafts, with reduction of the fracture with external fixator in one of the patients. Transient peroneal nerve palsy occurred in one patient. One patient had intra-articular leakage of PMMA; the PMMA that leaked was surgically removed two weeks after the initial surgery.
Functional outcome was measured on the basis of the MSTS score at the time of the latest follow-up was comparable among the three cohorts (p=0.52). The mean MSTS score was 26 (range 11-30) in 67 patients treated with phenol and PMMA, 26 (range 8-30) in 22 patients treated with liquid nitrogen and PMMA,

Table 3 Non-oncological complications after curettage with different types of local adjuvants and reconstruction methods for giant cell tumor

	n	Complications		Osteo-arthritis*	Infection	Fracture **	Nonunion	Nerve palsy	PMMA leakage	p-value
		n	%							
Total	132	24	18	13	4	3	2	1	1	-
Local adjuvant type										0.019
Phenol and PMMA	82	9	11	6	1	-	2	-	-	-
Liquid nitrogen and PMMA	26	7	27	4	1	1	-	-	1	-
Liquid nitrogen and bone grafts	24	8	33	3	2	2	-	1	NA	-
Reconstruction type										0.038
PMMA	108	16	15	10	2	1	2	-	1	-
Bone grafts	24	8	33	3	2	2	-	1	NA	-

NA = not applicable
*In both the cohort treated with liquid nitrogen and PMMA and liquid nitrogen and bone grafts, one patient had radiocarpal osteoarthritis; one was treated with wrist arthrodesis. All other patients had osteoarthritis of the knee, which was objectified as Kellgren-Lawrence grade 3 or 4 at final follow-up.
**After liquid nitrogen and PMMA, one patient had a postoperative fracture, which was treated with PMMA replacement. After liquid nitrogen and bone grafts, two patients had a femoral condyle collapse; one was treated with total knee arthroplasty and one expectative due to severe co-morbidities.NA = not applicable
*In both the cohort treated with liquid nitrogen and PMMA and liquid nitrogen and bone grafts, one patient had radiocarpal osteoarthritis; one was treated with wrist arthrodesis. All other patients had osteoarthritis of the knee, which was objectified as Kellgren-Lawrence grade 3 or 4 at final follow-up.
**After liquid nitrogen and PMMA, one patient had a postoperative fracture, which was treated with PMMA replacement. After liquid nitrogen and bone grafts, two patients had a femoral condyle collapse; one was treated with total knee arthroplasty and one expectative due to severe co-morbidities.

and 27 (range 13-30) in 24 patients treated with liquid nitrogen and bone grafts. There was also no clinically relevant difference between the two reconstruction methods with respect to the MSTS score, which averaged 27 (range 13-30) in 24 patients who received bone grafts and 26 (range 8-30) in 89 patients who received PMMA (p=0.039).

Discussion

Most retrospective case series involving treatment of GCTB by curettage followed by use of a local adjuvant have focused on only a single adjuvant. Comparisons among these series may be misleading as the centers may have had different study populations and different indications for selection of curettage with adjuvants or resection. To our knowledge, the effectiveness of phenol has never been compared directly with that of liquid nitrogen.

Recurrence rates did not differ significantly among the three treatment cohorts in the present study, but they were at the higher end of the ranges reported in the literature (Table 4). These high recurrence rates may be explained by the relatively broad indications for intralesional curettage applied at both centers, including patients with a pathologic fracture or soft-tissue extension. This is in accordance with extended indications for curettage in 80% to 88% of patients as described previously by some authors [7,9,10,42]. In contrast, other authors appear to prefer primary resection (in 32% to 55% of patients) for more complicated cases [1,5,6,12,43]. At the time of the latest follow-up in the present study, local control had been achieved with use of one or multiple intralesional procedures in 89% of the patients, indicating that repeated curettage with adjuvants is a safe alternative to resection. *En bloc* resection was rarely considered as the primary treatment at either center, and it was used in only eleven patients with (first or later) recurrences, as expected functional results are inferior [2-5]. The recurrence rate data indicate that cryosurgery is a good alternative to the more commonly used combination of phenol and PMMA; however, it is preferably performed at centers experienced with this technique, as complications are more common. Whereas bone grafts and PMMA were used equally often at Center 2 for filling of the cavity during the time period described in this study, most giant cell tumors of bone are now treated with curettage and use of liquid nitrogen and PMMA at that center.

Table 4 Overview of literature reporting recurrence rates after curettage with different local adjuvants for giant cell tumor of bone

Study	Year	Follow-up (months)	Total	No local adjuvants			Phenol and bone grafts			Phenol andPMMA			PMMA			Liquid nitrogen and bone grafts			Liquid nitrogen and PMMA		
		Mean (range)	n	n	rec	%	n	rec	%	n	rec	%	n	rec	%	n	rec	%	n	rec	%
Marcove et al. [21]*	1978	43 (3-120)	52	-	-	-	-	-	-	-	-	-	-	-	-	52	12	23	-	-	-
Jacobs et al. [29]	1985	(26-132)	12	-	-	-	-	-	-	-	-	-	-	-	-	12	2	17	-	-	-
Capanna et al. [47]	1990	NR	667	280	126	45	147	28	19	33	1	3	187	36	19	20	4	19	-	-	-
Marcove et al. [25]**	1994	147 (24-170)	7	-	-	-	-	-	-	-	-	-	-	-	-	7	2	29	-	-	-
O'Donnell et al. [48]	1994	48 (24-120)	60	-	-	-	-	-	-	17	3	18	43	12	28	-	-	-	-	-	-
Alkalay et al. [27]	1996	(24-48)	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	0	0
Dürr et al. [17]	1999	61 (6-178)	26	7	3	43	11	1	9	-	-	-	-	-	-	-	-	-	-	-	-
Malawer et al. [24]	1999	78 (48-180)	102	-	-	-	-	-	-	-	-	-	-	-	-	86	8	8	-	-	-
Schreuder et al. [26]	1999	34 (18-79)	13	-	-	-	-	-	-	-	-	-	-	-	-	13	4	31	-	-	-
Trieb et al. [16]	2001	121 (48-516)	47	14	3	21	12	3	25	-	-	-	-	-	-	-	-	-	-	-	-
Wittig et al. [49]***	2001	54 (49-62)	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	0	0
Boons et al. [13]	2002	84 (24-372)	21	-	-	-	-	-	-	-	-	-	4	1	25	12	5	42	5	1	20
Ghert et al. [50]	2002	62 (24-224)	75	-	-	-	-	-	-	9	3	33	38	6	16	-	-	-	-	-	-
Turcotte et al. [42]†	2002	57 (24-192)	148	-	-	-	37	NR	18	U	U	18	62	NR	18	10	0	0	-	-	-
Wada et al. [32]	2002	46 (24-188)	15	-	-	-	-	-	-	-	-	-	15	1	7	-	-	-	-	-	-
Ward et al. [51]	2002	59 (12-115)	24	-	-	-	9	1	11	13	1	8	1	0	0	-	-	-	-	-	-
Saiz et al. [52]	2004	76 (28-175)	40	-	-	-	-	-	-	40	5	13	-	-	-	-	-	-	-	-	-
Su et al. [43]	2004	62 (28-138)	87	-	-	-	56	10	18	-	-	-	-	-	-	-	-	-	-	-	-
Abdelrahman et al. [28]	2008	34 (24-40)	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	28	1	4
Balke et al. [7]††	2008	60 (8-281)	214	55	32	58	-	-	-	42	5	12	91	26	29	-	-	-	-	-	-
Becker et al. [9]	2008	64 (1-440)	256	65	32	49	-	-	-	50	13	27	69	15	22	-	-	-	-	-	-
Kivioja et al. [1]	2008	60 (3-216)	294	47	24	51	-	-	-	-	-	-	147	32	22	-	-	-	-	-	-
Errani et al. [5]	2010	91 (36-204)	349	-	-	-	136	24	18	64	8	13	-	-	-	-	-	-	-	-	-
Gaston et al. [33]	2011	77 (2-319)	330	246	73	30	-	-	-	-	-	-	84	12	14	-	-	-	-	-	-

Klenke et al. [10]	2011	108 (36-233)	118	22	7	32	32	11	34	40	6	15	1	0	0	-	-	-	-	-	-
Lin et al. [19]	2011	58 (36-156)	26	-	-	-	26	3	12	-	-	-	-	-	-	-	-	-	-	-	-
Benevenia et al. [53]	2012	55 (10-184)	93	-	-	-	18	4	22	-	-	-	-	-	-	-	-	-	-	-	-
Van der Heijden et al. [11]	2012	96 (24-288)	93	-	-	-	-	-	-	75	20	27	18	5	28	-	-	-	-	-	-
Current study	2013	93 (24-266)	132	-	-	-	-	-	-	82	23	28	-	-	-	24	9	38	26	8	31
Mean recurrence rate (range)				**41% (21-58)**			**19% (9-34)**			**19% (3-33)**			**20% (0-29)**			**19% (0-42)**			**15% (0-31)**		

Rec = recurrence, NR = not reported, U = unknown
*Only in later cases PMMA was used instead of bone grafts, but it is not stated in how many patients
**In this study only GCT of the sacrum were reported
***In this study only GCT of the small bones of the hand were reported
†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%).

Non-oncological complications were more common after use of liquid nitrogen and bone grafts (33%) or liquid nitrogen and PMMA (27%) compared with phenol and PMMA (11%). Non-oncological complications were more common after reconstruction with bone grafts (33%) compared with PMMA (mean 15% in two cohorts). However, as the difference in complication rates after cryosurgery (mean 30% in two cohorts) compared with phenolization (11%) was most striking, we conclude that this risk can be attributed to the use of liquid nitrogen and that it is especially elevated in combination with use of bone grafts for reconstruction.

The most common complication in all cohorts was secondary osteoarthritis. It has been hypothesized that a large subchondral bone defect close to the joint in combination with the hyperthermic reaction of PMMA may increase the risk for secondary osteoarthritis [33,36-39]. To our knowledge, this is the first study to evaluate the prevalence of osteoarthritis after cancellous bone grafting or PMMA use in the treatment of giant cell tumor of bone about the knee. Osteoarthritis was observed more frequently after cryosurgical treatment, especially if bone grafts were used for reconstruction. In theory, subchondral bone grafts may protect articular cartilage from degeneration by increasing the distance between the cartilage and PMMA, thus creating a barrier against thermal effects [33,36,37]. In the present study, subchondral bone grafts were used in patients with little remaining subchondral bone stock (<10 mm), and we only found a modest decrease in the prevalence of osteoarthritis compared with that in patients in whom subchondral bone grafts were not used. However, the numbers available were too small to draw conclusions and we did not study the influence of patient, treatment, and tumor characteristics on osteoarthritis development. A previous detailed analysis of the amount of subchondral bone involvement and the distance between giant cell tumors of bone and articular cartilage demonstrated that these factors both strongly increase the risk for osteoarthritis—thus, in the present study, patients in whom subchondral bone grafts were placed would have been at an *a priori* increased risk for osteoarthritis [39]. 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% [21,29] to 0%-7% [13,24,26,28]; Table 5). The postoperative fracture rate of 6% after cryosurgery in the present study confirms that the fracture risk with current cryosurgery techniques is relatively low.

In the present study, the functional outcome as assessed with the MSTS score was excellent for all adjuvants and reconstruction methods. However, even though joint salvage was achieved in all patients, different cavity fillings and complications might alter the functional outcome. For example, osteoarthritis was more common after cryosurgery, but this did not appear to negatively influence the mean functional outcome. The clinical impact of osteoarthritis appeared modest at intermediate-term follow-up, but longer follow-up is required as the study involved relatively young patients. One could hypothesize that the weight-bearing that is possible during the immediate postoperative period if PMMA is used for reconstruction would yield functional results during this period that are superior to those for reconstruction with bone grafts. However, because of the retrospective nature of this study, we were unable to compare such interim functional results. Our functional results were comparable with those reported in the literature for all adjuvants. For example, mean MSTS scores of 25 (range 16-30) after use of phenol and PMMA, 26 (range 14-30) after use of liquid nitrogen and PMMA, and 28 (range 21-30) after use of liquid nitrogen and bone grafts were reported in a previous study [13].

This study has several strengths: both centers had different but equally accepted standard treatments during the same period, applied identical criteria for the choice between intralesional and wide resection of the giant cell tumor, and had similar surgical expertise. Regional or inter-center differences in treatment have been used previously as instrumental variables [44].

In observational studies, analysis of instrumental variables can estimate the therapeutic effects of various standard treatments and deal with controlled and uncontrolled confounding [44-46]. Several assumptions should be met: an instrumental variable should directly affect the treatment decision, must not be related to patient prognosis, and may not affect the primary outcome measures other than through chance [44-46].

Our study has several limitations. First, it would have been interesting to analyze four cohorts (use of phenol and bone grafts, phenol and PMMA, liquid nitrogen and bone grafts, and liquid nitrogen and PMMA) to compare the unique effects of phenol and liquid nitrogen and the combined effects of these treatments with use or non-use of PMMA. However, as curettage followed by phenolization and bone grafting was performed in only four patients, this cohort was too small to include. In addition, this treatment was abandoned at Center 1 as the surgeons preferred using PMMA because of its advantages.

Table 5 Overview of literature reporting on complications after curettage with different local adjuvants for giant cell tumor of bone

	Year	Follow-up	Local adjuvant	Patients	Total complications	Fracture	Wound infection	Skin necrosis	Osteoarthritis	Nerve palsy	Other
		months (range)		n	n (%)	n	n	n	n	n	n
Marcove et al. [21]	1978	43 (3-120)	liquid nitrogen ± PMMA	52	31 (60)	13	8*	4	2	4	-
Jacobs et al. [29]	1985	(26-132)	liquid nitrogen	12	6 (50)	6	-	-	-	-	-
Marcove et al. [25]*	1994	147 (24-170)	liquid nitrogen	7	3 (43)	-	2	-	-	-	1 rectal fistula
Alkalay et al. [27]**	1996	(24-48)	liquid nitrogen and PMMA	5	0 (0)	-	-	-	-	-	-
Malawer et al. [24]	1999	78 (48-180)	liquid nitrogen	102	12 (12)	6	-	3	2	1	-
Schreuder et al. [26]	1999	34 (18-79)	liquid nitrogen	13	2 (15)	-	1	-	1	-	-
Wittig et al. [49]†	2001	54 (49-62)	liquid nitrogen and PMMA	3	0 (0)	-	-	-	-	-	-
Boons et al. [13]	2002	84 (24-372)	PMMA	4	1 (25)	-	1	-	-	-	-
			liquid nitrogen	12	4 (33)	-	1	-	-	3	-
			liquid nitrogen and PMMA	5	0 (0)	-	-	-	-	-	-
Ghert et al. [50]	2002	62 (24-224)	PMMA (with phenol)	47 (9)	8 (17)	5	-	-	3	-	-
Wada et al. [32]	2002	46 (24-188)	PMMA	15	2 (13)	1	-	-	1	-	-
Ward et al. [51]	2002	59 (12-115)	phenol and PMMA	13	5 (38)	-	-	-	3	-	1 non-union, 1 pain
Saiz et al. [52]	2004	76 (28-175)	phenol and PMMA	40	3 (8)	1	-	-	2	-	-

Abdelrahman et al. [28]	2008	34 (24-40)	liquid nitrogen and PMMA	28	4 (14)	2	1	1	-	-	-
Gaston et al. [33]	2011	77 (2-319)	None	246	14 (6)	4	1	-	3	3	1 neuroma, 2 pain
			PMMA	84	18 (21)	4	2	-	11	-	1 neuroma
Current study	2013	93 (24-266)	phenol and PMMA	82	9 (11)	-	1	-	6	-	2 non-union
			liquid nitrogen and PMMA	26	7 (27)	1	1	-	4	-	1 PMMA leakage
			liquid nitrogen	24	8 (33)	2	2	-	3	1	-

OSM = osteosynthesis material
*4 deep wound infections and 4 superficial wound infections
**In this study only giant cell tumors of the sacrum were reported
***Two-stage local excision with liquid nitrogen and PMMA was performed for GCT with intra-articular fracture, first aiming at fracture reduction and union with temporary bone graft and PMMA filling, followed by meticulous re-curettage with liquid nitrogen and PMMA.
†In this study only giant cell tumors of the small bones of the hand were reported

Second, the decisions for bone grafts, PMMA and osteosynthesis at Center 2 were made intraoperatively and were based on the structural integrity of the remaining bone after curettage. These choices were not standardized and this may have resulted in confounding by indication.

In conclusion, treatment of GCTB remains challenging as recurrence rates remain relatively high after curettage with local adjuvants. Recurrence rates in the present study were comparable for curettage with use of phenol and PMMA, liquid nitrogen and PMMA, and liquid nitrogen and bone grafts. The risk of complications, especially the development of osteoarthritis, was higher with cryosurgery. Functional outcome was excellent in all cohorts, making the relatively high recurrence rates (in comparison with the rate following *en bloc* resection and endoprosthetic reconstruction) acceptable.

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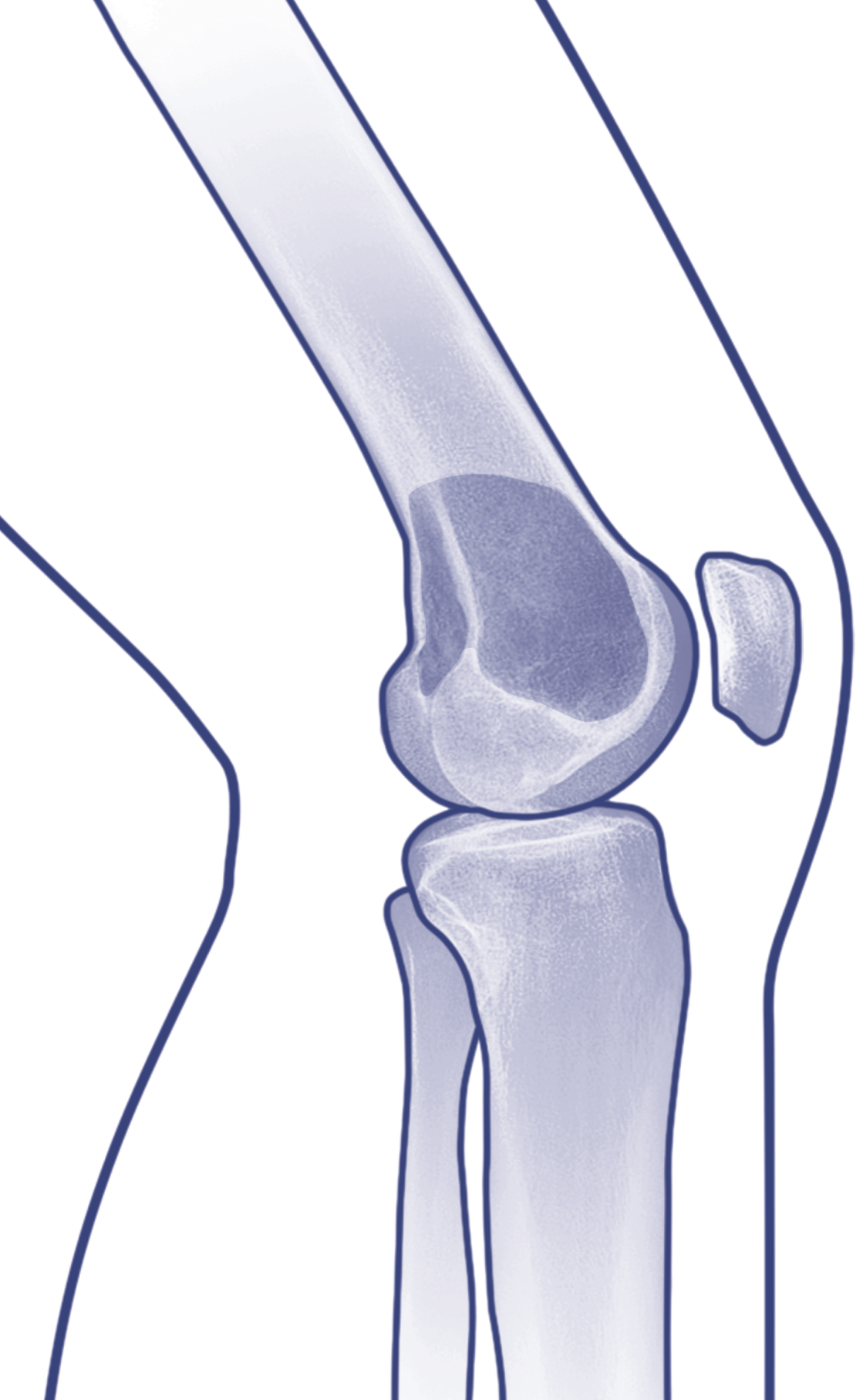

Chapter 4

Giant cell tumor with pathologic fracture: Should we curette or resect?

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Abstract

Background Approximately one in five patients with giant cell tumor of bone (GCTB) presents with a pathologic fracture. However, recurrence rates after resection or curettage differ substantially in the literature and it is unclear when curettage is reasonable after fracture. We therefore determined: (1) local recurrence rates after curettage with adjuvants or *en bloc* resection; (2) complication rates after both surgical techniques and whether fracture healing occurred after curettage with adjuvants; and (3) function after both treatment modalities for GCTB with a pathologic fracture.

Patients and methods We retrospectively reviewed 48 patients with fracture from among 422 patients treated between 1981 and 2009. The primary treatment was resection in 25 and curettage with adjuvants in 23 patients. Minimum follow-up was 27 months (mean 101 months; range 27–293 months).

Results Recurrence rate was higher after curettage with adjuvants when compared with resection (30% *vs.* 0%). Recurrence risk appears higher with soft tissue extension. The complication rate was lower after curettage with adjuvants when compared with resection (4% *vs.* 16%) and included aseptic loosening of prosthesis, allograft failure, and pseudoarthrosis. Tumor and fracture characteristics did not increase complication risk. Fracture healing occurred in 24 of 25 patients. Mean Musculoskeletal Tumor Society score was higher after curettage and adjuvants (mean 28; range 23–30; n=18) when compared with resection (mean 25; range 13–30; n=25).

Conclusions Our observations suggest curettage with adjuvants is a reasonable option for GCTB with pathologic fractures. Resection should be considered with soft tissue extension, fracture through a local recurrence, or when structural integrity cannot be regained after reconstruction.

Introduction

Giant cell tumor of bone (GCTB) is a primary benign bone tumor with a peak incidence between the third and fifth decades and a slight predominance for females [28]. It is most commonly found in the epimetaphyseal region of the long bones [28]. GCTB contains mononuclear histiocytic cells, multinucleated giant cells, and mononuclear stromal cells; the latter are believed to be neoplastic. Overexpression of receptor activator nuclear factor kappa-B ligand by mononuclear stromal cells promotes the recruitment of multinucleated giant cells [28]. Cathepsin K, exclusively expressed by these giant cells, is believed to be the principal protease in GCTB [18]. This indicates the osteoclast-like giant cells are responsible for the osteolysis seen in giant cell tumor of bone. Pathologic fractures occur at first presentation in 9% to 30% of all patients with GCTB [4–6, 19, 20, 27] and are often intra-articular as a result of the epimetaphyseal location.

Curettage with adjuvants and *en bloc* resection are both considered treatment options for GCTB with a pathologic fracture. The use of curettage with adjuvants reportedly is associated with relatively high local recurrence rates (12%–34%) [2, 3, 16]. Most local recurrences occur within the first 2 postoperative years [15]. Although based on a relatively small series, O'Donnell *et al.* [20] suggested the presence of pathologic fractures would be associated with a higher recurrence risk after curettage through fracture contamination of surrounding soft tissues. However, more recent studies have suggested that this may not be the case [2, 3, 16]. The majority of GCTB with a pathologic fracture about the knee have reportedly been treated with resection and reconstruction with either allograft or tumor prosthesis [19]. Some authors consider resection and reconstruction the preferred treatment in patients with severe joint destruction or dislocated, comminuted, or intra-articular fractures [6]. Although the risk for local recurrence is generally low after *en bloc* resection (0%–12%) [2, 9, 15, 27], it is not necessarily the most favorable primary treatment. Considering the benign nature of the disease, the young patient population, the substantial complications, and the need for revision surgery, the aim for joint preservation is generally justified [12, 13, 19, 22]. The preferred surgical treatment for primary GCTB with a pathologic fracture therefore remains controversial [7, 9, 11, 20, 21, 24].

Although presentation with a pathologic fracture is not uncommon for patients with GCTB, combining our collective experience is critical to the understanding

of this difficult to study subject. In the present study, we therefore reviewed our multicenter experience of patients with GCTB presenting with a pathologic fracture to determine if tumor and fracture characteristics led to universally better or worse outcomes.

We therefore determined: (1) local recurrence rates after curettage with adjuvants or *en bloc* resection; (2) complication rates after both surgical techniques and whether fracture healing occurred after curettage with adjuvants; and (3) function after both treatment modalities for GCTB with a pathologic fracture.

Patients and methods

We retrospectively evaluated 63 patients treated for GCTB with a pathologic fracture (15%) from a total of 422 consecutive patients with GCTB treated in one of three tertiary referral centers specializing in the interdisciplinary treatment of bone and soft tissue tumors between 1981 and 2009. We excluded eight patients with less than 2-year follow-up, three patients who underwent primary treatment other than mentioned, two with axially located GCTB, and two with rapidly progressive (malignant) GCTB with recurrent and metastatic disease eventually resulting in death at 4 and 9 months after initial surgery (Figure 1). Both patients had eventually undergone resection (distal and proximal femur) for local recurrences and they developed pulmonary metastases (3%). From the eight patients with less than 2-year follow-up (1–19 months; five resections, three curettage with adjuvants), none developed a local recurrence so far. These 15 exclusions left 48 patients with primary GCTB with a pathologic fracture for analysis in this tri-center retrospective study. Primary treatment consisted of *en bloc* resection (n=25) or curettage with adjuvants (n=23). Local adjuvants were combinations of phenol, hydrogen peroxide, and polymethylmethacrylate (PMMA). There were 27 male and 21 female patients. Mean age was 36 years (range 11–77 years). Most common locations of GCTB with a pathologic fracture were the distal femur (n=23; 48%), proximal humerus (n=9; 19%), and proximal tibia (n=6; 13%). Minimum follow-up of the living patients was 27 months (mean 101 months; range 27–293 months). One patient died from an unrelated disease. No patients were recalled specifically for this study; all data were obtained from medical records. The study was approved by the local ethics committee.

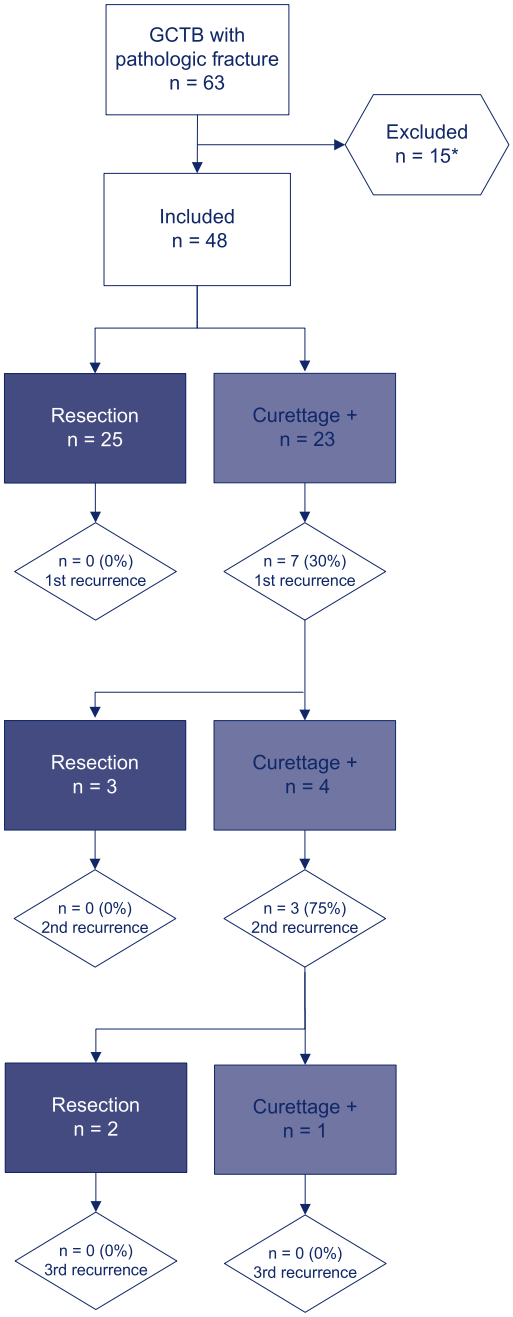

Figure 1 Surgical treatment of a primary giant cell tumor of bone (GCTB) with a pathologic fracture and subsequent recurrences. *Patients with a follow-up of less than 2 years (n = 10), other primary treatment (n = 2), or axial location (n = 2) were excluded.

Table 1 Patient demographics

Demographic	Mean	Range
Age at diagnosis (years)	39	11-77
Time to recurrence (months)	15	6-26
Follow-up (months)	101	27-293

	GCTB with a pathologic fracture	
	Number	Percent
Total	48	
Sex		
Male	27	56
Female	21	44
Location		
Proximal humerus	9	19
Distal radius	4	8
Distal ulna	1	2
Proximal femur	4	8
Distal femur	23	48
Proximal tibia	6	13
Distal tibia	1	2
Tumor characteristics		
Soft tissue extension	18	38
Complex fractures	13	27
Joint proximity (< 1 cm)	37	77
Intra-articular fractures	16	33
Surgical treatment		
En bloc resection	25	52
Curettage with adjuvants	23	48
PMMA	21	91
Phenol	20	87
Hydrogen peroxide	3	13

GCTB = giant cell tumor of bone; PMMA = polymethylmethacrylate.

We collected data from medical records and included patient demographics, imaging, histopathological evaluation, tumor localization, soft tissue extension, fracture characteristics, fracture healing, date and type of surgical intervention, method of reconstruction, local recurrences, complications, functional outcome, and follow-up (Table 1). All data were complete. Conventional radiographs were available for all patients; preoperative MRI for 42 patients; and preoperative CT for the other six patients. Soft tissue extension was assessed on preoperative MRI. We considered soft tissue involvement as an entity only

when this was a preexisting feature with cortex destruction and a tumor mass in the surrounding soft tissues; the fracture hematoma was not considered soft tissue extension.

The presumptive diagnosis was based on radiographic characteristics (i.e. conventional radiographs and MRI) and clinical findings and history (e.g. pain, swelling, preceding trauma); this was later confirmed by either preoperative (45) or intraoperative (six) biopsy. None of the patients underwent surgery without a proper histopathologic diagnosis. All patients were surgically treated by one of six fellowship trained oncological orthopaedic surgeons (Center 1: PDSD, MAJS, AHMT; Center 2: DAC, RC; Center 3: CLMHG). Treatment of GCTB with a pathologic fracture differed (chi square: $p<0.001$) among the three centers. In one of three centers, curettage with adjuvants was preferred over resection in the presence of a pathologic fracture (Table 2). Complex fractures, intra-articular fractures, and subchondrally located GCTB (less than 1 cm from the articular cartilage), which were assessed on imaging and operative reports, occurred equally in the three centers; only the incidence of soft tissue extension differed slightly (Table 3). Patient, tumor, and fracture characteristics were equal within both treatment groups (Table 4). Surgical management of the pathologic fracture consisted of two steps, namely surgical resection of the GCTB and fractured bone or joint reconstruction. Resection was performed within 1 week after the pathologic fracture occurred. In these cases, the tumor, fractured or involved bone, and contaminated soft tissue were resected and reconstructed (Table 1). In case of intra-articular fractures, the resection was performed transarticularly. *En bloc* resection was always followed by reconstruction with either allograft or cemented modular tumor prosthesis. Surgical margins were reviewed in operation and pathology reports. We performed intralesional treatment using curettage with adjuvants either before or after fracture healing. In 15 patients, immediate curettage with adjuvants and fracture reconstruction with use of PMMA only was performed. In only two patients internal fixation was necessary to maintain structural integrity after curettage. In two patients we awaited fracture consolidation using an external fixation and in six patients with use of a plaster cast before performing intralesional resection of GCTB. In all patients who underwent curettage, we used local adjuvants to reduce the risk for local recurrence (Table 1). In two patients, cancellous bone graft was applied instead of PMMA because of considerable loss of cortical and subchondral bone stock. We used hydrogen peroxide in three patients as an alternative for phenol.

Table 2 Treatment for GCTB with a pathologic fracture per center

	n	Center 1 (n=23)	Center 2 (n=15)	Center 3 (n=10)
Curettage with adjuvants	23	18 78%	1 7%	4 40%
En bloc resection	25	5 22%	14 93%	6 60%

Table 3 Distribution of tumor and fracture characteristics among the three participating centers

Fracture characteristic	Center 1 (n = 23)	Center 2 (n = 15)	Center 3 (n = 10)	p value
Soft tissue extension	7 30%	2 13%	7 70%	0.012
Complex fractures	3 13%	6 40%	4 40%	0.088
Intraarticular fractures	8 35%	7 47%	3 30%	0.719
Joint proximity (< 1 cm)	16 69%	14 93%	7 70%	0.216

Table 4 Distribution of tumor and fracture characteristics between treatment modalities

Treatment modality	Number	Curettage with adjuvants (n = 23)	En bloc resection (n = 25)	p value
Soft tissue extension	16	7 30%	9 36%	0.307
Complex fractures	13	4 17%	9 36%	0.123
Intraarticular fractures	18	6 26%	12 48%	0.092
Joint proximity (< 1 cm)	37	16 69%	21 84%	0.133

Postoperative treatment after curettage consisted of functional mobilization with partial weightbearing for at least 6 to 12 weeks. Weightbearing was increased when pain and radiographic follow-up indicated stable fusion of the fracture. Five patients needed additional immobilization using a (removable) cast for 6 to 12 weeks based on postoperative radiographs and clinical examination. In case of prosthetic reconstruction, immediate weightbearing was allowed; for allograft reconstruction, this was dependent on union as assessed on radiographs.

The follow-up protocol consisted of radiography at 1.5, 3, and 6 months postoperatively followed by half yearly radiographs until 2 years postoperatively and yearly radiographs in the next years to detect local recurrences or complications. We performed MRI at 1, 2, 5, and 10 years postoperatively. We recorded local recurrences, complication rates, fracture healing, and function for both curettage with adjuvants and *en bloc* resection. Musculoskeletal Tumor Society (MSTS) scores were obtained to evaluate functional outcome and pain in the affected extremity [8]. We took the questionnaire at latest follow-up

(mean 101 months). MSTS scores were available for 43 patients. Five patients did not return the questionnaire and could not be contacted by telephone. A distinction between major complications requiring surgical intervention and minor complications demanding nonsurgical treatment was made. The primary oncological end point was a radiological or histological-proven local recurrence and, for the complication rate, failure of the prosthesis or allograft requiring surgical revision. Radiological signs for loosening of prostheses were not evaluated. We evaluated several variables potentially increasing the recurrence and complication risk: complex or intra-articular fractures, soft tissue extension, and subchondral GCTB.

Statistical analysis

Recurrence-free survival was assessed using Kaplan-Meier survival analysis and differences in survival between treatment groups were assessed using a log rank test. Local recurrence and complication rates were calculated. Univariate and multivariate (two variables) Cox regression analysis was performed to determine independent factors of influence on the recurrence and complication risk. Functional outcome (MSTS score) for both groups was compared with an unpaired t-test. We used SPSS 17.0 (SPSS Inc, Chicago, IL, USA) to perform all statistical analysis.

Results

No recurrences occurred in the resection group, whereas in the curettage group, the recurrence-free survival rates were 74% and 70% at 2 and 5 years postoperative, respectively (p=0.003) (Figure 2). The local recurrence rate was 30% after curettage with adjuvants (seven of 23) and 0% after *en bloc* resection (zero of 25). Surgical margins were negative in 24 patients and marginal in one patient who underwent *en bloc* resection; no piecemeal resection was performed. All local recurrences were found at the site of the primary tumor and were confined to the bone in five patients and with an additional soft tissue component in two patients. No skip lesions or distant recurrences were reported. Because there were no recurrences in the resection cases, we only performed a risk analysis for local recurrence in the intralesional treatment

group. The only factor increasing (hazard ratio=4.8; p=0.046) recurrence risk after curettage with adjuvants in univariate analysis was preexisting tumor soft tissue extension (five recurrences in seven patients with soft tissue extension). Complex fractures (p=0.073), intra-articular fractures (p=0.76), or subchondral GCTB close to the articular cartilage (p=0.94) did not increase the recurrence risk (Table 5). For simple fractures without soft tissue extension, the recurrence rate after curettage with adjuvants was only 7% (one of 14). All but one recurrence occurred within the first 2 years postoperatively; mean time to local recurrence was 15 months (range 6–26 months; n=7). Surgical treatment of all first and second local recurrences is summarized in a flowchart (Figure 1).

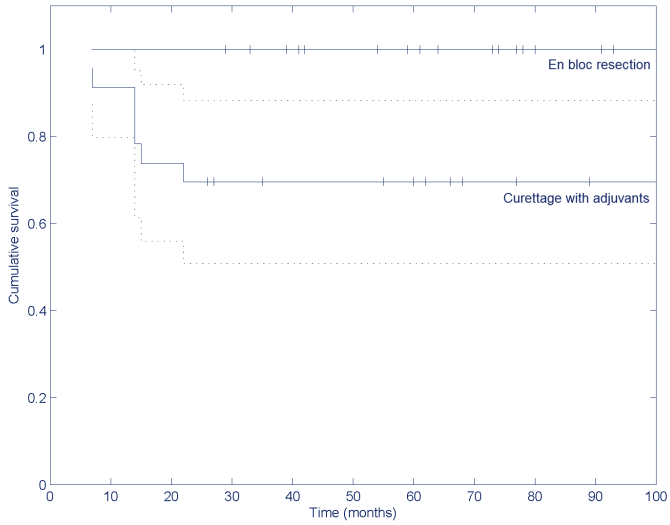

Figure 2 Recurrence-free survival (RFS) after curettage with adjuvants (with 95% confidence interval) and en bloc resection for giant cell tumor of bone with a pathologic fracture. After curettage with adjuvants, the RFS was lower than after resection (p = 0.003) and was estimated at 74% and 70% at 2 and 5 years postoperatively, respectively. After resection, the RFS was 100%.

The major complication rate was 4% after curettage with adjuvants (one of 23) and 16% after *en bloc* resection (four of 25). The one major complication in the intralesional treatment group was a pathologic fracture of the distal femur that did not heal after immediate curettage and cementation and developed a pseudarthrosis; this was successfully treated with cancellous bone graft and postoperative immobilization with a plaster cast. Minor complications after

Table 5 Factors of influence on recurrence and complication risk

Factors of influence	Number	Local recurrence	Hazard ratio	95% confidence interval	p value
Influence on recurrence risk after curettage with adjuvants (n = 23)					
Multivariate analysis					
Soft tissue extension	7	5	4.6	1.0-21	0.053
Complex fracture	4	3	3.8	0.83-17	0.086
Univariate analysis					
Soft tissue extension	7	5	4.8	1.0-22	0.046
Complex fracture	4	3	4.0	0.88-18	0.073
Intraarticular fracture	6	2	1.2	0.07-34	0.76
Joint proximity (< 1 cm from joint cartilage)	16	5	1.1	0.15-7.6	0.94
Influence on complication risk after en bloc resection (n = 25)					
Univariate analysis					
Soft tissue	9	0	1.8	0.25-13	0.55
Complex fracture	9	0	0.93	0.09-9.2	0.95
Intraarticular fracture	12	0	0.44	0.04-4.3	0.48
Joint proximity	21	0	0.27	0.04-1.9	0.19

curettage with adjuvants (three of 23; 13%) were chronic pain, superficial wound infection, and deep venous thrombosis; all were successfully treated nonsurgically. Fracture healing occurred in 22 of the 23 patients treated with curettage and adjuvants after a mean of 12 weeks (range 6–48 weeks) either after immediate curettage with adjuvants (n=14) or after treatment with external fixation (n=2) or a plaster cast (n=6) before surgery. Fracture healing was assessed by conventional radiographs and clinical examination. After resection, major complications were reported in four patients. Two patients had aseptic loosening of tumor prostheses (two of 25; 8%); both were successfully revised. In one patient, the allograft humeral head fragmented; this was successfully replaced by a shoulder hemiprosthesis. One patient developed subluxation of the wrist after distal radius reconstruction with an autologous vascularized fibula inlay graft and osteosynthesis. Surgical correction was performed resulting in decreased ROM and persistent pain. Minor complications after resection (four of 25; 16%) were reduced ROM (n=3) and joint effusion (n=1). Decreased ROM improved after physiotherapy in one patient and was persistent in two. Complication risk was not increased by soft tissue extension (p=0.55), complex fractures (p=0.95), intra-articular fractures (p=0.48), or joint proximity (p=0.19) in univariate analysis (Table 5). We performed risk analysis for major complications only after resection.

Functional ability and pain as reported by patients at latest follow-up were superior (p=0.013) after curettage with adjuvants when compared with resection. Mean MSTS score after curettage was 28 (range 23–30; n=18). Fourteen patients had an MSTS score over 90%, two 80% to 89%, and two 60% to 79%. Mean MSTS score after resection was 25 (range 13–30; n=25). Eleven patients had an outcome score greater than 90%, seven between 80% and 89%, five from 60% to 79%, and two less than 60%.

Discussion

Pathologic fracture is a relatively infrequent complication of GCTB, being a purely osteolytic primary skeletal lesion. It was commonly believed that pathologic fracture was associated with a higher recurrence risk as a result of the expected contamination of surrounding tissues [20]. *En bloc* resection reduces the recurrence risk dramatically and has therefore been preferred as the primary treatment [14]. However, more recent studies could not confirm pathologic fractures as a risk factor for local recurrence. Furthermore, articular resection may result in important morbidity and functional impairment. This created opportunities for further studies investigating the indication for and outcome of curettage with adjuvants for GCTB with a pathologic fracture [6, 7, 14]. Deheshi *et al.* [6] compared recurrence-free survival and functional outcome after curettage for both patients with and without pathologic fracture; outcomes were comparable. Dreinhöfer *et al.* [7] analyzed 10 of 15 patients with a pathologic fracture treated with curettage and PMMA and reported a recurrence rate of four of 10. Jeys *et al.* [14] evaluated treatment options for different types of fractures and concluded that curettage can be safe for cortical breach but that discrete fractures more often require resection. Thus, the appropriate treatment remains controversial. To address these controversies in the literature, we determined (1) local recurrence rates after curettage with adjuvants or *en bloc* resection; (2) complication rates after both surgical techniques and whether fracture healing occurred after curettage with adjuvants; and (3) functional outcome after both treatment modalities for GCTB with a pathologic fracture.

Our study has several limitations. First, patients were treated in three centers where indications for surgical treatment differed, possibly resulting in selection

and treatment bias. This multicenter approach was needed to accrue sufficient numbers of cases of this relatively infrequent occurrence with its variable presentation. Indications for curettage were more extended in Center 1 than in the other centers; a majority of cases with soft tissue extension and/or intra-articular or complex fractures in this center were treated with curettage and adjuvants. It is therefore probable that the high overall recurrence rate after curettage is a result of selection bias based on different indications for curettage or resection. Second, long-term clinical outcomes of GCTB with pathologic fracture were not compared with outcomes of GCTB without pathologic fracture. We can draw conclusions from our results as to which surgical treatment option would be most favorable in the presence of a pathologic fracture, but a relative interpretation of results on local recurrences, complications, and functional outcome is possible only considering available literature. Third, patients received different local adjuvants after curettage; the creation of subgroups for local adjuvants could have addressed this inconsistency. However, because treatment groups were small, statistics would not be reliable. Furthermore, only two patients did not receive PMMA as cavity fill-up and hydrogen peroxide was used as an alternative for phenol in only three patients. We therefore compared an *en bloc* approach with an intralesional approach with due consideration of small differences regarding local adjuvant treatment.

In our study, the local recurrence rate for primary GCTB with a pathologic fracture was higher after curettage with adjuvants and lower after *en bloc* resection when compared with recent literature [2–4, 9, 15, 16]. However, we also treated difficult cases with curettage plus adjuvants; this probably resulted in the relatively high recurrence rate after curettage. If we consider only simple fractures without soft tissue extension, the recurrence rate was only 7%, which is even lower than recurrence rates reported in the literature (Table 6). The pulmonary metastasis rate was comparable to that previously reported in the literature (0%–4%) [16]. Therefore, we do not believe the relatively high recurrence rate affected the metastasis rate. Soft tissue extension is a known risk factor for local recurrence [2, 3, 21]; this was confirmed in our risk analysis. Regression analysis showed a higher recurrence risk only for patients with preexisting soft tissue extension (five of seven). Performing a thorough curettage is technically challenging in the presence of a pathologic fracture and soft tissue mass, because there is no adequate local adjuvant available that is applicable on soft tissues without inducing severe tissue necrosis. In principle,

each dislocated fracture can also induce contamination of surrounding soft tissues. Complex fractures indeed had a high recurrence rate after curettage with adjuvants (three of four) and intralesional treatment was insufficient to obtain immediate local control. In these cases, *en bloc* resection can be considered to improve local control. In the near future, systemic targeted neoadjuvant therapy with receptor activator of nuclear factor kappa-B ligand inhibitor denosumab may facilitate wider indications for curettage in these cases. Such treatments result in calcification in GCTB and affected soft tissues, facilitating surgical removal through curettage and application of adequate adjuvants (e.g. phenol, PMMA) [17, 25]. Intra-articular fractures did not demonstrate a higher recurrence rate after curettage with adjuvants (two of six). In the literature, intra-articular pathologic fractures were often resected as a result of technical difficulties in performing curettage and a presumed high risk for local recurrence [9, 16]. Likewise, in our series, 12 of 18 patients with an intra-articular fracture underwent primary resection. However, the recurrence risk was not influenced by the presence of an intra-articular fracture when treated with curettage plus adjuvants. Curettage can therefore be considered a feasible treatment option for intra-articular fractures. Subchondrally located GCTB had a similar acceptable recurrence rate after curettage with adjuvants (five of 16). Subchondral bone stock may be augmented by cancellous bone grafting before applying PMMA to prevent damage to the articular cartilage by the heat of the bone cement. Within our study population, this was performed only in case of an intra-articular fracture or complete loss of subchondral bone stock. A layer of approximately 1 cm is considered sufficient. Subsequent local recurrences were only reported in patients who underwent recurettage for a local recurrence, not for those who underwent resection (Figure 1). This indicated local recurrences after GCTB with a pathologic fracture can be successfully treated with *en bloc* resection.

Table 6 Overview of literature reporting on the treatment and outcomes of giant cell tumor of bone with a pathologic fracture

Study	Year	n	Pathologic fracture		Surgical treatment			Local recurrences		Complications		Functional outcome	Follow-up
			n	(%)		n	(%)	n	(%)		(%)		yrs (range)
McDonald et al. [19]	1986	146	24	16%	En bloc resection	16	67%	NR		NR		NR	7 (2-21)
					Curettage	8	33%	NR		NR		NR	
Campanacci et al. [5]	1987	327	29*	9%	En bloc resection	8	28%	1	13%	NR		NR	(2-44)
					Marginal resection	8	28%	0	0%	NR		NR	
					Curettage	3	10%	0	0%	NR		NR	
O'Donnell et al. [20]	1994	60	6	10%	Curettage + PMMA	6	100%†	3	50%	NR		NR	4 (2-10)
Dreinhöfer et al. [7]	1995	98	15	15%	Resection	3	27%	0	0%	None		Overall: Excellent (7), good (7), fair (1)§	4 (1-22)
					Curettage	2	7%	2	100%	None			
					Curettage + PMMA	10	67%	2	20%	Osteoarthritis (2)	20%		
Blackley et al. [4]	1999	59	17	29%	Curettage	17	100%†	4	24%	Knee stiffness (2), non-union (1)	18%	NR	7 (2-11)
Ghert et al. [11]	2002	75	12	16%	NR‡			1	6%	NR		NR	5 (2-19)
Turcotte et al. [27]	2002	186	56	30%	Resection	11	20%	NR		NR		Overall: Lower when compared with giant cell tumor without fracture**	5 (2-16)
					Curettage ± PMMA	45	80%	7	16%	NR			
Su et al. [23]	2004	87	13	15%	NR‡			3	23%	NR		NR	5 (2-11)
Prosser et al. [21	2005	137	29	21%	Curettage	29	100%†	4	14%	Non-union (1)	3%	NR	6 (2-18)
Jeys et al. [14]	2006	54	12	22%	Resection	6	50%	0	0%	NR		NR	NR
					Curettage	6	50%	3	50%	NR		NR	

Deheshi et al. [6]	2007	139	43	31%	Resection	7	16%	0	0%	Overall: Arthrofibrosis (3), non-union (2)	12%	NR TESS: 88 (42-100) MSTS-87: 30 (21-35) MSTS-93: 26 (14-30)***	7 (2-15)
					Curettage ± PMMA	36	84%	7	19%				
Becker et al. [3]	2008	256	50	13%	Resection	22	44%	NR		NR		NR	5 (1-37)
					Curettage ± PMMA	28	56%	NR		NR		NR	
Kivioja et al. [15]	2008	294	60	20%	NR‡			17	28%	NR		NR	5 (0.2-18)
Gaston et al. [10]	2011	330	62	19%	Curettage	34	55%	18****	29%	NR		NR	6 (0.2-26)
					Curettage + PMMA	28	45%			NR		NR	
Klenke et al. [16]	2011	118	17	14%	Resection	8	47%	NR		NR		NR	9 (3-19)
					Curettage ± PMMA	9	53%	NR		NR		NR	
The current study	2012	422	48	11	Resection	25	42%	0	0%	Aseptic loosening (2), allograft fracture (1), subluxation (1)	16%	MSTS-93: 25 (13-30)	8 (2-12)
					Curettage + PMMA	23	48%	7	30%	Non-union (1)	4%	MSTS-93: 28 (23-30)	

NR = Not reported
*Surgical treatment was only specified for patients with Campanacci grade II lesions with pathologic fracture (n=19), but not for grade III lesions with pathologic fracture (n=10).
†Study reporting only on intralesional treatment. Indications for resection were among others displaced intraarticular pathologic fractures.
‡Surgical treatment was not specified for patients with a pathologic fracture. Most giant cell tumors were treated with curettage and PMMA; indications for resection were among others displaced intraarticular pathologic fractures.
§Functional outcome was assessed with MSTS-87, but no numerical values were reported.
**Functional outcome was assessed with MSTS-87, Toronto Extremity Salvage Score (TESS) and SF-36 questionnaires; but was not numerically specified for patients with a pathologic fracture.
***Functional outcome did not differ for intraarticular and extraarticular pathologic fractures treated with curettage.
****This is the overall recurrence rate after intralesional treatment for giant cell tumor with a pathologic fracture; it was not specified for curettage with or without PMMA.

The major complication rate was higher after resection when compared with curettage with adjuvants (16% versus 4%). In the literature, complications were even more frequent after resection and reconstruction with allograft or tumor prosthesis when compared with our results (e.g. allograft fracture 16%, nonunion 19%, aseptic loosening prosthesis 19%, periprosthetic infection 11%–34%) [1, 12, 13, 16, 19, 22], but only few articles have reported on complications after surgical treatment for GCTB with a pathologic fracture in specific [6, 7, 14]. In one study, it has been postulated that the complication rate for GCTB with and without pathologic fractures is comparable [6]. As mentioned, we did not evaluate data on complications after treatment of GCTB without a pathologic fracture in this study. Multivariate regression analysis showed the complication risk after resection was independent of the complexity of fractures, soft tissue extension, intra-articular fractures, or joint proximity; the complication risk is thus inherent in the surgical treatment itself.

As expected, higher MSTS scores were reported after curettage with adjuvants (range 23–30) when compared with resection (range 13–30). Functional outcome after both treatment modalities was comparable to outcomes described in the literature [7, 8, 26]. However, wide variations in function after resection possibly make this finding less clinically relevant. Outliers with a poor function were patients with multiple surgical interventions for recurrences and/or complications; the number of surgical interventions should therefore be minimized.

The observations from our multicenter experience suggest a higher overall local recurrence rate after curettage with adjuvants for GCTB with a pathologic fracture when compared with resection. The local recurrence rate after curettage with adjuvants for simple fractures without soft tissue extension was not elevated. The risk for recurrence was only increased for coexistence of a pathologic fracture and soft tissue extension. Also, further recurrences only occurred after curettage with adjuvants. Fewer complications were reported after curettage when compared with resection. No tumor or fracture characteristics (including intra-articular fractures) influenced the risk for complications after surgery. Fracture healing was not impaired after curettage with adjuvants. Finally, functional outcome was better after curettage with adjuvants. Therefore, we believe that curettage can be considered in case of GCTB with a relatively simple pathologic fracture. In more complicated fractures, the higher recurrence risk but better functional results and lower

complication rates should be valued when performing intralesional treatment. *En bloc* resection should be considered in case of soft tissue extension, complex fractures, local recurrences, and when structural integrity cannot be regained after reconstruction.

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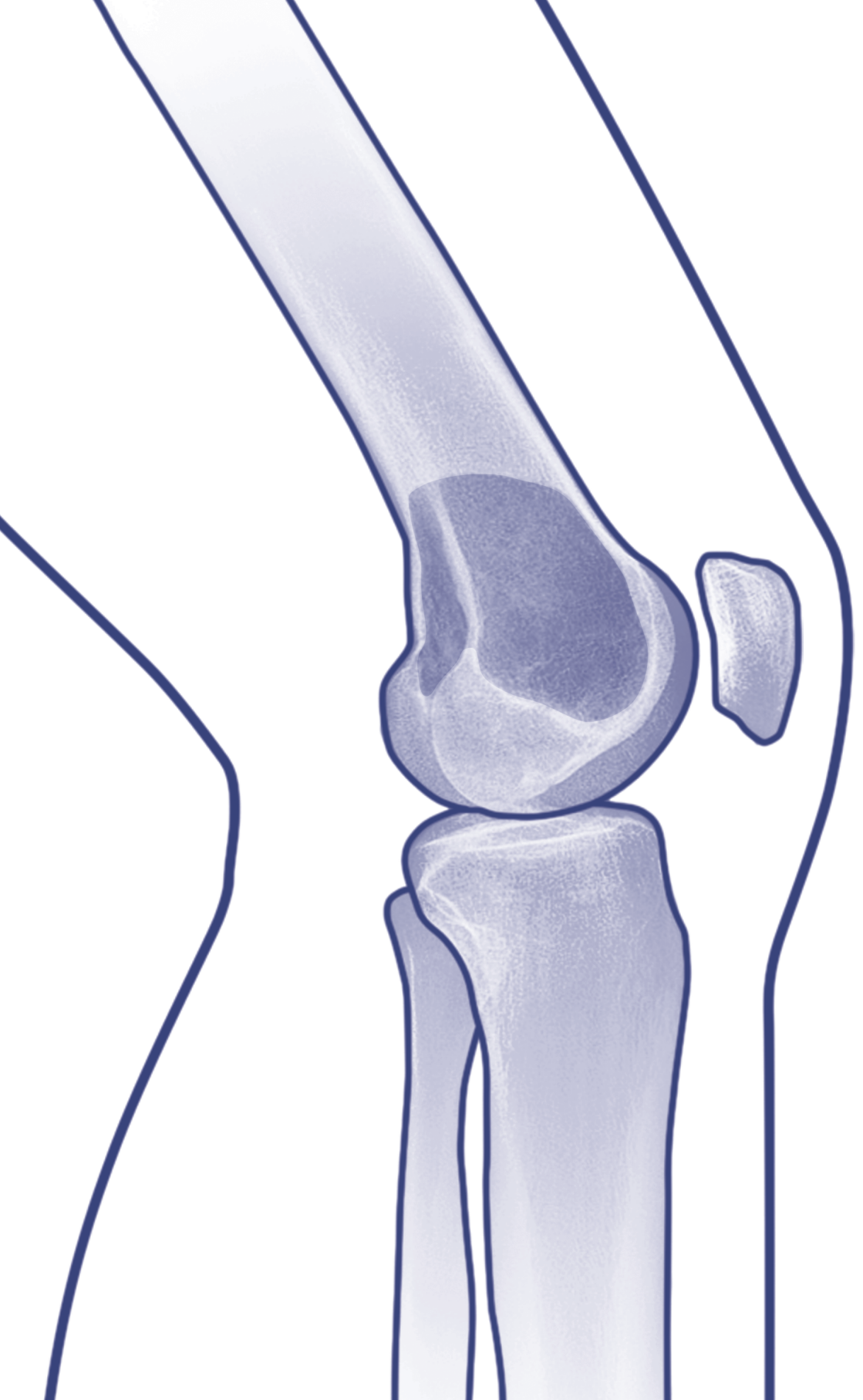

Chapter 5

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.

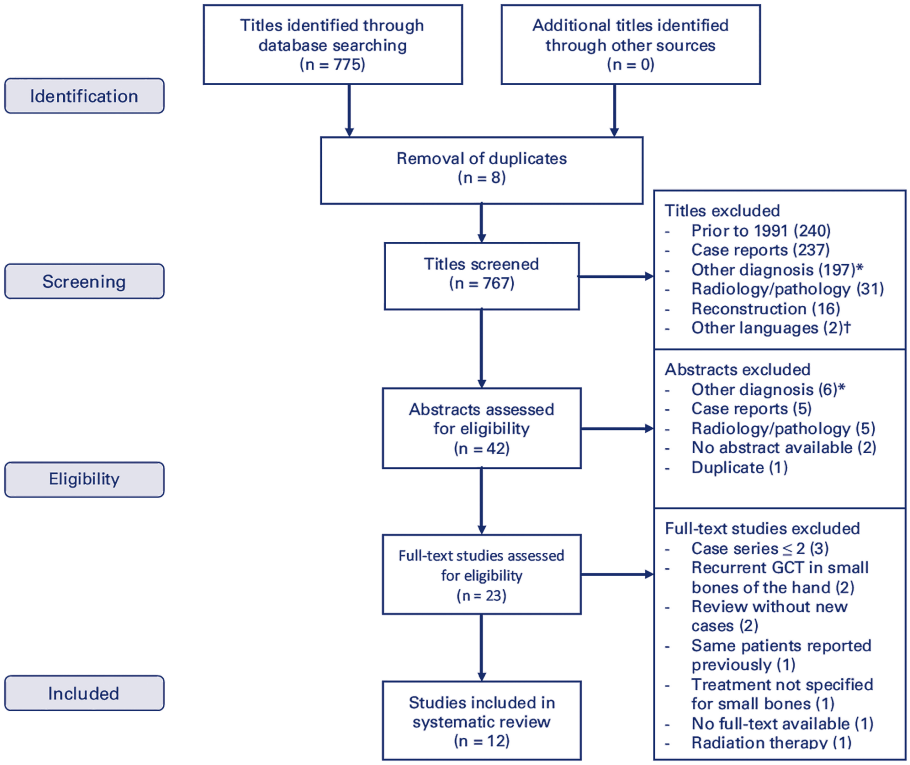

Figure 1 Flowchart of systematic literature search

*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).

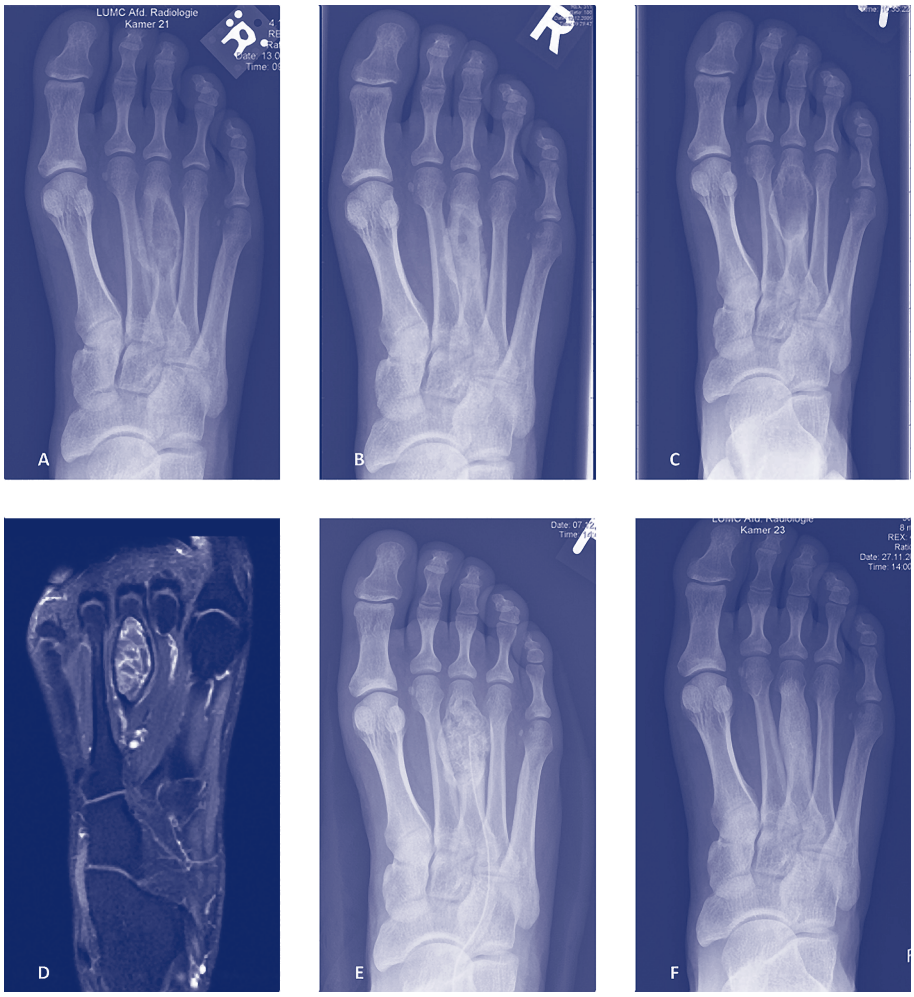

Figure 2 GCTB of the 3rd metatarsal bone of the right foot in a 22-year old female patient. (A) Preoperative conventional AP radiograph demonstrating an expansive lytic lesion without cortical disruption in the metaphysis of the 3rd metatarsal bone of the right foot. (B) Conventional AP radiograph taken 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.

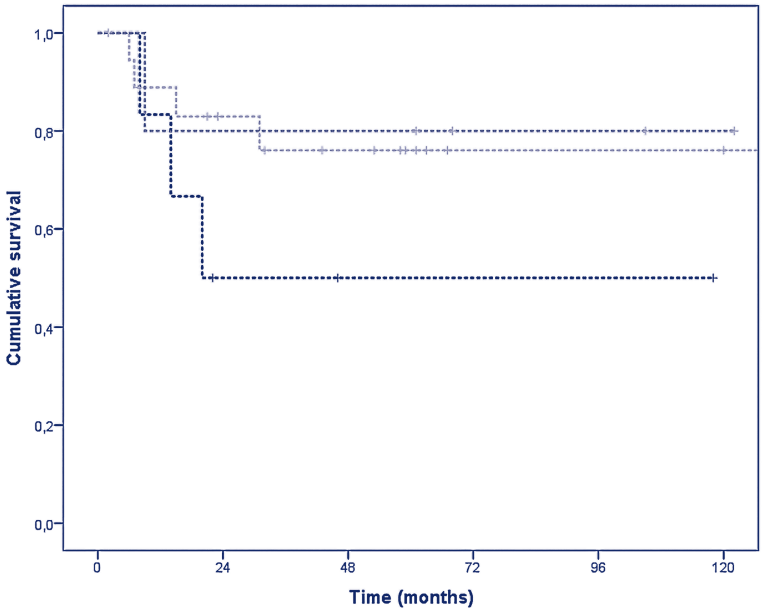

Figure 3 Kaplan Meier survival curve showing the estimated 5-years recurrence free survival after curettage (0.50; black line), curettage with adjuvants (0.75; light gray line) and resection (1.0; dark gray line) for GCTB of the small bones (p=0.160).

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).

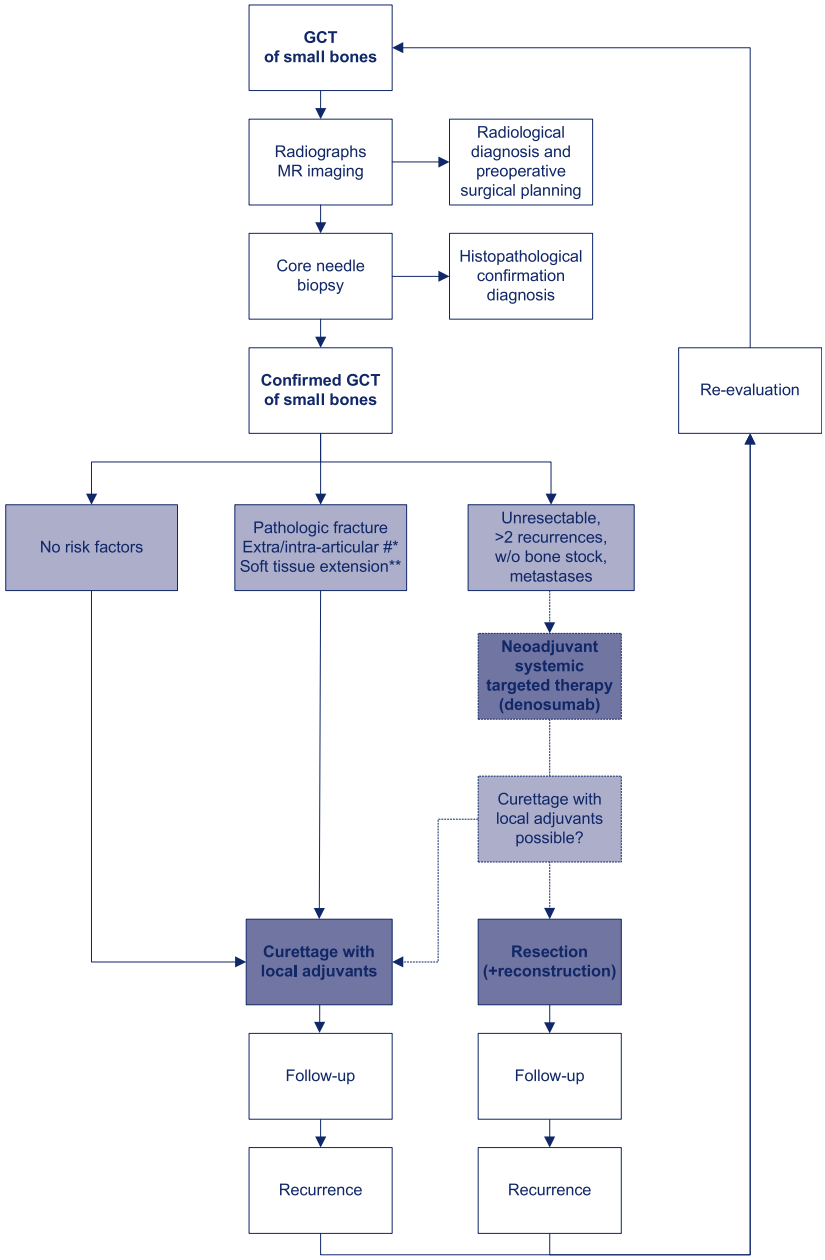

Figure 4 Flowchart of evaluation and treatment of GCTB of the small bones of the hands and feet. *With extra-articular pathologic fractures, preoperative fracture healing may be awaited before curettage with adjuvants, while immediate surgery is required with intra-articular pathologic fractures. **Attention 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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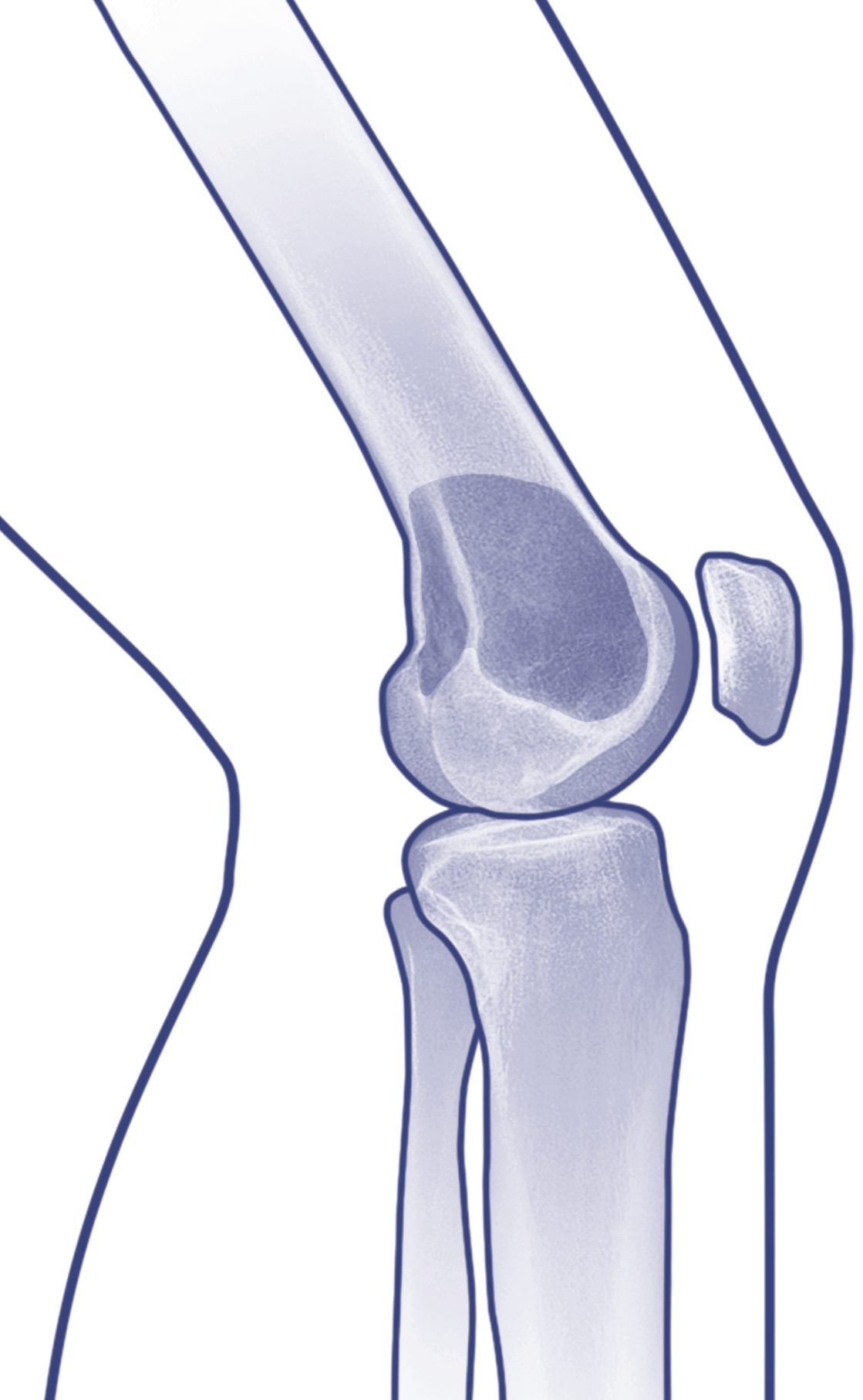

Chapter 6

Giant cell tumors of the sacrum – A nationwide study on midterm results in 26 patients after intralesional excision

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Abstract

Purpose Evaluation of recurrences, complications and function at mid-term follow-up after curettage for sacral giant cell tumor of bone (GCTB).

Methods We retrospectively studied all 26 patients treated for sacral GCTB in the Netherlands (from 1990 to 2010). Median follow-up was 98 (6-229) months. All patients underwent intralesional excision, 21 with local adjuvants, five radiotherapy, three IFN-α, one bisphosphonates. Functional outcome was assessed using Musculoskeletal Tumor Society (MSTS) score. Statistics were performed with Kaplan-Meier, Cox regression, log rank and Mann-Whitney U.

Results Recurrence-rate was 14/26 after median 13 (3-139) months and was highest after isolated curettage (4/5). Soft tissue masses >10cm increased recurrence risk (HR=3.3, 95%CI=0.81-13, p=0.09). Complications were reported in 12/26 patients. MSTS was superior in patients without complications (27 vs. 21; p=0.024).

Conclusion Recurrence rate for sacral GCTB was highest after isolated curettage, indicating that (local) adjuvant treatment is desired to obtain immediate local control. Complications were common and impaired function.

Introduction

Giant cell tumor of bone (GCTB) is a benign, locally aggressive primary bone tumor, mostly affecting meta-epiphyseal regions of long bones. The sacrum is the most affected bone of the axial skeleton, accounting for 2-8% of all GCTB [1-3]. Patients present with lower back pain, frequently radiating to the legs, and sometimes with bladder, rectal or sexual dysfunction. Surgical management of sacral GCTB is challenging because of large size due to late discovery, spinal instability and involvement of sacral nerve roots. Cortical destruction and soft tissue extension by expansive tumor growth are common [4]. Because of its rareness, only small case series on sacral GCTB have been published [1-3,5-12], and optimal treatment remains under debate.

Selective arterial embolization can be performed to prevent extensive intraoperative hemorrhage [1,13], or repeatedly as primary treatment [1,14-16]. Radiation therapy may be given as adjuvant treatment for residual or recurrent disease; only rarely as primary treatment for inoperable tumors [1,3,10,17]. On the long term, it may result in radiation induced sarcoma (3-11%) [10,18].

In case of extended involvement of at least the proximal part of the sacrum, total sacrectomy has been advocated, as recurrence rates are low (0-8%) [1,2,5,6,8,19]. However, as there is a high risk of infections (18-46%), neurological deficits (24-38%) and bladder, rectal or sexual dysfunction (18-47%) [8,20], it could be considered overtreatment of this benign tumor. Partial sacrectomy is less mutilating and can be performed when distal from S2 [1], as pelvic support remains intact. Damage to lower sacral nerve roots results in less severe neurological complications compared with upper sacral nerve roots. Recurrence rates after marginal resection without local adjuvants range from 18-54% [3,6,19].

Curettage is less invasive but higher recurrence rates (10-75%) are reported [1-3,6,7,10-12,19] compared to GCTB of long bones, because of difficulties in complete tumor removal at this anatomical site and in application of local adjuvants including phenol or liquid nitrogen [3,11]. Advantages of curettage are salvage of nerve roots and visceral structures and maintenance of pelvic support.

To summarize, sacral GCTB is a difficult condition, none of current treatment options are satisfactory and possibilities for using (local) adjuvant treatment with intralesional surgery need to be further explored. The aim of this study

was to evaluate mid-term results including recurrences, complications and functional outcome after intralesional excision of sacral GCTB in one country.

Methods

In this nationwide retrospective study, we reviewed all 28 patients treated for sacral GCTB between 1990 and 2010, via the Netherlands Committee on Bone Tumors. Two patients were excluded due to inoperability; one with extremely vascularized GCTB underwent repetitive selective arterial embolization; one with morbid obesity underwent primary radiation therapy. We included all 26 patients that underwent surgery (15 females). Median age was 41 years (range 14-66). All patients had a minimum follow-up of two years, except one patient who died from disease six months after surgery. Median follow-up was 98 months (range 6-229).

Data were collected from medical records, imaging and histopathological reports: age, gender, preoperative symptoms, localization, tumor size, cortical destruction, soft tissue extension, involvement of sacral nerve roots, preoperative embolization, surgical treatment, (local) adjuvant treatment, reconstruction, recurrences, metastases, postoperative symptoms and complications, functional outcome and duration of follow-up.

Preoperative selective arterial embolization was performed in 19 patients. All patients underwent intralesional excision. In all but one patient, a standard midline posterior approach was used. Exposed sacral nerve roots were carefully detached and the cavity thoroughly curetted. In eight patients with extensive cortical destruction and/or large presacral soft tissue masses, no chemical adjuvant was used. Surgical margins were extended in four patients with anterior sacral wall excision (ASWE), performed with burring, milling or piecemeal excision of the anterior sacral wall after detachment and protection of sacral nerve roots. Two-stage curettage with combined anterior and posterior approach was indicated in five patients due to large presacral tumor masses (>10cm). One patient had an anterior approach because of ventral localization. Local adjuvants were liquid nitrogen (n=9), phenol (n=4), argon beam coagulation (n=3) and polymethylmethacrylate (PMMA; n=3). Two patients underwent adjuvant radiotherapy for suspected incomplete curettage. One patient underwent preoperative radiotherapy for suspected metastasis

of unknown primary tumor, before histopathological confirmation of GCTB after resection. Three patients received adjuvant IFN-α, one bisphosphonates. Median duration of surgery was 3.6 hours (range 1.5-11) for posterior and 6.2 hours (range 5.3-8) for combined anterior and posterior approaches. Median estimated blood loss was 1,600ml (range 350-32,000) for posterior and 8,500ml (range 4,500-25,000) for combined anterior and posterior approaches. Despite selective arterial embolization, four patients had >12,000ml blood loss (two posterior and two combined approaches).

After tumor removal, stability of remaining sacral segments and its potential for weight-bearing was assessed. When at least S1 remained intact after surgery, weight-bearing capacity was considered sufficient and no reconstruction was performed. Stability and weight-bearing capacity were insufficient in eleven of 20 patients with S1 involvement. Posterior stabilization with lumbopelvic fixation with PMMA or bone grafts was indicated in three patients, reconstruction with bone grafts in seven and with PMMA in one. Lumbopelvic instrumentation consisted of transpedicular screws L4-L5 with rods connected to 2-3 iliac screws and at least one rod connector (Figure 1). Double rods were used in case of large sacral destruction without remaining proximal sacral bone (S1-S2). In all patients, special attention was paid to soft tissue coverage; routine transposition of gluteal muscles was performed, but no free flaps were deemed necessary.

In patients with sacral instability, postoperative treatment consisted of immobilization in a brace for 3-6 months. After lumbopelvic fixation and/or ingrowth of bone grafts, patients could mobilize immediately.

Current follow-up protocols generally consist of radiographs every six months up to two years and annually up to 10 years after surgery to detect recurrences or complications. Magnetic resonance (MR) imaging may be performed after 1, 2, 5 and 10 years. In this study, all available imaging was reviewed. Functional outcome was evaluated with Musculoskeletal Tumor Society (MSTS) scores at latest follow-up [21], which were available from 22 patients and could not be obtained from three who died and one who relocated.

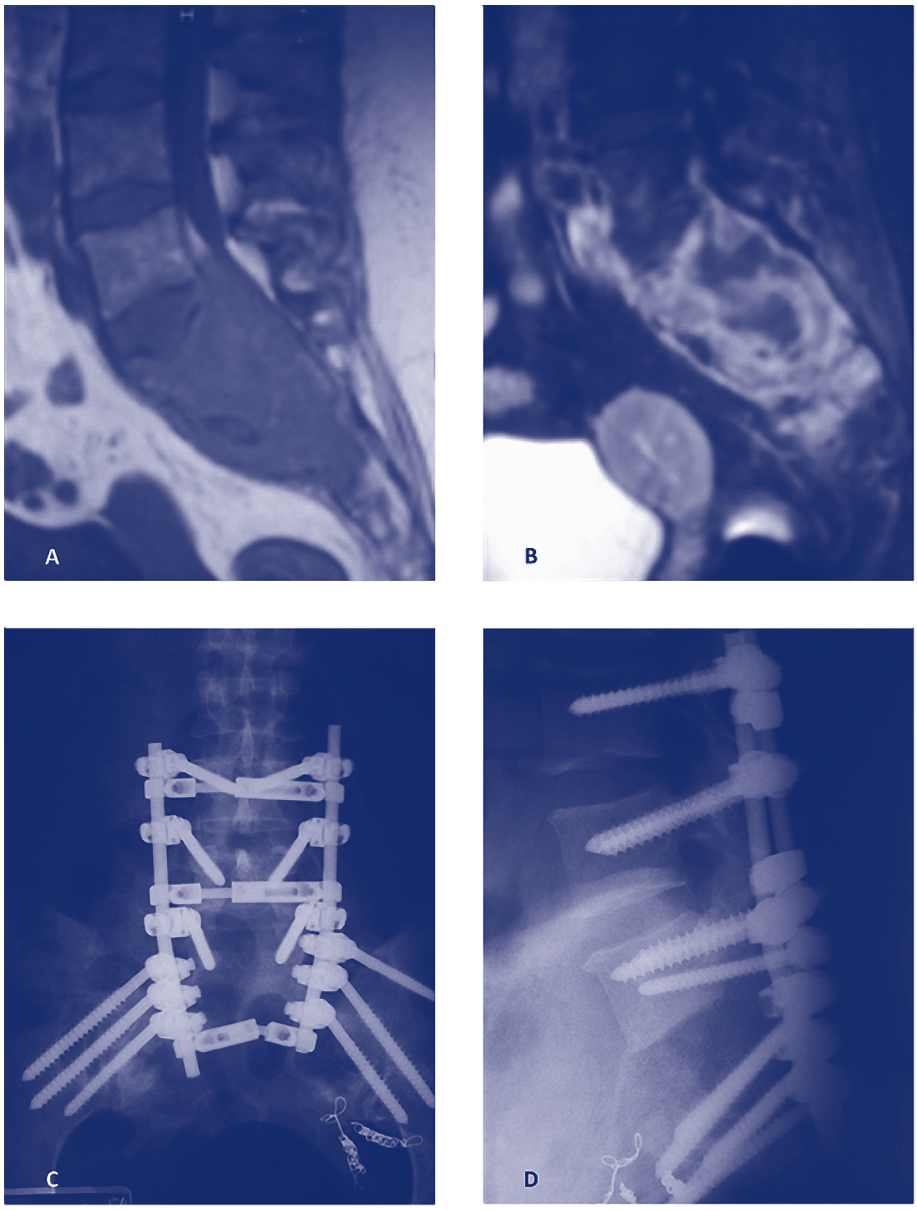

Figure 1 (a, b) Preoperative sagittal T1-weighted MR images and T1-weighted SPIR images with fat suppression after gadolinium administration in a 58-year old female patient with centrally located primary GCTB in S1-S3. (c, d) Anteroposterior and lateral conventional radiographs after repeated intralesional surgery for a first recurrence and reconstruction with transpedicular screws L3-L5 with rods connected to six iliac screws, three rod connectors and bone grafts. The patient is continuously disease free at 10 years follow-up.

Statistical analysis

Kaplan-Meier survival analysis was performed to assess recurrence-free survival; log-rank to compare different treatments. Univariate Cox regression was performed to evaluate risk factors for recurrence. Mann-Whitney U tests were performed to compare numerical results.

Results

GCTB was confined to upper sacral segments (S1-S2) in fifteen patients, upper and lower sacral segments in ten, and lower sacral segments (S3-S5) in one; five had extension into the ilium (Tables 1 and 2). Sacral nerve roots were involved in 20 patients. Twenty-five had cortical destruction. Twenty-three had soft tissue extension. Preoperative symptoms included pain in all patients, sensory impairment in 11, motor deficits in six, bladder dysfunction in five and rectal dysfunction in two (Tables 1 and 2).

Table 1 Patient and tumor characteristics

	n	%
Localization		
S1 (+ ilium)	7 (3)	27
S1-S2	8	30
S1-S3 (+ilium)	2 (1)	8
S1-S4 (+ilium)	2 (1)	8
S1-S5	1	4
S2-S3	2	8
S2-S5	3	11
S3-S5	1	4
S1 involvement	**16**	**62**
Complete (>75)	8	31
Over midline (51-75%)	6	23
Until midline (26-50%)	5	19
In sacral wing (≤25%)	1	4
No involvement of S1	6	23

Table 1 continued

	n	%
Cortical destruction [a]	**25**	**96**
Extensive destruction both cortices (>75%)	9	36
Extensive destruction one cortex (>75%)	3	12
Moderate destruction both cortices (50-75%)	5	20
Moderate destruction one cortex (50-75%)	3	12
Minor destruction both cortices (<50%)	2	8
Minor destruction one cortex (<50%)	3	12
SI joint destruction [b]	**16**	**62**
Ingrowth into ilium or vertebra (L5) [b]	**10**	**38**
Soft tissue extension	**23**	**88**
<1 cm	8	35
1-5 cm	7	30
5-10 cm	3	13
10-15 cm	4	18
>15 cm	1	4
Sacral nerve root involvement	**15**	**58**
S1	5	33
S1-S2 (bilateral)	3 (3)	20
S1-S4 (bilateral)	1 (1)	7
S2 (bilateral)	2 (1)	13
S2-S3 (bilateral)	3 (1)	20
S3-S5 (bilateral)	1 (1)	7
Number of sacral nerve roots involved	**15**	**58**
1 sacral nerve root (bilateral)	7 (1)	47
2 sacral nerve roots (bilateral)	5 (3)	33
3 sacral nerve roots (bilateral)	2 (2)	13
4 sacral nerve roots (bilateral)	1 (1)	7
Preoperative complaints		
Pain	26	100
Sensory impairment	11	42
Loss of motor function (e.g. dropped foot)	6	23
Bladder dysfunction	5	19
Rectal dysfunction	2	8

[a]Either both anterior and posterior sacral cortices were affected, or the anterior or posterior sacral cortex
[b]This includes all sacro-iliac joints and os ilium that were affected (i.e. one or two sides in every patient)

Table 2 Individual patient and tumor characteristics before surgery for sacral GCTB

Pt.	Sex	Age (yr)	Localization	S1 involvement	Size (mm)	Cortical destruction	Soft tissue extension	Involved sacral nerve roots	Preoperative symptoms
1	M	16	S2-S3	-	60x70x70	Moderate destruction anterior and posterior (<50%), right SI joint	Moderate extension anterior (<5cm), minor extension posterior (<1cm), into gluteus muscles	S2-S3 right	Pain, breeches anesthesia, acute urinary retention
2	M	52	S1-S2	Central (75%)	60x50x30	Moderate destruction anterior (<50%)	Minor extension into neuroforamen S1 (<1cm)	S1 right	Pain
3	F	45	S1-S2	Central (100%)	60x70x50	Extensive destruction anterior and posterior (>75%), left SI joint	Extensive extension anterior (>5cm), minor extension posterior	S2 bilateral	Pain
4	F	35	S1-S2	Right until midline (50%)	60x60x40	Moderate destruction posterior (<50%), minimal destruction anterior, right SI joint	-	-	Pain
5	M	49	S1-S2	Central (100%)	100x35x35	Minor destruction anterior and posterior (<25%), left SI joint, left ilium	Minor extension (<1cm)	-	Pain, impaired pain perception, cauda syndrome
6	F	14	S1-S4-Ilium	Left over midline (75%)	90x70x60	Extensive destruction anterior and posterior (50%), left and right SI joints, left ilium	Extensive extension anterior caudal from S1 (>5cm), minor extension posterior into dorsal muscles	S1-S2 bilateral	Pain
7	M	27	S1-S2	Central (100%)	90x150x150	Extensive destruction anterior (>75%), right SI joint	Extensive extension anterior into entire pelvic area (>15cm), within spinal canal, extends to rectum	S1-S2 bilateral	Pain, rectal dysfunction, vena cava inferior syndrome, obstructive ileus
8	F	56	S1-S2	Central (100%)	100x60	Extensive destruction anterior and posterior (>75%)	Extensive extension anterior until acetabular roof (>10cm), minor extension posterior into dorsal muscles, within spinal canal	-	Pain, sensory impairment, bladder and rectal dysfunction

9	F	31	S1-Ilium	Left until midline (50%)	150x130x80	Extensive destruction posterior (50%), left SI joint, left ilium	Extensive extension posterior into dorsal and gluteus muscles (>10cm)	-	Pain
10	M	47	S2-S5	-	60x60x40	Extensive destruction anterior and posterior (50%), os coccygis	Moderate extension anterior and posterior (<5cm), into gluteal muscles	S2-S3 right	Pain, sensory impairment
11	M	66	S1-S2	Right until midline (50%)	70x50x40	Minor destruction anterior, moderate destruction posterior (<50%)	Minor extension into neuroforamen S1 (<1cm)	S1 right	Pain
12	F	32	S1-S3-Ilium	Left over midline (75%)	50x60x55	Extensive destruction anterior and posterior (50%), left SI joint, left ilium	Moderate extension anterior (<5cm)	S1 left	Pain
13	M	44	S1-Ilium	Left over midline (75%)	150x120	Extensive destruction anterior and posterior (75%), left SI joint, left ilium	Moderate extension anterior (<5cm)	-	Pain
14	M	39	S1	Left until midline (50%)	40x30x30	Minor destruction posterior (<33%)	Minor extension into neuroforamina S1-S2 (<1cm)	S1 left	Pain, sensory impairment
15	F	58	S1-S3	Central (100%)	85x70x40	Extensive destruction anterior and posterior (>75%), into intervertebral disc L5	Moderate extension anterior and posterior (<5cm), within spinal canal	-	Pain, sensory impairment
16	M	23	S1-S5	Central (100%)	90x80x75	Extensive destruction anterior and posterior, (>75%), destruction of L5, left and right SI joints, right ilium	Moderate extension anterior and posterior from sacrum and L5 (<5cm), into dorsal muscles, within spinal canal	S1-S2 bilateral	Pain, neurological deficit, sensory impairment
17	F	24	S1-Ilium	Left (25%)	55x40x30	Minor destruction anterior (25%), left SI joint, left ilium	Minor extension ventral from iliac wing (<1cm)	-	Pain, sensory impairment

Table 2 Continued

Pt.	Sex	Age (yr)	Localization	S1 involvement	Size (mm)	Cortical destruction	Soft tissue extension	Involved sacral nerve roots	Preoperative symptoms
18	F	63	S2-S3	-	40x40x20	Minor destruction anterior and posterior	Minor extension posterior into dorsal muscles and anterior (<1cm), and into neuroforamina S2-S4 (without involvement of sacral nerve roots)	-	Pain, neurological deficit, sensory impairment, bladder dysfunction
19	F	50	S2-S5	-	65x90x65	Extensive destruction anterior (50%), moderate destruction posterior (<50%)	Moderate extension anterior (<5cm)	S1 right, S2-S3 bilateral	Pain, bladder dysfunction
20	M	17	S1	Left until midline (50%)	65x55x50	Extensive destruction anterior and posterior (50%), left SI joint	Minor extension posterior (<1cm)	S1 left	Pain, neurological deficit
21	F	22	S1-S2	Central (100%)	75x45x50	Extensive destruction posterior (>75%), moderate destruction anterior (<50%), pathologic fracture	Minor extension anterior (<1cm), moderate extension posterior into dorsal muscles (<5cm)	-	Pain, sensory impairment, neurological deficit, cauda syndrome after fracture
22	F	49	S1-S4	Central (100%)	100x90x80	Extensive destruction anterior and posterior (75%), left and right SI joints, right ilium	Extensive extension anterior (>10cm), into neuroforamen S1, into gluteus muscles, extends to rectum	S1-S4 bilateral	Pain, sensory impairment
23	F	19	S1	Central (75%)	60x35x25	-	-	-	Pain
24	F	38	S3-S5	-	115x120x90	Extensive destruction anterior (>75%), os coccygis	Extensive extension anterior into entire pelvic area (>10cm), involves rectum	S3-S5 bilateral	Pain, bladder dysfunction, sensory impairment
25	M	20	S2-S5	-	55x40x25	Minor destruction anterior (<50%)	-	S2 right	Pain
26	F	45	S1	Central (75%)	80x40x50	Moderate destruction anterior (50%) within neocortex and minor destruction posterior (25%)	Minor extension posterior into spinal canal (<1cm)	-	Pain

Pt. = patient; M = male; F = female; yr = year; mm = millimeter; cm = centimetre

Two patients had residual GCTB confirmed on postoperative MR imaging three months after surgery; both underwent adjuvant radiotherapy (50-60 Gy). Fourteen of 26 (54%) patients had recurrence after median 13 months (range 3-139); one was a soft tissue recurrence (Table 3). Two years recurrence-free survival was 20% for isolated curettage and 65% for curettage with local adjuvants (liquid nitrogen, phenol, argon beam coagulation or PMMA) (p=0.035). The only factor that increased risk for recurrence was soft tissue mass >10cm (hazard ratio 3.3, 95% confidence interval 0.81-13, p=0.09) (Table 4). Of 14 first recurrences, 11 underwent second curettage (five with liquid nitrogen, two with ASWE, two adjuvant bisphosphonates, one adjuvant radiotherapy), one computed tomography (CT)-guided argon beam coagulation, one receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor denosumab and one remained expectative. Of four second recurrences, two underwent curettage and liquid nitrogen and two radiotherapy. A third recurrence was treated with curettage, liquid nitrogen and radiotherapy. Four patients had pulmonary metastases (after 4-17 months). Three died of metastatic disease (after 6-102 months); one had radiation-induced sarcoma, in the other two patients radiation-induced sarcoma was not confirmed.

Table 3 Individual surgical treatment and outcome for sacral GCTB

Pt.	Year	Preop embo	Primary treatment	Reconstruction	Rec.	Time to rec. (mo)	Treatment recurrence	Reconstruction recurrence	Metastases	Postoperative symptoms	Postoperative complications	MSTS	FU (mo)	Status
1	1990	No	Curettage[a], LN	None	-	-	-	-	-	-	-	30	100	NED
2	1994	No	Curettage, phenol	BG	-	-	-	-	-	-	-	29	52	NED
3	1994	Yes	Curettage, EBRT, bisphosphonates	BG, lumbopelvic fixation	-	-	-	-	-	Pain	Radiation-induced menopause, massive intraoperative bleeding	15	229	NED
4	1995	Yes	Curettage, phenol	BG	Yes	139	Curettage, burr, bisphosphonates	BG, lumbopelvic fixation	-	Pain	-	28	218	NED
5	1997	Yes	Curettage, LN, EBRT	None	-	-	-	-	-	Pain, permanent nerve palsy	Wound infection, persisting fistula, chronic osteomyelitis	21	177	NED
6	1997	Yes	Curettage[b]	BG	Yes, 2x	7; 5	1. Curettage 2. EBRT 50Gy	None	Lungs	Pain	-	-	42	DOD
7	1999	Yes	Curettage[b], EBRT 50Gy	None	-	-	-	-	Lungs, liver, mesentery	Pain, progressive neurological deficits (unable to walk shortly before death)	Massive intraoperative bleeding	-	6	DOD
8	1999	Yes	Curettage, ASWE, EBRT 60Gy	None	Yes	5	Expectative	None	-	Pain, permanent cauda syndrome	-	15	168	AWD[c]
9	2000	Yes	Curettage	BG	Yes[d]	7	Curettage	BG	-	-	-	30	152	NED

10	2000	No	Curettage, LN	None	-	-	-	-	-	Transient nerve palsy	S3 frozen by liquid nitrogen	30	106	NED
11	2001	Yes	Curettage, ASWE, argon beam coagulation	BG	Yes	19	Argon beam coagulation	None	-	Sensory impairment	-	28	94	NED
12	2002	Yes	Curettage, LN	None	Yes, 2x	29; 48	1.Embo, curettage, LN 2.Embo, curettage, LN	None	-	Mild pain	-	30	121	NED
13	2002	Yes	Curettage, LN	BG	Yes, 3x	41; 10; 8	1. Curettage, LN 2. Curettage, LN 3. Curettage, LN, EBRT 64Gy	BG	-	Transient nerve palsy	Massive intraoperative bleeding	23	126	AWD
14	2003	Yes	Curettage	None	Yes	7	Curettage, partial ASWE, burr, bisphosphonates	BG, lumbopelvic fixation	-	Transient partial cauda syndrome	Delayed wound healing	21	113	NED
15	2003	Yes	Curettage, IFN-α	None	Yes	9	Curettage, partial ASWE	BG, lumbopelvic fixation	-	Transient cauda syndrome	Wound infection, failure of instrumentation	18	123	NED
16	2003	Yes	Curettage[b], LN	None	Yes, 2x	10; 20	1. Embo, curettage, LN 2. EBRT	None	Lungs	Permanent nerve palsy, bladder and rectum insufficiency	Radiation induced sarcoma	-	102	DOD

Table 3 Continued

Pt.	Year	Preop embo	Primary treatment	Reconstruction	Rec.	Time to rec. (mo)	Treatment recurrence	Reconstruction recurrence	Metastases	Postoperative symptoms	Postoperative complications	MSTS	FU (mo)	Status
17	2004	No	Curettage, burr, LN	None	Yes	10	Curettage, LN	None	Lungs	Transient nerve palsy	S1-S3 frozen by liquid nitrogen, massive intraoperative bleeding	-	28	NED
18	2004	Yes	Curettage	None	-	-	-	-	-	-	-	27	111	NED
19	2005	Yes	Curettage, ASWE	None	-	-	-	-	-	-	-	29	95	NED
20	2005	Yes[e]	Curettage, H_2O_2, argon beam coagulation, IFN-α	BG	-	-	-	-	-	Mild pain	-	26	94	NED
21	2006	Yes	Curettage[b], H_2O_2, phenol, argon beam coagulation, IFN-α	PMMA, lumbopelvic fixation	-	-	-	-	-	Permanent nerve palsy (bilateral dropped foot)	-	21	77	NED
22	2008	Yes	Curettage, LN, EBRT	None	-	-	-	-	-	Bladder and rectum insufficiency	Dissociation fracture symphysis pubis (osteopenia)	15	52	NED
23	2008	No	Curettage, LN	PMMA	Yes	5	Curettage, LN, EBRT	BG	-	Partial cauda syndrome, bladder insufficiency, sexual dysfunction	S1 frozen by liquid nitrogen	24	59	NED
24	2008	No	Curettage[b,f]	None	Yes	3	Curettage	None	-	-	Wound infection	24	54	NED
25	2009	Yes	Curettage, ASWE	None	Yes	34	Denosumab	-	-	-	-	24	44	AWD
26	2009	No	Curettage	PMMA, lumbopelvic fixation	-	-	-	-	-	-	-	17	48	NED

[a]Curettage through anterior approach
[b]Curettage in two tempi through combined anterior and posterior approach
[c]Patient remains under observation for stable residual disease after radiation therapy
[d]Soft tissue recurrence
[e]This patient had arterial embolization three years prior to surgery to reduce tumor size and stop tumor growth
[f]Colostomy was performed during initial surgery because tumor involved rectum
Pt. = patient; preop embo = preoperative embolization; rec. = recurrences; mo = months; MSTS = Musculoskeletal Tumor Society score; FU = follow-up; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease; LN = liquid nitrogen; EBRT = external beam radiation therapy; ASWE = anterior sacral wall excision; IFN-α = interferon-α; PMMA = polymethylmethacrylate; BG = bone graft

Table 4 Univariate Cox regression analysis on risk factors for recurrence after intralesional excision for sacral GCTB

	n	recurrences	recurrence rate	hazard ratio	95% confidence interval		p-value
					lower	upper	
Confined to S1-S2	15	8	53%	1.1	0.37	3.3	0.85
Anterior cortex destruction >50%	14	7	50%	1.0	0.35	2.9	0.98
Soft tissue extension	23	11	48%	0.54	0.15	2.0	0.35
<5cm	16	7	44%	-	-	-	0.25
5-10cm	2	1	50%	1.1	0.13	8.6	0.96
>10cm	5	3	60%	3.3	0.81	13	0.09
Use of any local adjuvant*	18	9	50%	0.48	0.16	1.5	0.19
Use of any systemic adjuvant**	8	2	25%	0.32	0.04	2.4	0.27
Use of radiotherapy***	5	1	20%	0.24	0.03	2.0	0.19

*Local adjuvants at primary treatment included phenol, liquid nitrogen, argon beam coagulation, PMMA, ASWE
**Systemic adjuvants at primary treatment included bisphosphonates, IFN-α
***Radiotherapy was given as palliative treatment in two patients; complete response or local control was never aimed at in these patients

Complications were reported in twelve of 26 (46%) patients and included massive intraoperative hemorrhage (12,000-32,000ml; n=4), infection (n=3), permanent neuropraxia after freezing of sacral nerve roots (n=3), hardware failure (n=1), radiation-induced sarcoma (n=1), radiation-induced menopause (n=1), delayed wound healing (n=1) and pubic dissociation fracture due to osteopenia after radiotherapy (n=1) (Table 3). In eight patients, all preoperative symptoms resolved after surgery. Persistent pain was reported by eight patients. In five patients, neurological symptoms resolved completely during follow-up, including transient cauda syndrome (n=2) and transient nerve palsy

(n=3; after 12-30 months). Five patients sustained motor deficits during follow-up, including permanent nerve palsy (n=3), permanent cauda syndrome (n=1), progressive motor deficits shortly before death (n=1), and bladder and rectum insufficiency (n=1). Two patients newly developed motor deficit after surgery: bladder and rectum dysfunction (n=1) and partial cauda syndrome including bladder and sexual dysfunction (n=1).
Overall median MSTS score was 24 (range 15-30). Similar functional results were reported by patients without recurrence (median 26, range 15-30) and with multiple surgeries for recurrences (median 24, range 15-30; p=0.95). Superior functional results were reported by patients without complications (median 29, range 15-30) compared with patients with complications (median 21, range 15-30; p=0.024). Functional status was very poor shortly before death in three patients; all had progressive loss of motor function and were wheelchair bound. From all living patients, walking distance was normal in nineteen and limited in three (crutches outdoors); one patient with permanent cauda syndrome is currently wheelchair bound.

Discussion

Sacral GCTB is a rare lesion which is difficult to treat, and optimal treatment remains controversial. Several treatment options have been proposed, but all have disadvantages regarding tumor control, complications and functional outcome. Additionally, published case series are small and surgical approaches heterogeneous, impeding comparison of results. In this study, we evaluated mid-term results after intralesional excision for all patients treated for sacral GCTB in the Netherlands between 1990 and 2010.
Recurrence rates reported in literature range from 0-8% for wide, 18-54% for marginal and 10-75% for intralesional resection (Table 5). Recurrence-rate in this study (14/26; 54%) was high but within ranges reported for marginal and intralesional surgery. As local adjuvant use depended on the center the patients were treated in, its use was not uniform in this series and different combinations of local adjuvants were used by different surgeons. Therefore, we were unable to specify which local adjuvant provided better oncologic results in sacral GCTB. However, recurrence rate was remarkably higher after isolated curettage (4/5; 80%), indicating that this should not be performed as primary surgery.

Table 5 Overview of literature on surgical treatment of sacral GCTB

Study	Year	n	Age (yr)[a]	FU (mo)[a]	Embo-lization	Surgery	Surgical margin	Adjuvant treatment	Rec.	Treatment recurrences	Adjuvant treatment recurrences	Metastases	Complications	Status at FU
						(n)		(n)	n (%)	(n)	(n)	n (%)		(n)
Sung et al. [5]	1987	12	(30-50)	60 (24-180)[b]	9	Resection (12)	NR	-	1 (8%)	NR	NR	None	NR	NED (6) DOD (1)
Turcotte et al. [6]	1993	26	29 (15-77)	94 (6-300)	0	Curettage (19)	Intral-esional (17) Marginal (2)	Radiation (19)	14 (54%)	NR	NR	4 (15%)	Massive intraop-erative bleeding (1), pulmonary embolism (1), radiation-induced sarcoma (3)	NED (20) AWD (2) DOD (3) DOUD (1)
						Resection (2)	Wide (2)	Radiation (2)	None				Cauda equina syndrome (2)	
Mar-cove et al. [7]	1994	7	20 (14-48)	147 (24-170)	0	Curettage, LN (7)	Intrale-sional (4) Marginal (3)	Radiation (6)	4 (57%)[c]	Curettage, LN (4)	None	2 (28%)	Skin necrosis (2), infection (2), rectal fistula after radiation (1)	NED (7)
Sar et al. [8]	2002	7	23 (17-31)	74 (31-203)	4	Resection (7)	Wide (7)	-	None	-	-	None	Bladder dysfunc-tion (3), dropped foot (2)	NED (7)
Kollen-der et al. [9]	2003	3	23 (21-25)	92 (60-132)	0	Curettage, LN (3)	Intrale-sional (3)	-	None	-	-	None	None	NED (3)
Leggon et al. [10]	2004	2	33 (27-39)	96 (11-254)	0	Curettage (2)	Intrale-sional (2)	Radiation (1)	1 (50%)	-	Radiation (1)	-	NR	NED (1) AWD (1)
Guo et al. [3]	2009	24	35 (18-63)	58 (25-132)	24	Curettage (4)	Intrale-sional (4)	-	3 (75%)	NR	NR	2 (8%)	Delayed wound healing (2)	NED (20) AWD (1) DOD (1)

Table 5 Continued

Study	Year	n	Age (yr)[a]	FU (mo)[a]	Embo-lization	Surgery	Surgical margin	Adjuvant treatment	Rec.	Treatment recurrences	Adjuvant treatment recurrences	Metastases	Complications	Status at FU
						Resection (20)	Intral-esional (18) Marginal (2)	Radiation (2)	4 (20%)	NR	NR		Bladder dysfunc-tion (7), rectal dysfunction (8), delayed wound healing/wound infection (5), deep venous thrombo-sis (1)	DOUD (2)
Martin et al. [2]	2010	8	31 (13-49)	32 (0-84)	6	Curettage (6)	Intrale-sional (6)	Radiation (3)	2 (33%)	Emboliza-tion (1) Curettage (1)	Radiation (2) Chemother-apy (1)	None	Bladder dysfunc-tion (1)	NED (6) AWD (4)
						Resection (2)	Wide (2)	Radiation (1) Chemother-apy (1)	None	-	-		Rectal dysfunc-tion (1)	
Ruggieri et al. [11]	2010	31	29 (14-68)	108 (36-276)	23	Curettage, phenol (15), LN (3)	Intral-esional (31)	Radiation (21)	3 (10%)	NR	NR	NR	Delayed wound healing (8), mas-sive intraopera-tive bleeding (7)	NED (29) DOD (2)
Thanga-raj et al. [1]	2010	9	34 (15-52)	(24-252)	5	Curettage (7)	Intrale-sional (7)	-	3 (43%)	Curettage (2) Emboliza-tion (3)	Radiation (1)	None	Massive intraop-erative bleeding (2), bladder dys-function (1)	NED (7) AWD (2)
						Resection (1)	Wide (1)	-	None	-	-		Sexual dys-function (1), radiation-induced menopause (1)	
Balke et al. [12]	2011	10	28 (17-61)	52 (15-133)	4	Curettage, PMMA (10)	Intral-esional (10)	Radiation (2) Chemother-apy (1)	2 (20%)	Curettage (2)	-	None	Infection (3), bladder dysfunc-tion (2), rectal dysfunction (1), cauda equina syndrome (1), dropped foot (1)	NED (6) AWD (4)

Li et al. [19]	2012	32	31 (19-74)	42 (18-115)	32	Resection (25)	Wide (2)	Radiation (5)[e]	None	-	-	2 (6%)	Bladder dysfunction (1), delayed wound healing (1), radiation-induced sarcoma (2)	NED (30) DOD (2)
							Marginal (11)	Bisphosphonates (3)[e]	2 (18%)	NR[e]	Radiation (8)[e]		Lower limb dysfunction (4), delayed wound healing (3), bladder dysfunction (1)	
							Intralesional [d] (12)		5 (42%)				Delayed wound healing (6), bladder dysfunction (3), rectal dysfunction (2)	
						Curettage (7)	Intralesional (7)		5 (71%)				Delayed wound healing (1)	
Current study	2013	26	38 (14-66)	100 (6-229)	19	Curettage, LN (9) phenol (4), argon beam coagulation (3), PMMA (3)	Intralesional (22) Marginal (4)	Radiation (5), IFN-α (3), bisphosphonates(1)	14 (54%)	Curettage (11), LN (5)	Bisphosphonates (1), radiation (4), argon beam coagulation (1), denosumab (1)	4 (15%)	Massive intraoperative bleeding (4), infection (3), freezing of sacral nerve roots (3), hardware failure (1), radiation-induced sarcoma (1), radiation-induced menopause (1), delayed wound healing (1), fracture (1)	NED (20) AWD (3) DOD (3)

[a] Mean value with range given in parenthesis
[b] Follow-up was only available for seven patients with GCT of the sacrum
[c] Two were microscopic recurrences detected through routinely performed postoperative biopsies
[d] Marginal resection of distal GCT and curettage of proximal GCT
[e] This (adjuvant) treatment was given within the entire study population; it is unknown what primary treatment was.
Yr = year; FU = follow-up; mo = months; rec. = recurrence; LN = liquid nitrogen; PMMA = polymethylmethacrylate; MSTS = Musculoskeletal Tumor Society score; NR = not reported; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease; DOUD = died of unrelated disease

Soft tissue extension is the only factor strongly increasing the risk for recurrence after curettage for GCTB of long bones [22,23]. From the limited risk analysis performed in this study, large soft tissue masses (>10cm) increased risk for recurrence three-fold. Possibly, volume measurements on CT or MR imaging may provide information regarding risk factors for recurrence of sacral GCTB in the future. Surgical management of recurrences is difficult due to adhesions and involvement of sacral nerve roots, bladder and rectum [5]. Therefore, immediate local control is key in order to avoid surgery for recurrent or residual disease. Since isolated curettage leads to 80% recurrence within two years, some kind of local adjuvant or systemic therapy is necessary—equal to surgical management of GCTB of long bones. The choice for wide or intralesional resection of sacral GCTB depends mainly on tumor size and localization. Intralesional surgery is preferred for large tumors involving upper sacral segments (S1-S2); marginal or en bloc resection can be recommended for small GCTB in lower sacral segments (S3-S5), for malignant GCTB (e.g. radiation-induced sarcoma) and for preexistent severe neurological deficits [2,5,12,24].

Chemical and thermal agents phenol and liquid nitrogen have been used as local adjuvants in sacral GCTB treatment [7,9,11]. Advantages are preservation of lumbopelvic continuity, shorter operative time and less intraoperative blood loss. However, chemical agents are not recommended in vicinity of soft tissue and sacral nerve roots because of its necrotizing effects. Furthermore, phenol has demonstrated only limited penetration in cortical bone [25,26]. Additionally, it has been postulated that whenever chemical agents are not applicable on all cavity borders, which is often the case in sacral GCTB, complication risk may surpass expected clinical benefits [11], and its use should be discouraged. Thermal agent liquid nitrogen has variable penetration capacities which can be monitored, and may be used in proximity of sacral nerve roots as it often causes only transient nerve damage. Therefore, cryosurgery may be useful in relatively large GCTB and tumors proximal to S3. However, complication risk after cryosurgery is higher compared to chemical agents and with large presacral soft tissue masses it may damage the posterior rectal wall [7].

Mechanical adjuvants include high-speed burring and, in this study, anterior sacral wall excision (ASWE). The anterior sacral wall is not required for maintenance of structural integrity, especially in lower sacral segments. Furthermore, tumor removal from the thin rim of remaining cortex can be

difficult [4]. Thus, complete removal of anterior cortex is a logical and safe method to increase surgical margins.

Radiotherapy has been used as adjuvant treatment for residual or recurrent disease; only rarely as primary treatment [1,3,10,17]. In this study, 9/26 patients underwent radiotherapy for residual or recurrent disease. Four patients are free of disease, two patients are alive with stable disease and three patients died of disease (one with confirmed radiation-induced sarcoma). Radiotherapy is not recommended for primary sacral GCTB, as lifelong risk for radiation-induced sarcoma is noteworthy (3-11%) [10,12,18]. With the advent of denosumab, the role of radiotherapy in the treatment of GCTB needs to be redefined. Given the promising short-term results of denosumab so far, use of radiotherapy should be restricted to rare cases of unresectable, residual or recurrent GCTB in which treatment with denosumab is not possible or proven to be ineffective, and when surgery would lead to unacceptable morbidity which is often the case in sacral GCTB.

Systemic treatment included bisphosphonates, IFN-α and denosumab in this study. After bisphosphonates, none of three patients had recurrence. After IFN-α, one of three patients had recurrence. One patient with recurrence is enrolled in a trial with denosumab, which showed clear clinical benefits in GCTB treatment and has recently been approved for unresectable GCTB [27,28]. Intralesional surgery may be facilitated after neoadjuvant denosumab, especially in difficult localizations including axial skeleton and sacrum. To date, it remains unknown whether systemic therapy with denosumab lowers the recurrence rate. The number of patients treated with systemic therapy in this study was small and its effect on oncological outcome needs to be further explored.

Complication rates reported in literature range from 50-100% after wide and marginal resection and 0-71% after intralesional excision for sacral GCTB (Table 5). In this study, complications were reported in 12/26 (46%) patients. Nineteen patients had selective arterial embolization to minimize intraoperative bleeding; yet, four patients had >12,000ml blood loss, possibly due to extreme vascularity of GCTB in these patients. In general, preoperative embolization is crucial for intraoperative hemorrhage control and although blood loss may be used to estimate its success, embolization of afferent arteries is not always feasible. Nerve palsy was most commonly reported after cryosurgery. This neuropraxia was often transient and may be taken for granted in exchange for a lower expected recurrence risk. Fortunately, with current cryosurgical

techniques, freezing temperatures can be monitored accurately and measures are undertaken to prevent nerve and other soft tissue damage, diminishing the complication risk [29]. Cauda syndrome can be caused by sacral nerve root involvement and multiple surgical interventions with subsequent adhesions in the operational area; another reason to advocate immediate local control. Radiotherapy related complications as reported in this study are considered very severe, which is the reason that the use of radiotherapy should be minimized in this relatively young patient category.

Functional outcome was comparable in patients with and without recurrences, but superior in patients without complications. Worst function was seen in three patients with progressive disease shortly before death. In the literature, functional results were only expressed in terms of neurological, bladder and rectum dysfunction. Worse functional results were reported for involvement of multiple sacral nerve roots and after wide resection (Table 5).

Our study has several limitations. First, we present a small cohort with patients treated by different surgeons in different centers over a long time period. However, it represents our nationwide experience with sacral GCTB and to date, only two larger series have been published of which one with comparable follow-up duration [11,19]. Second, treatment was uniform regarding intralesional surgery, but not when it comes to (local) adjuvant treatment, because patients were treated in different centers, each applying their standard treatment of musculoskeletal tumors. Overall recurrence and complication rates became visible with this study, and as both were high, the need for adequate local or systemic therapy is emphasized.

As sacral GCTB is rare and may present in many variations, different multidisciplinary approaches are required that seem favorable for each individual patient; treatment options are proposed in Figure 2. Definitive diagnosis should be obtained by accurate imaging and histopathological confirmation. In all patients, preoperative embolization should be considered to decrease risk of hemorrhage. Although accompanied by a higher recurrence risk, the preferred treatment for all patients is intralesional excision with local adjuvants, as this provides for better postoperative functional and quality of life results. If primary curettage is impossible, e.g. due to soft tissue extension and/or neurovascular involvement, neoadjuvant systemic targeted therapy with denosumab should be considered. Recent results showed that denosumab is effective in facilitating intralesional surgery instead of performing more

mutilating surgery for the most complex cases of GCTB [27,28]. However, it remains unknown whether denosumab also lowers the recurrence risk. Until more becomes known, surgery will remain mainstay of sacral GCTB treatment. If intralesional excision remains impossible after systemic therapy, en bloc resection may be considered as this results in a lower recurrence risk. After surgery, spinopelvic stability should be assessed and reconstruction performed if necessary. Radiotherapy should be restricted to rare cases of multiple recurrent or refractory GCTB in which denosumab is unavailable, contraindicated or ineffective.

In conclusion, recurrence rate after intralesional excision for sacral GCTB was high, especially after isolated curettage. Complications were common and impaired functional outcome. (Local) adjuvant treatment is desired to obtain immediate local control, this would likely result in fewer recurrences and complications and superior functional outcome.

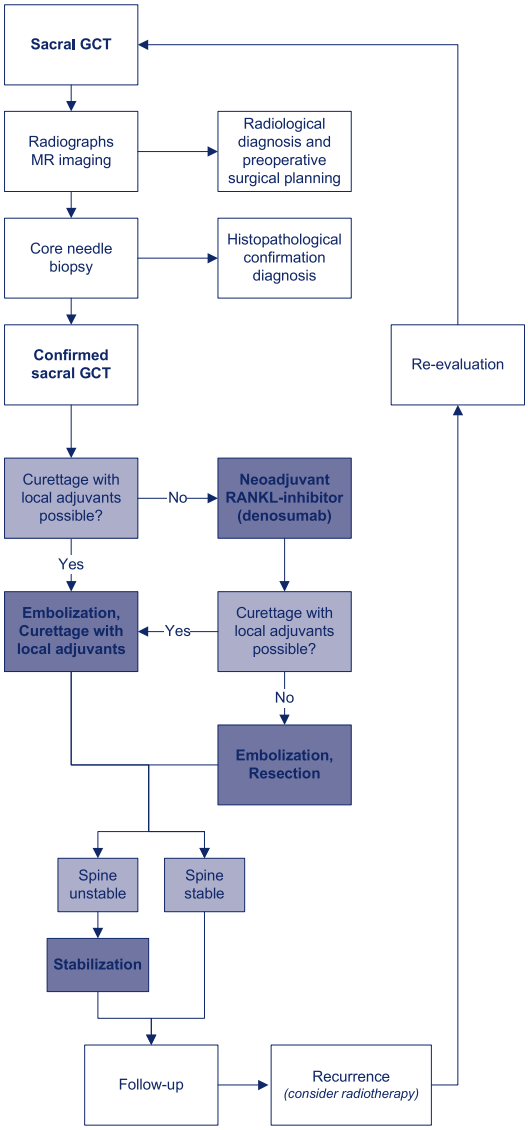

Figure 2 Multidisciplinary treatment recommendations for sacral GCTB. Definitive diagnosis should be obtained by accurate imaging and histopathological confirmation through either preoperative core needle biopsy or intraoperative frozen section. In all patients, preoperative embolization should be considered. Preferred treatment for all patients is intralesional excision. If primary curettage is impossible, e.g. due to soft tissue extension and/or neurovascular involvement, neoadjuvant systemic targeted therapy with denosumab should be considered. This may facilitate intralesional excision by creating a calcified rim around the tumor and its soft tissue component. It is yet unknown whether it also lower recurrence risk and therefore surgery remains mainstay of treatment. If intralesional excision remains impossible after systemic therapy, en bloc resection may be considered. After surgery, spinopelvic stability should be assessed and reconstruction performed if necessary. Radiotherapy should be restricted to rare cases of multiple recurrent or refractory GCTB, and when denosumab is unavailable, contraindicated or ineffective.

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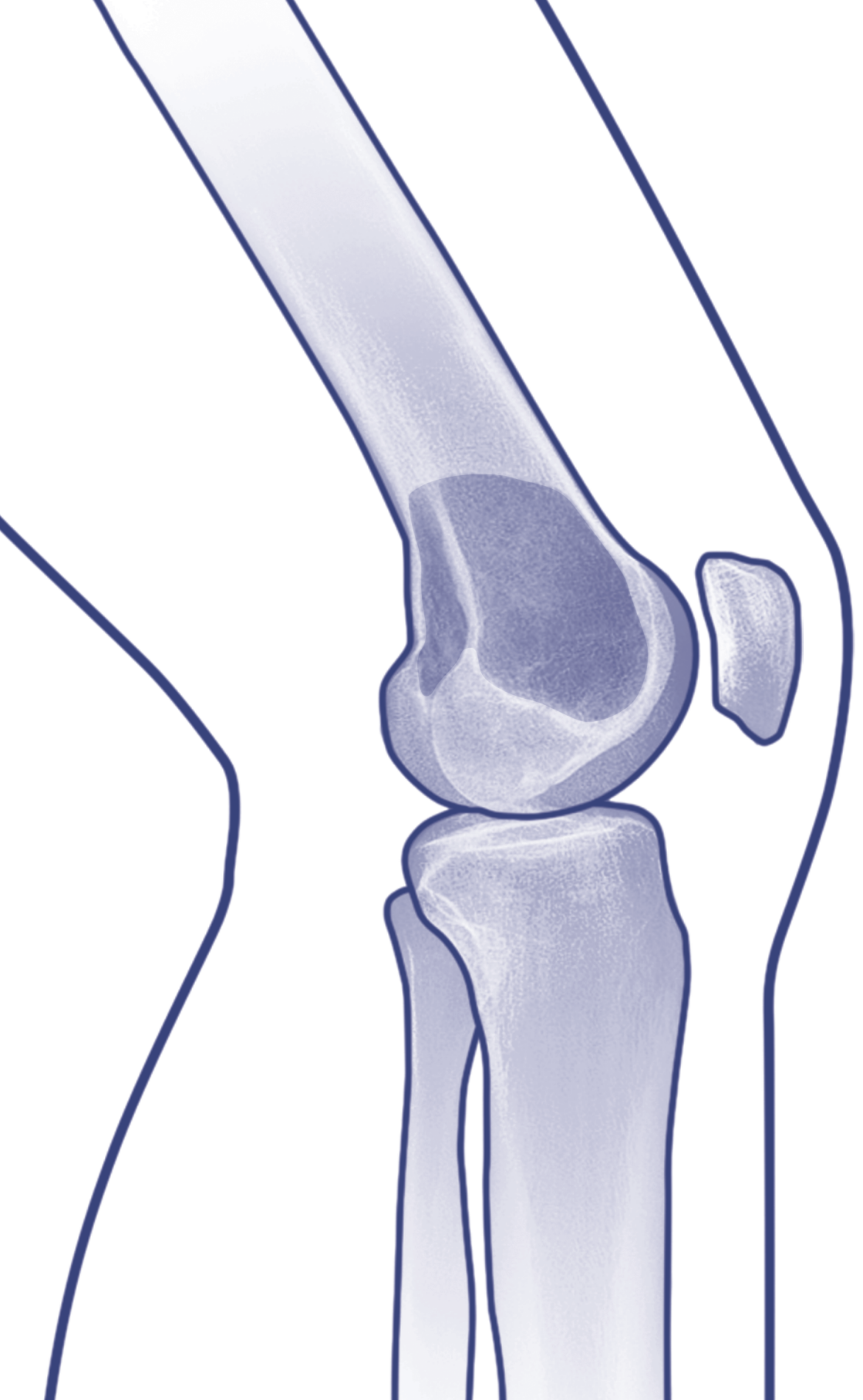

Chapter 7

Soft tissue extension increases the risk of local recurrence after curettage with adjuvants for giant cell tumor of the long bones – A retrospective study of 93 patients

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Abstract

Background Risk factors for local recurrence of giant cell tumor of bone (GCTB) have mostly been studied in heterogeneous treatment groups, including resection and intralesional treatment. The aim of the study was the identification of individual risk factors after curettage with adjuvants in GCTB.

Patients and methods Of 147 patients treated for primary GCTB between 1981 and 2009, 93 patients were included in this retrospective single-center study. All patients were treated with curettage and polymethylmethacrylate (PMMA) with (n=75) or without (n=18) phenol. Mean follow-up was 8 years (range 2–24). Recurrence-free survival was assessed for treatment modalities. Age, gender, tumor localization, soft tissue extension and pathologic fractures were scored for every patient and included in a Cox regression analysis.

Results The recurrence rate after the first procedure was 25 out of 93. Recurrence-free survival for PMMA and phenol and for PMMA alone was similar. Eventually, local control was achieved using one or multiple intralesional procedures in 85 patients. Resection was required in eight patients. A higher risk of local recurrence was found for soft tissue extension (hazard ratio 5; 95% confidence interval 2–12), but not for age below 30, gender, localization (distal radius versus other) or pathologic fracture.

Conclusions Curettage with adjuvants is a feasible first choice treatment option for GCTB, with good oncological outcome and joint preservation. Soft tissue extension strongly increased the risk of local recurrence, whereas age, gender, localization and pathologic fractures did not.

Introduction

Giant cell tumor of bone (GCTB) is aggressive locally with recurrence rates of 27 to 65% after curettage with bone grafting [1,2], 12 to 27% after curettage with adjuvants such as high-speed burr, phenol and polymethylmethacrylate (PMMA) [2-4], and 0 to 12% after *en bloc* resection [2,5]. In clinical practice, the choice of surgical procedure depends mostly on the feasibility of curettage and cementation versus resection, but in part also on the expected risk of local recurrence in individual patients. Cortex destruction, soft tissue extension, pathologic fractures, young age and localization in the distal radius have been suggested to be risk factors for local recurrence [2-8], but these have not been confirmed by others [9-11]. Most studies that aimed at identification of risk factors for local recurrence have included both resection and curettage in risk analyses [2-4,8], which results in a selection bias because of lower recurrence rates after resection.

At our tertiary referral center for musculoskeletal oncology, curettage with phenol and PMMA is the preferred standard treatment for all GCTB. Over 75% of patients with primary or recurrent GCTB presenting at our center underwent curettage with adjuvants; the rest underwent *en bloc* resection. The indications for resection were localization in the axial skeleton or severe joint destruction. In contrast to other studies [4,5,12,13], soft tissue extension and pathologic fracture were not contraindications for intralesional treatment; this is in accordance with extended indications for curettage as described previously [1-3,8,10]. The advantage is avoidance of prosthetic reconstruction at a relative young age. The disadvantage may be an increased risk of local recurrence.

We retrospectively evaluated risk factors for local recurrence and recurrence-free survival with these wide indications in 93 patients with primary GCTB and 30 patients with recurrent GCTB.

Patients and methods

In this retrospective single-center study, we identified 147 patients with primary GCTB who had been treated at our tertiary referral center for orthopedic oncology between 1981 and 2009 (Figure 1). All patients had a minimum follow-up of 2 years. As primary treatment, curettage with adjuvants (n=113; 77%), *en bloc* resection (n=28; 19%) or other treatment (n=6; 4%) was performed. We did

not evaluate patients who were primarily treated with resection (n=28); nor did we evaluate patients primarily treated with curettage without PMMA (n=10), with bisphosphonates (n=2), with denosumab (n=2), with radiotherapy (n=1) or with arterial embolization (n=1) because it was not standard treatment protocol. There was no statistically significant difference in the patient characteristics or tumor characteristics of excluded patients and of those who were included.

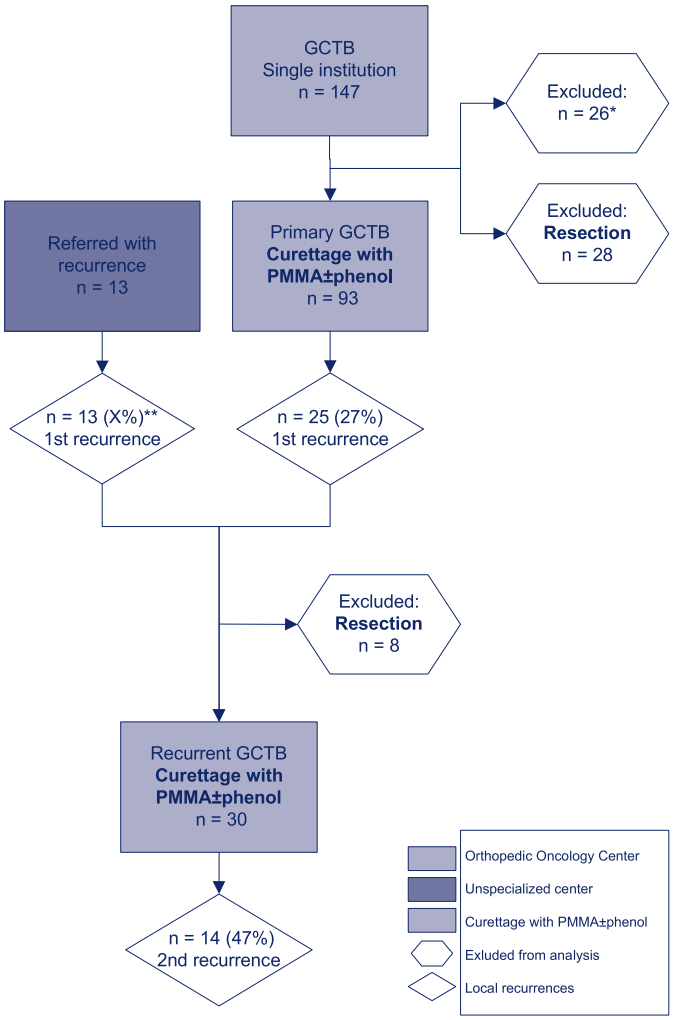

Figure 1 Flowchart of patients with primary and recurrent GCTB

*Excluded are patients primarily treated with curettage without PMMA (n=10), systemic treatment (n=5) or embolization (n=1) or follow-up of less than 24 months (n=10).
**Patients who were primarily treated for GCTB by curettage with adjuvants in a center not specialized in orthopedic oncology and who were later referred with a first recurrence to our Orthopedic Oncology Center for repeat curettage with adjuvants.

We evaluated 93 patients (55 males) who underwent curettage with adjuvants for primary GCTB. Mean age was 33 years (range 11–61). In all patients, PMMA was used as filling of the cavity after curettage. Additional phenol was applied on cavity borders whenever adequate protection of surrounding tissues was possible (n=75).

We also identified 38 patients who developed local recurrence after primary curettage with adjuvants either at our center (n=25) or elsewhere (n=13). Eight patients who underwent resection for a first recurrence were excluded. The other 30 patients underwent re-curettage with adjuvants for recurrent GCTB at our center (17 from our center and 13 referred). Mean age was 35 years (range 18–65). PMMA was used in all 30 patients and additional phenol in 21 of them.

Data were collected from the medical records and they included information on age, gender, tumor localization, soft tissue extension and pathologic fracture (Table 1). We defined soft tissue extension as a complete breakthrough of the cortex and additional extension into adjacent soft tissue (i.e. a tumor mass). Cortex destruction was first assessed on plain radiographs in all patients. Subsequently, extension into the surrounding soft tissues was assessed on MR imaging (unless the tumor was centrally located, confined strictly to bone, and with no cortex destruction in two planes on conventional radiographs). Preoperative MR imaging results were available for 84 patients and preoperative CT results for four patients. At our center, we had had access to an MRI scanner since 1987 but five patients were operated before this date. Nineteen patients had a pathologic fracture at presentation. Soft tissue extension in these cases was classified in the same way as in the other cases; pathologic fracture in itself was not classified as soft tissue extension. Preoperative MR imaging results were available for 17 of 19 patients with a pathologic fracture, preoperative CT results were available for one patient and conventional radiographs alone were available for one patient. Eight of 17 patients with preoperative MR imaging results also had a pathologic fracture and a soft tissue component. Only a fissure was reported in two patients (no soft tissue extension), none or a slight dislocation in 10 patients (three with soft tissue extension) and a moderate to substantial dislocation of the fracture was reported in seven patients (five with soft tissue extension). All the data were complete. Mean follow-up time was 8 years (range 2–24). The follow-up protocol consisted of conventional radiography at 1.5, 3, and 6 months postoperatively, followed

by half-yearly radiographs until 2 years postoperatively, and then radiographs taken annually over the next 10 years. MR imaging was performed at 1, 2, 5, and 10 years.

Table 1 Patient demographics

	Primary GCTB	Recurrent GCTB
	n = 93	n = 30
Sex		
Male	55	9
Female	38	21
Location		
Proximal humerus	3	1
Distal radius	13	5
Proximal femur	2	2
Distal femur	52	13
Proximal tibia	16	8
Distal tibia	5	1
Fibula	2	-
Tumor characteristics		
Soft tissue extension	25	8
Pathologic fracture	19	-
Curettage with adjuvants		
PMMA and phenol	75	21
PMMA	18	9

Statistical analysis

Recurrence-free survival (RFS) of curettage with PMMA with or without phenol was determined (Kaplan-Meier) for primary GCTB (n=93) and recurrent GCTB (n=30). Differences were assessed with log rank test. Time to recurrence was defined as time from primary surgery to the date on which a recurrence was confirmed by biopsy. Risk factors for local recurrence after primary curettage with adjuvants (n=93) were assessed by Cox regression analysis. Age below 30, gender, tumor localization (distal radius versus other), soft tissue extension and pathologic fractures were included. Interaction terms of variables that might interact (soft tissue extension, localization, pathologic fractures and young age) were assessed by successive incorporation in the regression model. There was

some evidence of interaction (interaction with soft tissue extension, $p<0.05$) but the numbers in this series were too small (n=4–10) for reliable estimation of this interaction effect and the results are not reported. Statistical analysis was performed with SPSS.

Results

Twenty-five out of 93 patients with primary GCTB had a local recurrence. Mean time to first recurrence was 19 months (range 4–78). Overall recurrence-free survival rates at 2 and 5 years were 0.82 and 0.74, respectively, and for recurrent GCTB they were 0.63 and 0.45 (Table 2). Four patients died after 4–9 years, all for reasons unrelated to GCTB. None of these patients had local recurrence or metastases at final follow-up. Local control was achieved using one or multiple intralesional procedures in 85 of 93 patients at 5 years postoperatively. Recurrence-free survival was similar in both primary and recurrent tumors that were treated with or without phenol in addition to PMMA (Figures 2 and 3).

Table 2 Recurrence-free survival of primary and recurrent GCTB

	n	recurrence	2-yrs RFS	95%CI	5-yrs RFS	95% CI	*p*-value
Primary							
Curettage with adj.	93	25	0.82	0.73-0.90	0.74	0.65-0.83	
PMMA + phenol	75	20	0.83	0.74-0.91	0.74	0.64-0.84	0.9
PMMA	18	5	0.78	0.59-0.97	0.72	0.51-0.93	
Recurrent							
Curettage with adj.	30	14	0.63	0.45-0.81	0.45	0.25-0.65	
PMMA + phenol	21	9	0.55	0.31-0.79	0.47	0.23-0.72	1.0
PMMA	9	5	0.56	0.23-0.88	0.44	0.12-0.77	

RFS = Recurrence-free survival
Yrs = years
CI = Confidence interval
Adj. = Local adjuvants

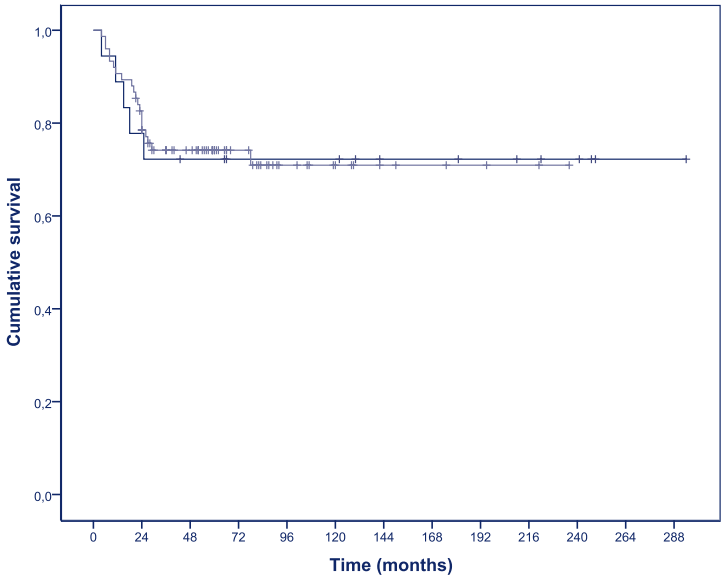

Figure 2 Kaplan-Meier estimated recurrence-free survival of primary GCTB treated with curettage with PMMA and phenol (n=75; light gray) or PMMA alone (n=18; black) ($p = 0.94$).

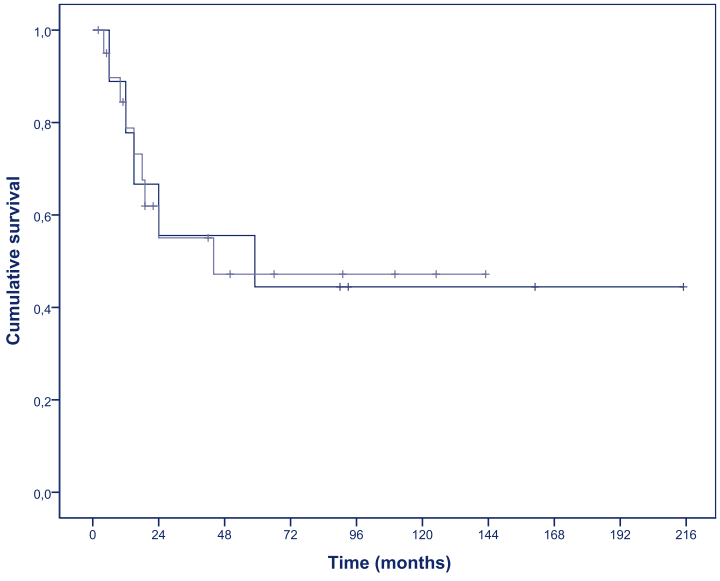

Figure 3 Kaplan-Meier estimated recurrence-free survival of recurrent GCTB treated with curettage with PMMA and phenol (n=21; light gray) or PMMA alone (n=9; black) ($p = 0.99$).

Potential risk factors for local recurrence were soft tissue extension (14 out of 25 recurred) and pathologic fracture (5 out of 19 recurred). For primary GCTB without soft tissue extension, the local recurrence rate was 12 out of 68; the risk of local recurrence was 5 times higher in tumors with soft tissue extension (Table 3). Age below 30, gender, presence of pathologic fracture or localization in the distal radius had no apparent influence on the risk of local recurrence.

Table 3 Potential individual and combined risk factors for recurrence in GCTB

	n	recurrence	HR	95% CI	*p*-value
Potential individual risk factors					
Soft tissue extension	25	14	5	2-12	0.001
Distal radius	13	6	2	0.8-5	0.1
Pathologic fracture	19	5	1.3	0.5-3.5	0.7
Age under 30	46	13	1.4	0.6-3.2	0.4
Gender	93	25	0.8	0.3-1.8	0.6
Local adjuvants					
PMMA	18	5	-	-	-
Phenol and PMMA	75	20	0.8	0.3-2.1	0.6

HR = Hazard ratio
CI = Confidence interval

Discussion

This study demonstrates that curettage with adjuvants is a feasible first choice treatment option for GCTB, even in the case of soft tissue extension or pathologic fracture. We performed intralesional treatment in the majority of GCTB with soft tissue extension, either alone or combined with pathologic fractures. This would explain the relatively high local recurrence rate, but if we only consider GCTB without a soft tissue component, the local recurrence rate is comparable to that reported in the recent literature (Table 4). However, the risk of a second recurrence after repeated curettage was relatively high (47%).

Table 4 Overview of recent studies on risk factors and surgical management of primary GCTB

	Institution	Total	Resection*	No adjuvants*	Phenol + burr*	PMMA*	PMMA + phenol*	PMMA + burr*	PMMA + phenol + burr*	Risk factors
O'Donnell et al. 1994	Single	60	-	-	-	30 (42%, n=13)	-	30 (17%, n=5)	-	Pathological fracture, soft tissue extension
Becker et al. 2008	Multi	256	48 (2%, n=1)	65 (49%, n=32)	-	69 (22%, n=15)	50 (27%, n=13)	-	-	Soft tissue extension***
Balke et al. 2008**	Multi	214	18 (0%)	55 (58%, n=32)	-	52 (36%, n=19)	-	39 (18%, n=7)	42 (12%, n=5)	Soft tissue extension, distal radius***
Kivioja et al. 2008	Multi	294	92 (12%, n=11)	47 (51%, n=24)	-	147 (22%, n=32)	-	-	-	Age***
Klenke et al.2011	Single	118	22 (5%, n=1)	22 (32%, n=7)	32 (34%, n=11)	-	-	1 (n=0)	40 (15%, n=6)	Age***
Current study 2011	Single	93	-	-	-	18 (28%, n=5)	75 (27%, n=20)	-	-	Soft tissue extension

*Number of cases of primary treatment in numbers, with corresponding recurrence rates in percentages and numbers in parentheses.
**In this study, H_2O_2 was used as alternative for phenol.
***Risk analysis performed using the whole patient population including resections.

The survival rates were similar for curettage with PMMA and phenol and for curettage with PMMA alone. The beneficial effect of using additional phenol has been debated [4,8]. Phenol may have a limited additive effect on the recurrence rate; however, the risk-reducing effect of PMMA may be of greater importance.

We found a 5-times higher risk of recurrence of tumors with soft tissue extension. This confirms the previously reported increase in recurrence risk with soft tissue extension: hazard ratio 2.7 (p=0.007) [3] and likelihood ratio 4.0 (p=0.05) [2]. This can be explained by technical difficulties in the complete removal of tumor tissue when performing intralesional treatment and the lack of adequate applicable local adjuvants, in the presence of soft tissue extension. Previously proposed risk factors—age below 30, localization in distal radius, or pathologic fracture—could not be identified as risk factors for local recurrence in the present study. This may be due to the fact that most studies analyzing risk factors for local recurrence have included both intralesional treatment and resection, with a lower expected overall recurrence rate [2-4,8].

Young age has been suggested to be a risk factor [4,8], but it may in part be explained by selection bias. Younger patients could have been selected to have intralesional treatment instead of resection. We could not confirm localization in distal radius as a risk factor for local recurrence, as has been suggested previously. Balke *et al.* [2] found that 8 out of 9 GCTB located in the distal radius recurred, as compared to 6 out of 13 in our study. However, six of their cases had soft tissue extension and in five cases no PMMA was applied, which may have increased the local recurrence risk. Finally, we found no correlation between recurrence risk and pathologic fracture as reported by O'Donnell *et al.* [6]. This indicates that curettage with adjuvants could be a feasible treatment option for GCTB with a pathologic fracture [14,15].

In the near future, the treatment strategy could be changed given promising results from systemically targeted neoadjuvant therapy with RANKL inhibitor denosumab [16,17]. With this therapy, calcification of affected soft tissues occurs, which may extend the indications for curettage with adjuvants.

In summary, curettage should at least include PMMA as local adjuvant, and the role of phenol after curettage with PMMA as local adjuvant is questionable. The recurrence risk after curettage with adjuvants is only increased with soft tissue extension—but not with age below 30, pathologic fracture or localization in distal radius.

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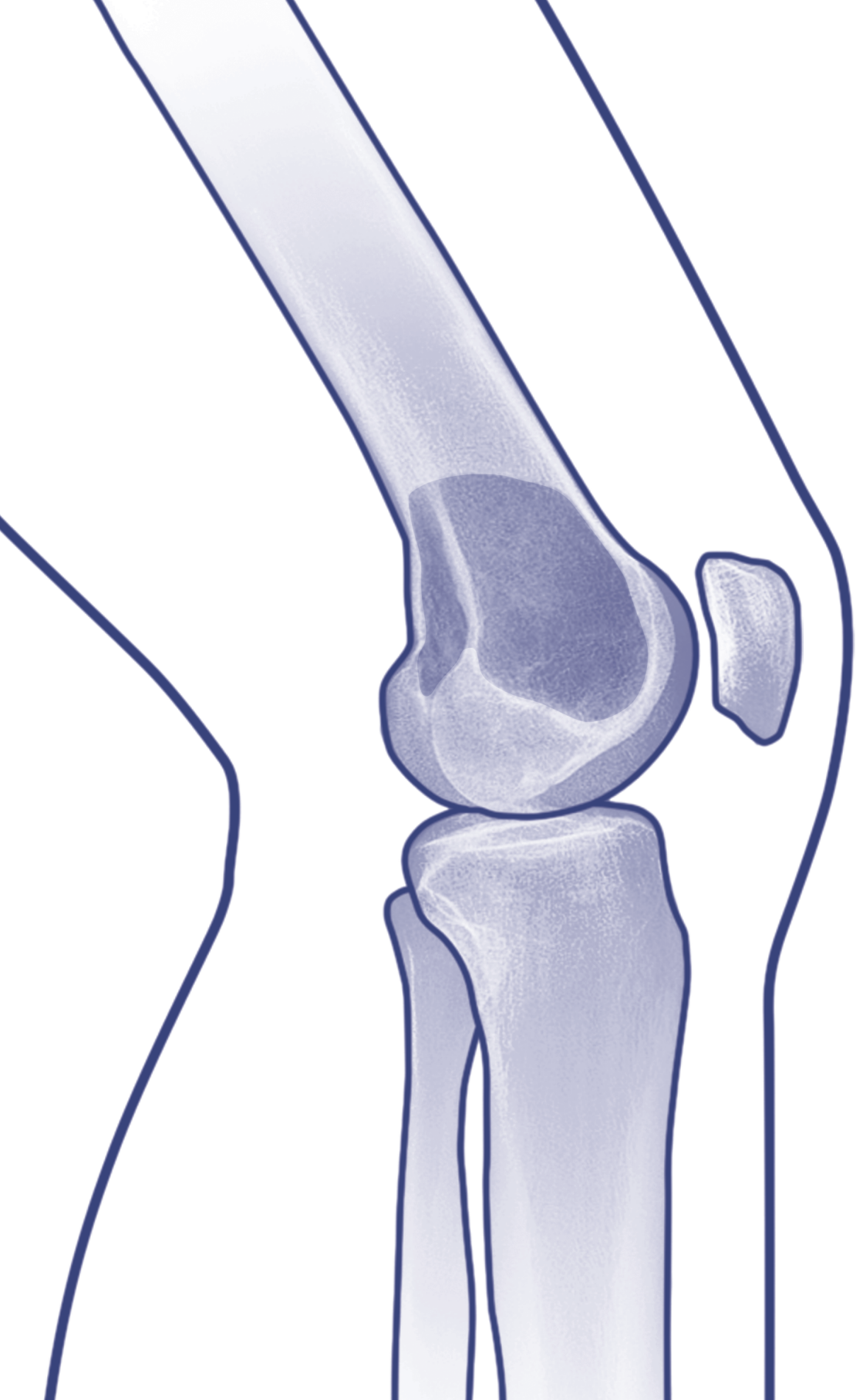

Chapter 8

Mid-term outcome after curettage and polymethylmethacrylate for giant cell tumor around the knee: Higher risk of radiographic osteoarthritis?

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Abstract

Background It has been suggested that, when a patient has giant cell tumor of bone (GCTB), subchondral bone involvement close to articular cartilage and a hyperthermic reaction from polymethylmethacrylate (PMMA) are risk factors for the development of osteoarthritis. We determined the prevalence, risk factors, and clinical relevance of osteoarthritis on radiographs after curettage and application of PMMA for the treatment of GCTB around the knee.

Methods This retrospective single-center study included 53 patients with GCTB around the knee treated with curettage and PMMA between 1987 and 2007. The median age at the time of follow-up was 42 years (range 23-70 years). There were 29 women. Radiographic evidence of osteoarthritis was defined, preoperatively and postoperatively, as Kellgren and Lawrence grade 3 or 4 (KL3-4). We studied the influence of age, sex, tumor-cartilage distance, subchondral bone involvement (≤3 mm of residual subchondral bone), subchondral bone grafting, intra-articular fracture, multiple curettage procedures, and complications on progression to KL3-4. Functional outcomes and quality of life were assessed with the Short Form-36 (SF-36), Musculoskeletal Tumor Society (MSTS) score, and Knee injury and Osteoarthritis Outcome Score (KOOS).

Results After a median duration of follow-up of 68 months (range 60-285 months), six patients (11%) had progression to KL3, two (4%) had progression to KL4, and one had preexistent KL4. No patient underwent total knee replacement. The hazard ratio for KL3-4 was 9.0 (95% confidence interval [CI]=2.0-41; p=0.004) when >70% of the subchondral bone was affected and 4.2 (95%CI=0.84-21; p=0.081) when the tumorcartilage distance was ≤3 mm. Age, sex, subchondral bone-grafting, intra-articular fracture, multiple curettage procedures, and complications did not affect progression to KL3-4. Patients with KL3-4 reported lower scores on the KOOS symptom subscale (58 versus 82; p=0.01), but their scores on the other KOOS subscales, the MSTS score (21 versus 24), and the SF-36 (76 versus 81) were similar to those for the patients with KL0, 1, or 2 (KL0-2).

Conclusion Seventeen percent of patients with GCTB around the knee had radiographic findings of osteoarthritis after treatment with curettage and PMMA. A large amount of subchondral bone involvement close to articular cartilage increased the risk for osteoarthritis. The function and quality of life

of the patients with KL3-4 were comparable with those for the patients with KL0-2, suggesting that radiographic findings of osteoarthritis at the time of intermediate follow-up had a modest clinical impact. Treatment with curettage and PMMA is safe for primary and recurrent GCTB, even large tumors close to the joint.

Introduction

Giant cell tumor of bone (GCTB) is a benign primary bone tumor with a locally aggressive character. Usually, giant cell tumor occurs between thirty and fifty years of age [1-3]. GCTB is usually localized to the meta-epiphyseal area of long bones; 50% are located around the knee [1]. Approximately 1% to 4% of patients develop benign pulmonary metastases [1,4-8].

Standard treatment for GCTB consists of extended curettage and chemical adjuvants such as phenol, alcohol, hydrogen peroxide, argon laser, or liquid nitrogen [3,9-15]. The remaining cavity can be left empty awaiting new bone formation during partial immobilization [16-18], or it may be filled with cancellous bone graft [2,19,20]. However, reported recurrence rates following both options are high (27% to 65%) [1,10]. At present, the most commonly used filling material is polymethylmethacrylate (PMMA), which is associated with a lower recurrence risk (12% to 34%), provides immediate mechanical support, and facilitates easy and early detection of local recurrences [9,10,21]. PMMA is therefore widely recommended to fill the cavity left after curettage [3,9-13,21]. However, it has been suggested that curettage and PMMA may result in secondary osteoarthritis, although risk factors for this development remain unclear (Figure 1) [2,13,17,22-29]. PMMA is a thermal adjuvant increasing surgical margins up to 1.5 to 2 mm in cancellous bone and 0.5 mm in cortical bone [23-25]. Degenerative changes may be caused by this hyperthermic polymerization of PMMA [13,17,23,24], but a close relation of the tumor with articular cartilage and extensive subchondral bone involvement may be more important risk factors [22,25-27]. In addition, often large volumes of PMMA are used after curettage for GCTB, with possible increased thermal damage [24]. Finally, intra-articular pathologic fracture [28,29] and repeated curettage with application of PMMA for recurrences are also believed to increase the risk for degenerative changes [2,28].

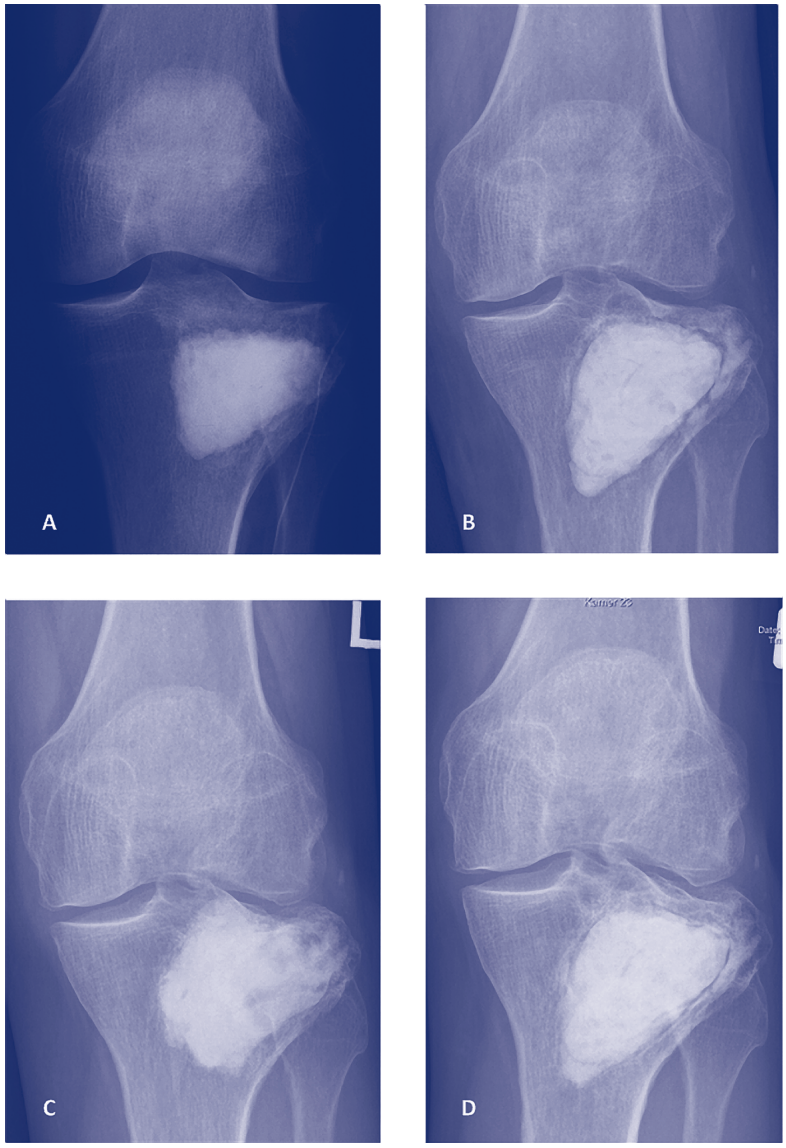

Figure 1 (A) Anteroposterior radiograph of a forty-two-year-old man demonstrates KL0 after curettage with application of subchondral bone graft and PMMA for primary GCTB in the proximal part of the tibia. (B) Follow-up radiographs demonstrate KL1-2 after fifty-five months, (C) KL3 after sixty-seven months and (D) KL4 after ten years. This patient underwent repeated curettage and application of PMMA for three recurrences. There was no evidence of GCTB at the time of final follow-up.

Therefore, we evaluated (1) the prevalence of radiographic findings of osteoarthritis after treatment for GCTB around the knee with curettage and PMMA; (2) which patient, treatment, and tumor characteristics are associated with the risk of progression to osteoarthritis; and (3) the clinical relevance, as determined with functional outcome and quality-of-life scores, of radiographic findings of osteoarthritis.

Materials and methods

We retrospectively evaluated 68 patients treated with curettage and PMMA for GCTB in the distal part of the femur or the proximal part of the tibia from 1987 to 2007. These patients were identified from the total group of 189 consecutive patients who had been treated for GCTB at our tertiary referral center during that period. The minimum duration of follow-up was five years. Fifteen patients were excluded: nine patients had missing preoperative radiographs, four patients had been treated with resection and endoprosthetic reconstruction for recurrence, and two patients had died of causes unrelated to the GCTB, all within five years after index surgery. We included 53 patients (29 of whom were female) with GCTB around the knee, with a median duration of follow-up of 86 months (range 60-285 months). The median age at the index surgery was 32 years (range 16-62 years). Two patients had multicentric GCTB. None of the included patients developed pulmonary metastases. No patient was recalled specifically for this study. This study was approved by the institutional medical ethics committee.

The initial surgery was performed by fellowship-trained oncological orthopaedic surgeons. At our center, intralesional treatment was preferred for GCTB even in the presence of soft-tissue extension and intra-articular pathologic fracture [30,31]. *En bloc* resection was almost never performed as primary treatment for GCTB. Standard treatment consisted of curettage, local application of phenol and ethanol, and rinsing the cavity with high-speed pulse lavage with saline solution. During the evaluated time frame, high-speed burring was not standard at our center. In eight patients, no phenol was applied as adequate protection of surrounding tissues was impossible due to cortical defects. Subchondral cancellous bone grafting was considered after curettage when <10 mm of subchondral bone remained, and was performed in 25 patients. The cavity was

filled with PMMA in all patients. Cementation was performed under tourniquet control. The cement volume depended on the size of the GCTB and averaged 30 to 60 mL. Postoperative treatment consisted of functional mobilization and immediate weight-bearing for most patients. Those with a pathologic fracture were permitted only partial weight-bearing for 6 to 12 weeks. There were no restrictions on sports or activities six months postoperatively. The follow-up protocol consisted of conventional radiographs after 1.5, 3, 6, 12, 18 and 24 months and yearly up to ten years to detect recurrences and complications. Chest radiography to detect pulmonary metastases and magnetic resonance imaging (MRI) were performed after one, two, five, and ten years.

Table 1 Patient demographics

	Number	Median	Mean	Range
Age at primary intervention *(yr)*	53	32	34	16-62
Age at latest follow-up *(yr)*	53	42	43	23-70
Follow-up *(mo)*	53	86	120	60-285
Time to local recurrence *(mo)*	15	21	57	6-217
	Mean	Range	Number	Percent
Localization				
Distal part of femur			38	72
Proximal part of tibia			15	28
Tumor-cartilage distance *(mm)*	4.9	0-23	53	100
< 1 mm			15	28
1-3 mm			11	21
3-5 mm			5	9
> 5 mm			22	42
Subchondral bone involvement*	49	7-100	26	49
<30%			8	31
30-49%			6	23
50-69%			5	19
≥70%			7	27
Intra-articular pathologic fracture			4	8
Soft-tissue extension			11	21
Preoperative KL grade**				
KL0			33	62
KL1			18	34
KL2			1	2
KL3			0	0
KL4			1	2

*The amount of subchondral bone involvement was defined as the area of the involved knee compartment in which ≤3 mm of subchondral bone thickness remained. Thus, for example, <30% indicates that ≤3 mm of subchondral bone thickness remained in <30% of the involved knee compartment. **KL = Kellgren and Lawrence.

Medical records and radiographs were reviewed to determine age, sex, localization, tumor-cartilage distance, subchondral bone involvement, intra-articular pathologic fractures, subchondral bone grafting, multiple curettage and PMMA procedures for recurrence, complications, preoperative and postoperative Kellgren and Lawrence (KL) grades, and duration of follow-up (Table 1). All data were complete.

KL grading was used to assess osteoarthritis on preoperative and postoperative anteroposterior non-weight-bearing radiographs [32]. Two observers each performed the grading twice. When three of four KL grades corresponded, that grade was assigned. When the two observers assigned different KL grades, consensus was reached. We defined KL grade-3 or 4 (KL3-4) osteoarthritis [32-34] as moderate to pronounced osteophyte formation, definite joint space narrowing, and subchondral sclerosis (Table 2; Figure 1). The time until signs of osteoarthritis appeared was determined on follow-up radiographs.

Table 2 Kellgren and Lawrence grading for radiographic evidence of osteoarthritis

Grade	Description	Radiographic findings of osteoarthritis
KL0	Normal joint	None
KL1	Possible osteophytes, no joint space narrowing or sclerosis	Mild
KL2	Definite osteophytes, possible joint space narrowing and sclerosis	Mild
KL3	Moderate osteophytes, definite joint space narrowing, some sclerosis, and possible bone contour deformity	Moderate
KL4	Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone contour deformity	Severe

We assessed the influence of age, sex, follow-up duration, tumor-cartilage distance, subchondral bone involvement, subchondral bone grafting, intra-articular pathologic fractures, number of curettage and PMMA procedures, and complications on osteoarthritis development. The amount of subchondral bone involvement was defined as the area of the involved knee compartment in which ≤3 mm of subchondral bone thickness remained (Figure 2); this was calculated as a percentage with a method similar to that described by Chen et al. [26]. Measurements were performed once by each of two observers.

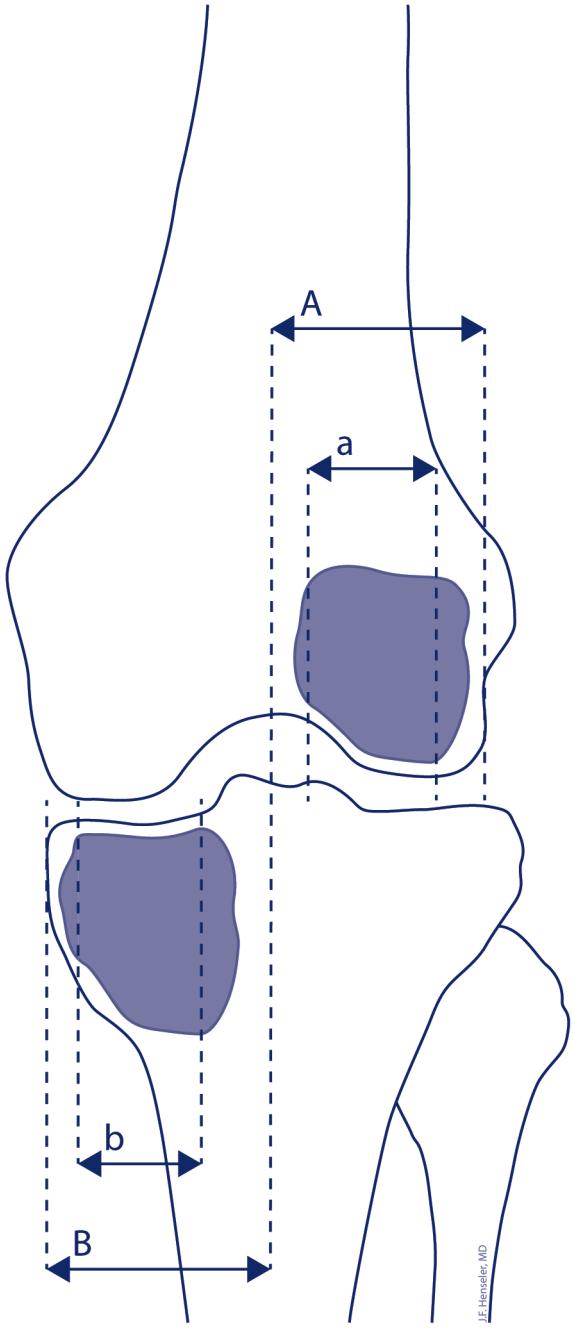

Figure 2 The amount of subchondral bone involvement by the GCTB was defined as the area of the femoral or tibial condyle in which there was ≤3 mm of subchondral bone thickness remaining. This was calculated, with a method similar to that described by Chen et al. as a percentage: (a/A) x 100% or (b/B) x 100% [26].

Functional outcomes and quality of life were evaluated with the Musculoskeletal Tumor Society (MSTS) score, Knee injury Osteoarthritis Outcome Score (KOOS), and Short Form-36 (SF-36) [35-37]. Questionnaires were obtained by mail at a mean of 11 years (range 5-25 years) after the initial surgery. Nine patients did not return questionnaires, so patient-reported outcome measures were available for 44 patients (83%).

Statistical analysis

Kaplan-Meier methodology was applied to assess the probability of progression to KL3-4. As no patient died, this probability can be estimated as one minus survival function. Univariate and multivariate (for relevant variables) Cox regression was performed to determine risk factors for radiographic osteoarthritis. Chi-square and Fisher exact tests were employed for dichotomous variables whereas nonparametric Mann-Whitney U tests were used for numerical data. Cohen's kappa statistic was used to determine interobserver and intraobserver agreement for KL3-4 and interobserver agreement for subchondral bone involvement. Outstanding agreement was defined as $\kappa>0.80$; substantial agreement as $\kappa=0.60$-0.79; moderate agreement as $\kappa=0.40$-0.59; and poor agreement as $\kappa<0.40$ [38,39].

Results

Six patients (11%) had progression from KL0-1 to KL3 and two (4%) from KL0-1 to KL4, the signs of which appeared on postoperative radiographs after a median of 57 months (mean 98 months; range 33-285 months); one patient had preexistent KL4. At the time of writing, none of these patients had required total knee arthroplasty. Figure 3 shows that the probability of progression to KL3-4 has not reached a plateau phase by the time of this study, indicating that the prevalence of KL3-4 grades may increase with time. In all patients, degenerative changes were localized to the involved knee compartment. Eighty-three percent of the patients did not develop radiographic findings of osteoarthritis: for 20 patients (38%), the grade remained stable at KL0-2; 14 patients (26%) had progression from KL0 to KL1; five (9%) had progression from KL0 to KL2; and five (9%) had progression from KL1 to KL2. Cohen's

kappa statistic for KL3-4 was outstanding for interobserver agreement, with κ=0.90 (95% confidence interval [CI]=0.76-1.0; p<0.001); it was outstanding for intraobserver agreement, with κ=0.83 (95%CI=0.66-1.0; p<0.001), for one observer and substantial, with κ=0.76 (95%CI=0.53-0.99; p<0.001), for the other [38,39].

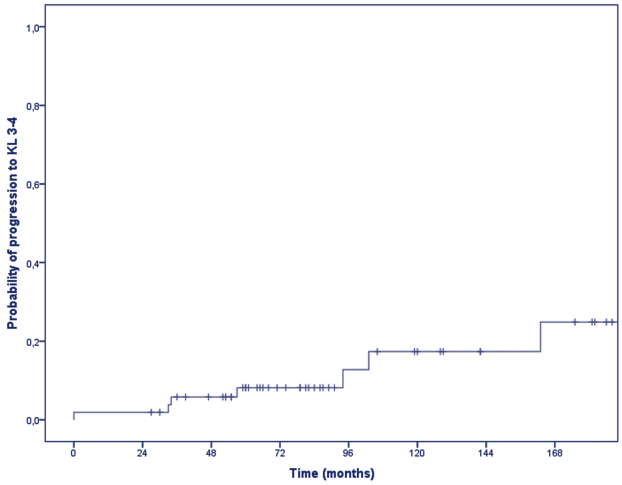

Figure 3 Kaplan Meier one minus survival curve of the probability of progression to KL3-4, which was 8% at five years and 18% at ten years after curettage and application of PMMA for GCTB around the knee joint.

In 26 patients, ≤3 mm of subchondral bone remained after curettage; their mean subchondral bone involvement was 49% (range 7%-100%). Sixteen of these patients were treated with subchondral bone graft. The mean subchondral bone involvement was 56% (range 10%-100%) in patients treated with subchondral bone graft and 38% (range 7%-85%) in patients not treated with subchondral bone graft (p=0.007). Six of the 16 patients who received bone graft and one of the ten patients who did not receive bone grafts developed radiographic evidence of osteoarthritis (KL3-4). When more subchondral bone was affected, the risk of development of KL3-4 increased, with a hazard ratio (HR) of 18 (95%CI=2.4-140; p=0.005) (Table 3). This risk was most apparent when >70% of the subchondral bone was involved by giant cell tumor, with an HR of 9.0 (95%CI=2.0-41, p=0.004). The HR for a tumor-cartilage distance of ≤3 mm was 4.2 (95%CI=0.84-21; p=0.081). Fifteen patients (28%)

Table 3 Risk factors for progression of radiographic findings of osteoarthritis after curettage with PMMA for giant cell tumor around the knee

	Number	KL3-4		Hazard ratio	95% confidence interval		p value
		n	%		lower	upper	
Univariate Cox regression analysis							
Affected subchondral bone							
%	26	7	27	18	2.4	140	0.005
>70%	7	4	57	9.0	2.0	41	0.004
>50%	12	5	42	4.9	1.2	20	0.032
>30%	18	6	33	3.7	0.89	16	0.073
Tumor-cartilage distance							
0-1 mm	15	5	33	12	1.4	103	0.024
1-3 mm	11	2	18	5.4	0.47	63	0.18
0-3 mm	26	7	27	4.2	0.84	21	0.081
Longer distance to articular cartilage (mm)	53	9	17	0.73	0.54	0.99	0.045
Complications	7	2	29	3.2	0.58	17	0.18
Subchondral bone grafting	25	7	28	2.5	0.49	13	0.28
Follow-up >10 years	21	7	33	1.5	0.24	10	0.66
Multiple curettage and PMMA procedures	15	3	19	1.2	0.56	2.6	0.63
Age at the time of follow-up >60 years	8	2	25	0.34	0.04	3.9	0.41
Female sex	29	3	10	0.22	0.04	1.1	0.063
Multivariate Cox regression analysis							
Affected subchondral bone (%)	-	-	-	18	2.3	148	0.006
Multiple curettage and PMMA procedures	-	-	-	1.0	0.34	3.0	1.0
Affected subchondral bone (%)	-	-	-	19	2.4	149	0.005
Age at the time of final follow-up	-	-	-	1.0	0.95	1.1	0.69
Affected subchondral bone (%)	-	-	-	19	1.9	186	0.013
Subchondral bone grafting	-	-	-	0.97	0.15	6.3	0.98
Affected subchondral bone (%)	-	-	-	16	2.1	118	0.007
Complications	-	-	-	2.4	0.42	14	0.33

underwent repeat curettage and application of PMMA because of recurrences (nine had two repeat curettage procedures, four had three, and two had four). Three of the 15 patients with repeat curettage had KL3-4 at the time of follow-up. The prevalence of KL3-4 in patients with repeat curettage was not higher than that in the patients with a single surgical intervention (six of 38; p=0.63). The recurrence rate was comparable between the patients treated

with subchondral bone graft and PMMA (nine of 25) and those treated with PMMA alone (six of 28) (p=0.36). Of the nine patients with recurrence after subchondral bone grafting, only two had the recurrence in the subchondral area; the other recurrences were at the PMMA-bone junction.

There were seven complications: three patients had pain, two had postoperative fracture, one had pseudoarthrosis, and one had infection. In all cases, the PMMA was replaced with bone graft. Two of these patients had KL3-4 at the time of follow-up; one underwent high tibial osteotomy to correct varus deformity after fracture.

An age at the time of final follow-up of more than 60 years, a follow-up duration of more than ten years, female sex, and intra-articular fracture did not significantly influence the development of KL3-4 at the time of follow-up (Table 3). Cohen's kappa statistic for interobserver agreement on subchondral bone involvement was substantial with κ=0.76 (95%CI=0.58-0.94; p<0.001) [38,39].

The functional outcome and quality of life were compared between different KL grades. There were no data from the one patient with preexistent KL4. Patients with KL3-4 reported lower scores only on the KOOS symptom subscale compared with patients with KL0-2 (p=0.01). The scores on the other KOOS subscales, MSTS, and all SF-36 subscales were similar between groups (Table 4). Patients with KL4 reported lower scores only on the KOOS sports/recreation subscale when compared with patients with KL0-3 (p=0.044).

Discussion

The intralesional treatment of GCTB with curettage, local adjuvants, and PMMA was hypothesized to increase the risk for degenerative changes [13,17,23,24]. A close relation with the articular cartilage, extensive subchondral bone defects, and larger tumor size, all characteristic of GCTB, are the most important factors for the development of osteoarthritis [22,24-27]. Additionally, intra-articular pathologic fractures [28,29] and multiple curettage and PMMA procedures have also been mentioned as possible risk factors [2,28]. In summary, risk factors for knee osteoarthritis after this surgical procedure remain unclear. Furthermore, quantification of degenerative changes after treatment for GCTB around the knee was presented in only two prior studies [28,40]. Therefore,

Table 4 Patient and tumor characteristics, functional outcomes, and quality of life of patients with and without radiographic findings of osteoarthritis at the time of final follow-up

	KL0-2		KL3-4		
	mean	**range**	**mean**	**range**	**p**
Age at the time of follow-up *(yr)*	42	23-67	51	37-70	0.034
Duration of follow-up *(mo)*	107	60-283	184	60-285	0.011
Tumor-cartilage distance *(mm)*	5.6	0-23	2.1	0-6.9	0.037
Subchondral bone involvement *(%)*	42	7-85	68	28-100	0.009
Number of curettage and PMMA procedures	1.4	1-4	1.6	1-4	0.80
MSTS score	24	11-30	21	16-30	0.094
KOOS	76	30-99	61	32-99	0.05
Pain	84	39-100	75	28-100	0.26
Symptoms	82	46-100	58	32-100	0.01
Activities of daily living	89	35-100	84	62-100	0.20
Sports / recreation	59	5-100	34	0-100	0.058
Quality of life	67	0-100	52	19-94	0.078
SF-36	81	42-95	76	48-99	0.38
Physical functioning	78	30-100	61	40-100	0.33
Role limitations due to physical problems	85	0-100	72	0-100	0.35
Bodily pain	86	45-100	73	45-100	0.08
General health	73	10-100	72	25-100	0.92
Vitality	71	30-100	82	50-100	0.092
Social functioning	90	38-100	84	38-100	0.54
Role limitations due to emotional problems	92	0-100	96	67-100	0.85
Mental health	79	52-100	87	72-100	0.21

KOOS = Knee injury Osteoarthritis Outcome Score, MSTS = Musculoskeletal Tumor Society, and SF-36 = Short Form 36

we determined the prevalence of radiographic findings of osteoarthritis after curettage and application of PMMA for giant cell tumor around the knee, risk factors for progression to KL3-4 after this surgical procedure, and the functional outcomes and quality of life following the procedure.

Seventeen percent of patients had KL3-4 after curettage and application of PMMA for GCTB around the knee, a ten-fold increase compared with age-matched cohorts (0.3% to 1.8%) of the general population [34]. In the literature, the prevalence of osteoarthritis after curettage and application of PMMA has ranged from 4% to 25% in the upper and lower extremities [2,3,13,17,18,22,28,41,42] (Table 5). At the time of writing, none of our patients had required total knee replacement.

Table 5 Literature overview of degenerative changes after curettage with polymethylmethacrylate for giant cell tumor around the knee

Study	Year	n	Surgical treatment			Recurrence rate		Degenerative changes		Complications		Functional outcome	Duration of follow-up
				n	(%)	n	(%)	n	(%)	n	(%)		mean (range)
Bini et al. (1)	1995	28*	Curettage, burr, H_2O_2, PMMA	28	100	1	4	4**	11	1 pain PMMA remnants	4	32 patients good / excellent MSTS(93)**, ***	5 (2-16)
Wada et al. (2)	2002	14*	Curettage, burr, phenol, PMMA	14	100	1	7	1†	7	1 stress fracture	7	-	4 (2-16)
Ward et al. (3)	2002	14	Curettage, burr, phenol, PMMA	13	93	1	8	3††	23	1 pseudoarthrosis 1 pain PMMA remnants	15	6 patients good / excellent function***	5 (1-10)
			Curettage, burr, BG	1	7	-	-	-	-	-	-		
Szalay et al. (4) †††	2006	64*	Curettage, PMMA	36**	45	-	-	7**	20	-	-	30 patients: MSTS(87) mean 32; SF-36 mean 80	7 (4-12)
			Curettage, BG	44**	55	-	-	7**	16	-	-	41 patients: MSTS(87) mean 32; SF-36 mean 80	
Suzuki et al. (5)	2007	30	Curettage, PMMA	12	40	10**	33	3	25	4 postoperative fractures **	-	-	5 (2-10)
			Curettage, BG	18	60			7	39		-	-	
Vult von Steyern et al. (6)	2007	9	Curettage, PMMA	9	100	4	44	1†	11	1 pain PMMA remnants 1 postoperative fracture	22	LKS mean 92 (83-100)	11 (6-16)
Fraquet et al. (7)	2009	26*	Curettage, burr, PMMA	26	100	7	23	1	3	1 infection	3	MSTS(93) mean 28 (26-30)	6 (0.5-13)
Gaston et al. (8)	2011	180*	Curettage, burr, PMMA	64	36	12**	14	11§	17	4 postoperative fractures 2 infections 1 neuroma**	11	-	6 (0.2-27)

			Curettage, BG	116	64	73 **	30	3§§	3	4 postoperative fractures 3 ulnar abutment 2 pain 1 infection 1 neuroma**	9	-		
Present study	2013	53	Curettage, phenol, PMMA	53	100	15	28	KL3: 6 KL4: 3	11 6	3 pain PMMA remnants 2 postoperative fractures 1 pseudoarthrosis 1 infection	13	KL3-4: KOOS mean 61; MSTS(93) mean 21; SF-36 mean 76 KL0-2: KOOS mean 76; MSTS(93) mean 24; SF-36 mean 81	10 (5-24)	

*Only patients with GCT around the knee are listed in this table
**Number given for total group and not specified for GCT around the knee
***Not definition of *good* and *excellent*
†This patient presented had intra-articular pathologic fracture
††One patient underwent total knee replacement
†††This study compared degenerative changes after curettage with either bone grafts or PMMA. The authors controlled for confounding by excluding GCT with potential risk factors for secondary osteoarthritis (e.g. pathologic fractures, complications and recurrences).
§Eight patients underwent endoprosthetic replacement and three patients total knee replacement
§§Three patients underwent total knee replacement
PMMA – polymethylmethacrylate, BG – bone grafts, LKS – Lysholm Knee Score, MSTS – Musculoskeletal Tumor Society score, SF-36 – Short-Form Health Survey 36, OA – osteoarthritis

In our study of GCTB treated with curettage and PMMA, tumor size and proximity to joint surface were strongly associated with radiographic findings of osteoarthritis, confirming earlier results [24-27]. The risk of arthritis was increased nine-fold when >70% of the subchondral bone within 3 mm of articular cartilage was affected. If ≤3 mm of cancellous bone is spared by tumor, both the subchondral bone layer and articular cartilage can be exposed to necrotic effects of curettage, phenol application, and PMMA polymerization [25]. Along with others, we could not confirm whether the risk of osteoarthritis could be attributed to the use of PMMA, intralesional treatment, or characteristics of the GCTB, as there was no control group in this study [3]. Szalay et al. compared degenerative changes in two groups, treated with cement or bone graft, and found that the risk of osteoarthritis was increased for the bone graft group in the first two postoperative years, until full incorporation of the bone graft, and was increased in the PMMA group thereafter [22]. Placing subchondral bone graft in large subchondral bone defects may protect cartilage from degenerative changes by increasing the distance between the articular cartilage and the bone cement, thus creating a buffer against the thermal effects of PMMA on the joint cartilage [2,17,22]. In the present study, subchondral bone graft was used in patients with subchondral bone defects close to the joint, but we found no decrease in the prevalence of osteoarthritis, probably because the subchondral defects were larger in the patients treated with bone graft. These patients had a higher a *priori* risk for developing KL3-4 osteoarthritis compared with patients with less tumor involvement of subchondral bone. This suggests that articular damage may be caused by the curettage itself or by tumor characteristics rather than by thermal damage from PMMA; however, without a control group, this remains uncertain. Furthermore, it was hypothesized that recurrences would be more likely to appear at the site of bone grafting because of absent thermal effects of PMMA, but we could not confirm this finding. Repeat curettage and PMMA procedures for recurrences have been suggested to increase the risk of osteoarthritis [2,28], but that was not found in our series. The relatively high recurrence rate in our study may partly be explained by the fact that we did not perform extended curettage including high-speed burring during the evaluated time frame. Now, high-speed burring is performed whenever it is technically possible. However, the largest confounder of the high recurrence rate is our wide indication for curettage, including the majority of patients with soft-tissue extension and pathologic fracture. *En bloc* resection is rarely

the primary treatment for GCTB at our center [30,31]. Intra-articular pathologic fractures have also been suggested to increase the risk for osteoarthritis, but we could not confirm that finding [28,29]. Finally, we found no association between osteoarthritis and sex, age over sixty years, follow-up longer than ten years, or complications, but most patients were relatively young and osteoarthritis may appear with longer follow-up [34].

The functional outcome and quality-of-life scores were comparable between the patients with KL3-4 and those with KL0-2, and quality of life was comparable with that of age-matched cohorts of the general population [37]. Despite radiographic evidence of osteoarthritis in a small group of our patients, it is likely not a clinical concern at the time of mid-term follow-up. Yet this clinical relevance may increase with time, and longer follow-up is required. The discrepancy between the degree of osteoarthritis and clinical symptoms was found in 33% of patients with osteoarthritis in a previous study [34]. Other investigators have reported similar functional results and quality of life after curettage with and without PMMA [3,12,13,22,26], but no previous study to our knowledge compared functional results and quality of life between patients with and those without osteoarthritis after curettage and PMMA. Only Chen et al. demonstrated a decrease of 3% in the MSTS score for every 10% increase in subchondral bone involvement [26].

Since the risk of osteoarthritis was not increased after repeat curettage and application of PMMA, we concluded that PMMA is a safe material and that curettage is a good treatment option for primary and recurrent GCTB. When progression to KL3-4 is noted and patients have severe physical symptoms, PMMA may be removed and replaced with cancellous bone graft, potentially facilitating total knee replacement in the future. In future, PMMA substitutes with similar hyperthermic effects, better osteoconductive and osteoinductive properties, and more favorable elasticity may be used [43-45]. Resection and endoprosthetic replacement as primary treatment for GCTB close to the joint surface is not advocated, as the expected risk for eventual joint arthroplasty remains low.

Our study has several limitations. First, a control group without use of PMMA was not available. Ideally, we would have compared the results with the contralateral knees in the same patients or with curettage without use of PMMA. However, as radiographs were made for oncological follow-up, the contralateral knees were not depicted. Second, measurement of joint space

narrowing would have been valuable for objective assessment of radiographic findings of osteoarthritis. The KL graded is determined on non-weight-bearing radiographs, as proposed in the original publication on this system [32], and joint space narrowing could not be measured accurately.

In conclusion, the prevalence of osteoarthritis on the latest follow-up radiograph was increased after curettage and application of PMMA for GCTB around the knee. Large subchondral bone defects and close proximity to the joint surface increased the risk of osteoarthritis. The role of PMMA in osteoarthritis development remains unclear. Overall, functional outcomes and quality of life were unaltered for patients with radiographic findings of osteoarthritis. None of the patients required surgery for osteoarthritis at the time of intermediate follow-up, but the clinical relevance may increase over time as our study population was young and prolonged follow-up is advocated. Curettage and application of PMMA is a safe option for primary and recurrent GCTB, even with a large amount of subchondral bone involvement close to articular cartilage.

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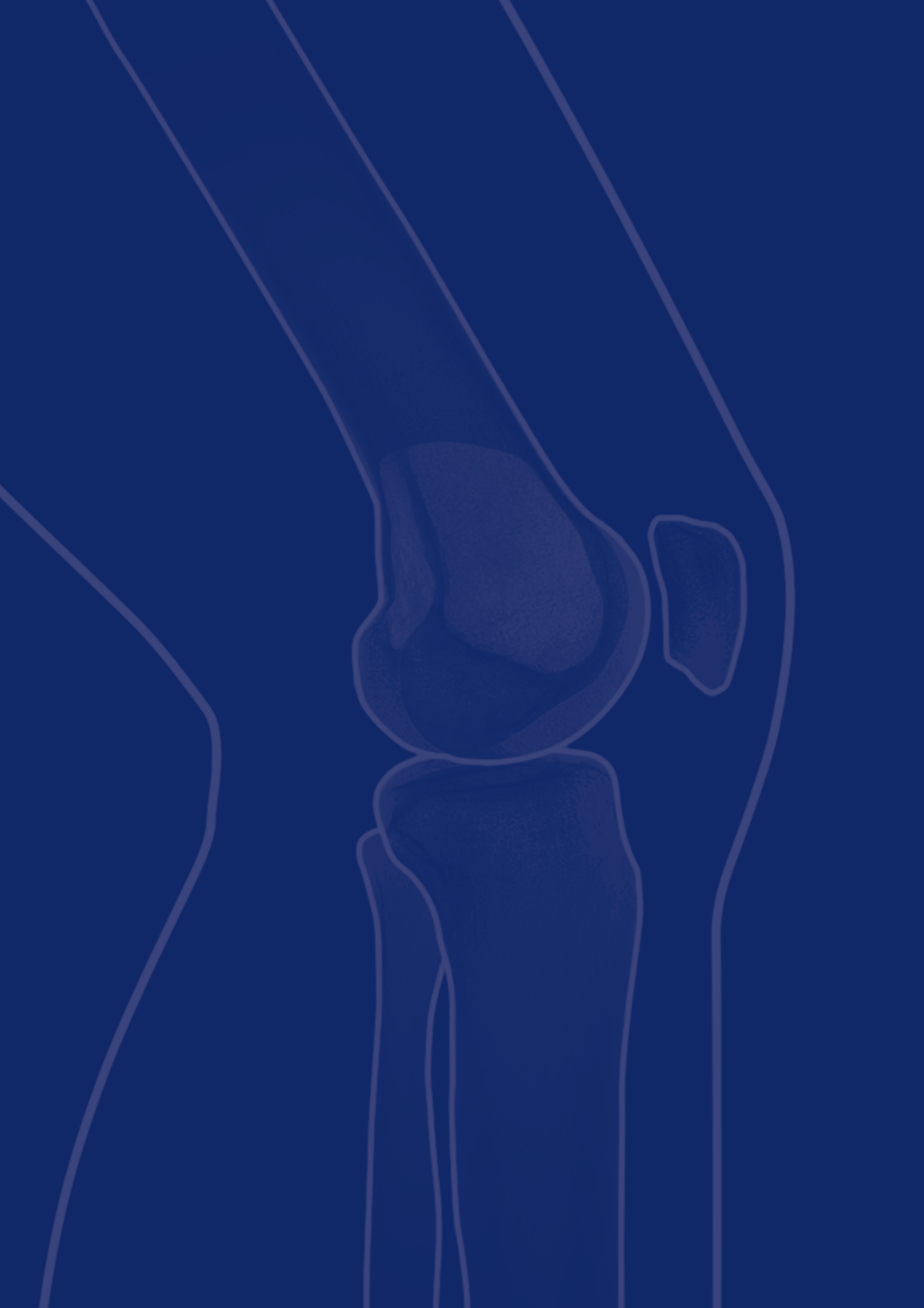
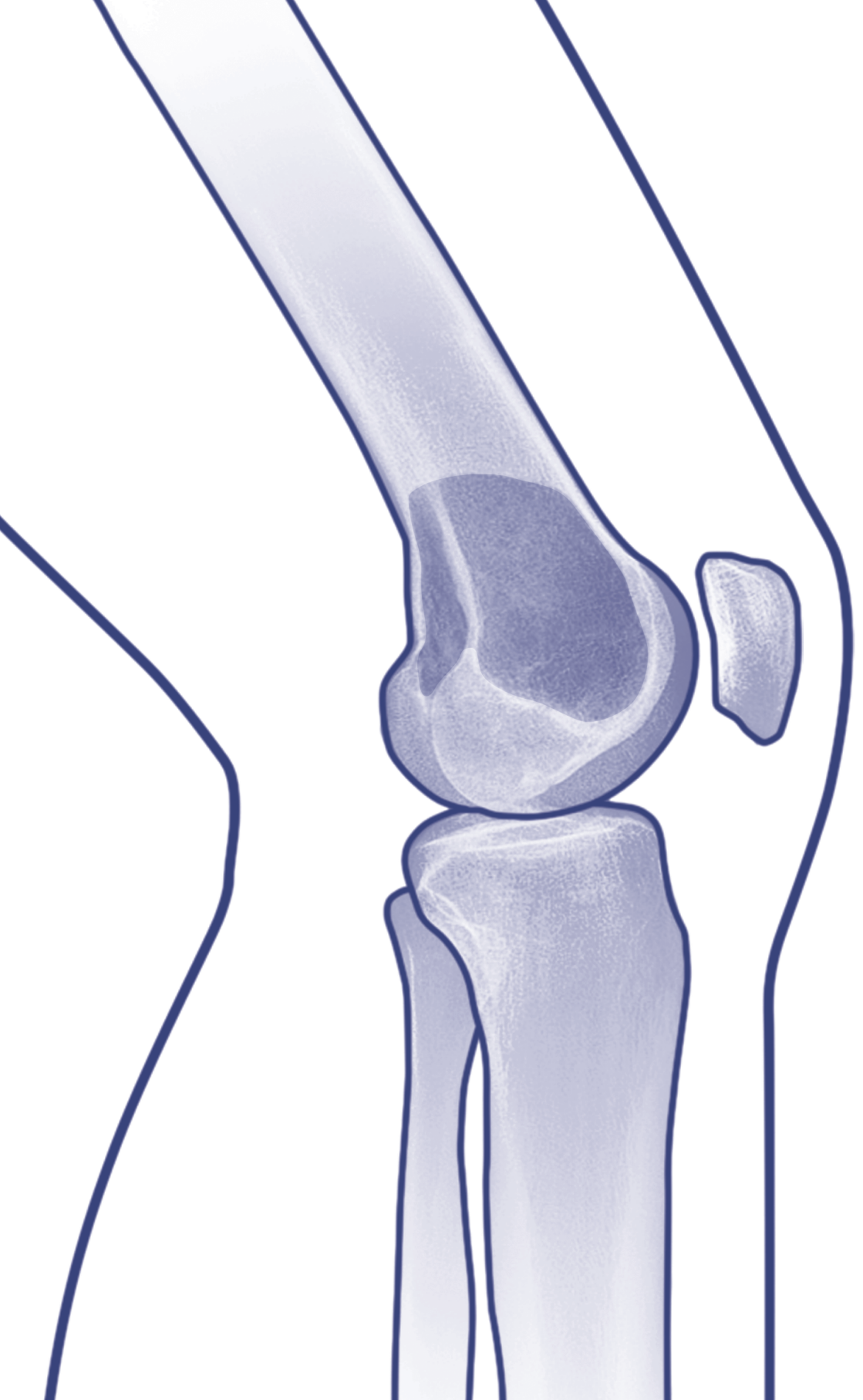


Part II

Giant cell tumor of tenosynovial tissue



Chapter 9

The management of diffuse-type giant cell tumor (pigmented villonodular synovitis) and giant cell tumor of tendon sheath (nodular tenosynovitis)

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Abstract

Background Giant cell tumors of the synovium and tendon sheath can be classified into two forms: localized (giant cell tumor of the tendon sheath, GCT-TS; or nodular tenosynovitis) and diffuse (diffuse-type giant cell tumor, Dt-GCT; or pigmented villonodular synovitis, PVNS). The former principally affects the small joints. It presents as a solitary slow-growing tumor with a characteristic appearance on MRI and is treated by surgical excision. There is a significant risk of multiple recurrences with aggressive diffuse disease. A multidisciplinary approach with dedicated MRI, histological assessment and planned surgery with either adjuvant radiotherapy or systemic targeted therapy is required to improve outcomes in recurrent and refractory Dt-GCT.

Treatment Although arthroscopic synovectomy through several portals has been advocated as an alternative to arthrotomy, there is a significant risk of inadequate excision and recurrence, particularly in the posterior compartment of the knee. For local disease, partial arthroscopic synovectomy may be sufficient, at the risk of recurrence. For both local and diffuse intra-articular disease, open surgery is advised for recurrent disease. Marginal excision with focal disease will suffice, not dissimilar to the treatment of GCT-TS. For recurrent and extra-articular soft-tissue disease adjuvant therapy, including intra-articular radioactive colloid or moderate-dose external beam radiotherapy, should be considered.

Introduction

Giant cell-rich tumors are classified according to their site of origin, namely bone, soft tissue, synovium or tendon sheath. Those that arise from tendons and synovium are now classified into two forms: localized (nodular tenosynovitis) and diffuse (pigmented villonodular synovitis). In the World Health Organization (WHO) classification [1] the former is described as giant cell tumor of tendon sheath (GCT-TS), whereas the latter, which was first recognized and described by Jaffe, Lichtenstein and Sutro [2] in 1941 as a reactive or inflammatory disorder of the synovium of large and small joints, is described as diffuse-type giant cell tumor (Dt-GCT). The disease is mono-articular, and chromosomal aberrations are seen in both forms, suggesting a neoplastic rather than a reactive origin [3].

Giant cell tumor of tendon sheath (GCT-TS)

This local form of the disease can occur in any age group but principally affects those between 30 and 50 years of age, with a female predominance [4]. Most commonly it presents as a soft-tissue swelling in the hand or foot, adjacent to a small joint and arising from a tendon sheath or the synovial lining of a joint or bursa. It is often painless and slow growing, fixed to deep structures and abutting the bone, which can be eroded by pressure to cause scalloping [4]. In >10% of patients it arises from the synovium [5]. Solitary disease is also common in the knee and may present as an incidental finding on MRI or, more commonly, with mechanical symptoms mimicking a meniscal injury or 'loose body', which suggests a pedunculated tumor (Figure 1A). Extra-articular disease presents as a slow-growing non-painful, often palpable peri-articular mass. It is a benign condition, but may recur if incompletely excised [6].

Diffuse-type GCT (Dt-GCT)

This is a rare, usually benign proliferative tumor that develops in the synovium, with an incidence of two per 1,000,000 per year [1] in patients ≤40 years old, with an equal gender distribution. The knee is the most common site (Figure 1B); the elbow, ankle and hip are less common, and rarely the foot and temporomandibular joint may be involved. The spine may be affected, notably

the sacroiliac joints and posterior vertebral elements [7]. Characteristically there is a long history, with a delay in diagnosis. The patient often presents with an intermittently tender and painful joint. In the knee and ankle there may be recurrent swelling with spontaneous haemarthrosis. Although considered to be a benign condition, the diffuse form is more aggressive, with a high recurrence rate after surgery of 25% with intra-articular and 25% to 50% with extra-articular disease [8].

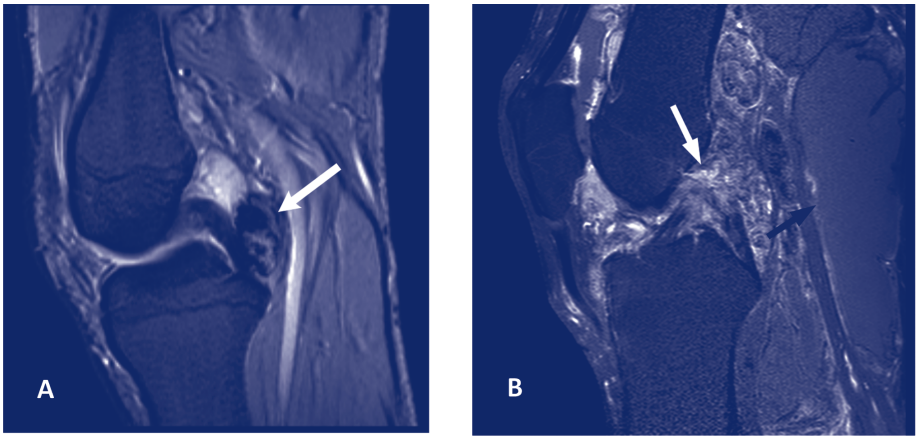

Figure 1 (A) Sagittal gradient echo MRI in a 41-year-old man with persistent pain in the right knee, showing the local form of the disease (giant cell tumor of tendon sheath, GCT-TS). MRI shows a well-defined soft-tissue mass dorsal to the posterior cruciate ligament and in close relationship to the knee capsule (white arrow). The lesion shows focal hypointense areas, owing to the 'blooming' artifact from haemosiderin. (B) Sagittal T1-weighted MRI in a 61-year-old man showing recurrence of the diffuse form of disease (Dt-GCT) (white arrow). MRI after intravenous gadolinium with fat suppression reveals an extensive proliferative synovial process of the left knee with a heterogeneous enhancement and areas of low signal intensity typical of iron deposition. Here, Dt-GCT is localized diffuse and intra-articular in relation to a large Baker's cyst (black arrow).

A review of the management of this disease is merited for a number of reasons:
The reclassification of the disease, according to the site and the tissue of origin, recognizes two distinct forms, nodular and diffuse, with the latter behaving in a more aggressive manner.
With improvements in imaging, notably MRI, a radiological and pathological diagnosis of the condition can be made, identifying the extent of disease and allowing for planned treatment and resection.
Recognition of this condition as a tumor rather than a reactive or inflammatory disorder, with a chromosome aberration identified in both the local and diffuse forms.

The need for a multidisciplinary approach to the management of diffuse disease, with selective histology and planned surgical resection to avoid the high incidence of local recurrence.
The potential use of adjuvant radiation and novel targeted therapies, such as macrophage colony-stimulating factor 1 receptor (M-CSFR)-targeted tyrosine kinase inhibitors (e.g. imatinib) as non-surgical treatment for aggressive Dt-GCT (PVNS) or for recurrent disease.

Imaging

Conventional radiographs combined with MR imaging will establish the diagnosis of Dt-GCT and accurately determine the extent of the disease. Although the appearance can be characteristic, image-guided percutaneous needle biopsy for histopathological examination may be indicated, particularly if there is doubt about the diagnosis.
Conventional radiographs are often not diagnostic. With advanced disease there may be evidence of soft-tissue swelling, loss of joint space and peri-articular erosion of bone. The peri-articular erosions are more notable in joints with a tight capsule, such as the hips, elbows, hands and feet (Figure 2).
The joint space is preserved until late in the disease. In addition to the absence of peri-articular osteopenia this feature is helpful in differentiating Dt-GCT from an inflammatory synovitis.

On MRI the appearance of Dt-GCT is often characteristic owing to the presence of haemosiderin [9]. The lesions demonstrate predominantly low signal intensity on T1- and T2-weighted spin echo sequences. The presence of haemosiderin deposits causes local changes in susceptibility ('blooming effect'), especially on gradient echo sequences, resulting in disproportionately lower signal intensity areas. Marked enhancement is seen on T1-weighted MR images after the intravenous injection of gadolinium.
The differential diagnosis on MRI includes rheumatoid pannus, amyloid arthropathy, synovial haemangioma, haemophilia, and desmoid-type fibromatosis, which can be resolved on the basis of clinical history and laboratory findings. MR morphology and enhancement characteristics can be confirmed with biopsy and formal histological examination.

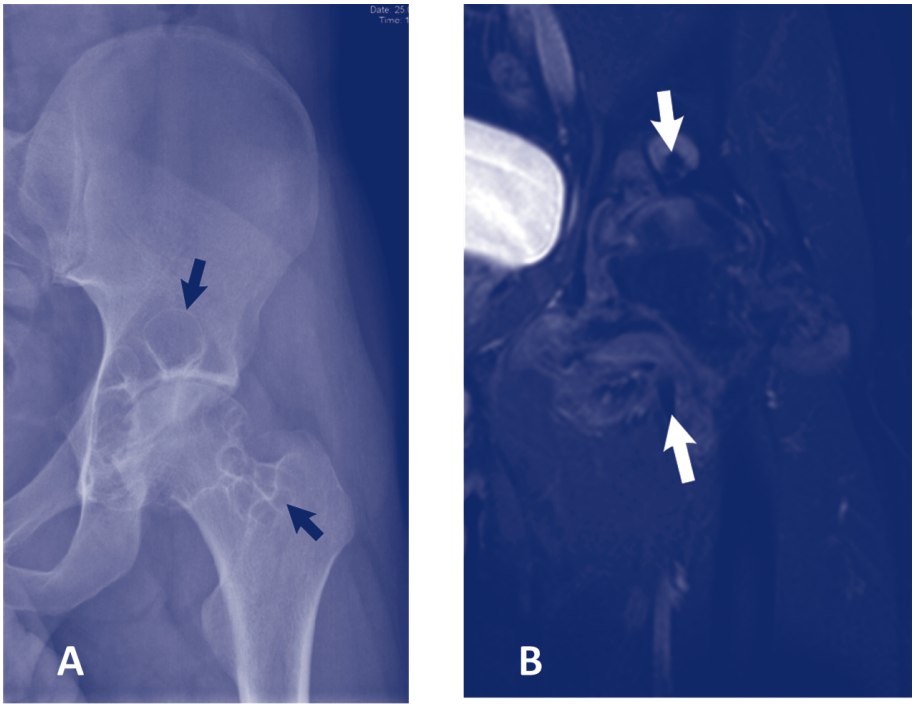

Figure 2 (A) Radiograph of the left hip of a 22-year-old man with a three-year history of progressive pain in his left groin, showing diffuse-type giant cell tumor (Dt-GCT) with erosive destruction of the hip joint. There are lytic lesions with well-defined sclerotic margins on both sides of the joint, (black arrows) consistent with a synovial process. (B) Corresponding coronal T2-weighted MRI with fat suppression demonstrates the erosive destruction of the acetabulum, femoral head and neck as a result of extensive synovial proliferation. The areas of low signal intensity within the synovial mass indicate the presence of haemosiderin deposits characteristic of Dt-GCT (white arrows).

Genetics

Dt-GCT and GCT-TS are giant cell tumors that both express an osteoclast-like antigenic phenotype; the cells show calcitonin receptors and are capable of lacunar resorption of bone [10-13]. It is thought that osteoclast-like giant cells are formed from mononuclear macrophage precursors by a receptor activator of nuclear factor-kappa B ligand (RANKL)-dependent mechanism similar to that seen in giant cell tumors of bone and soft tissues [10, 14-16].

The tumors are driven by overexpression of macrophage colony-stimulating factor 1 (M-CSF1). In 30% to 60%, M-CSF over-expression results from a t(1;2) translocation, which fuses the M-CSF gene on chromosome 1p13 to the collagen 6A3 (COL6A3) gene on chromosome 2q35 [3, 17]. M-CSF1 is only expressed by

a minority of tumor cells, which in turn attract non-neoplastic inflammatory cells that express M-CSF1R through a paracrine or so-called landscape effect [3]. M-CSF is produced by synovial fibroblasts with increased expression of M-CSF by proliferating cells, leading to the accumulation of macrophages and the formation of a tumor-like mass [3]. In benign disease mitotic activity is less but in the aggressive form, mitotic rates are increased to > 20 mitoses per ten high-power fields.

This molecular characterization of Dt-GCT has resulted in the development of new systemic targeted therapies for the aggressive form and for recurrent disease [18]. A malignant form of the disease was first reported by Bertoni *et al.* [19] but is thought to be a debatable entity that needs to be proven by linear studies [20].

Pathology

Macroscopically, Dt-GCT is red-brown or yellow and contains numerous capillary fronds and nodular areas that in the diffuse form often involve the whole synovium. However, focal interrupted areas in normal synovium may be a feature of disease in the knee [1].

Histological examination reveals villous hypertrophy of the synovial membrane with subintimal macrophage infiltration. There are numerous lipid-laden foamy macrophages and scattered multinucleated giant cells. The tumor has a fibrous stroma and may contain bands of collagen with brisk mitotic activity in the subintimal stromal cells. Haemosiderin may be present within the synovial lining cells and the subintimal macrophages (siderophages), and it may be extracellular within the subintima. Its presence is significant because it produces the characteristic signal appearances noted on MRI, which are useful for diagnosis of this disease.

Surgery

Giant cell tumor of tendon sheath (GCT-TS)

In the hand and foot this presents as a solitary swelling next to a small joint, whereas in the knee and ankle it may be an intra-articular solitary lesion or a peri-articular lesion fixed to a tendon sheath or bursa.

As with any solitary solid tumor that is fixed to the deep tissues it is important that imaging supports the diagnosis of GCT-TS; if there is any doubt about the diagnosis a formal tissue biopsy must be undertaken. Rarely peri-articular malignant conditions may mimic GCT-TS, including synovial, epithelioid and clear cell sarcoma in the hand; these conditions can present in similar fashion as can other common benign solid soft-tissue lesions (such as haemophilia, synovial hemangioma, rheumatoid pannus, amyloid arthropathy and desmoid-type fibromatosis) [4]. Careful clinical examination, MR morphology and enhancement characteristics can usually differentiate between these conditions. Planned surgical excision, aiming for a clear margin, is advised when a solid diagnosis is established.

In the hand and the foot GCT-TS is a solitary non-invasive firm tumor, generally 0.5 cm to 3.5 cm in size [4]. As it is a slow-growing lesion it displaces adjacent structures and rarely involves nerves and blood vessels. In our opinion an extensile approach centered over the lump in the long axis of the digit is recommended, so that adjacent neurovascular structures can be identified first and separated from the pseudo-capsule. Skin flaps need to be developed carefully, fully identifying the tumor, which has the characteristic appearance of a well-circumscribed lobular mass. The cut surface has a variegated pink-grey appearance with flecks of yellow and brown tissue. In principle, a solitary tumor can be excised marginally with associated affected soft tissue. After careful excision of solitary tumors of the digits and of the larger joints, a recurrence rate of <15% is expected [21]. Histological confirmation is mandatory, and the patient must be advised that if further soft-tissue masses develop they should seek review that should include MR imaging.

Arthroscopic resection has been advocated for solitary tumors of the large joints, notably the knee [22, 23], which in expert hands can be technically successful for focal intra-articular disease and small accessible solitary solid tumors. However, if the lesion is misdiagnosed pre-operatively and afterwards appears to be malignant (i.e. not Dt-GCT), intra-articular spread of a malignant tumor and incomplete excision of the disease may result.

We would recommend open excision for extra-articular solitary tumors of large joints and for inaccessible intra-articular disease, such as for the posterior knee or fixed synovial disease, an extensile approach should be used, with arthrotomy, which can be extended if revision surgery is required [22, 23].

Formal excision, either marginally or with a cuff of tissue, is required and histological examination mandatory.

Diffuse-type giant cell tumor (Dt-GCT)

The current management of this is controversial, owing in part to the rarity and heterogeneity of the disease and the limited evidence available, particularly in the knee. What is recognized is the high recurrence rate, at 25% for intra-articular and 50% for extra-articular disease, which is dependent on the site, volume of disease, intra- or extra-articular extent and previous surgery [1, 8].
In the knee arthroscopic synovectomy has been advocated, with better functional results and lower rates of post-operative stiffness. Local recurrence can occur if excision is incomplete [24].
Arthroscopic synovectomy requires technical expertise, and complete excision is rarely achieved even by experienced arthroscopic surgeons. In order to treat diffuse disease, many portals may be required to access the posterior and collateral joint recesses, with the risk of seeding the disease into the soft tissues around the portals.
The posterior joint, collateral ligaments and cruciate attachments are often difficult to visualize and treat arthroscopically. The recommended treatment for large-volume diffuse disease therefore remains open arthrotomy [25-27]. Combined or staged surgery may be considered if there is limited anterior disease that is accessible to arthroscopic synovectomy. However, with posterior disease an open posterior approach is required. We prefer an extensile approach, with a lazy-S incision, and elevation of the origin of the medial or lateral heads of gastrocnemius to allow protection of the neurovascular structures. Formal arthrotomy to visualize the posterior cruciate ligament and articular surfaces must be undertaken to obtain access to the synovium.
A midline anterior approach is advised for anterior disease, as this allows good visualization of the synovial cavity, fat pad, cruciate and collateral ligaments. Residual tumor adjacent to the joint line and unilateral gutters can be safely resected.
Although an open approach with complete synovectomy for diffuse disease remains the standard treatment, high recurrence rates can still be expected. A multidisciplinary approach, including careful assessment with MRI of the knee and complete synovectomy, either as a single or a staged procedure, results in

a lower recurrence rate and fewer complications [28]. However, arthrotomy of the knee is associated with a prolonged hospital stay and rehabilitation, with the incidence of joint stiffness as high as 24% [29].

Dt-GCT is also not uncommonly found in the elbow and ankle joints. A similar approach as for the knee is advised, with careful imaging and a tissue diagnosis with planned open surgery [30]. An extensile approach with identification and protection of the neurovascular structures should be undertaken, and attention should be paid to complete clearance of the synovium under direct vision.

With extensive joint destruction or the development of secondary arthritis, arthroplasty is indicated. In the hip, ankle or knee a conventional procedure is advocated, although with Dt-GCT the failure rate is reported as higher than with conventional arthritis [31, 32]. A failure rate of 22% has been reported following total knee replacement and complete synovectomy for Dt-GCT [32]. A marginally improved rate is reported in the hip [33]. These patients are generally younger than those who undergo conventional joint replacement and often have multiple procedures, with an increased risk of complications.

Radiosynovectomy

Intra-articular injection of yttrium-90 (^{90}Y)-labeled colloid can be used as a local adjuvant after synovectomy, but only for localization of intra-articular disease. At present, doses of 15 mCi to 25 mCi (555 MBq to 925 MBq) are administered six to eight weeks post-operatively, depending on the volume of the joint and body size [34-37]. Although caution is needed when using radioactive agents in the treatment of benign lesions, instillation of intra-articular radioactive colloids seems safe and effective after subtotal synovectomy. Recurrence rates of 0% to 25% are reported, but there is little evidence regarding outcomes, as the number of cases in most series is small [34, 35, 38]. Ottaviani *et al.* [39] presented the largest, albeit mixed, group of patients with Dt-GCT (n=122) treated by radiosynovectomy with a relatively high recurrence rate of 30% in the knee (15 of 50) and 9% in other locations (two of 23). However, it is unclear from their report whether the lesions were localized or diffuse, and for which lesions an open or arthroscopic approach was used. Both parameters significantly influence the recurrence rate.

Radiation therapy

External beam radiotherapy can be used as primary treatment for unresectable disease or as local adjuvant treatment in incompletely resected or extensive Dt-GCT, improving local tumor control [40-44]. An average dose of 30 Gy to 50 Gy (in 15 to 20 fractions) has the advantage of staying under the threshold for fibrosis formation and avoiding long-term radiotherapy-related toxicity. Recurrence is reported to be between 7% and 67% for different tumor sites [41, 43, 45-47]. No significant complications of radiotherapy were seen in this group of patients [7, 34, 44, 45, 48, 49].

Neo-adjuvant systemic targeted therapy

The molecular characterization of Dt-GCT facilitates the use of systemic targeted therapies as a novel method of treatment for patients in whom surgery would produce significant functional impairment, or for those with unresectable Dt-GCT.

Although M-CSF over-expression is present in a minority of neoplastic cells, the majority of mononuclear and multinucleated stromal cells in Dt-GCT express high levels of M-CSFR, which is thought to be responsible for the formation of a tumor mass [3, 17, 50]. This signaling pathway seems a promising target for systemic therapy with tyrosine kinase inhibitors such as imatinib or related compounds. Imatinib is an approved drug for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST); it acts on cells of the monocyte/macrophage lineage with M-CSFR [50]. Recently, it has been shown to induce some tumor regression in patients with advanced Dt-GCT [18, 28, 51].

In 2008, the first case report of the activity of imatinib in recurrent M-CSFR-dependent Dt-GCT was published [51]. The patient was treated with imatinib 400 mg/day. After a complete response at five months, the Dt-GCT recurred when the drug was stopped. At re-introduction a secondary complete remission was reported.

Additionally, it showed promising activity in two preliminary case series [18, 28]. In one, five of six patients reported pain relief, three had regression of disease, and two patients found the disease stabilized with this treatment [28]. The second series revealed one complete remission, four partial remissions,

and in 20 of 27 patients the disease was stabilized [18]. The most common side effects were mild fluid retention, fatigue, nausea and skin toxicity.

Although blockade of M-CSFR by imatinib in Dt-GCT would seem to be the most likely mechanism of action, the potential contribution of blockade of other tyrosine kinases by imatinib cannot be ruled out. Currently the role of imatinib and other tyrosine kinase inhibitors (e.g. nilotinib and sunitinib) is under investigation as a neo-adjuvant systemic treatment in advanced Dt-GCT (www.clinicaltrials.gov, NCT01261429 and NCT01207492). There may also be a therapeutic role for blockade of M-CSFR through other cytokines, notably interleukin (IL)-34, which interacts with this receptor [52]. In addition, as the formation of giant cells in Dt-GCT is known to be by a RANKL-dependent mechanism [16], there may be a role for RANKL antibody treatment to inhibit the formation of giant cells in this lesion, as in giant cell tumor of bone [14].

Summary

GCT of the tendons and synovium is now classified into two forms: localized (GCT-TS, nodular tenosynovitis) and diffuse (Dt-GCT, pigmented villonodular synovitis). The former principally affects the small joints and presents as a solitary slow-growing tumor with a characteristic MRI appearance, and is treated by planned surgical excision.

Dt-GCT is a more aggressive intra-articular form affecting both small and large joints, most commonly the knee. Both local and diffuse diseases were previously thought to be of reactive inflammatory origin; however, both forms are now regarded as tumors of peri-articular tissue, as they share a common chromosomal aberration.

There is a significant risk of multiple recurrences in diffuse disease. A multidisciplinary approach with dedicated MR imaging, histological assessment and planned surgery, with either adjuvant radiotherapy or systemic targeted therapy, is required to improve outcome in recurrent and refractory Dt-GCT (Figure 3).

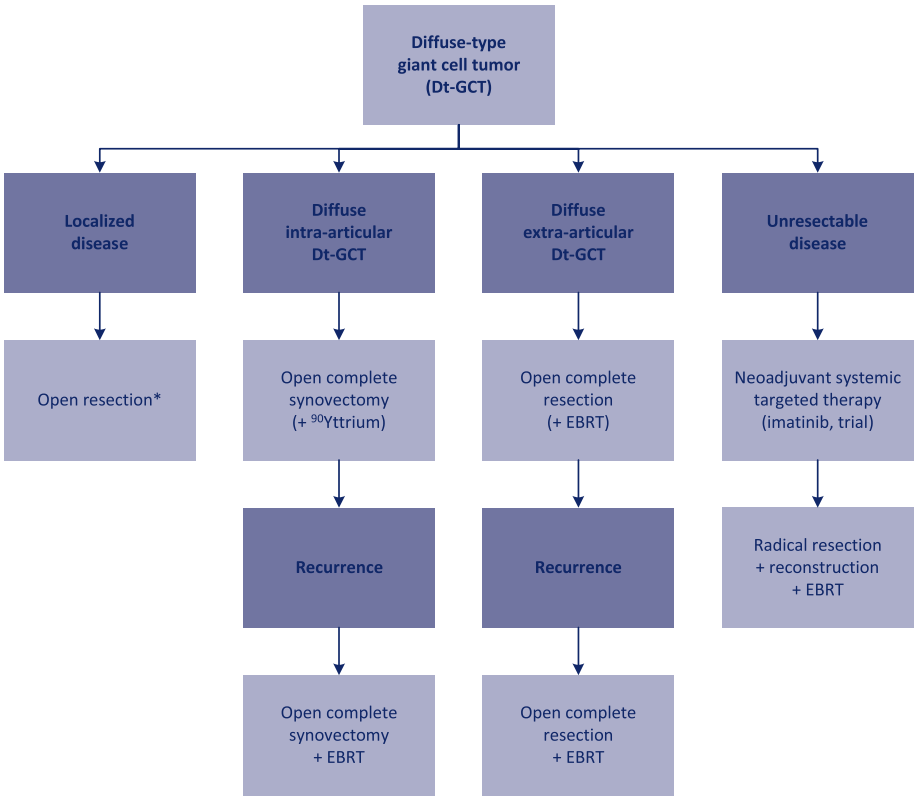

Figure 3 Multidisciplinary integrated treatment protocol for local (GCT-TS) and diffuse (Dt-GCT) forms of disease (* although good results have been published on arthroscopic treatment, an open approach prevents contamination and potentially reduces the risk of recurrence); EBRT, external beam radiation therapy.

Although good results have been published for arthroscopic treatment of diffuse intra-articular disease [23-25], particularly of the knee, an open approach allows a more complete resection and potentially reduces the risk of recurrence. It is recommended that with both local and diffuse forms of the disease, resection and formal histological examination of the lesion should be undertaken.

Open synovectomy is recommended for diffuse intra-articular involvement of the joint. After arthroscopic synovectomy for Dt-GCT of the knee, there is a high risk of incomplete excision and hence a risk of recurrence. Arthroscopy is advised to obtain a tissue diagnosis or for treatment of easily accessible solitary or focal disease.

In selected cases without extra-articular spread, instillation of intra-articular radioactive colloid can be a safe and potentially effective local adjuvant treatment, although there is still little evidence to support its universal application.

Diffuse local recurrences in the knee can be treated with open two-stage synovectomy and resection of all affected tissues, possibly followed by moderate-dose external beam radiation. Moderate-dose radiotherapy will improve midterm local control (75% to 98%) and minimize long-term radiotherapy complications. Radiotherapy is recommended prior to advanced joint destruction, particularly in recurrent disease; it can safely be used for the knee, shoulder and hip, but is not advocated for the hands and feet.

If the Dt-GCT has an extra-articular component, one- or two-stage open synovectomy with resection of all affected soft tissues is advised. Radioactive colloid instillation is not indicated, and external beam radiotherapy should be considered in the presence of extensive soft-tissue disease.

For unresectable disease, MRI with radical planned resection, joint reconstruction with joint replacement and consideration of radiotherapy is advised. Inclusion in a trial of neo-adjuvant systemic targeted therapy (targeting MCSFR, for example imatinib or related tyrosine kinase inhibitors) can be considered, notably when radiotherapy is contraindicated. Data on systemic treatment in large study populations will follow in the near future, and with the new systemic targeted treatments for Dt-GCT treatment optimization will require review and validation. This includes mono versus combination therapy, obtaining the optimal balance between the benefits of alleviating functional impairment against the potential toxicity of the treatment and its duration, the timing of operation and the mechanism of resistance to treatment.

Although arthroscopic synovectomy through multiple portals has been advocated as an alternative to arthrotomy [20, 39-41], there is a significant risk of inadequate excision and subsequent recurrence, particularly in the posterior compartment of the knee. For local disease, partial arthroscopic synovectomy may be sufficient at the risk of recurrence. Open surgery for both local and diffuse intra-articular disease is advised for recurrent disease. Marginal excision with focal disease will suffice, not dissimilar to the treatment of GCT-TS [42]. With recurrent and extra-articular soft-tissue disease adjuvant therapy, including intra-articular radioactive colloid or moderate-dose external beam radiotherapy should be considered.

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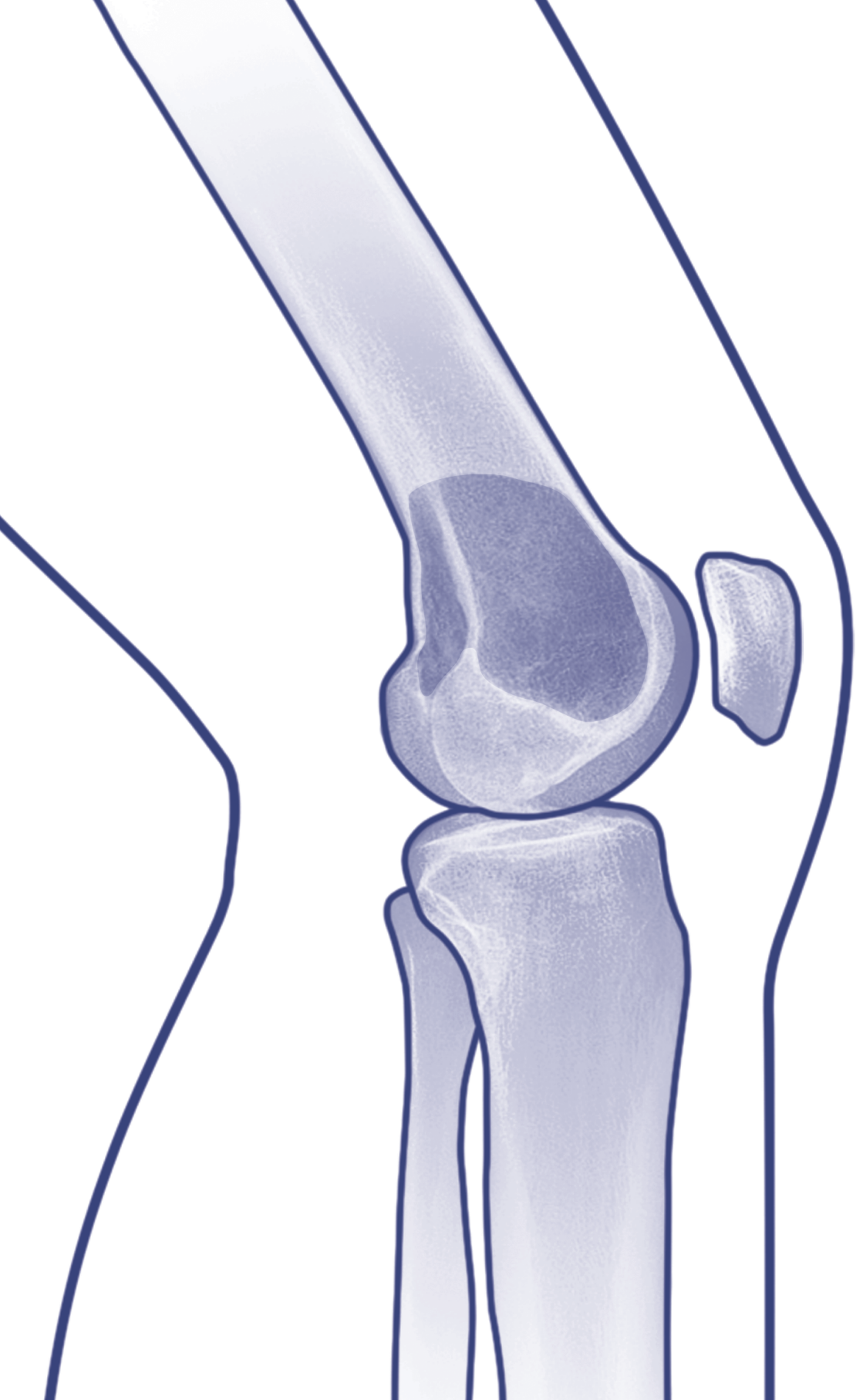

Chapter 10

A multidisciplinary approach to giant cell tumors of tendon sheath and synovium – A critical appraisal of literature and treatment proposal

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Abstract

Background Giant cell tumors deriving from synovium are classified into a localized (giant cell tumor of tendon sheath; GCT-TS) and diffuse form (diffuse-type giant cell tumor, Dt-GCT). We propose a multidisciplinary management based upon a systematic review and authors' opinion.

Treatment Open excision for GCT-TS and open synovectomy (plus excision) for Dt-GCT is advised to reduce the relatively high recurrence risk. External beam radiotherapy should be considered in severe cases, as Dt-GCT commonly extends extra-articular.

Introduction

Although pigmented villonodular synovitis (PVNS) was first described as entity by Jaffe *et al.* in 1941 [1], the histological, clinical and radiological definition of this lesion remained unclear for years. Ambiguous naming was used for synovial lesions resulting in controversies in literature [2, 3]. In 2002, the World Health Organization differentiated giant cell-containing tumors to their origin: bone, soft tissue, synovium and tendon sheath (Table 1). Diffuse PVNS was renamed to diffuse-type giant cell tumor (Dt-GCT) and local PVNS into giant cell tumor of tendon sheath (GCT-TS) [4].

Table 1 WHO classification of giant cell rich soft tissue tumors

	Location	Epidemiology	Diagnostics	Histopathology	Treatment
Diffuse type GCT	75% knee, 15% hip, ankle, elbow, shoulder	Age 20-45	Magnetic resonance. Decreased signal intensity in T1- and T2-weighted images.	Infiltrative. Less osteoclastic giant cells. Small histiocyte-like cells, rounded cells with haemosiderin granules.	Open synovectomy. Adjuvant radiotherapy in unresectable or recurrent disease (18-46%).
GCT of tendon sheath	85% fingers	Age 30-50	Radiography, magnetic resonance	Lobulated, well circumscribed, covered in fibrous capsule. Mononuclear cells, multinucleate giant cells, foamy macrophages, siderophages.	Local excision. Re-excision in recurrent disease (4-30%).
GCT of soft tissue	70% superficial in upper and lower extremity	Age 40-50	Magnetic resonance	Multinodular, haemosiderin-laden macrophages, mononuclear round cells, multinucleated osteoclast-like giant cells	Local excision. Re-excision in recurrent disease (12%).

Dt-GCT is a benign proliferative lesion which develops in the synovial lining of joints, tendon sheaths and bursae [5]. The incidence is approximated at two per million people per year, mostly under the age of 40 and with an equal distribution between the sexes [4]. Multiple joint involvement is rare [6]. A distinction is made between localized and diffuse lesions. Local forms (GCT-TS)

are confined to a distinct area of synovium (Figure 1), whereas diffuse forms (Dt-GCT) demonstrate extensive involvement of the whole synovial membrane and capsule (Figure 2; Table 1).

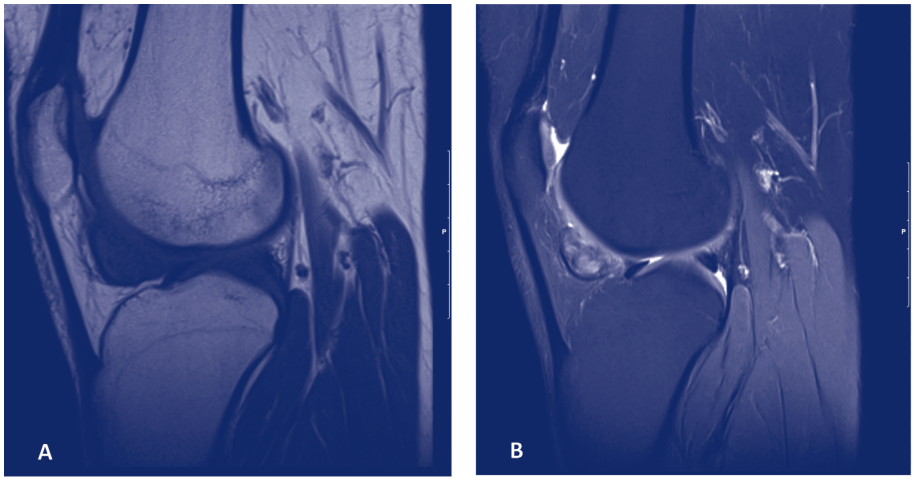

Figure 1 (A) Sagittal T1-weighted and (B) sagittal fast spin-echo proton density-weighted MR images of localized GCT-TS of the knee in a 43-year old male patient, presenting with locking symptoms. A well-defined soft tissue mass is revealed in Hoffa's fat pad.

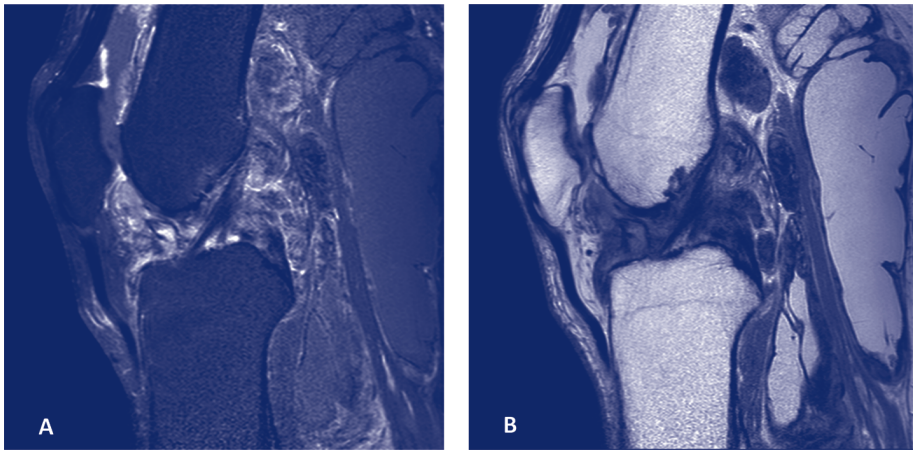

Figure 2 (A) Sagittal T1-weighted MR image after intravenous contrast injection with fat suppression in a 61-year old man with recurrent Dt-GCT reveals an extensive proliferative synovial process of the left knee with a heterogeneous enhancement with areas of low signal intensity typical for iron deposition. (B) Sagittal fast-spin echo proton density-weighted MR image shows Dt-GCT located in both anterior and posterior knee compartments, intra-articular around the anterior and posterior cruciate ligaments and in relation to a large Baker's cyst.

Main complaints are pain, (hemorrhagic) joint effusion and a limited range of motion [7]. With slow-growing tumors of synovium it is important to exclude other diagnoses prior to surgical intervention: e.g. synovial hemangioma, synovial chondromatosis and synovial sarcoma (the latter is usually extra-articular but may be seen in the joint occasionally and should not be missed). The atypical pattern of complaints and wide differential diagnosis can result in delays of years in diagnosing this disease.
The purpose of this article is outlining a framework for the diagnosis and management of giant cell tumors of synovium and tendon sheaths. Making use of recent literature (1990–2011)—containing all available cases with clear descriptions of disease extent—and local experience we aim for a multidisciplinary integrated recommendation on treatment for local and diffuse forms of synovial giant cell tumors.

Literature search

We performed a systematic literature search reviewing all available literature on Dt-GCT until October 7, 2011. We limited ourselves to the systematic review of literature on Dt-GCT, since there are fewer consensuses about its optimal treatment when compared with localized GCT-TS. Search terms and MeSH headings were 'PVNS', 'pigmented villonodular synovitis', 'synovitis, pigmented villonodular', 'diffuse type giant cell', 'giant cell tumors' and 'GCT' and we laid particular emphasis on the large joints such as the knee, hip, and ankle. We identified 1,057 titles in PubMed, EMBASE, Web of Science and ScienceDirect.

All titles and abstracts were screened by one reviewer (LH) according to the following inclusion and exclusion criteria. We included only case series of five or more patients published after 1990 and articles must have been written in the English, Dutch, French, Italian or German language; other languages were excluded. Furthermore, we excluded articles focusing purely on radiological and/or pathological assessment of Dt-GCT, reviews without new clinical cases and articles on Dt-GCT in animals. Finally, we included 59 articles for systematic review (Figure 3) and critical appraisal according to the Newcastle-Ottawa Scale (NOS) for quality assessment of cohort studies (Table 2; Figure 4); this was performed by two independent reviewers (LH and MAJS).

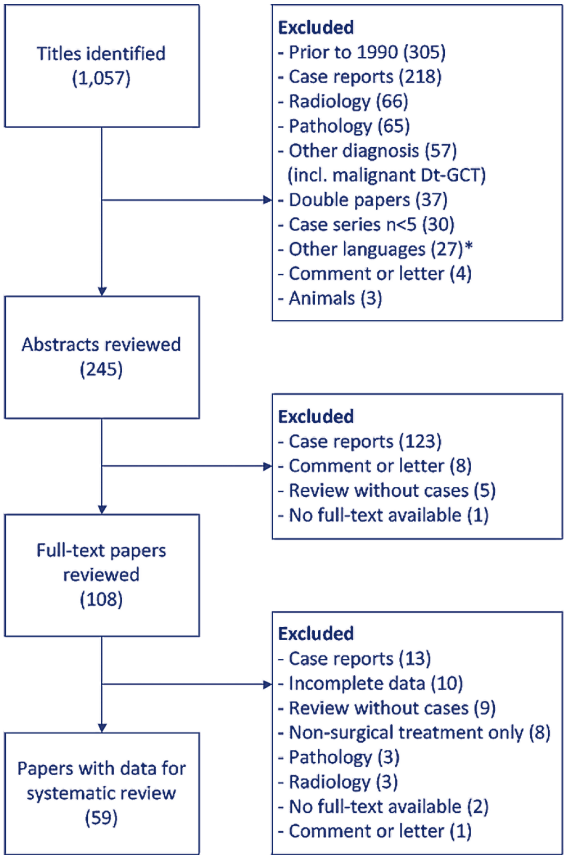

Figure 3 Flowchart of systematic literature search. Articles in the Chinese, Danish, Japanese, Norwegian, Russian, Serbian, and Spanish languages were excluded.

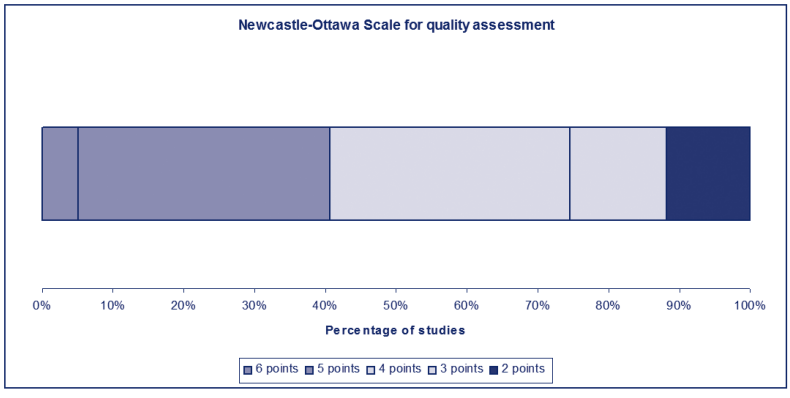

Figure 4 Newcastle-Ottawa Scale for quality assessment of cohort studies; overview of all studies. Studies with 5–6 points were considered of good quality, 3–4 points intermediate quality, and 2 points poor quality. Results correspond with NOS scores as provided in Tables 3-8.

Table 2 Critical appraisal of all included studies (n=59) by means of Newcastle-Ottawa quality assessment Scale (NOS); one point could be obtained for each item of the NOS.

	n	%
Selection		
Representativeness of the exposed cohort	59	100%
Selection of non-exposed cohort*	N.A.	N.A.
Ascertainment of exposure**	45	76%
Demonstration that outcome of interest was not present at start of study†	13	22%
Comparability of cohorts*		
Study controls for most important factor	N.A.	N.A.
Study controls for any factor	N.A.	N.A.
Outcome		
Assessment of outcome‡	45	76%
Follow-up long enough (minimum 2 years)	25	42%
Adequacy of follow-up (≥ 90% of all patients)	51	86%
Scores		
6 points	3	5%
5 points	21	36%
4 points	20	34%
3 points	8	14%
2 points	7	12%

N.A. = Not applicable
*In this modified NOS, no points were accredited for selection of the non-exposed cohort and comparability of cohorts, because all studies were descriptive and contained only one cohort.
**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 Dt-GCT and not for local recurrence; this might induce bias.
‡Through independent blind assessment (e.g. by independent surgeons, radiologists or pathologists) or record linkage.

Imaging

Conventional radiographs are followed by MR imaging to establish a proper diagnosis and determine the extent of the lesion. Although Dt-GCT has in most cases a characteristic appearance on MR imaging, image guided percutaneous needle biopsy can be necessary to confirm the diagnosis. In experienced centers, small localized intra-articular lesions with characteristic MR imaging appearances may be removed open or arthroscopically without prior biopsy.
Conventional radiographs often appear normal or demonstrate a nonspecific

peri-articular soft tissue swelling or joint effusion [3]. Associated bone erosions with a sclerotic margin may be present on both sides of the affected joint, especially in joints with a tight capsule such as the hip (Figure 5). The preservation of the articular joint space until relatively late in the disease, and the absence of peri-articular osteopenia is helpful to differentiate between Dt-GCT and inflammatory synovitis.

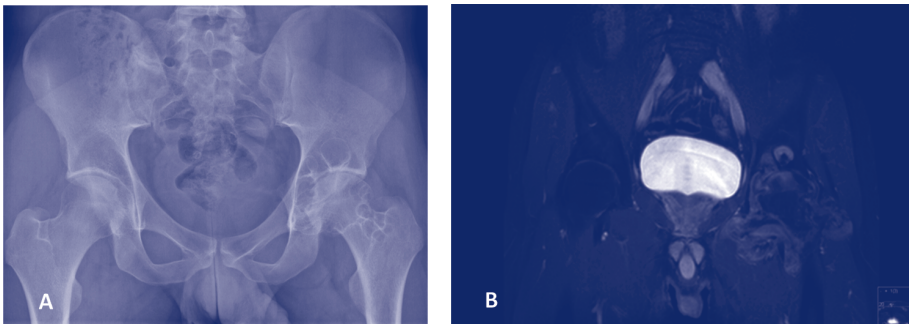

Figure 5 (A) Anteroposterior conventional radiograph of the pelvis demonstrates Dt-GCT with erosive destruction of the hip joint in a 22-year old man with a history of progressive pain in his left groin since three years. The right hip joint is normal. Conventional radiograph of the left hip shows geographic lytic lesions with well-defined sclerotic margins on both sides of the joint consistent with a synovial process. (B) Corresponding coronal T1-weighted MR image demonstrates the erosive destruction of the acetabulum and femoral neck as a result of extensive synovial proliferation. The lesions show areas of remarkable low signal intensity indicating the presence of hemosiderin depositions characteristic for Dt-GCT.

Hemosiderin depositions cause local changes in susceptibility—the so-called blooming effect—resulting in the characteristic appearance of Dt-GCT on MR images, demonstrating predominantly low signal intensity on T1- and T2-weighted spin echo sequences (Figure 1) [8]. After intravenous Gadolinium administration marked enhancement is often noted. The differential diagnosis on MR includes hemophilia, synovial hemangioma, rheumatoid pannus, amyloid arthropathy, and desmoid-type fibromatosis. One can differentiate between these diagnoses on the basis of clinical history (in case of rheumatoid arthritis and hemophilia), laboratory findings (for amyloid arthropathy in patients with renal failure undergoing long-term hemodialysis), and MR morphology and enhancement characteristics. Pathognomonic MR imaging findings of synovial hemangioma consist of a lobulated intra-articular mass with marked hyperintensity on T2-weighted MR images reflecting blood within

vascular spaces in combination with septae and serpiginous vascular structures. Desmoid-type fibromatosis are usually centered in an intermuscular location with irregular infiltrative margins. Extension along fascial planes ('fascial tail sign') is also a common manifestation which helps in the differential diagnosis with Dt-GCT.

Genetics

Giant cells within Dt-GCT express an osteoclast-like antigenic phenotype (CD45+, CD68+, CD14–, CD11/18–, HLA-DR–, CD51) [9–12]. They also express calcitonin receptors and are capable of lacunar bone resorption. Only recently it was identified that the osteoclast-like giant cells in Dt-GCT are formed from CD14+ macrophage precursors and that CD14– subintimal stromal cells express receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [13]. It is thus likely that the osteoclast-like giant cells in Dt-GCT are formed from CD14+ mononuclear macrophage precursors by a RANKL-dependent mechanism in a manner similar to that seen in giant cell tumor of bone and soft tissues [12, 14, 15].
M-CSF is produced by synovial fibroblasts and abnormal expression of M-CSF and its receptor (M-CSFR) has been noted in mononuclear cells in Dt-GCT [16]. M-CSF is required for macrophage formation and survival and it plays a role in osteoclast formation [17–19]. A translocation involving chromosome 1p13, a locus that includes M-CSF gene, has been noted in local and diffuse forms of Dt-GCT [20–22]. It has been postulated that Dt-GCT arises on the basis of a tumor landscaping effect in which there is increased M-CSF expression by proliferating cells within the lesion; this would lead to an abnormal accumulation of macrophages that expressed M-CSFR, resulting in the formation of a tumor-like mass [23]. This signaling pathway could potentially be a good target for systemic therapies as a new treatment for Dt-GCT requiring mutilating surgery, diffuse unresectable and recurrent Dt-GCT.

Histopathology

Grossly, the synovium in Dt-GCT is thickened, red-brown or yellow, and contains numerous papillary frond or larger nodular areas. Local lesions (GCT-TS) have a pedunculated, lobular form and are confined to one area of the synovium.

Diffuse lesions (Dt-GCT) usually involve all of the synovium, but focal areas of normal synovium may be found.

Histologically, there is villous hypertrophy of the synovial membrane with intimal thickening and heavy subintimal macrophage infiltration. Synovial lining cells contain hemosiderin and extracellular hemosiderin deposits are present in the subintima (Figure 6). Hemosiderin is also present within subintimal macrophages (siderophages). Collections of lipid-laden foamy macrophages and multinucleated giant cells are present. Scattered lymphocytes, plasma cells, and occasionally large lymphoid aggregates are also commonly found. The lesion has a fibrous stroma which may contain broad bands of collagen. Brisk, typical mitotic activity may be seen in subintimal stromal cells.

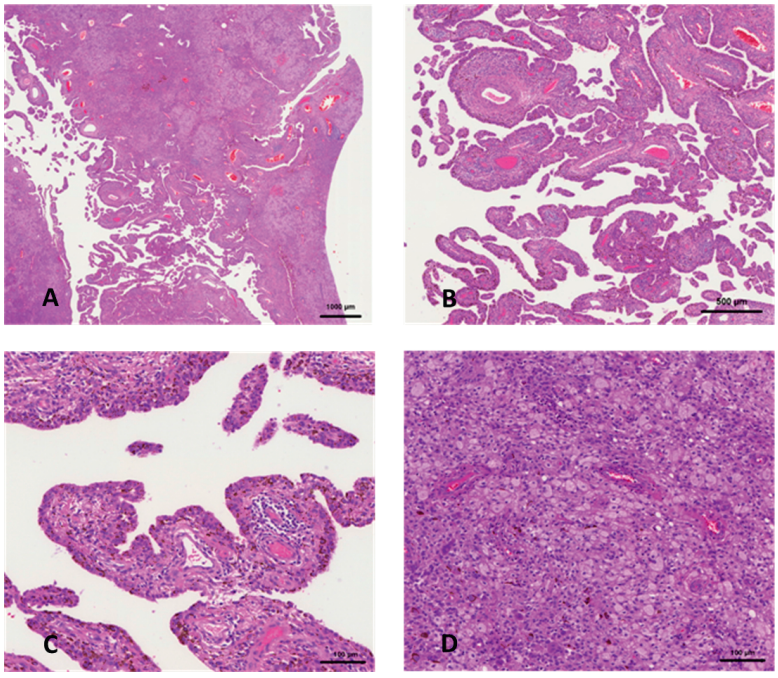

Figure 6 Hematoxylin eosin staining showing histologic characteristics of Dt-GCT. (A) Overview photograph of Dt-GCT. (B, C) Close-up photographs of Dt-GCT. Villonodular protrusions are seen with overlying synovial lining cells. There is villous hypertrophy with intimal thickening and subintimal macrophage infiltration. Characteristic brownish intracellular hemosiderin is seen in synovial lining cells and macrophages (siderophages) and extracellular hemosiderin depositions in the subintima. (D) Close-up photograph of Dt-GCT showing brown cytoplasmic intracellular hemosiderin and the presence of multinucleated giant cells.

Surgery

Arthroscopy

Arthroscopic synovectomy through multiple portals has been advocated as alternative for open synovectomy in localized GCT-TS in the knee [7, 24–26]. At the cost of a higher recurrence risk, arthroscopy has been advocated as it presents possibilities for biopsy and other pathology can be treated simultaneously. Morbidity, joint stiffness, postoperative infections, and reported pain may be reduced [7]. Either partial or complete arthroscopic synovectomy can be performed, dependent on disease extension. For local disease in the knee and other large joints, partial arthroscopic synovectomy (limited to the lesion) can be sufficient (Tables 3 and 4).

Table 3 Surgical resection of localized GCT-TS in the knee

	Year	NOS	n	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Arthoscopic resection							
Stroz [52]	1990	4	6	40 (30-60)	0	0%	
Moskovich [53]	1991	5	9	48 (25-108)	0	0%	
Ogilvie-Harris [24]	1992	5	5	54 (24-120)	0	0%	
Rader [54]	1995	5	8	58	0	0%	
LeTiec [55]	1998	4	5	108 (36-204)	1	20%	Arthroscopic synovectomy
Rochwerger [56]	1998	4	3	64 (24-168)	0	0%	
Zvijac [7]	1999	4	2	48 (42-53)	0	0%	
Kim [57]	2000	5	11	30 (24-48)	0	0%	
Muscolo [58]	2000	4	5	37 (12-55)	0	0%	
Perka [59]	2000	5	2	(36-108)	0	0%	
Rauh [60]	2002	5	3	66 (47-83)	0	0%	
Akgün [61]	2003	2	7	24 (12-33)	0	0%	
Calmet [62]	2003	2	5	36 (12-84)	0	0%	
De Ponti [26]	2003	2	4*	60 (12-128)	0	0%	
Pinaroli [63]	2006	3	2	97 (12-309)	1	50%	Open synovectomy
Dines [64]	2007	3	12	21 (3-47)	0	0%	
Neubauer [65]	2007	5	4	30 (12-60)	1	25%	Synovectomy
Sharma [66]	2009	5	5	74 (12-156)	2	40%	Open synovectomy (n=2)
Baroni [67]	2010	6	4	102 (46-143)	0	0%	

Table 3 Continued

	Year	NOS	n	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Rhee [68]	2010	6	11	112 (25-223)	2	18%	Open synovectomy (n=2), tibial osteotomy (n=2), TKA (n=1)
Kubat [69]	2010	5	4	84 (28-127)	0	0%	
Total			**117**		**7**	**6% (0-50%)**	
Open resection							
Groulier [70]	1991	4	5	N/A	0	0%	
Rader [54]	1997	5	2	58	0	0%	
LeTiec [55]	1998	4	2	108 (36-204)	0	0%	
De Visser [28]	1999	4	9	48 (12-228)	1	11%	Synovectomy + EBRT (n=1)
Perka [59]	2000	5	16	(36-108)	0	0%	
Dürr [71]	2001	4	8	18 (1-54)	1	13%	None
Calmet [62]	2003	2	4	36 (12-84)	0	0%	
Akgün [61]	2003	2	1	24 (12-33)	0	0%	
Chiari [72]	2006	5	9	80 (26-294)	0	0%	
Pinaroli [63]	2006	3	7	97 (12-309)	0	0%	
Dines [64]	2007	3	14	21 (3-47)	0	0%	
Sharma [73]	2007	5	4	72 (12-168)	0	0%	
Pannier [74]	2008	5	2*	58 (36-81)	0	0%	
Sharma [66]	2009	5	7	74 (12-156)	2	29%	Open synovectomy (n=2)
Akinci [75]	2011	2	4	80 (15-156)	0	0%	
Total			**94**		**4**	**4% (0-29%)**	

EBRT = External beam radiation therapy
*All patients were children
NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies

Table 4 Surgical resection of localized GCT-TS in other locations

	Year	NOS	n	Location	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Arthoscopic resection								
Stroz [52]	1990	4	1	Shoulder	40 (30-60)	0	0%	
Neubauer [65]	2007	5	1*	Ankle	30 (12-60)	0	0%	
Total			**2**			**0**	**0% (0%)**	
Open resection								
Looi [76]	1999	3	55	Hand	(12-60)	4	7%	Open synovectomy (n=1)
Chiari [72]	2006	5	12	Hand	80 (26-294)	0	0%	
Neubauer [65]	2007	5	1	Hand	30 (12-60)	1	100%	Open synovectomy
Groulier [70]	1991	4	1	Hip	N/A	0	0%	THA (n=1)
Scapinelli [77]	1993	4	8	Hip	(8-156)	0	0%	THA (n=8)
Bisbinas [78]	2004	4	7*	Ankle	41 (12-150)	0	0%	
Sharma [79]	2006	5	9	Ankle	55 (2-121)	0	0%	
Rochwerger [80]	1999	4	3	Foot	48 (13-110)	1	33%	Amputation
Chiari [72]	2006	5	2	Foot	80 (26-294)	0	0%	
Carpintero [81]	2007	3	1	Foot	95 (12-174)	0	0%	
Total			**99**			**6**	**6% (0-100%)**	

NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies
* All patients were children
THA = Total hip arthroplasty
N/A = Not available

For diffuse disease located in the knee, complete arthroscopic synovectomy is preferred over partial arthroscopic synovectomy as it lowers the recurrence risk (Table 5) [7, 24, 26, 27]. However, the risk of a subtotal synovectomy remains present because of the difficulty in visualizing the posterior compartment of the knee when performing a complete arthroscopic synovectomy and the recurrence risk remains high (~40%). Modern arthroscopic techniques and the approach through multiple portals are believed to reduce this risk [25].

Table 5 Arthroscopic and open synovectomy for Dt-GCT in the knee

	Year	NOS	Synovectomy	n	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Arthroscopic synovectomy								
Stroz [52]	1990	4	Complete	5	40 (30-60)	0	0%	
Ogilvie-Harris [24]	1992	5	Complete	11	54 (24-120)	1	9%	Arthroscopic synovectomy + Yttrium (n=2)
			Partial	9		5	55%	Open synovectomy (n=4), TKA (n=2)
Rader [54]	1995	5	Complete	4	58	1	25%	Open synovectomy (n=1)
LeTiec [55]	1998	4	Complete	4	108 (36-204)	2	50%	Arthroscopic synovectomy (n=2)
Zvijac [7]	1999	4	Complete	12	41 (8-83)	2	17%	Arthroscopic synovectomy (n=2)
Martin [27]	2000	4	Complete	3	56 (17-148)	1	33%	Arthroscopic synovectomy (n=1)
Rauh [60]	2002	5	Complete	5	66 (47-83)	4	80%	Arthroscopic synovectomy (n=3)
De Ponti [26]	2003	2	Complete	7	60 (12-128)	1	14%	N/A
			Partial	9		4	44%	N/A
Pinaroli [63]	2006	3	Complete	7	97 (12-309)	5	71%	TKA (n=3), open synovectomy (n=7), synoviorthesis (n=3) (total group)
Pannier [74]	2008	5	Complete	3	58 (36-81)	1	33%	Arthroscopic synovectomy + synoviorthesis (n=1)
Sharma [66]	2009	5	Complete	13	74 (12-156)	12	92%	Open synovectomy (n=12)
Kubat [69]	2010	5	Complete	9	84 (28-127)	1	11%	Open synovectomy (n=1)
Total				**101**		**40**	**40% (0-92%)**	
Open synovectomy								
Groulier [70]	1991	4	Complete	5	N/A	0	0%	TKA (n=1)
Flandry [2]	1994	4	Complete	25	58	2	8%	None (n=2)
Rader [54]	1995	5	Complete	3	58	2	67%	TKA (n=1), open synovectomy (n=1)
Rochwerger [56]	1998	4	Complete	16	64 (24-168)	4	25%	TKA (n=4), open synovectomy (n=2)
LeTiec [55]	1998	4	Complete	6	108 (36-204)	3	50%	Open synovectomy (n=3)
De Visser [28]	1999	4	Complete	3	48 (12-228)	0	0%	

Table 5 Continued

	Year	NOS	Synovectomy	n	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
			Partial	16		7	44%	EBRT (n=8), partial (n=2) or complete synovectomy (n=1)
Martin [27]	2000	4	Complete	9	56 (17-148)	1	11%	TKA (n=1)
Dürr [71]	2001	4	Complete	6	18 (1-54)	0	0%	TKA (n=1)
Chin [82]	2002	4	Complete	5	60 (18-96)	0	0%	TKA*
Ohnuma [83]	2003	5	Complete	5	83 (40-97)	1	20%	Open synovectomy (n=1)
Pinaroli [63]	2006	3	Complete	27	97 (12-309)	11	41%	See above
Chiari [72]	2006	5	Complete	3	80 (26-294)	1	33%	TKA (n=2)
Sharma [73]	2007	5	Complete	10	72 (12-168)	1	10%	Open synovectomy (n=1)
			Partial	3		2	67%	Open synovectomy (n=1), none (n=1)
Sharma [66]	2009	5	Complete	24**	74 (12-156)	5	21%	Open synovectomy (n=5)
Baroni [67]	2010	6	Complete	5	102 (46-143)	0	0%	
Mankin [5]	2011	3	Complete	125	N/A		2%***	Arthrodesis (n=6), TKA (n=6)
Akinci [75]	2011	2	Complete	14	80 (15-156)	5	36%	Open synovectomy (n=4), EBRT (n=1), TKA (n=5)
			Partial	1		0	0%	
Total				**311**		**45**	**14% (0-67%)**	

NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies
TKA = Total knee arthroplasty
EBRT = External beam radiation therapy
N/A = Not available
* Overall, four TKA were performed in this paper (n=40)
** Eight patients had combined anterior arthroscopy and posterior arthrotomy
*** Overall, three recurrences were reported in this paper

Open synovectomy

An open approach can be desirable for both GCT-TS and Dt-GCT and can be performed in all joints.

For local disease, open resection limited to the lesion is sufficient (Tables 3 and 4). Although local recurrences are rare for local lesions, open instead of arthroscopic resection is recommended to keep the recurrence risk as low as possible.

For diffuse lesions about the knee, (two-stage) open synovectomy with a separate anterior and posterior approach is reported to be a safe surgical treatment option [2, 5, 27, 28]. Average recurrence rates are considerably lower than for arthroscopic synovectomy (14% versus 40%; Table 5). In other joints, open complete synovectomy is more often performed than arthroscopic synovectomy, with acceptable results (Table 6) [5, 27–31].

Table 6 Arthroscopic and open synovectomy with or without radiation therapy for Dt-GCT in other locations

	Year	NOS	Synovectomy	n	Location	FU (months)	Recur-rences	Recurrence rate (range)	Re-interventions
Arthroscopic synovectomy									
Chiang [84]	2009	5	Complete	5	Shoulder	22 (12-33)	0	0%	Cuff tear repair (n=5)
Rochwerger [80]	1999	4	Complete	1	Ankle	48 (13-110)	0	0%	
Stroz [52]	1999	4	Complete	1	Ankle	40 (30-60)	0	0%	
Total				**7**			**0**	**0% (0%)**	
Open synovectomy									
Martin [27]	2000	4	Partial	2	Shoulder	56 (17-148)	0	0%	TSA (n=1)
Chiari [72]	2006	5	Complete	1	Shoulder	80 (26-294)	1	100%	N/A
Martin [27]	2000	4	Partial	3	Elbow	56 (17-148)	1	33%	Partial synovectomy (n=1)
			Partial	3	Hand		0	0%	
Chiari [72]	2006	5	Complete	6	Hand	80 (26-294)	2	33%	N/A
Giannini [29]	1996	5	Complete	17	Spine	43 (6-132)	3	18%	Resection (n=2)
			Partial	3	Spine		0	0%	
Groulier [70]	1991	4	Complete	2	Hip	N/A	0	0%	THA (n=2)
Scapinelli [77]	1993	4	Complete	1	Hip	(8-156)	0	0%	THA (n=1)
De Visser [28]	1999	4	Partial	3	Hip	48 (12-228)	0	0%	THA (n=2)
Martin [27]	2000	4	Complete	5	Hip	56 (17-148)	1	20%	THA (n=3)
Gonzalez [85]	2000	6	Complete	5	Hip	156 (24-276)	1	20%	Primary THA (n=1), THA for recurrence (n=1)
Dürr [71]	2001	4	Complete	1	Hip	18 (1-54)	0	0	
Vastel [31]	2005	5	Complete	8	Hip	200 (12-336)	0	0%	THA (n=4)
Chiari [72]	2006	5	Complete	3	Hip	80 (26-294)	3	100%	N/A
Yoo [86]	2010	5	Complete*	8	Hip	107 (52-162)	0	0%	THA (n=8), revision THA (n=2)
Mankin [5]	2011	3	Complete*	12	Hip	N/A			THA (n=11)
Rochwerger [80]	1999	2	Complete	3	Ankle	48 (13-110)	0	0	Arthrodesis (n=3)

	Year	NOS	Synovectomy	n	Location	FU (months)	Recur-rences	Recurrence rate (range)	Re-interventions
Ghert [87]	1999	4	Complete	2	Ankle	13 (1-41)	0	0	
De Visser [28]	1999	4	Complete	1	Ankle	48 (12-228)	0	0%	
			Partial	1	Ankle		1	100%	EBRT (n=1)
Martin [27]	2000	4	Partial	2	Ankle	56 (17-148)	0	0%	
Dürr [71]	2001	4	Complete	1	Ankle	18 (1-54)	0	0	
Saxena [30]	2004	4	Complete	10	Ankle	54 (12-132)	2	20%	EBRT (n=1)
Brien [88]	2004	5	Complete	5	Ankle	111 (24-180)	0	0%	
Sharma [79]	2006	5	Complete	5	Ankle	55 (2-121)	2	40%	Synovectomy (n=2)
Chiari [72]	2006	5	Complete	3	Ankle	80 (26-294)	3	100%	N/A
Pannier [74]	2008	5	Complete	1	Ankle	58 (36-81)	1	100%	Synovectomy + synoviorthesis + arthrodesis (n=1)
Groulier [70]	1991	4	Complete	1	Foot	N/A	0	0%	Resection arthrodesis (n=1)
Ghert [87]	1999	4	Complete	4	Foot	13 (1-41)	1	25%	Lisfranc amputation (n=1)
Rochwerger [80]	1999	4	Complete	1	Foot	48 (13-110)	0	0	Arthrodesis (n=1)
Bisbinas [78]	2004	4	Complete	2	Foot	41 (12-150)	2	100%	Complete synovectomy + EBRT (n=2)
Brien [88]	2004	5	Complete	2	Foot	111 (24-180)	1	50%	Resection (n=1), arthrodesis (n=1)
Chiari [72]	2006	5	Complete	3	Foot	80 (26-294)	0	0%	
Mankin [5]	2011	3	Complete	48	Foot	N/A		2%*	Arthrodesis (n=5)
Total				**178**			**25**	**14% (0-100%)**	
Open synovectomy with RT or isotopic synoviorthesis									
O'Sullivan [40]	1995	4	Complete + EBRT	3	Hand		0	0%	
Berger [42]	2007	4	Complete + EBRT	1	Hand	29 (3-112)	0	0%	
Giannini [29]	1996	5	Partial + EBRT	1	Spine	43 (6-132)	0	0%	
Scapinelli [77]	1993	4	Complete + EBRT	1	Hip	(8-156)	0	0%	

	Year	NOS	Synovectomy	n	Location	FU (months)	Recur-rences	Recurrence rate (range)	Re-interventions
De Visser [28]	1999	4	Partial + EBRT	1	Hip	48 (12-228)	1	100%	THA (n=1)
Shabat [38]	2002	3	Partial + ^{90}Y	1	Hip		0	0%	
Berger [42]	2007	4	Complete + EBRT	1	Hip		0	0%	THA (n=1)
Shabat [38]	2002	3	Partial + ^{90}Y	3	Ankle	72 (30-144)	0	0%	
Brien [88]	2004	5	Complete + EBRT	4	Ankle	111 (24-180)	0	0%	
Lee [89]	2005	5	Complete + EBRT	3	Ankle		0	0%	
Bickels [90]	2008	2	Partial + ^{90}Y	7	Ankle	47 (12-114)	0	0%	Full thickness skin necrosis (n=2), draining sinus (n=1)
O'Sullivan [40]	1995	4	Complete + EBRT	7	Foot	69 (13-250)	0	0%	
Lee [89]	2005	5	Complete + EBRT	4	Foot	24 (18-36)	0	0%	
Carpintero [81]	2007	3	Complete + EBRT	7	Foot	95 (12-174)	1	14%	EBRT (n=1)
Total				**44**			**2**	**5% (0-100%)**	

NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies
THA = Total hip arthroplasty
TSA = Total shoulder arthroplasty
EBRT = External beam radiation therapy
^{90}Y = 90 Yttrium
N/A = Not available
* All patients had severe joint destruction and underwent primary THA

Arthroplasty

Arthroplasty is indicated in case of joint destruction or development of secondary osteoarthritis. The hip, ankle, hand, and foot joints have tight capsules and lack the capacity to expand and provide space for larger tumor masses. As a consequence, the lesion can erode articular cartilage and extend into bone and surrounding soft tissues. Total hip replacement is therefore more often necessary than in joints with a less tight capsule. Expected revision rates for standard arthroplasty, i.e., for primary osteoarthritis, are 6% after 5 years and 12% after 10 years and are identical for hip and knee [32]. Expected functional results are worse and risk for failure of prostheses placed for Dt-GCT (22% at 10 years) is higher when compared to standard arthroplasty [33].

Intra-articular radioactive isotopes treatment

Instillation of 90-Yttrium (^{90}Y) labeled colloid in the affected joint can be a safe local adjuvant after subtotal synovectomy. ^{90}Y is a pure beta emitter with an energy of 935Kev, physical half-life of 64 hr, penetrating up to 10.8 mm in soft tissue although the effective therapeutic range is 2.8 mm (defined as the distant soft tissue in which 90% of the absorbed dose is deposited) [34]. Despite high radiation doses to (peri)articular tissues, there are no reports of subsequent synovial, chondral or periarticular bone tumor formation. However, some activity may escape from the joint and since this is in colloidal form, draining lymph nodes can receive significant absorbed dose and lymphocyte chromosomal damage may occur. The clinical impact of this chromosomal damage is unknown.

For many years, dosages of 5 mCi (185 MBq) were given out of fear of inducing chromosomal damage by higher dosages, resulting in high recurrence rates (~50%) [35, 36]. At present, doses of 15–25 mCi (555–925 MBq) are administered at 6–8 weeks postoperatively, with dose adjustment according to joint volume and body size [36–39]. Intra-articular radioactive colloids seem safe and effective after subtotal synovectomy, even if caution is advised when treating benign lesions with radioactive agents. However, there is little evidence to support this practice, as case series are small and prospective trials are lacking (Table 7).

Table 7 Arthroscopic and open synovectomy followed by isotopic synoviorthesis for Dt-GCT in the knee and hip joints

	Year	NOS	Synovectomy	n	Location	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Arthroscopic synovectomy with isotopic synoviorthesis									
Ozturk [39]	2008	3	Partial + ^{90}Y	3	Knee	48 (24-97)	0	0%	
Zook [91]	2011	3	Partial + Phosphorus-32	1	Hip	20 (2-48)	1	100%	None (n=1)
Kat [92]	2000	4	Complete + ^{90}Y	3	Knee	12	1	33%	N/A
Kat [92]	2000	4	Partial + ^{90}Y	1	Knee	12	0	0%	
Total				**9**			**2**	**22% (0-100%)**	
Open synovectomy with isotopic synoviorthesis									
Groulier [70]	1991	4	Complete + ^{90}Y	1	Knee	N/A	0	0%	
Kat [92]	2000	4	Complete + ^{90}Y	4	Knee	12	1	25%	N/A
Kat [92]	2000	4	Complete + Rhenium-186	3	Hip	12	0	0%	
Shabat [38]	2002	3	Partial + ^{90}Y	6	Knee	72 (30-144)	0	0%	
Chin [82]	2002	4	Complete + Dysprosium-165	30	Knee	60 (18-96)	5	17%	Open synovectomy + Dysprosium (n=2)
Ozturk [39]	2008	3	Partial + ^{90}Y	4	Knee	48 (24-97)	0	0%	
Zook [91]	2011	3	Complete + Phosphorus-32	8	Knee	20 (2-48)	2	25%	Phosphorus-32 (n=1), open synovectomy (n=1)
Total				**52**			**8**	**15% (0-25%)**	

NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies
N/A = Not available

Radiation therapy

External beam radiation can be a primary treatment in unresectable disease or an adjuvant treatment in incompletely resectable or recurrent Dt-GCT, improving local tumor control [25, 40–43]. Moderate dose external beam radiation (total of 35 Gy) offers a high chance of local control (75–98%) with avoidance of long-term radiotherapy induced toxicity. Most authors recommend radiotherapy prior to the moment that significant joint destruction occurs, particularly in recurrent disease. Radiotherapy is not advocated in the joints of hand and foot. Results of arthroscopic and open synovectomy followed by adjuvant radiotherapy for Dt-GCT in the knee are listed in Table 8. Radiation doses ranged between 16–50 Gy. All patients had unresectable primary disease, unresectable residual disease after subtotal synovectomy or recurrent disease. Average recurrence rates ranged between 6 and 13% and were comparable for different tumor sites (Tables 6 and 8). No significant complications of radiotherapy were seen in any of the patients.

Systemic targeted therapy

Systemic targeted therapy against the M-CSFR can be a novel treatment—given the molecular characterization of Dt-GCT—for patients in whom surgery would result in significant functional impairment or who present with unresectable or rapidly recurring Dt-GCT.

Although the M-CSF overexpression is present in a minority of neoplastic cells, the majority of mononuclear and multinucleated stromal cells in Dt-GCT express high levels of M-CSFR, responsible for the earlier described landscape effect and formation of a tumor mass (see Genetics section) [23, 44]. This signaling pathway seems a promising target for systemic therapy targeting M-CSFR such as imatinib, nilotinib or sunitinib [45].

This section focuses on the available literature for imatinib. This is a small molecule registered for chronic myeloid leukemia (CML), dermatofibrosarcoma protuberans (DFSP), and gastrointestinal stromal tumor (GIST). Besides the Abelson (Abl), Arg (abl-related gene), stem cell factor receptor (Kit) and platelet-derived growth factor receptor A and B (PDGFRA and PDGFRB) tyrosine kinases, M-CSFR is one of its main targets [46]. Tumor regression is seen in patients with advanced Dt-GCT after treatment with imatinib [47–49].

Table 8 Arthroscopic and open synovectomy with external beam radiation for extensive Dt-GCT located in the knee

	Year	NOS	Synovectomy	n	FU (months)	Recurrences	Recurrence rate (range)	Re-interventions
Arthroscopic synovectomy with EBRT								
Blanco [25]	2001	4	Partial + EBRT	22	33 (26-76)	3	14%	Arthroscopic synovectomy (n=3)
Berger [42]	2007	4	Complete + EBRT	1	29 (3-112)	0	0%	
Total				**23**		**3**	**13% (0-14%)**	
Open synovectomy with EBRT								
Groulier [70]	1991	4	Complete + EBRT	1	N/A	0	0%	
De Visser [28]	1999	4	Partial + EBRT	3	48 (12-228)	2	67%	Partial synovectomy (n=1), partial synovectomy + EBRT (n=1)
Chin [82]	2002	4	Complete + EBRT	5	60 (18-96)	2	40%	TKA*
O'Sullivan [40]	2005	4	Complete + EBRT	15**	69 (13-250)	1	7%	Partial synovectomy (n=1)
Berger [42]	2007	4	Complete + EBRT	4	29 (3-112)	0	0%	TKA (n=1)
Wu [93]	2007	5	Complete + EBRT	9**	67 (37-103)	1	11%	None (n=1)
Ozturk [39]	2008	3	Partial + EBRT	3	48 (24-97)	0	0%	
Nassar [94]	2009	4	Partial + EBRT	12	27 (20-36)	0	0%	
Total				**52**		**6**	**12% (0-67%)**	

NOS = Newcastle-Ottawa Scale for quality assessment of cohort studies
TKA = Total knee arthroplasty
EBRT = External beam radiation therapy
N/A = Not available
* Overall, four TKA were performed in this paper (n=40)
** All patients had extra-articular disease

In 2008, the first case report of the activity of imatinib in recurrent M-CSFR dependent Dt-GCT was published [47]. The patient was treated with imatinib 400 mg/day and a complete response was induced after 5 months of therapy. Following discontinuation of imatinib, the disease recurred. Reintroduction induced a secondary complete remission.

In two case series, promising results of imatinib therapy were reported [45, 49]. Pain reduction (5 out of 6), disease regression (3 out of 6), and stable disease (2 out of 6) were achieved in the first report [45]. Additionally, results from 27 evaluable patients were presented in a multi-center retrospective study. This series revealed one complete remission, four partial remissions, and 20 patients with stable disease. Two patients had pulmonary or bone metastases. In 16 patients, symptomatic improvement was seen. Six patients discontinued therapy because of side effects and four because of non-medical reasons [49]. The most common side effects were fatigue, nausea, mild fluid retention and skin toxicity. Therefore the risk-benefit ratio should be considered in determining the utility of this treatment approach.

Although the action of imatinib in Dt-GCT seems clear, the potential contribution of the blockade of other tyrosine kinases by imatinib cannot be ruled out. Currently, the role of nilotinib and PLX108-01 are investigated as systemic treatment in advanced Dt-GCT (www.ClinicalTrials.gov) [50, 51].

Conclusions

Results of a systematic literature search on surgical and adjuvant treatment, recurrence rates, and complications are listed in Tables 2-8. In all tables, the mean and range of the recurrence rates is provided for different treatment modalities, to estimate the true recurrence rates with more precision. The results were difficult to compare due to significant differences in location, disease extent, treatment protocols, and the small number of patients in reported case-series and the absence of randomized trials. Therefore, recurrence rates varied widely, suggesting heterogeneity of the included studies and lack of reliable evidence. Our multidisciplinary treatment recommendations, based on both authors' opinion and available evidence, are displayed in Figure 7.

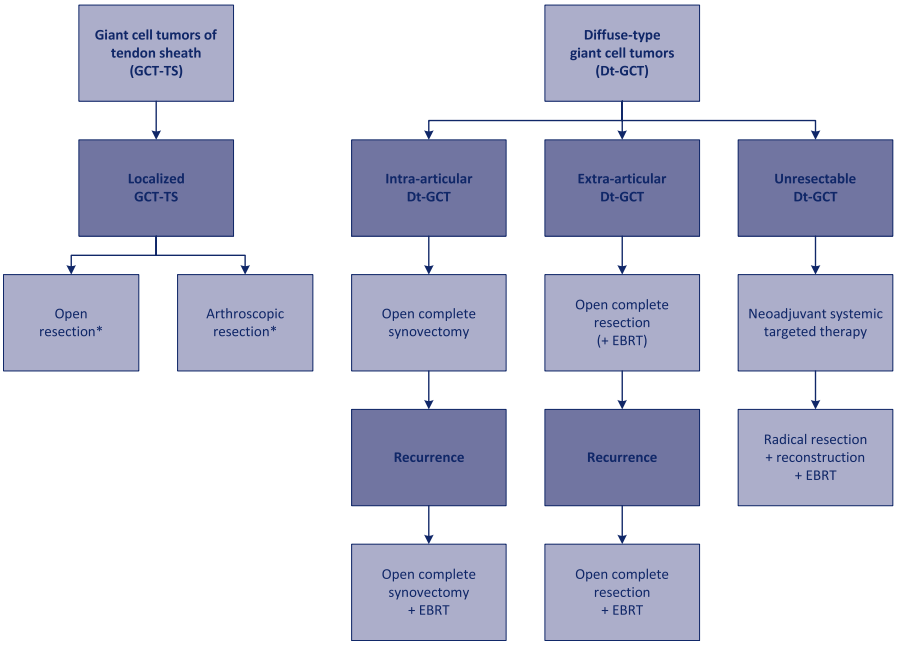

Figure 7 Multidisciplinary integrated treatment protocol for different forms of giant cell tumors of synovium and tendon sheath. Although good results have been published on arthroscopic treatment, an open approach is preferred preventing contamination and potentially reducing recurrence risk in the authors' opinion. EBRT = Moderate dose external beam radiation therapy.

First, good results have been published on arthroscopic treatment. However, an open approach prevents contamination and potentially reduces the (low) recurrence risk. Therefore, in the authors' opinion localized GCT-TS would require an open resection of the lesion, even though recurrences are rare.

Second, in case of diffuse intra-articular joint involvement, one or two-stage (separate) open complete synovectomy is recommended. We believe that an arthroscopic approach for Dt-GCT about the knee presents a high risk of leaving residual tumor behind and thus increasing the recurrence risk. In selected cases without extra-articular in-growth, instillation of intra-articular radioactive colloids can be a safe and effective local adjuvant, although there is little evidence. Local recurrences can be treated with open (two-stage separate) repeated synovectomy and resection of all affected tissue followed by moderate dose external beam radiation.

Third, in case of diffuse *extra*-articular joint involvement, we recommend one- or two-stage (separate) open synovectomy with resection of all affected

soft tissues. There is no indication for the use of *intra*-articular instillation of radioactive colloids for Dt-GCT with an *extra*-articular component. Recurrences can be treated by open complete synovectomy, resection of all affected surrounding tissues and postoperative moderate dose radiotherapy.

Fourth, in case of unresectable disease we recommend radical resection and joint reconstruction followed by radiotherapy. Treatment with neoadjuvant systemic therapy targeting M-CSFR (e.g. imatinib, nilotinib in studies) can be considered for unresectable disease and when radiotherapy is not an option. Data on large study populations will be available in the near future. The use of systemic targeted therapy as primary treatment or as neoadjuvant treatment before surgery would need further testing in prospective trials. Optimal agent, mono- versus combination therapy, optimal balance between benefits of alleviating functional impairment against potential toxicity of therapy, therapy duration, surgery timing and mechanisms of therapy resistance require further investigation to optimize systemic treatment of Dt-GCT.

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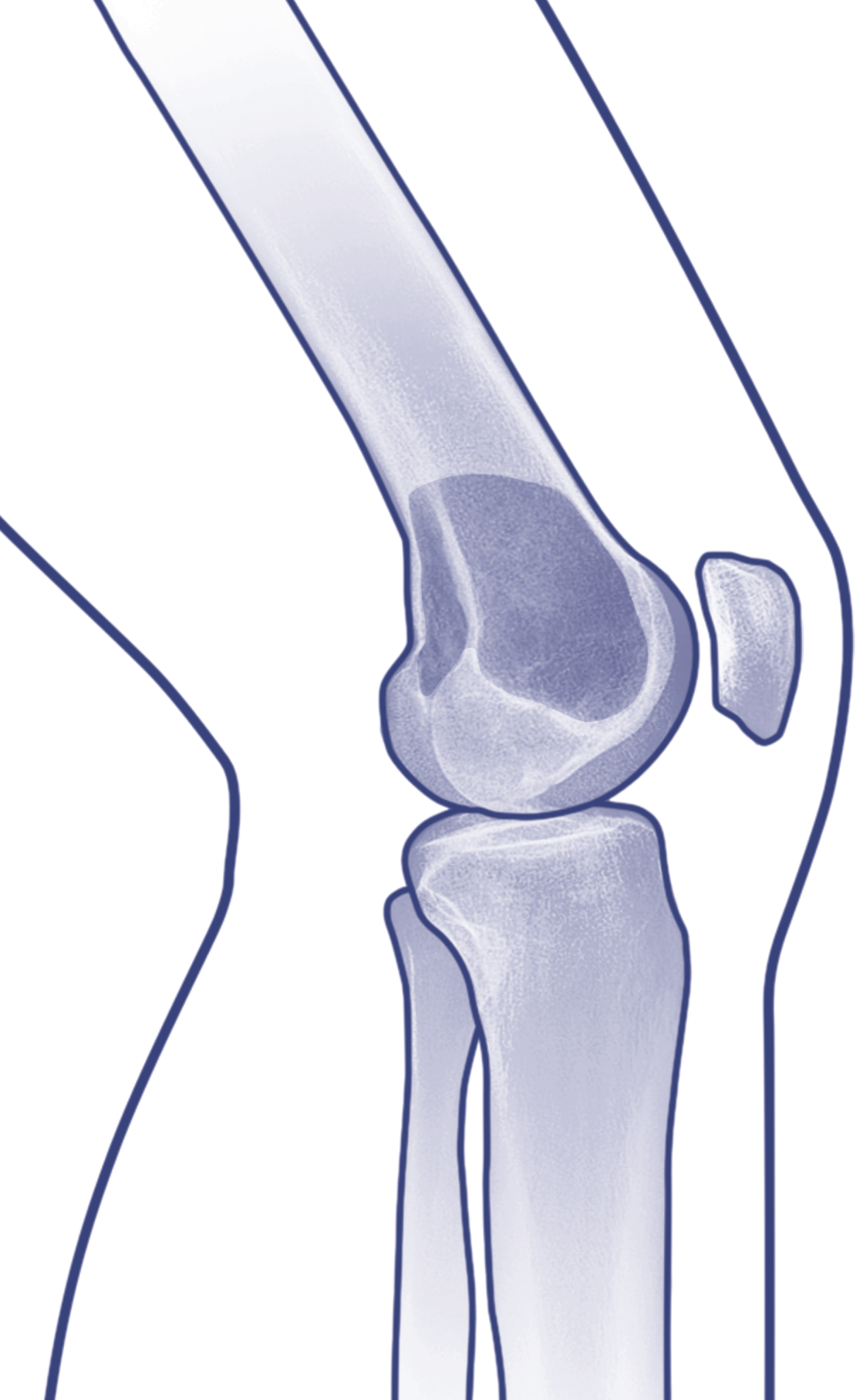

Chapter 11

Functional outcome and quality of life after surgical treatment of diffuse-type giant cell tumor about the knee – A retrospective analysis of 30 patients

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Abstract

Background We evaluated influence of type of surgery on functional outcome and quality of life (QOL) for diffuse-type giant cell tumor (Dt-GCT) about the knee, previously known as pigmented villonodular synovitis (PVNS).

Patients and methods We retrospectively reviewed 30 patients; 15 primarily treated at our tertiary center, 15 referred with recurrence (1980-2011). Median follow-up was 95 months (24-393). Functional outcome and QOL were assessed with range of motion, Knee injury and Osteoarthritis Outcome Score (KOOS), Musculoskeletal Tumor Society (MSTS) score, Toronto Extremity Salvage Score (TESS), SF-36. Results were compared with Chi-squared, Fisher's Exact and Mann-Whitney U tests.

Results From 14 patients with open synovectomy as index surgery, 4/14 recurred. Local control was achieved after second procedure in 75%. From 16 patients with arthroscopic synovectomy as index surgery, 15/16 recurred. These patients underwent mean 1.8 arthroscopies (range 1-8) before open synovectomy at our center; the latter resulting in local control after one attempt in 47% and two attempts in 73%. After initial arthroscopic synovectomy and subsequent surgical procedures, impaired function and QOL were reported compared to initial open synovectomy: range of motion (114*vs.*127 degrees, p=0.03), KOOS (48*vs.*71, p=0.003), MSTS (19*vs.*24, p=0.02), TESS (75*vs.*86, p=0.03) and SF-36 (62*vs.*80, p=0.01).

Conclusions The majority of patients referred with recurrence underwent initial arthroscopy and multiple re-synovectomies. At latest follow-up, these patients had impaired function and QOL compared to patients who underwent initial open synovectomy and fewer subsequent surgeries. We may therefore conclude that the course of extensive disease treated with arthroscopic synovectomy is not favorable and that primary open synovectomy should be treatment of choice for severe Dt-GCT to prevent recurrent or residual disease activity.

Introduction

Tenosynovial giant cell tumors are classified as localized and diffuse type [1,2]. In this study, we focused on diffuse-type giant cell tumor (Dt-GCT; previously known as pigmented villonodular synovitis), a benign but locally aggressive tumor with the capacity for autonomous growth and invasion of bone. The presence of chromosomal aberrations suggests a neoplastic rather than reactive origin [3]. Dt-GCT develops in synovial lining of joints, tendon sheaths and bursae [4]. It is mostly monoarticular and involves the knee in 75%, the hip in 15% and other localizations such as ankle, elbow and shoulder in 10%. It often involves the entire synovium and may have extra-articular, infiltrative soft tissue masses. There is an equal distribution between sexes, it mainly occurs between the ages of 30-40. Incidence is estimated at two per million annually [1,5]; but this may be an underestimation as the awareness on this disease is growing and diagnostic methods are improving. Patients present with nonspecific symptoms as pain, locking, limited range of motion and hemorrhagic joint effusion [1,6]. There may be delays of years between onset of complaints and diagnosis [6].

Several treatment options exist for Dt-GCT about the knee, including arthroscopic or open synovectomy, intra-articular radioactive colloids, radiation therapy, systemic targeted therapy, or a combination of the above [7]. At present, surgery remains treatment of choice as there is little evidence supporting single use of abovementioned therapies [5,7].

Arthroscopic synovectomy is commonly performed for Dt-GCT and is propagated in some papers for hypothesized better functional results and possibly lower complication rates (e.g. joint stiffness, infection) [8,9]. However, mean recurrence rate after arthroscopic synovectomy for Dt-GCT about the knee remains high at 40% (range 0-92) [7]. As it may be technically difficult to resect all tumor mass, especially with extra-articular spread, adjuvant treatments or multiple reoperations are often required to treat residual disease [7,10-12]. Additionally, there is a risk for disease progression with arthroscopic synovectomy due to use of a shaver and recurrences have been reported in the tract of arthroscopic portals [6,11].

Open synovectomy is mainly advocated to minimize recurrence rate [5,7,10]. Mean reported recurrence rate after open synovectomy for Dt-GCT about the knee is 14% (range 0-67) [7]. Although open synovectomy may

decrease risk for recurrence, this may be at the cost of prolonged hospital stay and rehabilitation time, joint stiffness, increased morbidity and possibly functional loss.
Residual disease and multiple recurrences may result in functional impairment and often necessitate multiple interventions and eventually even joint replacement. Therefore, primary treatment decision should decrease recurrence rates, minimize surgical morbidity and provide optimal functional outcome and quality of life (QOL). The purpose of this study was to evaluate influence of disease severity and surgical treatment on functional outcome and QOL for Dt-GCT about the knee. We hypothesize that open synovectomy as index surgery does not in itself result in impaired function and QOL compared to arthroscopic synovectomy and subsequent surgical procedures required for obtaining local control.

Patients and methods

In this retrospective single-center study, we evaluated 38 consecutive patients with Dt-GCT about the knee treated in a tertiary center for musculoskeletal oncology between 1980 and 2011. Eight patients were excluded: three died unrelated to Dt-GCT, three had incomplete data, one had an unclear diagnosis and in one patient Dt-GCT was an incidental finding during total knee replacement. Thirty patients were included, 17 were female. Mean age was 34 years (range 6-73). Median follow-up was 95 months (range 24-393). Fifteen patients were primarily treated at our center and fifteen patients were referred with recurrent Dt-GCT (Figure 1). No patients were recalled specifically for this study; all data were obtained from medical records, imaging, histopathological evaluation and questionnaires. We included demographic data, clinical presentation, imaging, histopathological evaluation, surgical treatment, recurrences, complications, functional outcome, QOL and follow-up. Initial disease severity was assessed on preoperative magnetic resonance imaging (MRI). Dt-GCT only includes the diffuse type of tenosynovial GCT, which was further subcategorized as mild and severe Dt-GCT. Mild Dt-GCT was defined as an isolated involvement of either anterior or posterior knee compartment. Severe Dt-GCT was defined as involvement of both the anterior and posterior knee compartment, with or without extra-articular

extension. Diagnosis was confirmed by preoperative (n=9) or intraoperative (n=21) biopsy. All data were complete. This study was approved by the local ethics committee.

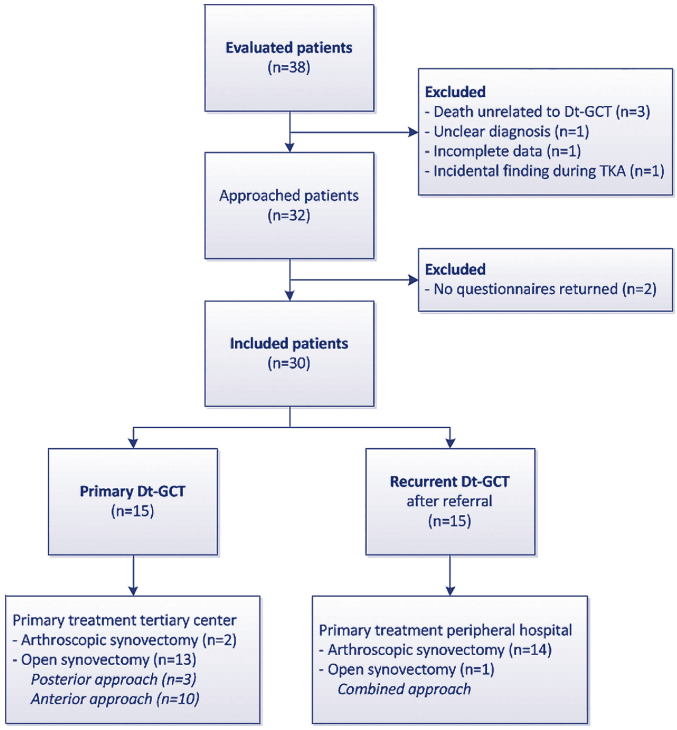

Figure 1 Flowchart of patients with Dt-GCT about the knee

Arthroscopic synovectomy was performed with the use of both a 30° and 70° arthroscope through standard portals and techniques [13,14]. As arthroscopic synovectomy was performed in referring hospitals, specifics on surgical techniques cannot be provided.

At our center, standard treatment consisted of open synovectomy, performed by fellowship-trained oncological-orthopedic surgeons. For good visualization, we use a midline anterior approach for anterior disease and an extensile lazy-S incision for posterior disease [5]. For primary and recurrent Dt-GCT in both anterior and posterior compartments, we nowadays standard perform combined surgery with posterior open synovectomy followed by anterior open synovectomy 4-6 weeks later. For severe recurrent disease and osteoarthritis

of the knee, resection with endoprosthetic replacement was considered in individual cases. Postoperative treatment involved early active and passive mobilization, including continuous passive motion after anterior open synovectomy and extension splint after posterior open synovectomy. Follow-up protocol included clinical evaluation at 2, 6 and 12 weeks postoperative, annually up to 5 years and biannually up to 10 years as local recurrence and osteoarthritis are likely to occur.

Diagnosis at presentation was not always certain and in some patients Dt-GCT was an incidental finding during knee surgery. Initial synovectomy in referring hospitals was therefore hypothesized to be incomplete and was often repeated. After referral, histopathological diagnosis of Dt-GCT was confirmed at our center and MR imaging was repeated for all patients; this allowed for optimal surgical planning in case of recurrent or residual disease.

Functional outcome was assessed with range of motion, Knee injury and Osteoarthritis Outcome Score (KOOS) [15], Musculoskeletal Tumor Society (MSTS) score [16], Toronto Extremity Salvage Score (TESS) [17]; QOL with SF-36 [18] at mean 8 years (range 2-32) after index surgery.

Statistical analysis

Differences in dichotomous data were calculated with Chi-squared and Fisher's exact tests and in numerical data with Mann-Whitney U tests. We used SPSS 20.0 (SPSS Inc, Armonk, NJ, USA) for statistical analysis. The level of statistical significance was set at $p<0.05$.

Results

Preoperative disease severity was mild in 15 and severe in 15 patients. Fourteen patients underwent initial open synovectomy (one in referring hospital) and 16 initial arthroscopic synovectomy (14 in referring hospital) at index surgery (Table 1).

Table 1 Patient, tumor and treatment characteristics for Dt-GCT about the knee

	Total	Initial open synovectomy		Initial arthroscopic synovectomy		p-value
	n	n	%	n	%	
Total	30	14	-	16	-	-
Primary treatment in tertiary center	15	13	93	2	12	<0.001
Referred with recurrence	15	1	7	14	88	-
Mild Dt-GCT	15	10	71	5	31	0.033
Severe Dt-GCT	15	4	29	11	69	-
		mean	range	mean	range	
Age (years)		44	11-77	43	17-69	1.0
Follow-up (months)		128	29-396	120	24-403	0.94
Number of recurrences		1.4	1-4	3.4	1-10	-
Number of open synovectomies		-	1-4	-	0-4	0.31
Number of arthroscopic synovectomies		-	0-1	-	1-8	<0.001

From 14 patients with initial open synovectomy, 10 had mild Dt-GCT and four had severe Dt-GCT. After initial open synovectomy, four of 14 had recurrence (three of four with severe Dt-GCT); three had one recurrence and one had three recurrences.
From 16 patients with initial arthroscopic synovectomy, five had mild Dt-GCT and 11 had severe Dt-GCT. After initial arthroscopic synovectomy, 15 of 16 had recurrence (11 of 11 with severe Dt-GCT); five had one recurrence and 10 had multiple recurrences (range 2-9) (Table 2).

From the patients initially treated with arthroscopic synovectomy, fifteen underwent open synovectomy after a mean of 1.8 surgical interventions (range 1-8) with arthroscopic synovectomy. Within this group, the first open synovectomy at our tertiary center resulted in local control for seven patients (47%) with a mean follow-up of 55 months (range 24-124). Secondary open synovectomy was performed in an additional four cases without any further recurrences (73%; mean follow-up 123 months; range 47-212) (Table 2) .

Table 2 Patient and tumor characteristics, surgical treatment, recurrences, functional outcome and quality of life results for patients with Dt-GCT about the knee

Pt	Sex	Age	Primary/ referred	Year	Severity of Dt-GCT	Surgical interventions			Recurrences	Adjuvant therapy	ROM	KOOS	MSTS	TESS	SF36	FU
		(years)				n	Primary treatment	Treatment for recurrences	n (months)[1]		(degrees)					(months)
Open synovectomy																
1	M	25	primary	1980	mild	2	OS (A)[2]	AS	1 (17)	-	110	12	10	46	56	372
2	M	43	primary	1996	mild	1	OS (A)		-	-	135	58	20	78	64	200
3	F	29	primary	2000	mild	1	OS (A)		-	-	140	53	23	76	80	156
4	F	47	primary	2000	severe	2	OS (P)	AS	1 (19)	-	140	94	27	99	85	152
5	F	17	primary	2004	severe	1	OS (P)		-	-	120	64	22	89	79	107
6	F	57	primary	2004	mild	1	OS (A)		-	-	100	72	26	84	76	95
7	M	21	primary	2004	mild	1	OS (P)		-	-	140	79	29	90	90	97
8	F	30	primary	2006	mild	1	OS (A)		-	-	140	70	26	96	71	79
9	F	24	referred	2006	severe	4	OS (C)	OS (P), OS (P), OS (EPR)	3 (12)	EBRT; TKI	95	58	22	82	69	82
10	M	6	primary	2007	mild	1	OS (A)		-	-	130	99	30	100	98	60
11	F	73	primary	2008	mild	1	OS (A)		-	-	140	68	17	69	72	51
12	F	58	primary	2008	mild	1	OS (A)		-	-	120	89	26	100	91	49
13	F	17	primary	2010	mild	1	OS (A)		-	-	140	95	30	100	94	34
14	F	31	primary	2010	severe	2	OS (A)	OS (C)	1 (20)	-	130	79	29	88	93	29
Arthroscopic synovectomy																
15	M	33	referred	1980	severe	10	AS	AS, AS, AS, AS, OS (A), AS, AS, AS, OS (TKR[6])	9 (41)	^{90}Y	120	35	18	83	80	393
16	F	11	referred	1995	severe	3	AS	OS (A), **OS (A)**	3 (9)	-	125	57	12	71	61	212
17	F	38	primary	1997	severe	7	AS[5]	OS (A), OS (A), OS (A), AS, AS, OS (A)	6 (4)	TKI	90	14	8	63	49	182

Table 2 Continued

Pt	Sex	Age	Primary/ referred	Year	Severity of Dt-GCT	Surgical interventions			Recurrences	Adjuvant therapy	ROM	KOOS	MSTS	TESS	SF36	FU
		(years)				n	Primary treatment	Treatment for recurrences	n (months)[1]		(degrees)					(months)
18	M	27	referred	1999	severe	4	AS	OS (A), OS (C), OS (A)	3 (19)	^{90}Y	120	37	17	84	83	160
19	F	16	referred	2001	severe	3	AS	OS (A), **OS (A)**	2 (13)	^{90}Y; TKI	120	44	18	73	64	137
20	M	35	referred	2002	severe	2	AS	**OS (C)**	1 (25)	^{90}Y	100	49	16	69	81	124
21	F	26	referred	2002	mild	2	AS	**OS (P)**	1 (3)	Anti-TNFα ; MTX	110	64	30	45	26	122
22	F	35	primary	2003	mild	1	AS		-	-	140	69	24	89	84	110
23	F	18	referred	2005	severe	2	AS	**OS (A)**	1 (82)	^{90}Y	90	25[3]	9[3]	52[3]	48[3]	92
24	M	41	referred	2005	mild	3	AS	OS (P), OS (P)	2 (45)	-	130	95	30	96	94	95
25	F	62	referred	2006	mild	3	AS	OS (A), AS[4]	2 (45)	-	140	43	21	88	44	84
26	M	40	referred	2008	mild	2	AS	**OS (A)**	1 (40)	-	110	45	22	72	50	50
27	M	59	referred	2009	severe	3	AS	OS (C), **OS (EPR)**	2 (26)	-	110	52	18	69	63	47
28	M	25	referred	2009	severe	4	AS	AS, AS, **OS (C)**	3 (12)	^{90}Y; EBRT	110	33	18	80	42	38
29	M	48	referred	2010	severe	3	AS	AS, **OS (C)**	1 (19)	-	95	37	22	68	38	34
30	M	15	referred	2011	severe	2	AS	**OS (C)**	1 (10)	-	110	72	28	95	78	24

Pt = patient, ROM = range of motion, FU = follow-up, OS = open synovectomy, AS = arthroscopic synovectomy, (A) = anterior approach, (P) = posterior approach, (C) = combined anterior and posterior approach, EPR = endoprosthetic replacement, TKR = total knee replacement, ^{90}Y = ^{90}Yttrium, EBRT = external beam radiation therapy, MTX = methotrexate, TKI = tyrosine kinase inhibitor, anti-TNF-α = anti tumor necrosis factor α.

[1]First recurrence after n months

[2]Postoperative complication: recurrent haemarthros and secondary osteoarthritis

[3]Scores obtained during postoperative rehabilitation period

[4]Final AS was performed elsewhere

[5]Postoperative complication: urinary tract infection

[6]Three AS and final TKR were performed elsewhere

After initial open synovectomy, complications were reported in two patients. One patient had recurrent hemarthrosis that required repeated surgical debridement. This patient also developed secondary osteoarthritis at the age of 35, ten years after initial surgery; radiological and clinical progression of osteoarthritis was noted in the next years. Another patient had refractory Dt-GCT and knee osteoarthritis after three open synovectomies; this was treated with resection and endoprosthetic reconstruction. After initial arthroscopic synovectomy, complications were reported in three patients. Two patients had refractory Dt-GCT and developed knee osteoarthritis (after two and nine surgical interventions); both underwent open resection, one total knee replacement and one endoprosthetic reconstruction. One patient sustained a urinary tract infection, successfully treated with antibiotics.

Patients with initial open synovectomy reported higher scores for all functional and QOL results compared to initial arthroscopic synovectomy and all subsequent surgical procedures and similar scores as healthy controls from an age- and gender matched general population (Figure 2). Mean range of motion was 127 degrees (range 95-140) in the open synovectomy group and 114 (range 90-140) in the arthroscopy group (p=0.03). Similar differences were seen in reported outcomes of KOOS (71 *vs.* 48, p=0.003), MSTS (24 *vs.* 19, p=0.02), TESS (86 *vs.* 75, p=0.03) and SF-36 (80 *vs.* 62, p=0.01) (Table 3).

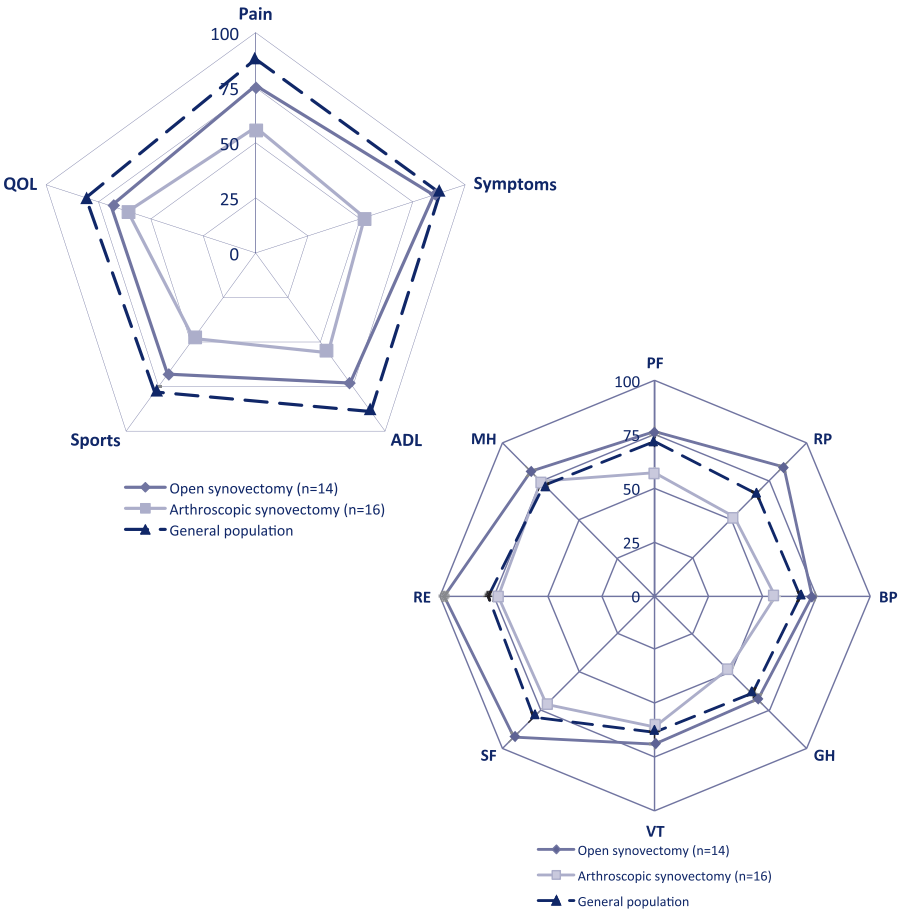

Figure 2 (A) KOOS and (B) SF-36 for patients with initial open or arthroscopic synovectomy for Dt-GCT about the knee, compared with age-matched healthy peer controls. ADL=Activities of daily living, QOL=Quality of life, PF=Physical functioning, RP=Role limitations due to physical functioning, BP=Bodily pain, GH=General health, VT=Vitality, SF=Social functioning, RE=Role limitation due to emotional functioning, MH=Mental health.

Table 3 Functional outcome and quality of life after initial open synovectomy or initial arthroscopic synovectomy and all subsequent surgeries before local control was obtained

	Initial open synovectomy		Initial arthroscopic synovectomy		p-value
	mean	range	mean	range	
Range of motion (degrees)	127	95-140	114	90-140	0.03
MSTS	24	10-30	19	8-30	0.02
TESS	86	46-100	75	45-96	0.03
KOOS	71	12-99	48	14-95	0.003
SF-36	80	63-98	62	26-94	0.01

Discussion

Most studies on tenosynovial GCT are case series including diffuse and localized types, primary and recurrent disease, different localizations, and arthroscopic and open synovectomy. Authors did not always distinguish between these factors when analyzing their data [13,19-22]. The majority of studies on treatment of Dt-GCT about the knee reported only oncological results; few studies described objectified functional results, and to our knowledge QOL has never been evaluated. Therefore, we evaluated influence of type of surgery on functional outcome and QOL for Dt-GCT about the knee.

Standard primary treatment of Dt-GCT at our center consisted of open synovectomy. From thirteen patients, three had recurrent Dt-GCT (23%)—all had severe Dt-GCT. Primary arthroscopic synovectomy was performed in referring hospitals, most of these patients had severe Dt-GCT. Disease eradication can be difficult in case of wide spread disease and multiple re-synovectomies were needed after initial arthroscopy, suggesting that disease extent increases the recurrence risk. Additionally, MRI was not routinely used after surgery in most series and recurrence rates after arthroscopy may be underestimated [9,13,23]. Complication rate was low in this study and was not altered after multiple synovectomies. In literature, most common complications were joint stiffness (8-32%) [12,13,24], wound healing disorders and infection (2-20%) [24-26]. Secondary osteoarthritis has been reported in 24-48% after open synovectomy [10,24,26], and was objectified with Kellgren and Lawrence grading in one study [10,27]. Total knee arthroplasty was required in 8-10% of patients with osteoarthritis [24,26]. We observed osteoarthritis in four patients (13%), two after open synovectomy with 1-3 reinterventions and two after arthroscopic synovectomy with 2-9 reinterventions. Three underwent resection and total knee or endoprosthetic replacement; one is under observation.

Functional results after surgical treatment for Dt-GCT have been reported [6,9,10,13,19-24,28-33], but comparison is difficult as studies were heterogeneous and functional results were not specified for diffuse and localized types, primary and recurrent disease and different localizations (Table 4). In this study, both knee function and QOL were impaired for patients with initial arthroscopic synovectomy, of whom the majority presented with severe Dt-GCT and underwent multiple surgeries, compared with patients with initial open synovectomy and with healthy controls from an age- and gender-

matched general population (Figure 2) [18,34]. The long course of disease and the need for multiple surgeries has previously been reported to result in worse functional results in a large number of patients [20]. Patients who underwent initial open synovectomy, often for mild Dt-GCT and with fewer reoperations, had good functional results and QOL compared with patients with initial arthroscopy and with healthy controls from an age- and gender-matched general population [18,34], suggesting that preventing recurrent disease with open synovectomy does not have a negative influence on functional outcome and QOL.

Our study has several limitations. First, it is unknown how many patients were treated successfully in peripheral hospitals, so we were unable to provide a reliable recurrence rate after arthroscopic synovectomy. This may have resulted in selection bias, probably overestimating the inferior results of arthroscopic synovectomy. Second, numbers in this study may have been too small to conclude that open synovectomy has a lower recurrence rate than arthroscopic synovectomy for severe Dt-GCT (3/4 *vs.* 11/11).

In conclusion, the majority of patients referred with recurrence presented with severe Dt-GCT and underwent arthroscopic synovectomy before referral. Multiple re-synovectomies were required with the intent to cure. At latest follow-up, these patients reported lower functional and QOL results compared with patients who underwent initial open synovectomy in a tertiary center, affirming our hypothesis that open synovectomy does not result in impaired function or QOL. We may therefore conclude that the course of extensive disease treated with arthroscopic synovectomy is not favorable and that primary open synovectomy should be treatment of choice for severe Dt-GCT to prevent recurrent or residual disease activity.

Table 4 Literature overview on functional results after arthroscopic and open synovectomy for Dt-GCT

Study	Year	n	Localization	Primary or recurrent	Surgery type	GCT type	Follow-up (months)	Functional outcome	
							mean (range)		mean (range)
De Visser et al. [28]	1999	38	knee, hip, ankle	27 primary 11 recurrent	unspecified	29 diffuse 9 localized	48 (12-228)	MSTS	24 (15-30)
Zvijac et al. [13]	1999	14	knee	10 primary 4 recurrent	arthroscopic synovectomy	12 diffuse 2 localized	42 (8-83)	other	10 excellent/good, 2 fair, 2 poor[1]
Shabat et al. [29]	2002	10	knee, ankle, hip	primary	unspecified	diffuse	72 (30-144)	MSTS	9 excellent, 1 unknown[1]
Chin et al. [23]	2002	40	knee	recurrent	open synovectomy	diffuse	60 (18-96)	KSS other[2]	92 (55-100) 92 (0-100)
De Ponti et al. [9]	2003	19	knee	primary	arthroscopic synovectomy[3]	15 diffuse 4 localized	60 (12-128)	other[4]	Complete arthroscopy: excellent[1] Partial arthroscopy: good[1]
Chiari et al. [20]	2006	42	knee, ankle, hip, foot, shoulder, hand	primary	open synovectomy	19 diffuse 23 localized	80 (26-194)	MSTS	28 (18-30)
Wu et al. [22]	2007	9	knee	5 primary 4 recurrent	open synovectomy	diffuse	67 (37-103)	KSS-knee KSS-function	94 (86-98) 97 (80-100)
Dines et al. [27]	2007	26	knee	primary	14 open synovectomy 12 arthroscopic synovectomy	localized	66 (46-123)	LKS[6]	95 (71-100)
Ozturk et al. [21]	2008	7	knee	primary	4 arthroscopic synovectomy 3 open synovectomy	diffuse	48 (24-97)	MSTS	21 (12-26)
Nassar et al. [32]	2009	12	knee	unspecified	open synovectomy	diffuse	27 (20-36)	MSTS	25.5 (24-27)
Liu et al. [33]	2009	22	knee	primary	arthroscopic synovectomy	localized	22 (18-28)	LKS IKDC	95 (SD 3.5) 93 (SD 2.4)

Table 4 Continued

Study	Year	n	Localization	Primary or recurrent	Surgery type	GCT type	Follow-up (months)	Functional outcome	
							mean (range)		mean (range)
Akinci et al. [30]	2011	19	knee	unspecified	open synovectomy	15 diffuse 4 localized	80 (15-156)	KSS	8 perfect, 9 good, 2 bad[1]
Griffin et al. [19]	2012	50	knee, ankle, hip, foot, hand, wrist	22 primary 28 recurrent	unspecified	diffuse	94 (19-330)	MSTS-87[5] MSTS-93[5] TESS[5] other[5]	31 (25-35) 28 (19-30) 90 (65-99) 7 excellent, 34 good, 5 fair, 4 poor[1]
Nakahara et al. [10]	2012	17	knee	primary	open synovectomy	diffuse	65 (10-146)	KSS	97 (76-100)
Chen et al. [6]	2012	19	knee	17 primary 2 recurrent	open synovectomy	diffuse	98 (42-143)	TLKS	93 (86-100)
Loriaut et al. [31]	2012	30	knee	primary	arthroscopic synovectomy	localized	75 (12-144)	LKS	86 (83-88)
Current study	2013	30	knee	15 primary 15 recurrent	14 open synovectomy 16 arthroscopic synovectomy	diffuse	95 (24-304)	KOOS MSTS TESS SF-36	59 (12-99) 21 (8-30) 80 (45-100) 70 (26-98)

KSS = Knee Society Score; TLKS = Tegner-Lysholm Knee Score; LKS = Lysholm Knee Scale; IKDC = International Knee Documentation Committee, SD = standard deviation

[1]Functional outcome was not further quantified

[2]Functional outcome was based on pain, walking status, joint swelling, effusion, crepitus, locking, instability and range of motion

[3]In one patient after arthroscopy, removal of a voluminous popliteal cyst was performed using a posterior open approach

[4]Functional outcome was based on pain, synovitis/swelling, range of motion and function

[5]Functional outcome was obtained for only 14/50 patients

[6]Functional outcome was obtained for only 10/26 patients

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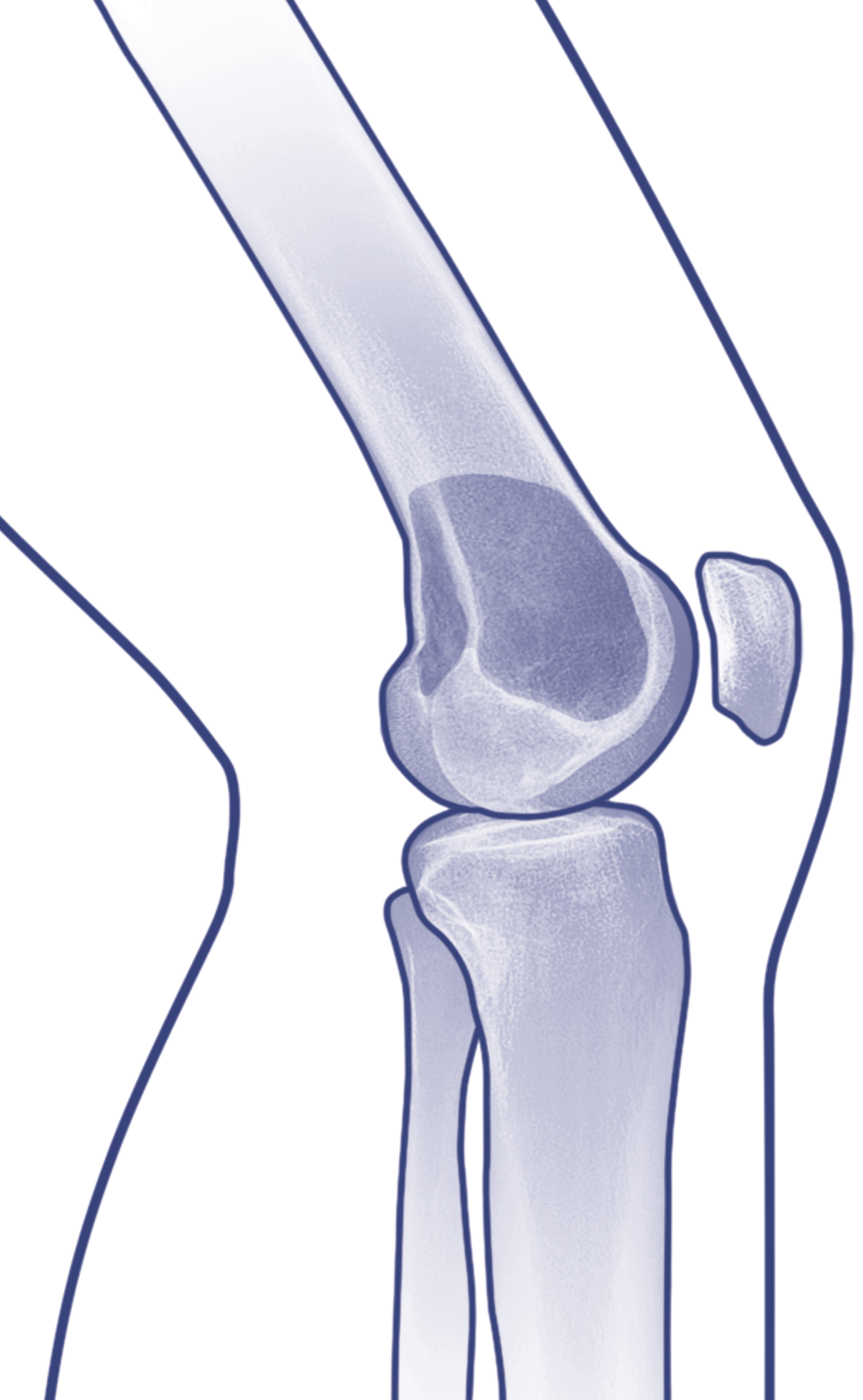


Chapter 12

General summary

General summary

Patients with giant cell tumor of bone and tenosynovial tissue pose challenging problems for surgical treatment. For giant cell tumor of bone (GCTB), the clinical challenge is to extend indications for intralesional excision, while providing optimal oncological, functional and quality of life results. For tenosynovial giant cell tumor (Dt-GCT), the clinical challenge is to improve oncological results and maintain a functional joint and quality of life. Therefore, the aims of this thesis were to improve patient selection for different types of surgery by identifying risk factors for recurrences and complications, to define indications for systemic targeted therapy and to evaluate clinical outcome after treatment for both diseases by providing a clinical decision analysis based on outcome data.

Giant cell tumor of bone

Chapter 2 provided an overview of imaging, genetics, histopathology and multidisciplinary treatment of GCTB. Overexpression of receptor activator of nuclear factor kappa-B ligand (RANKL) by mononuclear neoplastic stromal cells promotes recruitment of numerous reactive multinucleated giant cells capable of bone resorption. Radiologically, GCTB shows typical eccentric lytic lesions. Computed tomography can be performed to assess cortical thinning, pathologic fractures and (pending) joint involvement. MR imaging is required to evaluate extent of GCTB within the bone and surrounding soft tissues for surgical planning. MR imaging typically shows low to intermediate intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images. The preferred treatment for the majority of GCTB is extended curettage with local adjuvants. A large oval window is made in the cortex, creating sufficient exposure of the tumor cavity. The tumor is then carefully curetted with different sizes curettes followed by high-speed burring of cavity walls. Local adjuvants can be phenol, alcohol or liquid nitrogen. The remaining cavity may be filled with either bone grafts or polymethylmethacrylate (PMMA); advantages of the latter are a hypothesized lower recurrence risk through hyperthermic properties, immediate mechanical support and early radiographic detection of local recurrences. Reported recurrence rates are

comparable for different local adjuvants (27-31%); most recurrences occur within two years after surgery. Resection can be performed when joint salvage is not feasible and in expandable bones. Denosumab (RANKL-inhibitor) blocks and zoledronic acid (bisphosphonate) inhibits GCTB-derived osteoclast resorption. With zoledronic acid, 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 enabling less invasive forms of surgery. Denosumab was recently registered by the FDA for unresectable disease. Therefore, the role of systemic therapy in standard treatment of GCTB needs to be further explored. Moderate dose radiotherapy should be restricted to rare cases of unresectable, residual or recurrent GCTB when surgery would lead to unacceptable morbidity.

Chapter 3 compared the relative effectiveness of several local adjuvants in a retrospective cohort study in two tertiary referral centers in which different standard treatments are applied. Treatment assignment depended purely on the center patients were admitted to and both centers had similar indications for intralesional surgery and comparable surgical expertise (i.e. pseudo-randomization). Thus, 132 patients with primary GCTB who underwent either curettage with phenol and PMMA (P-PMMA; n=82), liquid nitrogen and PMMA (LN-PMMA; n=26) or liquid nitrogen and bone grafts (LN-BG; n=24) between 1990 and 2010 were retrospectively analyzed. Mean follow-up was 8 years (range 2 to 22). The three cohorts were comparable, except for tumor localization: bone grafts were more commonly applied instead of PMMA in non-weightbearing bones in the center specialized in cryosurgery. Recurrence rates were comparable for P-PMMA (28%; 23/82), LN-PMMA (31%; 8/26) and LN-BG (38%; 9/24) (p=0.52). Soft tissue extension increased risk for recurrence two-fold. When using liquid nitrogen, attention should be paid to the complication risk, as this was increased after LN-BG (33%; 8/24) and LN-PMMA (27%; 7/26) compared with P-PMMA (11%; 9/82) (p=0.019). In addition, preoperative pathologic fractures increased risk for complications four-fold. Functional outcome was excellent and comparable in all three cohorts (p=0.52).

Approximately 20% of patients with GCTB present with a pathologic fracture, which may impede adequate intralesional surgery. **Chapter 4** involved a retrospective multicenter analysis of 48 patients with a pathologic fracture, treated with curettage plus adjuvants (n=23) or *en bloc* resection (n=25) in one of three tertiary referral centers between 1981 and 2009. Mean follow-up was

8.4 years (range 2.3 to 24). Local recurrence rate was higher after intralesional surgery (30%; 7/23) compared with *en bloc* resection (0%) and was five-fold increased in patients with soft tissue extension. Complication rate was lower after intralesional surgery (4%; 1/23) compared with resection (16%; 4/25). Fracture healing after curettage occurred in all but one patient. Functional outcome was superior after intralesional surgery.

Approximately 2-5% of all GCTB occur in the small bones of the hands and feet. **Chapter 5** described a systematic review including twelve papers comprising a total of 91 patients with GCTB of the small bones. Published mean recurrence rates were 72% after curettage, 13% after curettage with local adjuvants, 15% after resection and 10% after amputation. Second, a retrospective multicenter analysis was performed of all 30 patients treated for GCTB of the small bones in one of five tertiary referral centers between 1987 and 2010. Mean follow-up was 7.9 years (range 2 to 26). Recurrence rates were 50% after curettage (3/6), 22% after curettage with adjuvants (4/18) and 17% after *en bloc* resection (1/6; p=0.40). No individual factors associated with a higher risk of recurrence or complication could be identified. Functional outcome was superior after intralesional surgery compared with resection. Repeated curettage and adjuvants finally resulted in cure of all patients.

Around 2-8% of all GCTB are localized in the sacrum. **Chapter 6** contained a nationwide retrospective evaluation of all 26 patients surgically treated for sacral GCTB in the Netherlands between 1990 and 2010. The majority of our patients had cortical destruction, large soft tissue components and sacral nerve root involvement at presentation. Preoperative selective arterial embolization was performed in nineteen patients. All patients underwent intralesional excision of which 21 with different local adjuvants, systemic therapy or adjuvant radiotherapy. In eight patients with extensive cortical destruction and soft tissue masses, no chemical adjuvants were used. Surgical margins were extended in four patients with anterior sacral wall excision. Posterior stabilization with lumbopelvic fixation with PMMA or bone grafts was indicated in three patients, reconstruction with bone grafts in seven and with PMMA in one. All but one patient had a minimum follow-up of two years (mean 8.3; range 0.5 to 19). Two patients died from tumor progression and metastases and one died from radiation-induced sarcoma (after 6-102 months). Overall recurrence rate was 54% (14/26). Soft tissue masses larger than 10 cm increased the risk for recurrence three-fold. Complications were reported in 46% (12/26) patients

and included massive hemorrhage, infection, neuropraxia, hardware failure, radiation-induced sarcoma, radiation-induced menopause, pubic dissociation fracture due to osteopenia after radiotherapy and delayed wound healing. Functional outcome in patients without complications was good. In eight patients, all preoperative symptoms resolved after surgery. Persistent pain was reported by eight patients. Neurological symptoms were transient in eight and permanent in five patients. Recurrence rate was highest after curettage alone (80%; 4/5), indicating that some kind of local or systemic adjuvant treatment is necessary.

Chapter 7 aimed at retrospectively analyzing individual risk factors for recurrence in 93 patients treated with curettage, phenol and PMMA (n=75) or curettage with PMMA (n=18) in one tertiary referral center between 1981 and 2009. Mean follow-up was 8 years (range 2 to 24). Twenty-five patients had recurrent GCTB (27%). Seventeen patients were disease free after second curettage with adjuvants and eight patients eventually required *en bloc* resection. We found a five-fold increased risk for recurrence in presence of soft tissue extension, whereas age, gender, localization and pathologic fracture did not increase recurrence risk.

Chapter 8 was a radiological study on the prevalence and impact of radiological osteoarthritis (Kellgren and Lawrence grades 3-4) in 53 patients who underwent curettage and PMMA for GCTB around the knee in one tertiary referral center between 1987 and 2007. Mean follow-up was 7 years (range 5 to 24). Radiological osteoarthritis was found in 17% of patients at a median of 57 months (range 33-285) after curettage and PMMA. None of these patients had surgery for clinical osteoarthritis at latest follow-up. A nine-fold increased risk for radiological osteoarthritis was found when more than 70% of subchondral bone was involved by GCTB and a four-fold increased risk for radiological osteoarthritis for a distance between GCTB and the articular cartilage of less than 3 mm. Functional outcome and quality of life were comparable for patients with Kellgren and Lawrence grades 3-4 and 0-2, suggesting modest clinical impact of radiological osteoarthritis at intermediate follow-up. However, this may increase with time and a prolonged follow-up is required.

Giant cell tumor of tenosynovial tissue

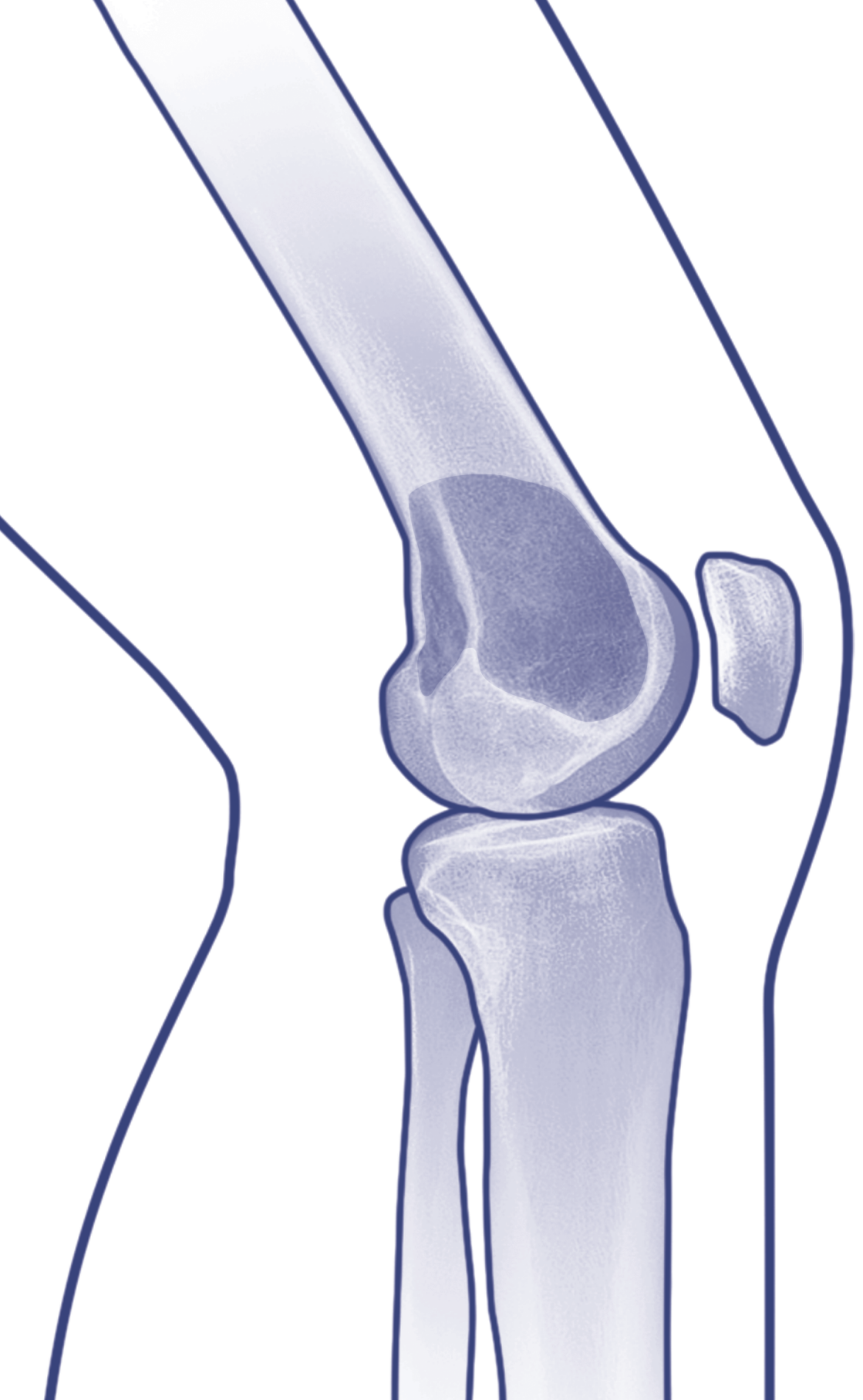
Chapter 9 outlined an overview of imaging, genetics, histopathology and multidisciplinary treatment of localized (GCT-TS) and diffuse type (Dt-GCT) tenosynovial giant cell tumor. Overexpression of macrophage colony-stimulating factor 1 (M-CSF) and its receptor (M-CSFR) by synovial fibroblasts promotes formation of a tumor-like mass. On MR images, hemosiderin depositions cause local changes in susceptibility, resulting in the characteristic low signal intensity appearance of Dt-GCT on T1- and T2-weighted spin echo and gradient echo sequences. Although arthroscopic synovectomy has been advocated as an alternative to open synovectomy, there is a significant risk of inadequate excision and recurrence, particularly in the posterior knee compartment. In addition, there is a risk of seeding the disease into the soft tissues around the portals. For GCT-TS or limited anterior Dt-GCT, arthroscopic synovectomy may be sufficient. For initial and recurrent Dt-GCT, especially in the posterior knee compartment, open synovectomy is advised. Combined or staged surgery may be considered. For posterior disease, a lazy-S incision is performed with elevation of the origin of the gastrocnemius muscle to protect neurovascular structures. This is followed by arthrotomy to visualize the posterior cruciate ligament and articular surfaces and a complete capsulotomy to achieve adequate synovectomy. For anterior disease, a midline anterior approach is advised, as this allows good visualization of the synovial cavity, fat pad, cruciate and collateral ligaments. Residual tumor adjacent to the joint line and unilateral gutters can also be safely resected. For recurrent and extra-articular disease, moderate dose radiotherapy or systemic targeted therapy can be considered. Although there is yet little evidence on the efficacy of neoadjuvant M-CSFR-targeted tyrosine kinase inhibitors (e.g. imatinib) for Dt-GCT treatment, it may in the future be incorporated in the treatment strategy for more extended disease, in analogy with systemic treatment for GCTB.

Chapter 10 presented a systematic review on tenosynovial giant cell tumor including 59 papers comprising a total of 313 patients with GCT-TS and 777 patients with Dt-GCT. Methodological quality (Newcastle-Ottawa Scale for quality assessment of cohort studies) was good in 40%, intermediate in 50% and poor in 10% of the included papers. Reported mean recurrence rates were 4% after open and 6% after arthroscopic synovectomy of GCT-TS in the knee and 14% after open and 40% after arthroscopic synovectomy of Dt-GCT in the

knee. With use of intra-articular radioactive colloids, mean recurrence rates were 15% after open and 22% after arthroscopic synovectomy for intra-articular Dt-GCT in the knee and hip. With adjuvant radiotherapy, mean recurrence rates were 12% after open and 13% after arthroscopic synovectomy for extra-articular Dt-GCT in the knee. In general, open synovectomy of the lesion plus excision of extra-articular disease is recommended to reduce the relatively high recurrence risk.

Chapter 11 retrospectively evaluated the influence of disease severity and type of surgery on functional outcome and quality of life in 30 patients treated for Dt-GCT in the knee between 1980 and 2011. Fifteen patients were primarily treated at our tertiary referral center; 15 were referred to our center with recurrence. Disease severity was assessed on preoperative MR imaging or imaging reports. Sixteen patients (53%) had simple disease, defined as a solitary pedunculated lesion or diffuse involvement of the anterior or posterior knee compartment. Fourteen patients (47%) had severe disease, defined as involvement of anterior and posterior compartments or extra-articular extension. Patients with initially severe Dt-GCT often underwent multiple surgeries including initial arthroscopic synovectomy and open synovectomy for latest recurrence. After a mean follow-up of 8 years (range 2-33), these patients reported significantly lower functional and quality of life results. In this study, primary open synovectomy did not result in impaired function or decreased quality of life when compared to arthroscopic synovectomy.

Conclusions, clinical implications and future perspectives for the subjects of this thesis are discussed in **Chapter 13**.



Chapter 13

General discussion

General discussion

Although giant cell tumors of bone and tenosynovial tissue are benign neoplasms, both have a locally aggressive character [1-3]. Therefore, treatment should be locally extended, which typically consists of intralesional excision with local adjuvants for giant cell tumor of bone and complete synovectomy with removal of all affected tissue for tenosynovial giant cell tumor. Local tumor control on the one hand and maintenance of a functional joint and quality of life on the other hand are the main pillars of surgical treatment for both disease entities.

Previously, treatment of both giant cell tumor of bone and tenosynovial tissue primarily consisted of surgical resection. Current knowledge and development in the fields of imaging, functional biology and systemic targeted therapy are forcing us into a paradigm shift from a purely surgical towards a multidisciplinary approach.

This thesis outlines the current state of the art concerning treatment of giant cell tumor of bone and tenosynovial tissue and the opportunities for further optimization of this multidisciplinary approach in the future. This thesis aims at improving patient selection for different types of surgery by identifying risk factors for recurrences and complications, defining indications for systemic targeted therapy and evaluating clinical outcome after treatment for both types of disease by providing for a clinical decision analysis based on outcome data.

Giant cell tumor of bone

Treatment decisions for giant cell tumor of bone (GCTB) should be made by a multidisciplinary team consisting of dedicated experts in the field of musculoskeletal oncology. This should include radiography, MR imaging, histopathological assessment and planned surgery, supplemented with systemic therapy if indicated, to improve oncological outcome especially in GCTB with a high risk for local recurrence or in uncurettable GCTB. These *high-risk* GCTB include, but are not limited to, cases with soft tissue extension, intra-articular pathologic fracture or localization in sacrum or spine.

Imaging

Existing classifications of Campanacci et al. [4] and Enneking et al. [5] are based on radiographic aspects of GCTB and became outdated with the advent of MR imaging. Hence, a new radiological classification is needed that incorporates other imaging modalities providing for a more accurate estimation of disease extent, evaluation of response to systemic therapy and detection of local recurrence. In addition, this should be integrated into a multidisciplinary classification with clinical and histopathological features in order to predict clinical behavior of GCTB and allow for optimal patient selection for specific treatment modalities based on individual risk profiles [6].

The appearance of GCTB on conventional radiographs is rather characteristic and this remains the first step in diagnosing primary and recurrent GCTB. Computed tomography (CT) may be used in selected patients to assess cortical thinning and pathologic fractures before intralesional surgery. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is required to evaluate the extent of GCTB within the bone and surrounding soft tissues in order to plan a surgical approach. On DCE-MRI, GCTB shows early and rapidly progressive enhancement followed by washout [7-9] and high signal intensity on T2-weighted images. On fluorodeoxyglucose-positron emission tomography (FDG-PET), GCTB demonstrates high FDG uptake due to high metabolic activity of osteoclast-like giant cells [10,11].

An important topic that needs to be evaluated in the future is monitoring of tumor activity during systemic therapy with use of DCE-MRI and FDG-PET. If GCTB responds well to denosumab, DCE-MRI signal-intensity curves are expected to change gradually and eventually mimic that of healthy bone. A reduction in FDG uptake during systemic therapy was shown to correlate with reduced tumor activity, making FDG-PET a second promising sensitive instrument to monitor response to systemic targeted therapy for GCTB. Differentiation between viable and necrotic tumor cells may be a valuable tool in future decision making for GCTB treatment, analogous to other musculoskeletal tumors [12].

Histopathology and genetics

To date, histopathological and genetic features of GCTB have not been clearly predictive for clinical behavior such as local progression and risk for recurrence or metastasis. With advancing fundamental knowledge on GCTB, this could

be further evaluated and merged with clinical and radiological features into a multidisciplinary classification of GCTB predicting its clinical behavior and creating individual risk profiles [6].

The following elements may predict clinical behavior. Macroscopically, GCTB associated with lung nodules commonly showed large areas of hemorrhage and thrombus formation, that were not seen in GCTB without recurrence or metastasis [13]. Microscopically, atypical mitotic figures are suggestive of malignancy, but a potential association between cellular atypia and a locally more aggressive behavior needs evaluation. Genetically, centrosome amplification and aneuploidy were reportedly higher in recurrent and metastatic GCTB, suggesting a relation with clinical behavior [14,15]. Expression of epidermal growth factor receptor (EGFR), a tyrosine kinase expressed by neoplastic stromal cells that promotes osteoclastogenesis in the presence of M-CSF, was more frequent in recurrent and metastatic GCTB, also suggesting a relation with disease progression [16].

To target tumor cells directly, more fundamental knowledge on the neoplastic stromal cells is necessary. An *in vitro* method involved isolation of neoplastic stromal cells to further study its capacities for osteoblastic differentiation and osteoclastogenesis [17]. Recently, a driver mutation has been identified in H3F3A in GCTB; these alterations were seen exclusively found in neoplastic stromal cells and not in precursor or mature osteoclasts [18]. Currently, there is a lack of suitable *in vivo* models for GCTB due to complex interactions between the neoplastic and reactive cellular components; therefore little is known about tumor growth, invasion, angiogenesis and metastasis. A method of grafting and growing GCTB on chick chorio-allantoic membranes (CAM) has been presented to further study interactions between all cellular components of GCTB [19]. This technique may be further exploited to gain vital insights in this disease and to test new therapeutic agents.

Surgical treatment

For GCTB, surgical treatment traditionally consists of either curettage with local adjuvants or *en bloc* resection. Ideally, curettage with local adjuvants should be treatment of first choice in all patients with GCT, achieving joint salvage and maintaining functionality. Concurrently, recurrence risk should be minimized to rates similar to those reported after *en bloc* resection (0-12%).

Overall recurrence rates in our studies varied between 27-31% after curettage with an adjuvant, i.e. phenol, liquid nitrogen and/or PMMA, and are therewith at the higher end of ranges reported in literature. This can be explained by the extended indications for intralesional surgery in participating centers, including *high-risk* GCTB. Contrariwise, lower recurrence rates of 7-18% were reported after curettage and local adjuvants for *low-risk* GCTB. Overall, local control was achieved after one or multiple intralesional procedures in 85-100% of patients with GCTB, indicating that primary intralesional surgery allows for acceptable results, even in patients with *high-risk* GCTB. Surgical treatment of axial GCTB is subject to multiple problems including complex anatomy for surgical resection and difficulty in using adequate local adjuvants near neurovascular structures. In our series on sacral GCTB, recurrence rate was high after intralesional excision (54%), especially after isolated curettage (80%). Therefore, oncological outcome after intralesional excision of sacral or spinal GCTB remains doubtful. An emerging phenomenon in general oncologic surgery is intraoperative optical imaging with systemic injection of tumor-specific fluorescence agents, which can help determining adequate resection margins [20,21]. Especially during intralesional surgery after systemic therapy, it may be valuable to be able to identify and remove viable neoplastic stromal cells and reactive giant cells, in order to further reduce recurrence risk.

Concerning the optimal combination of local adjuvants in terms of oncological outcome, effectiveness of liquid nitrogen and phenol appeared to be comparable. Phenol may have a limited effect when used combined with PMMA [22,23], as recurrence rates were similar for phenol and PMMA versus PMMA alone. Efficacy of PMMA with or without phenol has to be studied in a prospective randomized trial. The latter is also true for the role of mechanical adjuvants such as the use of a high-speed burr in a uniform and validated manner, although designing and executing such a trial will be challenging [24]. Soft tissue extension is the only individual parameter to strongly increase recurrence risk [25,26]. This can be explained by the locally aggressive character of GCT and by technical difficulties in complete tumor excision and application of local adjuvants in the presence of exposed neurovascular structures. In these cases, feasibility of intralesional surgery depends on the extent of the soft tissue component, which is likely to improve with the advent of systemic targeted treatment options.

The complication rate was higher after *en bloc* resection compared to curettage with adjuvants (16% versus 4%), including aseptic loosening of endoprosthetic replacement, allograft failure and non-union. With curettage, complications were observed more frequently after cryosurgical treatment (30% versus 11% with use of phenol), and this risk was especially elevated in combination with use of bone grafts for reconstruction. Complications included secondary osteoarthritis, infection, postoperative fracture, non-union and neuropraxia. Whereas postoperative fractures were the most important concern after cryosurgery in the past, current techniques with adequate monitoring of freezing temperatures and prophylactic osteosynthesis in selected cases have decreased fracture rates dramatically (from 25-50% to 0-7%). Secondary osteoarthritis of the knee was seen in 17% of patients after curettage and PMMA; risk factors were extensive subchondral bone involvement (>70%) and proximity to the articular cartilage (<3 mm). In the future, PMMA substitutes with a similar hyperthermic local adjuvant effect but with more favorable osteoconductive, osteoinductive and elasticity properties might be used to decrease the risk of secondary osteoarthritis [27-29]. When osteoarthritis does develop after curettage and PMMA, the bone cement can be replaced by bone grafts prior to total knee replacement, which is considered less invasive compared to primary *en bloc* resection.

Functional ability reported by patients at the latest follow-up was superior after curettage with different types of local adjuvants compared to *en bloc* resection. Functional outcome and quality of life were not impaired in patients with radiographic osteoarthritis of the knee at mid-term follow-up, but clinical relevance may become more important at longer follow-up since our patients were relatively young. In an ideal situation, the biggest gain in terms of functional outcome and quality of life can be achieved by expanding the indication for intralesional surgery to all patients, by means of neoadjuvant systemic therapy that creates a curettable situation in uncurettable GCT and thereby avoiding more rigorous and mutilating resections—especially for sacral and spinal GCT.

Finally, *en bloc* resection should be reserved for patients in whom intralesional surgery and systemic therapy are impossible, contra-indicated or unavailable, as it results in more complications and worse functional outcome. Thus, *en bloc* resection would only be indicated in patients with intra-articular pathologic fractures requiring immediate stabilization or in which reconstruction of bony

remains after curettage is impossible; with soft tissue components adjacent to vital structures; with acute myelum compression; and with GCT in "expandable" bones such as proximal fibula or distal ulna.

Systemic targeted therapy

Whereas *en bloc* resection previously constituted the only treatment option for uncurettable GCT, receptor activator of nuclear factor kappa-B ligand (RANKL)-inhibitor denosumab and bisphosphonate zoledronic acid have recently entered the arena of treatment armamentarium and are promising therapies for local down-staging of *high-risk* GCT before surgery. Rather than to divert to more mutilating resections for advanced disease adjacent to neurovascular structures, neoadjuvant therapy with denosumab may facilitate intralesional surgery by creating a calcified rim around the entire tumor including its soft tissue component [30,31]. A reduction in tumor size and a calcified rim around the tumor and its soft tissue component are already seen after an average of 3 months and further calcification is seen with longer therapy duration. In axial and sacral GCT, locally advanced disease is often seen and local recurrence risk is therefore high. Creating an operable situation and achieving immediate local control are of the utmost importance. It is, among others, precisely in those cases that denosumab may allow for intralesional surgery and in addition to that it may render radiotherapy redundant.

RANKL is expressed by neoplastic stromal cells and RANKL-inhibitor denosumab blocks osteoclast maturation and bone resorption [32,33]. The efficacy of denosumab has been proven in prospective randomized trials and it has recently been registered for advanced GCT by the FDA [30,31]. However, inhibition of RANKL only indirectly affects GCT, as the tumor cells are not directly targeted. Targets for systemic therapy which more specifically address neoplastic stromal cells should be identified in order to turn systemic therapy into a definite therapy for GCT. Currently, therapy effects of denosumab are hypothesized to be temporary—after discontinuation of denosumab, regrowth of GCT was seen in some patients—and until more becomes known on the subject, surgery is indicated as definite treatment in all patients. In addition, it remains unsure whether systemic therapy with denosumab reduces recurrence risk when used in an adjuvant postoperative setting. Finally, long-term toxicity and optimal therapy duration need to be further explored.

Bisphosphonates are assumed to bind to bone mineral, inhibit osteoclast formation, migration and osteolytic activity at sites of bone resorption and promote apoptosis of osteoclasts [34]. In small retrospective series, stabilization of local and metastatic disease was achieved with bisphosphonates [35-37]. A prospective randomized trial with adjuvant zoledronic acid is currently ongoing in patients with *high-risk* GCT. The efficacy of zoledronic acid in neoadjuvant setting has not yet been validated.

Thus far, there are no randomized trials comparing the clinical effectiveness of RANKL-inhibitors and bisphosphonates [38]. Although denosumab seems to be more potent compared to zoledronic acid in regulating the RANK/RANKL-pathway and inhibiting osteolytic properties of multinucleated giant cells in GCT, the latter may have a more direct anti-tumor effect by addressing neoplastic stromal cells. In a recent *in vitro* study, reduced cell growth and apoptosis were seen in neoplastic stromal cells treated with zoledronic acid, but not in those treated with denosumab [34]. Also, zoledronic acid inhibited mRNA expression of RANKL by neoplastic stromal cells, whereas denosumab did not [34]. These findings reinforce the hypothesis that recurrence may occur after discontinuation of denosumab.

Based on new findings in functional biology and genetics of GCT, new targets for systemic therapy may be studied in the future. First, Wnt/β-catenin and recombinant human bone morphogenetic protein-2 (BMP-2) are pathways that regulate osteoclast-inducing activity of neoplastic stromal cells and are potential clinical targets for direct anti-tumor targeted therapy [17]. Second, DD33+ is a characteristic feature of the osteoclast-like phenotype of multinucleated giant cells and may be targeted with gemtuzumab—an anti-CD33+ antibody—in analogy to the treatment of acute myeloid leukemia [39]. Third, there are RANKL-substitutes that demonstrated osteoclastogenesis and formation of multinucleated giant cells capable of lacunar bone resorption (e.g. TNF-α, IL-6, TGF-β, APRIL, BAFF, NGF, IGF-I and IGF-II). Although these mechanisms are less potent than the RANK/RANKL-pathway, they may be further investigated as new targets for systemic therapy.

Radiotherapy

Finally, radiotherapy should be restricted for rare cases of unresectable, residual or recurrent GCT (e.g. axial localizations) when surgery leads to

unacceptable morbidity. After radiotherapy, operability of the irradiated area becomes problematic and recurrences complicate further surgical treatment. Additionally, lifelong risk for radiation induced sarcoma is noteworthy (3-11%). Therefore, its use should absolutely be minimized and the possibilities of systemic therapy should be explored before considering radiotherapy.

Giant cell tumor of tenosynovial tissue

Awareness of giant cell tumors arising from synovium (diffuse-type GCT; Dt-GCT) and tendon sheath (GCT of tendon sheath; GCT-TS) has increased over the last decades and with improvements in radiological and histopathological techniques, diagnosis and disease extent can be identified more accurately. Treatment decisions for tenosynovial giant cell tumor, especially for Dt-GCT, should be made by a multidisciplinary team consisting of dedicated experts in the field of musculoskeletal oncology and should include MR imaging and histopathological assessment before surgery. The latter may be supplemented with systemic therapy or adjuvant radiotherapy, as optimal oncological outcome may interfere with maintaining a functional joint and quality of life.

Imaging

Although currently lacking, a multidisciplinary classification that combines clinical, radiological and histopathological features in order to predict clinical behavior of tenosynovial GCT is desirable as this would enhance patient selection for individually tailored treatment.
Conventional radiographs are often not diagnostic for tenosynovial GCT but can be performed to rule out other diagnoses, including malignancies. Only in case of advanced disease, there may be evidence of soft tissue swelling, diminished joint space width and periarticular bone erosion on radiographs. MR imaging of tenosynovial GCT has a highly characteristic appearance with low signal intensity on T1- and T2-weighted spin echo sequences and a "blooming effect" owing to the presence of haemosiderin; this is therefore the most important step in radiological evaluation of the lesion [40]. A distinction is easily made between localized and diffuse types of disease based on the dimensions and extent of the lesion. On DCE-MRI, tenosynovial GCT shows marked enhancement on T1-weighted images with a delayed wash-out. To

date, there is no evidence that DCE-MRI is helpful in differentiating tenosynovial GCT from other hemorrhagic joint effusions [41]. On FDG-PET, tenosynovial GCT shows high FDG uptake due to the high metabolic activity of osteoclast-like giant cells [42-45].
In the future, both DCE-MRI and FDG-PET should be evaluated as potentially sensitive instruments to monitor response of tumor activity to systemic targeted therapy in more advanced cases of tenosynovial GCT.

Histopathology and genetics

To date, no evident histopathological or genetic features have been identified that are associated with a more aggressive clinical behavior of tenosynovial GCT and its tendency for local recurrence, impeding the design of a histopathological classification. With advancing fundamental knowledge on tenosynovial GCT, this would need further evaluation, in order to combine histopathological with clinical and radiological features into a multidisciplinary classification of tenosynovial GCT to predict its clinical behavior based on individual risk profiles.
The following parameters may be related with more aggressive forms of tenosynovial GCT. Macroscopically, a distinction is made between localized and diffuse types of tenosynovial GCT, which show different clinical features and biological behavior, but share similar histopathological features and etiology. While the localized type is non-destructive and non-invasive, the diffuse type is locally aggressive and capable of bone resorption in the periarticular bone. Furthermore, Dt-GCT may recur as a secondary malignant neoplasm, but primary malignant tenosynovial GCT has also been reported. Malignant lesions show increased mitotic rates compared to benign lesions (>20 instead of >5 mitosis per 10 high power fields) [3]. In addition, areas of necrosis, presence of abundant eosinophilic cytoplasm and stromal myxoid changes are also seen, but none of those form solitary criteria for malignancy [3].
To target tumor cells directly, more fundamental knowledge on the neoplastic cell component of tenosynovial GCT should be gained in the future. Genetically, only a small subset of tenosynovial GCT has a t(1;2) translocation which fuses the M-CSF gene on chromosome 1 to the collagen 6A3 (COL6A3) gene on chromosome 2, resulting in high levels of M-CSF expression by neoplastic cells [46,47]. This overexpression of M-CSF and its receptor M-CSFR promotes

formation of a tumor mass, and forms a pathway for systemic targeted therapy [46]. Other pathways that are present in all patients with Dt-GCT still need to be identified.

Surgical treatment

For tenosynovial GCT, surgical treatment traditionally exists of either arthroscopic or open synovectomy, and differs for localized and diffuse types of disease. Surgical removal of localized type tenosynovial GCT is relatively easy, either through open excision of solitary lesions in the digits or arthroscopic or open partial synovectomy of intra-articular lesions in the knee. Although comparable recurrence rates are published for arthroscopic and open synovectomy confined to the lesion (6% and 4% respectively) [48-51], there is a significant risk of inadequate excision with arthroscopic synovectomy particularly in the posterior knee compartment. To minimize recurrence risk, open excision would be recommended in most cases of GCT-TS and arthroscopic synovectomy should be reserved for small and well-accessible lesions in the anterior knee compartment. Generally, GCT-TS is a non-invasive and non-destructive lesion, and recurrences may be treated with repeated surgical excision. Surgical removal of diffuse type tenosynovial GCT can be performed through arthroscopic or open complete synovectomy. As arthroscopic techniques have improved over the last decades and are continuously evolving, this is preferred by numerous knee surgeons. However, the arthroscopic endpoint, i.e. when the procedure is terminated, is often more dependent on maximum operating time than on macroscopically remaining Dt-GCT and suboptimal tumor removal is sometimes taken for granted. Unfortunately, oncological results have been disappointing due to the significant risk of incomplete tumor removal and high recurrence rates (~40%). Therefore, one or two-stage open complete synovectomy is recommended for Dt-GCT to prevent tumor spill, allow for complete resection and reduce risk of recurrence (~14%). There exists a wide variation in what is meant by open synovectomy in the literature. Open synovectomy may consist of only debulking or curetting macroscopically visible Dt-GCT, in addition it may involve dissection of the joint capsule, and even performing a true capsulectomy with removal of the entire synovium. This variation is logically directly associated with variable recurrence rates, with the latter leading to the best results. For *extra*-articular disease, attention should

be paid to the complete excision of all affected soft tissue. For diffuse disease in joints with a tight capsule such as the hip or ankle, joint destruction and secondary osteoarthritis may occur, which may necessitate joint arthroplasty. All recurrences, especially after primary arthroscopic synovectomy, would better be treated with open synovectomy.

With increasing knowledge regarding efficacy of systemic therapy for Dt-GCT, it would be interesting to compare oncological results after arthroscopic and open synovectomy combined with systemic therapy; less invasive forms of surgery may become standard treatment. As already performed in general oncological surgery and as previously proposed in this thesis for the surgical treatment of giant cell tumor of bone, there may be a place for optical surgery with tumor-specific fluorescent targeting agents to facilitate complete resection of advanced tenosynovial GCT, especially after systemic targeted treatment [20,21].

Recurrence rate is dependent on site, volume of disease, intra- or extra-articular extent, type of surgery and previous surgery. Besides, with arthroscopic synovectomy there is always a risk of seeding the disease into the soft tissues around the portals. In our series, patients with more severe Dt-GCT, defined as involvement of both anterior and posterior knee compartments or with extra-articular extension presented a higher risk for recurrence compared to patients with mild Dt-GCT, defined as a solitary pedunculated lesion (conform GCT-TS) or involvement of the anterior or posterior knee compartment. Furthermore, in our series half of the patients were referred to our center with recurrent or residual disease after one or multiple attempts of arthroscopic tumor removal. Subsequently, multiple open re-synovectomies were required with the intent to cure. The patients that initially underwent open synovectomy at our center developed fewer recurrences during follow-up.

The most commonly reported complication after open synovectomy is joint stiffness (24%) [52]. This is one of the arguments in favor of arthroscopic synovectomy, which hypothetically results in a shorter recovery time and a superior function without joint stiffness. Additionally, taking into account the high risk for reoperation after arthroscopy and the subsequent higher risk for complications including infection, deep venous thrombosis and joint stiffness, initial open synovectomy and the accompanying chance of immediate local tumor control may result in fewer complications in the end. A higher failure rate (22-25%) is reported after complete synovectomy and joint replacement

compared to joint replacement surgery for conventional osteoarthritis [53,54]. Regarding functional outcome, arthroscopic synovectomy may provide better results compared to open synovectomy. In our series, many patients underwent primary arthroscopy in a peripheral hospital with the intent of maintaining preoperative function and quality of life after surgery for Dt-GCT. Eventually, these patients were referred to our tertiary center with recurrent or residual disease after one or multiple attempts of arthroscopic tumor removal. Multiple open re-synovectomies were required with the intent to cure. At final follow-up, these patients reported worse functional outcomes and quality of life, compared to their counterparts that initially underwent open synovectomy at our center and who developed fewer recurrences and needed fewer reoperations during follow-up. This indicates that open synovectomy does not inevitably result in the hypothesized impaired function or quality of life compared to (repetitive) arthroscopy.

Finally, many patients with tenosynovial GCT still undergo primary surgical treatment in peripheral hospitals without multidisciplinary expertise in the field of musculoskeletal oncology, but as a severe course of disease is common, we recommend referral to a tertiary center. In concordance with recent suggestions, better care and cure would be achieved by centralization, especially with the advent of systemic targeted therapy [55].

Systemic targeted therapy

Patients with unresectable diffuse disease are particularly suitable for neoadjuvant systemic targeted therapy with imatinib or related tyrosine kinase inhibitors which block M-CSFR, as this could down-stage the disease and facilitate complete synovectomy on the long term in analogy to systemic therapy for giant cell tumor of bone. Imatinib has shown tumor regression in patients with advanced Dt-GCT in preliminary studies, and together with related tyrosine kinase inhibitors (e.g. nilotinib and sunitinib) it is currently studied in prospective randomized trials.

Based on new findings in functional biology and genetics of tenosynovial GCT, new targets for systemic therapy can be identified. First, there may be a role for blockade of M-CSFR through other cytokines than tyrosine kinase inhibitors that are currently under study and that interact with the same receptor, for example IL-34 [56]. Second, as the formation of multinucleated giant cells in Dt-GCT

is RANKL-dependent, there may be a place for therapy with RANKL-inhibitor denosumab, conform systemic targeted therapy in giant cell tumor of bone [57]. However, in Dt-GCT multinucleated giant cells are often less numerous or even absent and it remains unsure what the effect of therapy will be. With the introduction of systemic therapy for Dt-GCT, treatment optimization will require further review and validation, including optimal agent, toxicity profile, mechanism of resistance, therapy duration and timing of surgery.

Radiotherapy

Whereas radiotherapy is restricted to exceptional cases of unresectable, residual or recurrent giant cell tumor of bone, it is more commonly applied in the multidisciplinary treatment of tenosynovial GCT. For recurrent or refractory Dt-GCT with *extra*-articular extension, moderate dose external beam radiotherapy (30-50Gy) may be considered several weeks after surgical removal; the optimal dose should be investigated. Radiotherapy may kill residual tumor cells in case of incomplete resection and in this way it can prevent reoperation with its accompanying risk for complications and impaired functional outcome. However, if reoperation is indicated, the risk of complications is increased especially in the extremities. Another option for locally delivered radiotherapy in *intra*-articular Dt-GCT is instillation in radioactive colloids in the affected joint (i.e. synoviorthesis with ^{90}Yttrium). Although this treatment is most often used as adjuvant therapy with Dt-GCT, there is little evidence to support its universal application and one should be critical about its use.

Methodological considerations

Published case series on surgical treatment of giant cell tumor of bone and tenosynovial tissue are generally small and often provide only levels III-IV evidence. Also, most studies are retrospective and histopathology was not revised with respect to recent criteria for diagnosis of bone and soft tissue tumors. Hence, even systematic reviews of recurrence rates, complications and functional outcome after surgery and adjuvant treatment for different types of disease provide little evidence and meta-analysis of gathered data is often not warranted.

Randomized controlled trials (RCT) are preferred when comparing safety and efficacy of different interventions, but this design may be inappropriate for many musculoskeletal tumors due to rareness and heterogeneity of disease, required long-term follow-up, ethical objections and surgical expertise. However, several improvements of methodological approaches are imaginable. First, the role for alternative research methodologies that approximate RCTs, including stepped wedge cluster designs, expertise-based designs and instrumental variable analyses, all comparing treatment in different centers, should be further explored [58-64]. Second, a higher quality of non-randomized studies can be obtained by standardized data collection with use of (inter)national prospective databases and registries including technical, clinical and patient reported outcome measures (PROMs) [58,65]. Data from larger study populations and prolonged follow-up are required to that aim. In addition, studies should apply standard reporting protocols similar to CONSORT and STROBE requirements for randomized controlled trials and observational studies, respectively [66,67]. Third, with quickly advancing knowledge on genetics and molecular biology of musculoskeletal tumors, revision of histopathological diagnoses is recommended in future multicenter and international studies of retrospective nature. Finally, the IDEAL consortium proposed a five-stage model for the regulation of innovation of surgical techniques based on the principles of evidence-based medicine, analogous to the phased approach for drug development [68]. To achieve these objectives and to improve clinical decision making for the multidisciplinary treatment of giant cell tumors of bone and tenosynovial tissue, a high degree of (inter) national cooperation is key.

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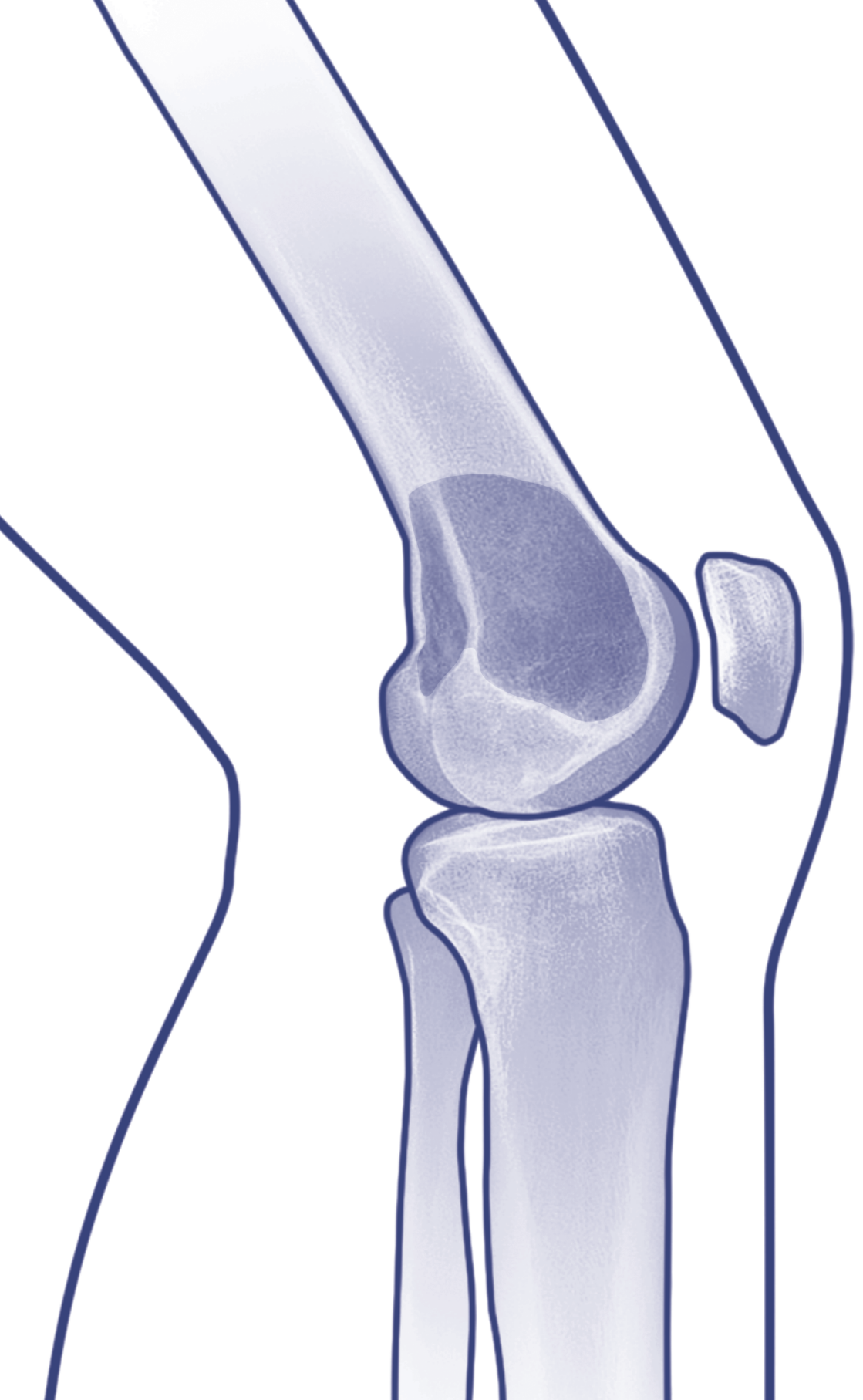


Chapter 14

Summary in Dutch

Nederlandse samenvatting

Patiënten met reusceltumoren van bot of tenosynoviaal weefsel vormen een uitdaging voor de orthopaedisch chirurg. De klinische uitdaging in de behandeling van reusceltumoren van bot is het verbreden van de indicatiestelling voor intralesionale excisie met inachtneming van het verkrijgen van optimale oncologische resultaten en het behoud van functionaliteit en kwaliteit van leven. Voor tenosynoviale reusceltumoren, in het bijzonder van het diffuus type, is de klinische uitdaging het verbeteren van oncologische resultaten en het behoud van een functioneel gewricht en kwaliteit van leven. Derhalve waren de onderzoeksdoelen van dit proefschrift het verbeteren van de selectie van patiënten voor verschillende chirurgische behandelingen door de identificatie van risicofactoren voor lokale recidieven en complicaties, het definiëren van indicaties voor systemische therapie en het evalueren van klinische en functionele uitkomstmaten na behandeling van beide typen reusceltumoren.

Reusceltumoren van bot

Hoofdstuk 2 schetst een overzicht van de beeldvorming, genetica, histopathologie en multidisciplinaire behandeling van reusceltumoren van bot. Over-expressie van receptor activator of nuclear factor kappa-B ligand (RANKL) door mononucleaire neoplastische stromacellen bevordert de werving van talrijke reactieve meerkernige reuscellen. Röntgenologisch gezien tonen reusceltumoren typische excentriek gelegen lytische laesies. Computertomografie (CT) kan worden uitgevoerd om corticale verdunning, dreigende pathologische fracturen en dreigende gewrichtsbetrokkenheid te beoordelen. Magnetische-resonantietomografie (MRI) is noodzakelijk om de uitbreiding van de reusceltumor binnen het bot en de omliggende weke delen te bepalen ten behoeve van de chirurgische planning. MRI toont doorgaans een lage tot gemiddelde signaalintensiteit op T1-gewogen beelden en intermediaire tot hoge signaalintensiteit op T2-gewogen beelden. De behandeling van eerste keuze voor de meeste reusceltumoren is curettage met lokale adjuvantia. Bij curettage wordt eerst een groot ovaal venster in de cortex gemaakt welke voldoende blootstelling geeft van de tumorholte. Vervolgens wordt de tumor

zorgvuldig gecuretteerd met verschillende maten curettes gevolgd door high-speed boren van de overgebleven wanden. Lokale adjuvantia kunnen fenol, alcohol of vloeibare stikstof zijn. De resterende holte kan worden gevuld met een autoloog of allogeen bottransplantaat of polymethylmethacrylaat (PMMA) botcement; voordelen van de laatste zijn een hypothetisch lagere recidiefkans door de hyperthermische eigenschappen, directe mechanische ondersteuning en belastbaarheid en vroegtijdige radiografische detectie van lokale recidieven. Gerapporteerde recidiefkansen zijn vergelijkbaar voor de verschillende lokale adjuvantia (27-31%); de meeste recidieven treden op binnen twee jaar na de eerste operatie. Wanneer behoud van het aangrenzende gewricht onmogelijk is en tevens in het geval van reusceltumoren in "misbare" botten kan de behandeling bestaan uit *en bloc* resectie. Denosumab (RANKL-remmer) blokkeert en zoledroninezuur (bisfosfonaten) onderdrukt de botresorptie door osteoclast-achtige reuscellen. Na gebruik van zoledroninezuur werd stabilisatie van lokale en gemetastaseerde ziekte gemeld, hoewel de mate van bewijslast laag was. Denosumab is uitgebreider bestudeerd in prospectieve gerandomiseerde trials en lijkt effectief voor de lokale down-staging van de tumor voor chirurgische behandeling. Denosumab is recent geregistreerd door de US Food and Drug Administration (FDA) voor inoperabele reusceltumoren. De plaats van systemische therapie binnen de standaard behandeling voor reusceltumoren moet in de toekomst verder ondergezocht worden. Een middelmatige dosis radiotherapie moet voorbehouden blijven aan zeldzame casus van inoperabele, residuele of multipel recidiverende reusceltumoren waarbij chirurgische behandeling tot een onacceptabele morbiditeit zou leiden.

Hoofdstuk 3 vergelijkt de relatieve effectiviteit van verschillende lokale adjuvantia in een retrospectieve cohort studie. De studie is uitgevoerd in twee topreferente centra met een regionale functie die beiden een verschillende standaardbehandeling hanteerden. De verwijzing en daarmee het type behandeling was slechts afhankelijk van de geografische locatie van de patiënt (pseudo-randomisatie). Beide centra waren gelijk qua indicatiestelling voor intralesionale chirurgie en chirurgische expertise. Tussen 1990 en 2010 ondergingen 132 patiënten met een primaire reusceltumor curettage met fenol en PMMA (F-PMMA; n=82), met vloeibare stikstof en PMMA (N-PMMA; n=26) of met vloeibare stikstof en een autologe of allogene bottransplantatie (N-BG; n=24). De gemiddelde follow-up duur was 8 jaar (range 2 tot 22). De drie

cohorten waren vergelijkbaar behoudens voor lokalisatie: bottransplantaten werden vaker toegepast in plaats van PMMA in niet-gewichtdragende botten in het centrum dat gespecialiseerd is in cryochirurgie. De recidiefkansen waren vergelijkbaar na curettage met F-PMMA (28%; 23/82), N-PMMA (31%; 8/26) en N-BG (38%; 9/24) (p=0.52). Een tweevoudig verhoogde recidiefkans werd gezien in geval van weke delen uitbreiding. Bij het gebruik van vloeibare stikstof moet men bedacht zijn op complicaties, aangezien het complicatierisico verhoogd was na curettage met N-BG (33%; 8/24) en N-PMMA (27%; 7/26) vergeleken met F-PMMA (11%; 9/82) (p=0.019). Preoperatief aanwezige pathologische fracturen leidden tot een viervoudig verhoogd complicatierisico. De functionele uitkomsten waren uitstekend en vergelijkbaar in alle drie de cohorten (p=0.52). Ongeveer 20% van de patiënten met een reusceltumor presenteert zich met een pathologische fractuur, welke adequate intralesionale chirurgie kan bemoeilijken. **Hoofdstuk 4** was een retrospectieve multicenter studie van 48 patiënten met een pathologische fractuur, behandeld met curettage en lokale adjuvantia (n=23) of *en bloc* resectie (n=25) tussen 1981 en 2009 in één van de drie deelnemende topreferente centra. De gemiddelde follow-up duur was 8.4 jaar (range 2.3 tot 24). De lokale recidiefkans was hoger na intralesionale chirurgie (30%; 7/23) dan na *en bloc* resectie (0%) en was vijfvoudig verhoogd in geval van weke delen uitbreiding. De complicatiekans was lager na intralesionale chirurgie (4%; 1/23) dan na *en bloc* resectie (16%; 4/25). Fractuurgenezing na curettage trad bij op één na alle patiënten op. De functionele uitkomst was het beste na intralesionale chirurgie.

Ongeveer 2-5% van alle reusceltumoren bevindt zich in de kleine hand- en voetbeentjes. **Hoofdstuk 5** bevat een systematische review van twaalf artikelen met in totaal 91 patiënten met een reusceltumor in de kleine hand- en voetbeentjes. De gemiddelde recidiefkansen in deze publicaties waren 72% na curettage, 13% na curettage met lokale adjuvantia, 15% na resectie en 10% na amputatie. Tevens is een retrospectieve multicenter studie verricht waarin alle 30 patiënten zijn geïncludeerd die behandeld zijn voor een reusceltumor in de kleine hand- of voetbeentjes tussen 1987 en 2010 in één van de vijf deelnemende topreferente centra. De gemiddelde follow-up duur was 7.9 jaar (range 2 tot 26). De recidiefkansen waren 50% na curettage (3/6), 22% na curettage met lokale adjuvantia (4/18) en 17% na *en bloc* resectie (1/6; p=0.40). Individuele factoren geassocieerd met een hogere recidief- of complicatiekans konden niet worden geïdentificeerd. Betere functionele resultaten werden

behaald na intralesionale chirurgie in vergelijking met *en bloc* resectie. Herhaalde curettage met lokale adjuvantia resulteerde uiteindelijk in de genezing van alle patiënten.

Ongeveer 2-8% van alle reusceltumoren is gelokaliseerd in het sacrum. **Hoofdstuk 6** bevat een landelijke retrospectieve studie van alle 26 patiënten die een chirurgische behandeling ondergingen voor een sacrale reusceltumor in Nederland tussen 1990 en 2010. Bij presentatie had de meerderheid van de patiënten enige mate van corticale destructie, uitbreiding in de weke delen en betrokkenheid van één of meerdere sacrale zenuwwortels. Negentien patiënten ondergingen preoperatieve selectieve arteriële embolisatie. Alle patiënten ondergingen intralesionale excisie en bij 21 patiënten werd dit aangevuld met lokale adjuvantia, systemische therapie of radiotherapie. Bij acht patiënten met uitgebreide corticale destructie en weke delen uitbreiding werden geen chemische adjuvantia gebruikt. Chirurgische marges werden bij vier patiënten uitgebreid door middel van anterieure sacrale wandresectie. Posterieure stabilisatie met lumbale fixatie en PMMA of bottransplantatie was geïndiceerd in drie patiënten, reconstructie met alleen bottransplantatie in zeven patiënten en met alleen PMMA in één patiënt. De minimale follow-up duur was twee jaar in op één na alle patiënten (gemiddelde follow-up 8.3 jaar; range 0.5 tot 9). Twee patiënten zijn overleden door lokale tumor progressie en metastasen op afstand en één vanwege een straling geïnduceerd sarcoom (na 6-102 maanden). De totale recidiefkans was 54% (14/26). Het recidiefrisico was drievoudig verhoogd in geval van weke delen uitbreiding groter dan 10 cm. Complicaties werden gerapporteerd in 46% (12/26) van de patiënten en omvatten massieve bloeding, infectie, neuropraxie, materiaalbreuk, radiatie-geïnduceerd sarcoom, radiatie-geïnduceerde menopauze, dissociatie fractuur van het os pubis vanwege osteopenie na radiotherapie en vertraagde wondgenezing. De functionele uitkomst was goed bij patiënten welke geen complicaties hadden. Bij acht patiënten waren alle preoperatieve symptomen verdwenen na de operatie. Aanhoudende pijn werd gemeld door acht patiënten. Neurologische symptomen waren van voorbijgaande aard bij acht en permanent bij vijf patiënten. De recidiefkans was het hoogst na geïsoleerde curettage (80%; 4/5), wat aangeeft dat enige vorm van lokale of systemische adjuvante behandeling noodzakelijk is voor lokale tumorcontrole.

Hoofdstuk 7 had tot doel de identificatie van individuele risicofactoren voor lokale recidieven in een retrospectieve studie met 93 patiënten die behandeld

zijn met curettage, fenol en PMMA (n=75) of alleen PMMA (n=18) tussen 1981 en 2009 in één topreferent centrum. De gemiddelde follow-up duur was 8 jaar (range 2 tot 24). Vijfentwintig patiënten ontwikkelden een lokaal recidief (27%). Zeventien patiënten waren ziektevrij na een tweede curettage met lokale adjuvantia en bij acht patiënten was *en bloc* resectie vereist voor lokale tumorcontrole. We vonden een vijfvoudig verhoogde recidiefkans in geval van uitbreiding in de weke delen; terwijl leeftijd, geslacht, lokalisatie en de aanwezigheid van een pathologische fractuur de recidiefkans niet beïnvloedden.

Hoofdstuk 8 was een radiologische studie naar de prevalentie en impact van radiologische gonartrose (Kellgren en Lawrence graad 3-4) bij 53 patiënten die curettage met PMMA ondergingen voor een reusceltumor rondom het kniegewricht tussen 1987 en 2010 in één topreferent centrum. De gemiddelde follow-up duur was 7 jaar (range 5 tot 24). Radiologische gonartrose werd gezien in 17% van de patiënten na een mediane follow-up van 57 maanden na curettage met PMMA. Geen van deze patiënten was ten tijde van laatste follow-up chirurgisch behandeld voor klinische gonartrose. Een negenvoudig verhoogd risico op radiologische gonartrose werd gevonden wanneer meer dan 70% van het subchondrale bot aangetast was door de reusceltumor en een viervoudig verhoogd risico voor een afstand van minder dan 3 mm tussen de reusceltumor en het gewrichtskraakbeen. De functionele uitkomst en kwaliteit van leven waren vergelijkbaar voor patiënten met Kellgren en Lawrence graad 3-4 en graad 0-2, hetgeen impliceert dat de klinische impact van radiologische gonartrose op middellange termijn bescheiden is. Dit kan echter nog toenemen met de tijd en langdurige follow-up is dan ook vereist.

Reusceltumoren van tenosynoviaal weefsel

Hoofdstuk 9 schetst een overzicht van de beeldvorming, genetica, histopathologie en multidisciplinaire behandeling van het lokaal en diffuus type tenosynoviale reusceltumoren. Over-expressie van macrophage colony-stimulating factor 1 (M-CSF) en zijn receptor (M-CSFR) door synoviale fibroblasten bevordert de formatie van een tumormassa. Op MRI veroorzaken hemosiderine deposities de lokale veranderingen in signaalopname waardoor men de karakteristieke lage signaalintensiteit van tenosynoviale

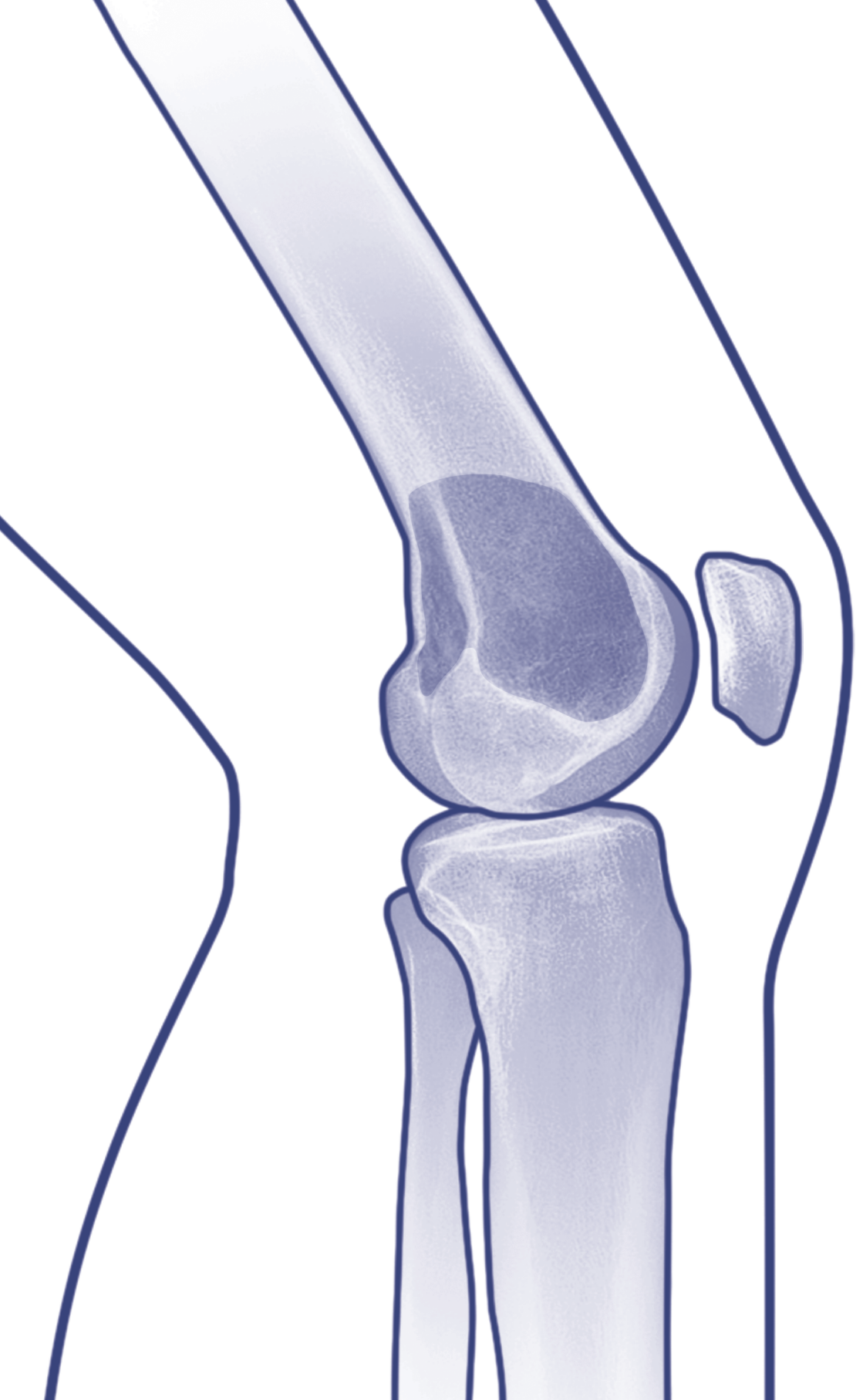
reusceltumoren krijgt op T1- en T2-gewogen spin echo of gradiënt echo sequenties. Hoewel arthroscopische synovectomie vaak als alternatief voor open synovectomie verdedigd wordt is er een aanzienlijk risico op onvolledige excisie en lokaal recidief, in het bijzonder in het achterste compartiment van de knie. Bovendien bestaat het risico van enten van de tumor rond de artroscopie portals. Voor het lokaal type tenosynoviale reusceltumoren en voor minimale ziekte in het anterieure knie compartiment kan arthroscopische verwijdering afdoende zijn. Voor primaire en recidiverende grote diffuus type tenosynoviale reusceltumoren is open synovectomie de aangewezen behandeling. Gecombineerde of gefaseerde operaties kunnen worden overwogen. Voor tumoren in het posterieure knie compartiment wordt een *lazy-S* incisie gemaakt met elevatie van de origo van de musculus gastrocnemius waardoor neurovasculaire structuren beschermd blijven. Dit wordt gevolgd door een artrotomie om de achterste kruisband en gewrichtsoppervlakte goed in zicht te krijgen en een volledige capsulotomie uit te kunnen voeren. Voor tumoren in het anterieure knie compartiment is een mediale parapatellaire artrotomie geadviseerd, omdat deze zorg draagt voor een goede visualisatie van de synoviale holte, het vetlichaam van Hoffa, de kruisbanden en de collaterale ligamenten. Resttumor grenzend aan de gewrichtsspleet kan ook veilig worden gereseceerd. In geval van recidiverende en extra-articulair uitbreidende tumoren kunnen matige doses radiotherapie of systemische therapie worden overwogen. Hoewel er momenteel slechts weinig bewijs is voor de effectiviteit van neoadjuvante M-CSFR-gerichte tyrosine kinase remmers (imatinib) voor de behandeling van diffuus type tenosynoviale reusceltumoren, kan systemische therapie in de toekomst in de behandelstrategie voor uitgebreidere ziekte opgenomen worden, in analogie met systemische behandeling voor ossale reusceltumoren.

Hoofdstuk 10 is een systematische review van 59 artikelen met in totaal 313 patiënten met lokaal type en 777 patiënten met diffuus type tenosynoviale reusceltumoren. De methodologische kwaliteit (Newcastle-Ottawa Scale voor kwaliteitsbeoordeling van cohortstudies) was hoog in 40%, middelmatig in 50% en laag in 10% van de geïncludeerde studies. De gerapporteerde recidiefkans was 4% na open en 6% na arthroscopische synovectomie van lokaal type en 14% na open en 40% na arthroscopische synovectomie van diffuus type tenosynoviale reusceltumoren in de knie. Na instillatie van intra-articulaire radioactieve colloïden was de recidiefkans 15% na open en 22% na

arthroscopische synovectomie van intra-articulaire diffuus type tenosynoviale reusceltumoren in de knie en heup. Na adjuvante radiotherapie was de recidiefkans 12% na open en 13% na arthroscopische synovectomie van extra-articulaire diffuus type tenosynoviale reusceltumoren. Open synovectomie en excisie van extra-articulaire uitbreiding verdient aanbeveling om de relatief hoge recidiefkans te minimaliseren.

Hoofdstuk 11 is een retrospectieve studie over de invloed van ziekte-ernst en het type operatie op de functionele resultaten en kwaliteit van leven bij 30 patiënten welke behandeld zijn voor tenosynoviale reusceltumoren in de knie tussen 1980 en 2011. Vijftien patiënten werden primair behandeld in één topreferent centrum; vijftien andere patiënten werden naar dit centrum verwezen voor de behandeling van een lokaal recidief. Ziekte-ernst werd vastgesteld aan de hand van preoperatieve MRI beelden of verslagen. Zestien patiënten (53%) hadden een milde vorm, gedefinieerd als een solitair gesteelde laesie of diffuse betrokkenheid van het voorste of achterste compartiment van de knie. Veertien patiënten (47%) hadden een uitgebreidere vorm, gedefinieerd als betrokkenheid van zowel het voorste als het achterste compartiment van de knie of extra-articulaire uitbreiding. Patiënten met aanvankelijk uitgebreidere ziekte hadden vaak al meerdere synovectomieën ondergaan, waaronder in de meeste gevallen primaire arthroscopische synovectomie, alvorens verwezen te worden. Allen ondergingen als laatste behandeling open synovectomie. Na een gemiddelde follow-up duur van 8 jaar (range 2 tot 23) rapporteerden deze patiënten significant slechtere functionele en kwaliteit van leven uitkomsten. In deze studie leidde primaire open synovectomie an sich niet tot een verminderde functie of kwaliteit van leven in vergelijking met herhaaldelijke arthroscopische synovectomie.

Conclusies, klinische implicaties en toekomstperspectieven voor de behandeling van reusceltumoren van bot en tenosynoviaal weefsel worden besproken in **Hoofdstuk 13.**



Chapter 15

Summary in French

Résumé en français

Les patients atteints de tumeurs à cellules géantes osseuses ou ténosynoviales posent des problèmes difficiles pour le traitement chirurgical. Pour les tumeurs osseuses à cellules géantes, le défi clinique est d´étendre les indications pour la résection intralésionnelle, tout en fournissant des résultats oncologiques, fonctionnels et de qualité de vie optimaux. Pour les tumeurs ténosynoviales à cellules géantes, en particulier celles du type diffus, le défi clinique est d´améliorer les résultats oncologiques et de maintenir une articulation fonctionnelle et la qualité de vie. Par conséquent, les objectifs de cette thèse de doctorat étaient d´améliorer la sélection des patients pour les différents types de chirurgie en identifiant les facteurs de risque de récidives et de complications, de définir les indications pour la thérapie systémique et d´évaluer les résultats cliniques après le traitement chirurgical de l´un des deux types de tumeurs à cellules géantes en fournissant une analyse de décision clinique.

Les Tumeurs à cellules géantes osseuses

Le **Chapitre 2** donne un aperçu de l´imagerie, de la génétique, de l´histopathologie et du traitement multidisciplinaire des tumeurs osseuses à cellules géantes. La surexpression de l´activateur du récepteur du facteur nucléaire kappa-B ligand (RANKL) par les cellules stromales néoplasiques mononucléaires favorise le recrutement de nombreuses cellules géantes multi-nucléées réactives. Radiologiquement, les tumeurs osseuses à cellules géantes montrent des lésions typiquement lytiques et excentriques. La tomodensitométrie peut être effectuée pour évaluer l´amincissement cortical, les fractures pathologiques et l´implication attente de l´articulation adjacente. L´imagerie par résonance magnétique (IRM) est nécessaire pour évaluer l´étendue des tumeurs à cellules géantes dans l´os et dans les tissus mous pour la planification chirurgicale. L´IRM montre généralement une faible à moyenne intensité sur les pondérations T1 et une intermédiaire à haute intensité sur les pondérations T2. Le traitement de choix pour la majorité des tumeurs à cellules géantes osseuses est le curetage intralésionnel avec des adjuvants locaux. Une grande fenêtre ovale est faite dans le cortex, en créant une exposition suffisante de la cavité tumorale. La tumeur est ensuite soigneusement curetée

avec de différentes tailles de curettes, suivi par l´ébavurage à haute vitesse des parois de la cavité. Les adjuvants locaux peuvent être le phénol, l´alcool ou l´azote liquide. La cavité restante peut être remplie soit avec des greffes osseuses ou avec du polyméthacrylate de méthyle (PMMA). Les avantages du PMMA sont le risque de récidive hypothétiquement inférieur à travers des propriétés hyperthermiques, le support mécanique immédiate et la détection des récidives locales précoce. Les taux de récidive rapportés sont comparables pour les différents adjuvants locaux (27-31%) ; la plupart des récidives surviennent dans les deux ans après la chirurgie initiale. La résection peut être effectuée lorsque le sauvetage de l´articulation adjacente n´est pas possible et dans les os extensibles. Le dénosumab (RANKL-inhibiteur) bloque et l´acide zolédronique (un bisphosphonate) inhibe la résorption des ostéoclastes dérivés des tumeurs à cellules géantes. Avec de l´acide zolédronique, la stabilisation de la maladie locale et métastatique a été signalé, bien que le niveau de preuve ait faible. Le denosumab a été étudié dans une plus large mesure et semble être efficace dans le « down-staging » de cette maladie avant le traitement chirurgicale. Le denosumab a récemment été homologué par la US Food and Drug Administration (FDA) pour les tumeurs à cellules géantes non résécables. Par conséquent, le rôle de la thérapie systémique dans le traitement standard des tumeurs à cellules géantes doit être davantage exploré. La radiothérapie à dose modérée devrait être limitée à des rares cas des tumeurs à cellules géantes non résécables, récidivantes, résiduelles ou lorsque la chirurgie conduirait à une morbidité inacceptable.

Le **Chapitre 3** a comparé l´efficacité relative de plusieurs adjuvants locaux dans une étude de cohorte rétrospective dans deux centres de référence tertiaires qui appliquent des traitements standards différents. L´affectation du traitement dépendait uniquement du centre de référence où les patients avaient été admis, les deux centres avaient des indications similaires pour la chirurgie intralésionnelle et l´expertise chirurgicale était comparable (c´est-à-dire une étude pseudo-randomisée). Ainsi, 132 patients atteints d´une tumeur à cellules géantes ayant subi un curetage soit avec du phénol et PMMA (P-PMMA ; n=82), de l´azote liquide et PMMA (AL-PMMA ; n=26) ou de l´azote liquide et des greffes osseuses (AL-GO ; n=24) entre 1990 et 2010 ont été analysés. Le suivi moyen était de 8 ans (allant de 2 à 22 ans). Les trois cohortes étaient comparables, sauf pour la localisation tumorale : les greffes osseuses ont été appliquées plus couramment au lieu de PMMA dans les os non porteurs dans le centre

spécialisé dans la cryochirurgie. Les taux de récidive étaient comparables pour P-PMMA (28% ; 23/82), AL-PMMA (31% ; 8/26) et AL-GO (38% ; 9/24 ; p=0,52). Le risque de récidive a été augmenté deux fois par la présence d´extension dans les tissus mous. À l´égard de l´usage de l´azote liquide, il faut se méfier des complications, comme cela a été le cas après AL-GO (33% ; 8/24) et AL-PMMA (27% ; 7/26) par rapport à P-PMMA (11% ; 9/82 ; p=0,019). En outre, le risque de complication a été augmenté quatre fois par les fractures pathologiques. Le résultat fonctionnel était excellent et comparable dans les trois cohortes (p=0,52).

Environ 20% des patients atteints de tumeurs à cellules géantes osseuses présente avec une fracture pathologique, ce qui peut gêner la chirurgie intralésionnelle. Le **Chapitre 4** comportait une analyse rétrospective multicentrique de 48 patients ayant subi une fracture pathologique, traité avec curetage intralésionnel avec adjuvants locaux (n=23) ou résection *en bloc* (n=25) entre 1981 et 2009 dans l´un des trois centres de référence tertiaires. Le suivi moyen était de 8,4 ans (allant de 2,3 à 24 ans). Les taux de récidive étaient plus élevés après chirurgie intralésionnelle (30% ; 7/23) par rapport à la résection *en bloc* (0%) et a été cinq fois plus élevé en cas d´extension dans les tissus mous. Moins de complications ont été rapportées après la chirurgie intralésionnelle (4% ; 1/23) par rapport à la résection *en bloc* (16% ; 4/25). La guérison des fractures après le curetage a eu lieu dans tous sauf un patient. Le résultat fonctionnel était supérieur après la chirurgie intralésionnelle.

Environ 2-5% des tumeurs à cellules géantes se produisent dans les petits os des mains et des pieds. Le **Chapitre 5** décrit une revue systématique de la littérature avec douze articles comprenant un total de 91 patients avec tumeurs à cellules géantes des petits os. Les taux de récidive publiés étaient de 72% après le curetage, 13% après le curetage avec adjuvants locaux, 15% après la résection *en bloc* et 10% après l´amputation. Deuxièmement, une analyse rétrospective multicentrique a été réalisée sur l´ensemble des 30 patients traités pour les tumeurs à cellules géantes des petits os entre 1987 et 2010 dans l´un des cinq centres de référence tertiaires. Le suivi moyen était de 7,9 ans (allant de 2 à 26 ans). Les taux de récidive étaient de 50% après curetage seul (3/6), 22% après curetage avec adjuvants locaux (4/18) et 17% après résection *en bloc* (1/6 ; p=0,40). Nous n´avons pas pu identifier des facteurs individuels associés aux risques plus élevés de récidive ou de complication. Le résultat fonctionnel était supérieur après la chirurgie intralésionnelle par rapport à la résection *en bloc*.

Le curetage avec adjuvants locaux répété a finalement abouti à la guérison de tous les patients.
Environ 2-8% des tumeurs à cellules géantes étaient localisées dans le sacrum. Le **Chapitre 6** contient une évaluation rétrospective nationale de l´ensemble des 26 patients traités chirurgicalement pour une tumeur à cellules géantes dans le sacrum entre 1990 et 2010 aux Pays-Bas. La majorité des patients avait une destruction corticale, une extension dans les tissus mous et avaient un rapport étroit avec les racines nerveuses lors de leur présentation. L´embolisation artérielle sélective a été réalisée dans dix-neuf patients avant le traitement chirurgical. Tous les patients ont subi une résection intralésionnelle, dont 21 avec des adjuvants locaux différents, un traitement systémique ou de la radiothérapie adjuvante. Chez huit patients ayant une vaste destruction corticale et masses des tissus mous, pas d´adjuvants chimiques ont été utilisés. Les marges chirurgicales ont été étendues en quatre patients par excision de la paroi antérieure du sacrum. La stabilisation postérieure avec fixation lombaire avec du PMMA ou des greffes osseuses a été indiquée chez trois patients, la reconstruction avec des greffes osseuses chez sept patients et avec du PMMA en un patient. Tous, sauf un patient avait un suivi minimum de deux ans (moyenne 8,3 ans ; allant de 0,5 à 19 ans). Deux patients sont décédés à cause de la progression tumorale et des métastases et un patient à cause d´un sarcome radio-induit. Le taux de récidive était de 54% (14/26). Le risque de récidive a été augmenté trois fois en cas d´extension dans les tissus mous de plus de 10 cm. Des complications ont été rapportées chez 46% (12/26) des patients et comprenaient des hémorragies massives, des infections, des neuropraxies, l´échec de l´instrumentation, un sarcome radio-induit, une ménopause radio-induite, une fracture de dissociation de l´os pubien en raison de l´ostéopénie après la radiothérapie et de la cicatrisation retardée. Les résultats fonctionnels étaient bons chez les patients sans complications. Chez huit patients, tous les symptômes préopératoires ont disparu après la chirurgie. De la douleur persistante a été rapportée par huit patients. Les symptômes neurologiques ont été transitoires chez huit patients et permanents chez cinq patients. Le taux de récidive était plus élevé après curetage sans aucun adjuvant local ou systémique (80% ; 4/5), ce qui indique que le traitement adjuvant est nécessaire pour obtenir le contrôle local de la tumeur.
Le **Chapitre 7** vise à analyser rétrospectivement les facteurs de risque de récidive individuels chez 93 patients traités par curetage, phénol et PMMA

(n=75) ou curetage avec PMMA (n=18) entre 1981 et 2009 dans un centre de référence tertiaire. Le suivi moyen était de 8 ans (allant de 2 à 24 ans). Vingt-cinq patients ont développé une récidive (27%). Dix-sept patients étaient indemnes de la tumeur après le deuxième curetage avec des adjuvants locaux et chez huit patients une résection *en bloc* a été nécessaire pour obtenir la guérison. Nous avons trouvé un risque de récidive cinq fois plus élevé en cas d´extension dans les tissus mous, tandis que l´âge, le sexe, la localisation et une fracture pathologique associée n´augmentaient pas le risque de récidive.
Le **Chapitre 8** rapporte une étude radiologique sur la prévalence et l´impact clinique de l´arthrose radiologique (Kellgren et Lawrence grades 3-4) chez 53 patients qui ont subi un curettage avec PMMA pour une tumeur à cellules géantes au niveau du genou entre 1987 et 2007 dans un centre de référence tertiaire. Le suivi moyen était de 7 ans (allant de 5 à 24 ans). L´arthrose radiologique a été trouvé chez 17% des patients après un délai médian de 57 mois après curettage avec PMMA. Aucun des patients n´a été opéré d´une arthrose au dernier suivi. Le risque de développer une arthrose du genou était neuf fois plus élevé lorsque l´os sous chondral était envahi et quatre fois plus élevé pour les tumeurs à cellules géantes en position sous chondrale. Les résultats fonctionnels et de qualité de vie étaient comparables pour les patients de grades 3-4 et 0-2 de Kellgren et Lawrence, suggérant un impact clinique modeste de l´arthrose radiologique avec un recul intermédiaire. Toutefois, cela peut augmenter avec le temps et un suivi prolongé est nécessaire.

Les Tumeurs à cellules géantes ténosynoviales

Le **Chapitre 9** décrit un aperçu de l´imagerie, de la génétique, de l´histopathologie et du traitement multidisciplinaire des types localisés et des types diffus de tumeurs ténosynoviales à cellules géantes. La surexpression du macrophage colony-stimulating facteur 1 (M-CSF) et de son récepteur (M-CSFR) par des fibroblastes synoviaux favorise la formation d´une masse tumorale. Sur l´imagerie par résonance magnétique (IRM), les dépôts d´hémosidérine provoquent des changements locaux de l´intensité du signal, ce qui entraîne l´apparition du signal de faible intensité caractéristique des tumeurs ténosynoviales à cellules géantes sur les pondérations T1 et T2 en séquences écho de spin et écho de gradient. Bien que la synovectomie arthroscopique

ait été préconisée comme une alternative à la synovectomie à ciel ouvert, il y a des risques de récidive et de résection insuffisante importants, en particulier dans le compartiment postérieur du genou. En outre, il existe un risque de semer la maladie dans les tissus mous autour des portails arthroscopique. Pour le type localisé et pour le type diffus limité au compartiment antérieur du genou, la synovectomie arthroscopique peut être suffisante. Pout le type diffus initial et récidivant, la synovectomie à ciel ouvert est conseillée. La chirurgie combinée ou en deux étapes peut être envisagée. Pour la maladie postérieure, une incision « lazy-S » est réalisée avec l´élévation de l´origine du muscle gastrocnémien permettant la protection des structures neurovasculaires. Il est suivi par l´arthrotomie pour visualiser le ligament croisé postérieur et les surfaces articulaires et pour faire une capsulotomie complète pour réaliser une synovectomie adéquate. Pour la maladie antérieure, une approche antérieure médiane est conseillée, car cela permet une bonne visualisation de la cavité synoviale, du coussinet adipeux de Hoffa et des ligaments croisés et collatéraux. De la tumeur résiduelle adjacente à l´interligne articulaire et à gouttières unilatérales peut également être réséquée en toute sécurité. Pour les récidives et pour l´extension extra-articulaire, la radiothérapie à dose modérée ou la thérapie systémique devraient également être considérées. Bien qu´il existe encore peu de preuves scientifiques sur l´efficacité des inhibiteurs de la tyrosine kinase M-CSFR (par exemple l´imatinib) pour le traitement des tumeurs à cellules géantes ténosynoviales, il pourrait à l´avenir être intégré dans la stratégie de traitement pour une maladie plus étendue, par analogie avec le traitement systémique pour les tumeurs à cellules géantes des os.

Le **Chapitre 10** présente une revue systématique de la littérature sur les tumeurs ténosynoviales à cellules géantes avec 59 articles comprenant un total de 313 patients avec le type localisé et 777 patients avec le type diffus. La qualité méthodologique (Newcastle-Ottawa échelle d´évaluation de la qualité des études de cohortes) était bonne dans 40%, intermédiaire dans 50% et médiocre dans 10% des articles inclus. Les taux de récidive rapportés étaient de 4% après synovectomie à ciel ouvert et 3% après synovectomie arthroscopique pour le type localisé dans le genou et de 14% après synovectomie à ciel ouvert et 40% après synovectomie arthroscopique pour le type diffus dans le genou. Avec l´utilisation de colloïdes radioactifs intra-articulaires (synoviorthèses) les taux de récidive étaient de 15% après synovectomie à ciel ouvert et de 22% après synovectomie arthroscopique pour le type diffus au genou et à la hanche.

Avec la radiothérapie adjuvante, les taux de récidive étaient de 12% après synovectomie à ciel ouvert et de 13% après synovectomie arthroscopique pour le type diffus avec extension extra-articulaire du genou. En général, la synovectomie à ciel ouvert ainsi que l´excision des tissus tumoraux extra-articulaires sont recommandées pour réduire le risque de récidive relativement élevé.

Le **Chapitre 11** a évalué de manière rétrospective l´influence de la mesure des tumeurs et du type de chirurgie sur les résultats fonctionnels et de qualité de vie chez 30 patients traités pour une tumeur ténosynoviale à cellules géantes du genou entre 1980 et 2011. Quinze patients ont été principalement traités dans notre centre de référence tertiaire et 15 patients ont été renvoyés dans notre centre pour le traitement d´une récidive. La mesure des tumeurs a été évaluée sur l´IRM préopératoire ou sur les rapports d´imagerie. Seize patients (53%) avaient une tumeur moins étendue, définie comme une lésion pédiculée solitaire ou l´atteinte diffuse du compartiment antérieur ou postérieur de genou. Quatorze patients (47%) avaient une tumeur plus étendue, définie comme l´atteinte des compartiments antérieurs et postérieurs du genou ou en cas d´extension extra-articulaire. Les patients ayant initialement une tumeur plus étendue ont souvent subi de multiples interventions chirurgicales, y compris une synovectomie arthroscopique initiale et une synovectomie à ciel ouvert pour la dernière récidive. Après un suivi moyen de 8 ans (allant de 2 à 33 ans), ces patients ont rapporté des résultats fonctionnels et de qualité de vie nettement inférieurs. Dans cette étude, la synovectomie à ciel ouvert comme intervention de première intention n´a pas entraîné de déficits fonctionnels ou une diminution de la qualité de vie par rapport à la synovectomie arthroscopique.

Les conclusions, les implications cliniques et les perspectives d'avenir pour les sujets de cette thèse de doctorat sont discutés dans le **Chapitre 13**.

List of publications

List of publications

Scientific articles

L van der Heijden, MJL Mastboom, PDS Dijkstra, MAJ van de Sande. Functional outcome and quality of life after surgical treatment of diffuse-type giant cell tumor about the knee – A retrospective analysis of 30 patients. *Accepted for publication in Bone Joint J.*

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L van der Heijden, MAJ van de Sande, ICM van der Geest, HWB Schreuder, BJ van Royen, PC Jutte, JAM Bramer, FC Öner, AP van Noort-Suijdendorp, HM Kroon, PDS Dijkstra. Giant cell tumor of the sacrum – A nationwide study on mid-term results in 26 patients after intralesional excision. *Eur Spine J 2014; e-pub ahead of print, DOI 10.1007/s00586-014-3263-5.*

L van der Heijden, ICM van der Geest, HWB Schreuder, MAJ van de Sande, PDS Dijkstra. Liquid nitrogen or phenolization for giant cell tumor of bone? A comparative cohort study on various standard treatments at two tertiary referral centers. *J Bone Joint Surg Am 2014;96(5):e35.*

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VC Oliveira, **L van der Heijden**, ICM van der Geest, DA Campanacci, CLMH Gibbons, MAJ van de Sande, PDS Dijkstra. Giant cell tumors of the small bones of hands and feet – Long-term results of 30 patients and systematic literature review. *Bone Joint J 2013;95-B(6):838-45.*

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RA Nout, KM Bradley, NA Athanasou, PCW Hogendoorn, MAJ van de Sande. The management of diffuse-type giant cell tumor (pigmented villonodular synovitis) and giant cell tumor of tendon sheath (nodular tenosynovitis). *J Bone Joint Surg Br 2012;94(7):882-8.*

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L van der Heijden, Facebook PVNS research group, MAJ van de Sande. Diffuse-type giant cell tumor of the knee and hip - First Facebook-based functional outcome and quality of life study after arthroscopic or open synovectomy in 71 patients. *Oral presentation at the 27th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Vienna, Austria, 22 May 2014.* Best Innovation Oral Presentation Award.

L van der Heijden, MAJ van de Sande, ICM van der Geest, HWB Schreuder, BJ van Royen, PC Jutte, JAM Bramer, FC Oner, AP van Noort-Suijdendorp, HM Kroon, PDS Dijkstra. Giant cell tumors of the sacrum – A nationwide study on mid-term results in 26 patients after intralesional excision. *Oral presentation at the 27th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Vienna, Austria, 23 May 2014.*

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L van der Heijden, AC Heineken, L Bollen, ICM van der Geest, HWB Schreuder, BJ van Royen, PDS Dijkstra. Giant cell tumor of the mobile spine - A multicenter study on midterm results in 18 patients after surgical excision. *Poster presentation at the 27th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Vienna, Austria, 21-23 May 2014.*

L van der Heijden, MAJ van de Sande, ICM van der Geest, HWB Schreuder, BJ van Royen, PC Jutte, JAM Bramer, FC Oner, AP van Noort-Suijdendorp, HM Kroon, PDS Dijkstra. Sacrale reusceltumoren – Landelijke studie naar resultaten van

intralesionale excisie in 26 patiënten. *Oral presentation at the annual meeting of the Dutch Orthopedic Association (Nederlandse Orthopaedische Vereniging, NOV), Rotterdam, the Netherlands, 6 February 2014.* Nomination Biomet Award.

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VC Oliveira*, **L van der Heijden**, ICM van der Geest, DA Campanacci, CLMH Gibbons, MAJ van de Sande, PDS Dijkstra. Giant cell tumors of the small bones of hands and feet – Long-term results of 30 patients and literature review. *Oral presentation at the 14th annual meeting of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Istanbul, Turkey, 7 June 2013.* *Presenting author.

L van der Heijden, AC Heineken, M Fiocco, MAJ van de Sande, RGHH Nelissen, PDS Dijkstra. Osteoarthritis after curettage with PMMA for giant cell tumors around the knee – Prevalence, risk factors and clinical relevance in 46 patients. *Poster presentation at the 14th annual meeting of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Istanbul, Turkey, 5-8 June 2013.*

L van der Heijden, CLMH Gibbons, AB Hassan, JR Kroep, H Gelderblom, CSP van Rijswijk, RA Nout, KM Bradley, NA Athanasou, PDS Dijkstra, PCW Hogendoorn, MAJ van de Sande. Multidisciplinary approach to giant cell tumors of tendon sheath and synovium – Critical appraisal of literature and treatment proposal. *Poster presentation at the 14th annual meeting of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Istanbul, Turkey, 5-8 June 2013.*

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L van der Heijden, CLMH Gibbons, AB Hassan, JR Kroep, H Gelderblom, CSP van Rijswijk, RA Nout, KM Bradley, NA Athanasou, PDS Dijkstra, PCW Hogendoorn, MAJ van de Sande. A multidisciplinary approach to giant cell tumors of tendon

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L van der Heijden, ICM van der Geest, HWB Schreuder, RPH Veth, MAJ van de Sande, PDS Dijkstra. Hot or cold? Clinical outcome of liquid nitrogen, phenol, PMMA and combinations as local adjuvant treatment after curettage in giant cell tumor of bone. *Oral presentation at the 25th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Bologna, Italy, 16 May 2012.*

L van der Heijden, AP van Noort-Suijdendorp, MAJ van de Sande, AHM Taminiau, BJ van Royen, PDS Dijkstra. Giant cell tumors of the sacrum – Midterm results in 14 patients after intralesional excision. *Poster presentation at the 25th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Bologna, Italy, 14-16 May 2012.*

L van der Heijden, CLMH Gibbons, AB Hassan, JR Kroep, CSP van Rijswijk, RA Nout, KM Bradley, NA Athanasou, PDS Dijkstra, PCW Hogendoorn, MAJ van de Sande. Multidisciplinaire behandeling van reusceltumoren van synovium en peesschede (PVNS) – Systematic review. *Oral presentation at the fall annual meeting of the Dutch Orthopedic Association (Nederlandse Orthopaedische Vereniging, NOV), Veldhoven, the Netherlands, 4 October 2011.*

L van der Heijden, PDS Dijkstra, DA Campanacci, M Ippolito, R Capanna, CLMH Gibbons, MAJ van de Sande*. Surgical management of giant cell tumor of bone presenting with a pathological fracture. *Oral presentation at the 16th general meeting of the International Society of Limb Salvage (ISOLS), Beijing, China, 15-18 September 2011.* *Presenting author.

L van der Heijden, MAJ van de Sande, MJ Nieuwenhuijse, PDS Dijkstra. Giant cell tumour of bone: risk analysis of local recurrence. *J Bone Joint Surg Br Proceedings 2012;94-B:(SUPP XXXVII)302. Oral presentation at the 12th annual meeting of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Copenhagen, Denmark, 2 June 2011*. Nomination Free Paper Award.

L van der Heijden, MAJ van de Sande, PDS Dijkstra. Giant cell tumour of bone: retrospective analysis of risk factors for local recurrence. *Oral presentation at the 24th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Ghent, Belgium, 19 May 2011*.

L van der Heijden, PDS Dijkstra, DA Campanacci, M Ippolito, R Capanna, CLMH Gibbons, MAJ van de Sande. Optimal adjuvant treatment after curettage for giant cell tumor of bone. *Poster presentation at the 25th annual meeting of the European Musculo-Skeletal Oncology Society (EMSOS), Ghent, Belgium, 18-19 May 2011*.

MAJ van de Sande*, **L van der Heijden**, PDS Dijkstra. Giant cell tumour of bone: retrospective analysis of risk factors for local recurrence. *J Bone Joint Surg Br Proceedings 2012;94-B:(SUPP XXX)4. Oral presentation at the annual meeting of the British Orthopaedic Oncology Society (BOOS), Oswestry, England, 8 April 2011*.
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Curriculum vitae

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Lizz van der Heijden was born in Veghel on April 11th 1987 and she grew up in Bergen op Zoom, the Netherlands. In 2003-2004 she spent a year as exchange student in Castellana Grotte, Italy, where she attended Liceo Linguistico 'Ettore Majorana' in Putignano. She graduated from Gymnasium 'Juvenaat' in Bergen op Zoom in 2006 and started medical school at Leiden University Medical Center (LUMC) in that same year. In 2007 she began her studies of French Language and Culture at Leiden University. From 2008 until today, she worked at BISLIFE Foundation (former Netherlands Bone bank Foundation–Bio Implant Services) as medical team leader and retrieval technician of bone and tendon tissue, heart valves and corneas in post-mortem tissue donors. Together with her passion for dancing, this enlarged her interest in the functioning of the musculoskeletal system.

In 2010 she started her research internship on risk factors for recurrence in giant cell tumor of bone at the Department of Orthopaedic Surgery at the LUMC. During this project, she also worked at the Centro Traumatologico Ortopedico of AOU-Careggi University Hospital in Florence, Italy (D.A. Campanacci MD and R. Capanna MD PhD) and at the Nuffield Orthopaedic Centre of Oxford University Hospitals in Oxford, United Kingdom (C.L.M.H. Gibbons MBBS MA FRCS(Orth) and N.A. Athanasou MD PhD MRCP FRCPath). This internship resulted in a series of clinical studies on giant cell tumor of bone and tenosynovial tissue that formed the basis of this PhD-thesis (R.G.H.H. Nelissen MD PhD, P.D.S. Dijkstra MD PhD and M.A.J. van de Sande MD PhD). Working as a PhD student also created the opportunity to present her research at multiple international scientific meetings, to follow courses on scientific methodology and epidemiology and to create and improve new connections in the international research field on this subject. At the Annual Meeting of the European Musculoskeletal Oncology Society Meeting in May 2014, she won the EMSOS Best Innovation Oral Presentation Award.

After obtaining her master's degree in French Language and Culture in 2012 and conducting most of the scientific work related to this PhD-thesis, she started her medical internships in April 2013 and she hopes to graduate in February 2015.