Giant cell tumor of bone and tenosynovial tissue : surgical outcome

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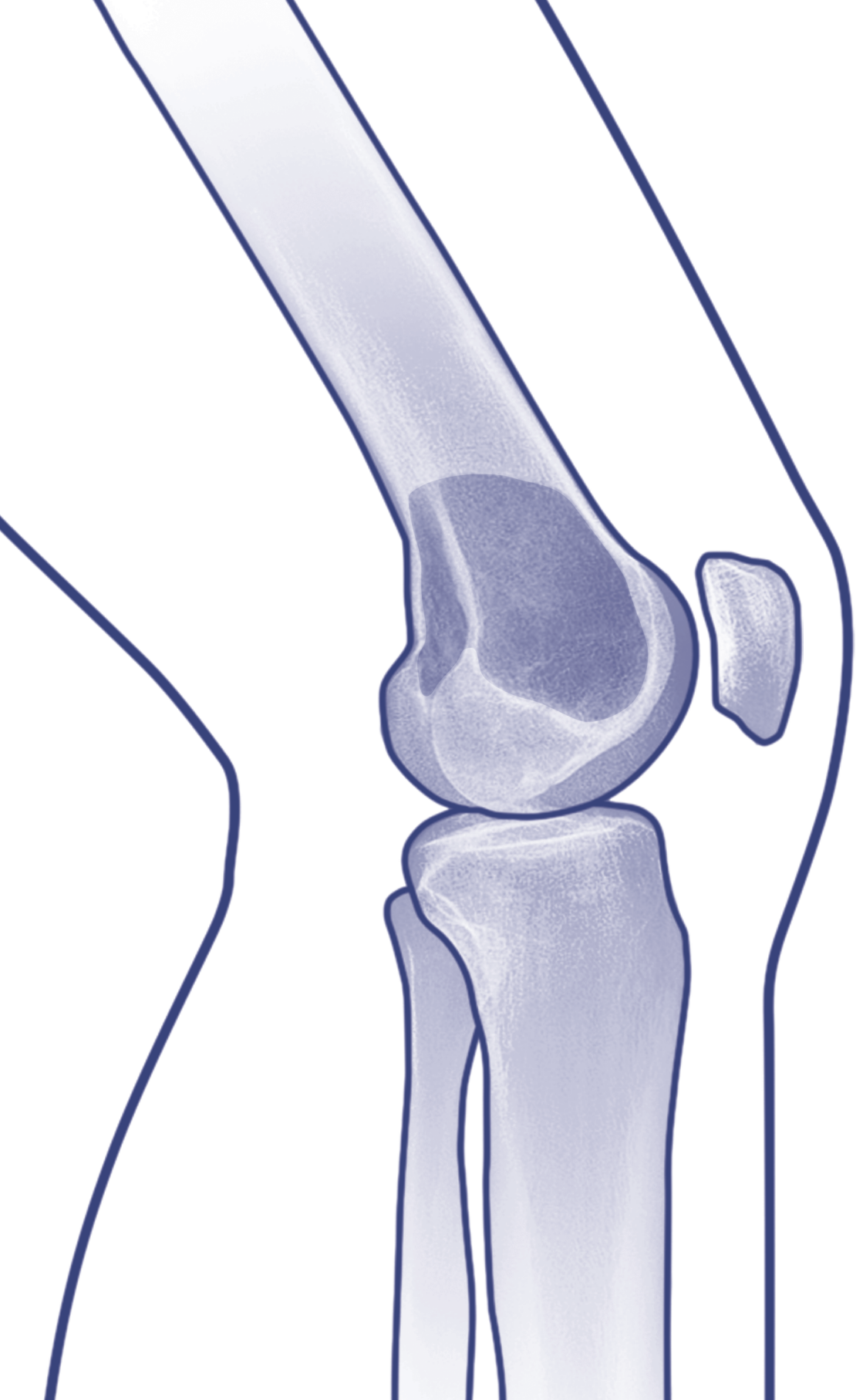

Chapter 13

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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