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Tenosynovial giant cell tumours

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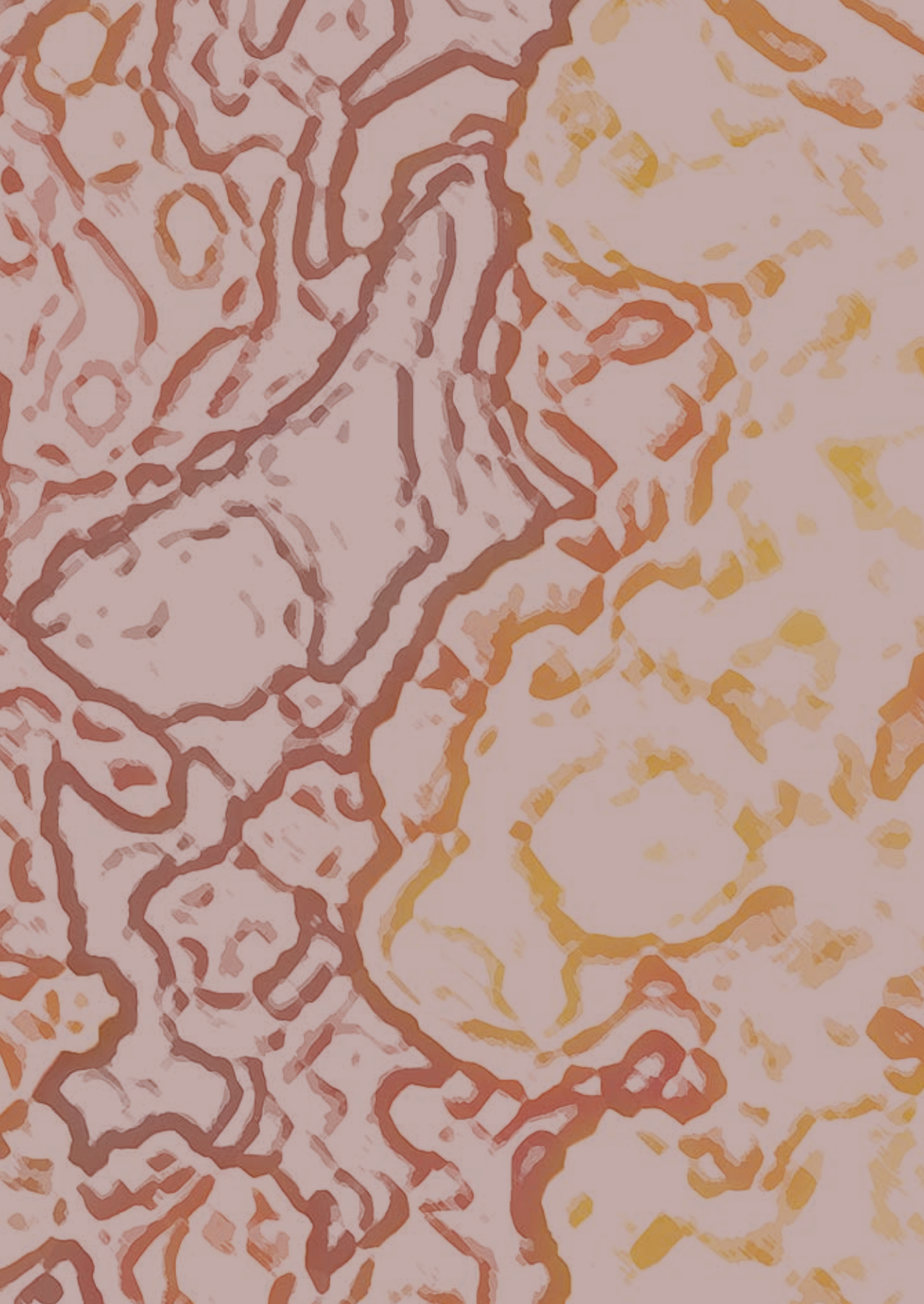


chapter fourteen

DISCUSSION

General discussion & Future perspectives

General discussion

In the 2013 WHO classification of tumours of soft tissue and bone, giant cell tumour of the tendon sheath and pigmented villonodular synovitis (PVNS) were unified in one overarching name: tenosynovial giant cell tumours (TGCT)[1, 2]. To date, among most treating physicians, the disease still remains best known with the term PVNS[3]. With this thesis, we want to create disease awareness and update knowledge on disease and treatment outcome.

TGCT is a rare heterogeneous disease (**chapter 2**) with a wide clinical spectrum; patients of all ages are affected (**chapter 5** and **6**), including different joints (both small and large), various disease stages and severities. This heterogeneity challenges research initiatives, as current literature mainly consists of relatively small single centre observational case-series that often compare apples to oranges. Frequently, series have a retrospective design and level of evidence is not exceeding level III-IV. To achieve solutions on unmet medical needs, we need to set up research projects that reach higher levels of evidence through thorough (inter)national, multicentre collaborative studies.

1. Translational research

The translocation (1;2)(p13;q35) that is responsible for overexpression of Colony Stimulating Factor 1 (CSF1), is thought to be the driver mechanism of this disease[4, 5]. It remains unclear when and why this translocation forms, but it remains a 'local problem' as TGCT is a mono-articular disease. An unravelled clinical question is how to differentiate the biological behaviour of different TGCT-types with clinical outcome (recurrence). All TGCT cases show CSF1 over-expression. By the use of correlative microscopy for CSF1 mRNA ISH and consecutive CSF1 split-apart FISH, we were able to detect CSF1-gene rearrangement in 76% of the TGCT cases; 77% for localized-TGCT and 75% for diffuse-TGCT. The relatively high percentage of rearrangement in our study could be attributed to our scoring on preselected areas, based on high CSF1 expression. In addition, our DNA FISH analysis, using bacterial artificial chromosome (BAC) clones (RP11-354C7 and RP11-96F24) bracketing CSF1 locus, identified not only a translocation, but also an inversion for CSF1 rearrangements. In diagnosing TGCT, CSF1 mRNA-ISH in combination with CSF1 split-apart FISH; using digital correlative microscopy, is an auxiliary diagnostic tool to identify rarely occurring neoplastic cells. Although this helps the diagnostic process, in **chapter 3** we were unable to use this technique and differentiate for biological behaviour of TGCT by evaluating CSF1 over-expression or rearrangement.

2. Individually tailored treatment

Physical joint examination is generally nonspecific in the clinical diagnosis of TGCT. A specialized musculoskeletal radiologist can however diagnose TGCT on magnetic resonance (MR) imaging, which is the most distinctive imaging technique[6-10]. MR imaging can also be a differentiating tool to determine tumour severity staging and for evaluation of disease extent during follow-up. The TGCT severity classification in **chapter 4** defines TGCT extension on MR imaging to classify disease severity. This classification, including four distinct severity-stages, could attribute to a treatment strategy flowchart and improve the homogeneity in clinical studies. Definitive diagnosis however is established by histopathology, either by biopsy or surgical resection.

The fundamental question whether curation is necessary in a locally aggressive disease often arises in literature. Debilitating symptoms and (progressive) joint destruction commonly result in treatment of the diseased tissue. At present, the choice of treatment is established by preference of the patient, treating physician and might differ per centre. Most common performed treatment is surgical excision, aiming for local tumour control. Localized-TGCT presents as a well circumscribed lesion and recurrence rates after arthroscopic and open synovectomy are reported similar (6% after arthroscopic and 4% after open synovectomy)[11]. Surgical treatment for the locally aggressive diffuse-TGCT is more challenging, as pathologic tissue can be widely spread and technically difficult to reach. In extensive disease (**chapter 4**, severe diffuse stage), irradical resection could be preferred with joint preservation in mind. However, higher rates of recurrences are described after macroscopically incomplete resections[12-15]. As primary treatment for diffuse-TGCT, either an arthroscopic- or (one- or two staged) open synovectomy or a combination of these two treatments is performed. Physicians in favour of arthroscopic resection claim fast recovery, a lower complication rate and less joint morbidity[13, 16-22]. However, frequently at the cost of inadequate excision, high recurrence rates (on average 40% in diffuse-TGCT) and a theoretical risk of joint seeding and portal contamination[11, 23]. A complete synovectomy is generally impossible with traditional arthroscopy, therefore Blanco et al. and Mollon et al. used multiple portals in arthroscopic synovectomy[24, 25]. Chin et al. stated that knee arthroscopy is an inferior treatment for extra-articular TGCT[26]. Nowadays, open synovectomy, either one- or two-staged, is the preferred surgical therapy in most centres, because of clear tumour visibility and lower short term recurrence rates (on average 14% in diffuse-TGCT)[11, 27, 28]. The disadvantage of a one- or two-staged

open resection, could be deteriorated joint function accompanied with decreased health-related quality of life (**chapter 9**)[29]. A combined anterior arthroscopic- and posterior open synovectomy in the knee is only incidentally reported. Mollon et al. described the combined approach of an anterior arthroscopy and posterior open synovectomy (N=15 patients), with low recurrence rates[25]. Colman et al. retrospectively subdivided 48 diffuse-TGCT patients in three groups; either treatment with an arthroscopy, the combined approach or an open approach. They concluded that the combined approach is a feasible option because of relatively low short term recurrence rates (9%)[30]. **Chapter 7** revealed that the longer the follow-up, the higher the recurrence rates. Localized-TGCT had a recurrence rate of 21% and diffuse-TGCT 69% after initial surgical resection at a tertiary oncology centre with a follow-up of more than 10 years. The suspicion arouses that most patients will develop a recurrence when you wait long enough. The main question remains: is the recurrent disease accompanied by debilitating symptoms or joint destruction?
In general, all surgical treatments harbour the risk of complications. Literature frequently lacks descriptions of complications. **Chapter 7** reports a complication rate of 4% in localized-TGCT and 12% in diffuse-TGCT after initial surgical treatment at a tertiary centre. Most common complication in diffuse-TGCT was joint stiffness, which might be difficult to prevent in surgical treatment of extensive disease.

In extensive diffuse disease, radical excision is next to impossible as residual tumour cells (micro- R1 or macroscopically R2) may persist. In diffuse-TGCT, joint destruction and secondary osteoarthritis is frequently present. When chronic symptoms persist, joint arthroplasty might become inevitable, especially in large joints with tight capsules including a higher risk of bone involvement, such as the hip and ankle[29, 31, 32].

A combination of surgery and external beam radiation is considered in extensive or recurrent diffuse-TGCT. Radiotherapy may kill residual tumour cells, but possibly at the cost of increased (delayed) complications, especially in re-operation, and impaired functional outcome[15, 33-35]. Blanco et al. reported that partial arthroscopic synovectomy of the knee combined with external beam radiation might reduce the risk of recurrence (N=22 patients)[24]. A meta-analysis suggested that open synovectomy (N=19 studies) or synovectomy combined with perioperative radiotherapy (N=11 studies) is associated with a reduced rate of recurrence[34]. Mollon et al. reserved additional

external beam radiation for patients at high risk for local recurrence, if they had the following characteristics: multiple recurrent intra-articular disease, extra-articular extension, or gross residual disease remaining following surgery[25]. Currently, sufficient data including adequate patient numbers is lacking to support the additional value of external beam radiation in primary cases and should only be performed in specific extensive or recurrent diffuse-TGCT cases.

Additional reported treatment modalities include radiation synovectomy with 90yttrium[36] and cryosurgery[37, 38], for which the therapeutic value is inconclusive and their long-term side effects and complications are unknown. Bickels et al. treated seven patients with diffuse-TGCT of the ankle with subtotal synovectomy and intra-articular ^{90}yttrium and warned not to use ^{90}yttrium as additional treatment because of unacceptable high rate of serious complications[39]. Gortzak et al. reported no significant differences in residual disease, complication rate and overall physical and mental health scores between patients surgically treated for TGCT of the knee with (N=34) or without (N=22) adjuvant 90Yttrium, after a mean follow-up of 7.3 years[36]. Chin et al. subdivided patients, after surgical resection without disease eradication, into three groups: group I combined arthroscopic and open synovectomy (five patients), group II combined synovectomy in combination with intra-articular radiation synovectomy (dysprosium-165) (30 patients), and group III combined resection and three months postoperatively external beam radiation (five patients). They concluded that group I and Group II showed similar increases in postoperative flexion compared with group III[15]. Verspoor et al. evaluated 12 patients treated with surgical synovectomy and additional cryosurgery. They did not find better results compared to surgical resection alone[37].

Diffuse-TGCT grows locally aggressive. Therefore, systemic therapy, with possible (severe) side effects, seems justified in this benign but debilitating disease. Colony Stimulating Factor1 (CSF1), due to genomic rearrangements, is believed to be the driver mechanism in tumour formation. By a paracrine loop, the CSF1 excreting tumour cells, attract non-neoplastic cells, carrying the CSF1 receptor. Interruption of this pathway is the aim of systemic targeted therapies. Targeted therapy might be used as treatment independently or to primarily down-stage the disease and facilitate consecutive surgical resection. Non-selective CSF1 inhibitor therapies with nilotinib[40] or imatinib (**chapter 8**) and newer, more potent selective CSF1 inhibitors such as pexidartinib[41], emactuzumab[42], cabiralizumab[43]; or a monoclonal antibody such as MSC110 (clinicaltrial.gov) seem promising.

Results are usually tumour-centric presented, using Response Evaluation Criteria in Solid Tumors (RECIST); complete response, partial response, stable disease and progressive disease; and patient centric, using symptom improvement evaluation. In a randomized, placebo-controlled phase 3 study, pexidartinib showed an improved overall response rate (complete response and partial response merged) of 39% in the pexidartinib-group (N=61) and 0% of placebo-group (N=59), after median six months follow-up. PROMIS physical function, worst stiffness and pain response was significantly better in patients treated with pexidartinib[41]. Emactuzumab (N=29) had an overall response rate of 86% and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months)[42]. Preliminary results of cabiralizumab showed partial response in 5 out of 11 patients and positive functional status improvements by Ogilvie-Harris score (from 2 to 7)[43]. Ogilvie-Harris score combines pain, synovitis, range of motion and functional capacity on a scale of 0 to 12.
Complete response was reported in a total of four patients; two patients treated with emactuzumab[42] and two patients treated with imatinib, presented in **chapter 8**.
Reported mild side effects include edema, change of hair colour, fatigue, nausea and skin rash/ dermatitis, but also moderate to severe side effects such as neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue. Despite these side effects, in selected patients with extensive and recurrent diffuse-TGCT, CSF1 inhibitors might offer a solution. Treatment optimization is yet to be established; optimal agent, therapy duration, timing of surgery, toxicity profile and mechanism of resistance.

A challenging rare subgroup of soft tissue sarcoma patients, comprises multifocal, malignant or metastatic disease resembling TGCT (four patients with metastatic TGCT in **chapter 8** and two patients in **chapter 11**). These patients are incidentally reported in case-series[44]. The largest series of Li et al. included seven patients with malignant TGCT and concluded that these tumours should be regarded as a distinct sarcoma with considerable morphologic variability, metastatic propensity, and lethality[45]. As specialized centres see these patients extremely rare, upcoming research should reveal whether TGCT is capable of malignant transformation or whether this malignant tumour should be regarded a different (malignant) entity.

To summarize, several treatment modalities in the heterogeneous disease TGCT are available. Current literature fails to specify patient characteristics per treatment modality and lacks randomized controlled trials, impeding definitive treatment of choice for each individual, based on efficacy and safety. A solution for the difficulty of performing a randomized controlled trial might be the so called stepped wedge cluster design. This is a special form of a randomised study in which an intervention at group level is implemented in stages[46]. To contribute to personalized treatment, careful evaluation of health-related quality of life and functional outcome (**chapter 9** and **10**), not just local recurrence and complications, should be included in patient follow-up. In addition, large scaled studies based on individual participant data meta-analysis provide a higher form of evidence in comparison with small heterogeneous case series. Advantages include that missing data can be accounted for at the individual level, subgroup analyses can be performed (e.g. per affected joint) and up to date disease status or follow-up information can be updated continuously (**chapter 7**)[47].

3. Centralized treatment in a multidisciplinary team

TGCT onset is typically slow and patients present with unspecified symptoms[1, 2, 48, 49]. Pain, swelling, and stiffness of the involved joint might be misinterpreted as osteoarthritis, rheumatoid arthritis, a meniscal tear, or other ligamentous injury[50]. Because of the rarity of the disease, definitive diagnosis may take several years and patients present with extensive disease[11, 51, 52]. After several (arthroscopic or open) synovectomies and even radiotherapy, patients are still referred to a tertiary hospital. Besides declined functional outcome and health-related quality of life, these patients are at risk of repeated recurrences, therapy resistant disease and higher risk of complications[29]. Continued inflammation, joint usuration and bone involvement may lead to articular destruction that might worsen (pre-existing) osteoarthritis[50]. By creating more public awareness, involving relevant dedicated health care providers (e.g. rheumatologists, general practitioners, physiotherapists), delay of diagnosis should be reduced by referring patients to specialized centres at an early stage to provide optimal treatment(s)[53]. Specialized centres treat multiple patients with TGCT and this rare disease is considered daily practice. Therefore, all members of the multidisciplinary team are highly trained to recognize disease specifics. Members of the multidisciplinary TGCT team include dedicated physicians with experience in musculoskeletal oncology in the field of pathology, radiology, orthopaedic oncology, arthroscopic orthopaedics, radiotherapy, medical

oncology and if necessary paediatric orthopaedics. To prevent end stage treatment options, such as limb amputation (**chapter 11**), centralization of treatment should become state of the art. Two examples of advantages of centralization of treatment are provided by the tertiary oncology centre in Leiden (LUMC). Every half year a patient centred newsletter is send to all patients with TGCT. This newsletter includes information on recent literature and (new) studies at patient level. In addition, the TGCT-team of the LUMC is active on Facebook, with their own up to date Facebook page ('TGCT study') and within the closed Facebook-group 'PVNS is pants' (**chapter 10**).

4. Patient-centred outcome measures

Outcome of TGCT treatments should be measured on how the patient is feeling. The mantra for patient-centred treatment is: don't make the treatment worse than the problem. Perhaps a debilitating operation costs more than the disease itself in the view of health-related quality of life and joint function preservation. Taking the factor time into account is necessary, as short term satisfying results could emerge into deteriorated outcome in the long run. Defining specific treatment options for each individual patient is of utmost importance. Would this individual patient benefit more from conservative treatment or side effects of targeted therapy? Mild side effects might be considered acceptable, however moderate to severe side effects seem less justifiable in a non-lethal disease.

Assessment of health-related quality of life and functional outcome in TGCT is necessary. However, specific patient reported outcome instruments have yet to be defined. A few studies, including **chapter 9** and **10**, have reported disease outcome from a patient perspective[15, 25, 29, 36, 48, 54, 55]. Used validated questionnaires included worst pain and worst stiffness numeric rating scale (NRS), short form (SF) health survey-12 and SF-36, Euroqol 5 (EQ5D5L), knee-injury osteoarthritis outcome score (KOOS), hip disability osteoarthritis outcome score (HOOS), Toronto extremity salvage score (TESS), musculoskeletal tumour society (MSTS) score, patient reported outcomes measurement information system physical function (PROMIS-PF) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). None of these patient reported outcome instruments are specifically designed for rarely lethal, but morbid musculoskeletal tumours. Gelhorn et al. performed research interviews regarding symptom experience to test the relevance and content validity of several existing patient reported outcome instruments. They recommended PROMIS-PF as most suitable questionnaire[48]. PROMIS-PF is subdivided in an upper- (11 questions) and lower-extremity part (13

questions). Since TGCT affects all joints, measurements eligible for all these locations would be the aim. In addition, general health-related quality of life measures are important to compare TGCT with other musculoskeletal disorders.

A major disadvantage of standardized questionnaires is that they include questions not applicable for each individual participant. Therefore, the item response theory (IRT) and Computer Adaptive Testing (CAT) are developed. IRT examines the response characteristics of individual items and the relationship between responses to individual items and the responses to each other item in a domain. By using IRT, CAT is a method that selects subsequent questions (from the item bank) based on the responses until predetermined termination criteria are met. Hereby only relevant questions are asked and the amount of questions is greatly reduced. This ensures a higher amount of patients willing to complete the questionnaire[56]. Relevant questions could be extracted from the PROMIS databank, including over 300 measures of physical, mental, and social health for use with the general population and with individuals living with chronic conditions (http://www.healthmeasures.net). For future self-reported outcome evaluations in TGCT, we would propose the CAT method by use of the PROMIS item bank.

Besides well-defined subjective outcome measures, objective outcome measures also need to be determined to structure clinical evaluation. The timed up and go test provides information on physical strength by measuring the time (seconds) to rise from and return to a chair with three meters walking in between[57]. Another functional measure is the six-minute walk test, not just determining joint range of motion, but looking at performance of the individual[58].

5. Limitations

This thesis consists of multiple cohort studies. At times, patients are present in several cohorts. Patients treated in the RadboudUMC or LUMC, were also present in the PALGA search to calculate the incidence (**chapter 2**). In the evaluation of impact on daily living (**chapter 11**), a Facebook cohort is used in which Dutch patients were present, which were also registered with the PALGA search. This overlap of patients in the cohort studies could have influenced the results. However, since each study had a unique research question to evaluate different aspects of the disease, this influence is considered minimal.

To conclude, TGCT is a chronic debilitating illness with large impact on daily living. It is a challenge for physicians to provide optimal personalized treatment, since TGCT patients present as a heterogeneous group, trials with targeted therapies are ongoing and a standardized treatment algorithm is lacking. Based on our experience, literature and the TGCT severity classification on MR imaging* (**chapter 4**), we propose a treatment algorithm for TGCT of all large joints as a foundation to build upon and to evolve (*figure 1 and figure 2*). In addition to the physical and financial burden for the patient, TGCT also involves a high healthcare burden with rising costs after diagnosis[59]. Current developments are promising: increasing disease awareness, centralization of care, several targeted therapy trials, evaluation of personalized follow-up questionnaires and ongoing prospective international collaboration studies. These initiatives should be expanded to achieve new insights in TGCT.

*The TGCT severity classification on MR imaging contains four distinct severity stages:

1. **Mild localized** contains localized-type, either intra- or extra-articular involvement without involvement of muscular/tendinous tissue/ligaments.
2. **Severe localized** includes localized-type, either intra- or extra-articular lesions and either or both involvement of muscular/tendinous tissue/ligaments.
3. **Moderate diffuse** comprises diffuse-type with intra- and/or extra-articular disease without involvement of muscular/tendinous tissue/ligaments.
4. **Severe diffuse** is diffuse-type including intra- and extra-articular involvement and involvement of at least one of the three structures (muscular/tendinous tissue/ligaments)

Future perspectives

1. Translational research

The driver mechanism in TGCT tumour formation seems to be over-expression of CSF1. Only a minority (2-16%) of cells in the tumorous tissue harbour the CSF1 rearrangement[4, 5]. Despite the few tumour cells, they disrupt the entire surrounding area in different degrees of extent. We expect the neoplastic cell to be a synovial like mononuclear cell, as was proposed by West et al.[4] They reported that CSF1 expressing cells also express CD68, without CD163 co-expression, and therefore expect CSF1 expressing neoplastic cells to be derived from synovial-lining cells. Identification of this neoplastic cell could attribute in investigations of new treatment modalities.

Dynamic contrast-enhanced MR imaging and histopathology research revealed high vascularization in both localized- and diffuse-TGCT, showing marked enhancement on T1-weighted images with a delayed wash-out[60, 61]. Angiogenesis is induced by CSF1 through vascular endothelial growth factor (VEGF)[62]. Formation of blood vessels is fundamental for tumour development. A possible therapeutic target would be to control this increased vascularity by inhibiting VEGF, for example with Bevacizumab (Avastin)[63].

2. Individually tailored treatment

It is unclear whether curation of diffuse-TGCT is possible at present, since residual tumour cells (micro- R1 or macroscopically R2) remain after surgical resection, optimal targeted therapy is under investigation and treatment with other therapies is inconclusive. A common question arises: is wait and see or conservative treatment justified in the locally aggressive diffuse-TGCT? Forthcoming research should provide answers on degree of joint destruction and (impaired) health-related quality of life in a wait and see or conservative treatment course.

Currently, data on tumour progression after quitting targeted therapy treatment is lacking. Future investigations should focus hereon. Also, several experimental studies with targeted therapy can be thought of, for example investigation of intermittent use (drug holidays), the possibility of intra-articular injection and the option of isolated limb perfusion with CSF1 blockers/inhibitors.

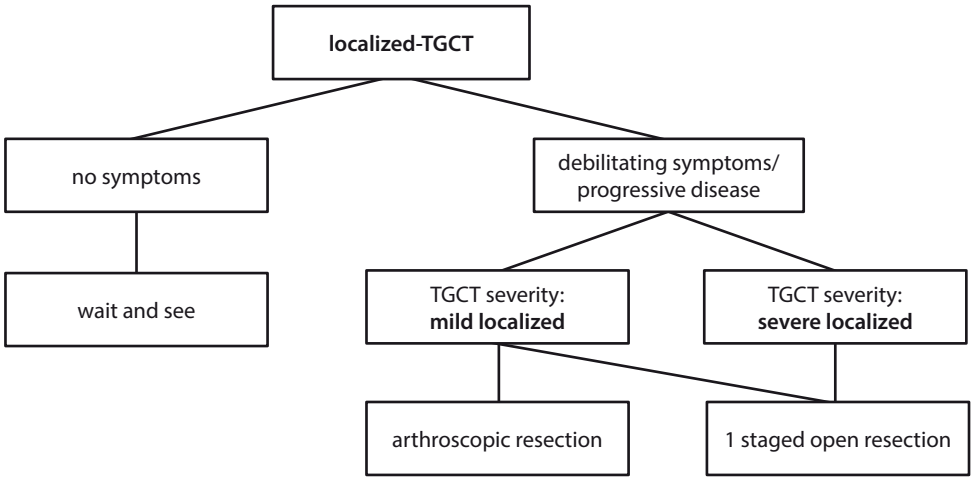
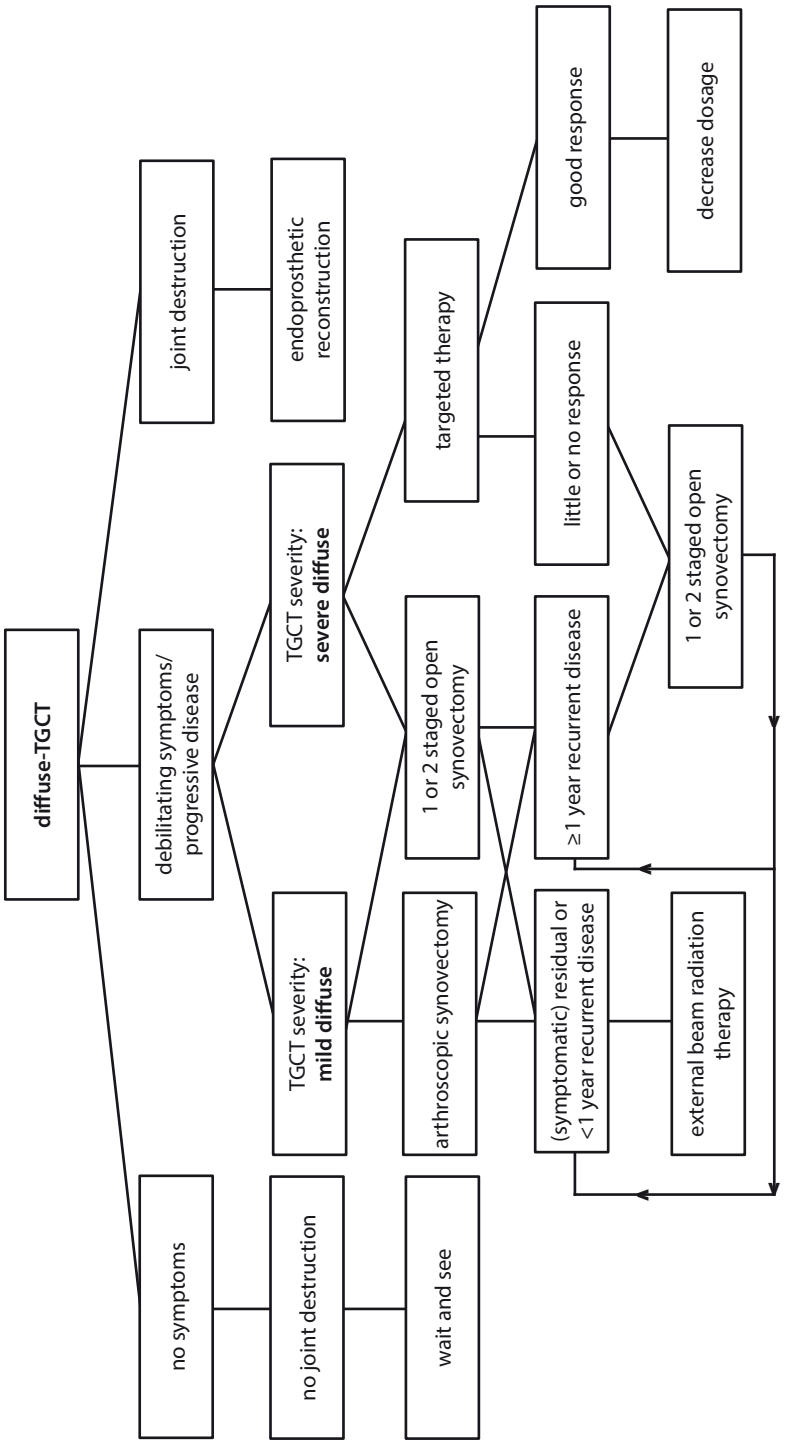


Figure 1 Proposed treatment algorithm for localized-TGCT of large joints. Balance between disease severity and potential treatment morbidity should be individually tailored for each patient. Wait and see and conservative treatment are considered similar. Open resection could be preferred above an arthroscopic resection to potentially reduce the risk of recurrence, but arthroscopic resection should not be excluded as a potentially curative surgical technique in selected cases.

Figure 2 ***(right page)*** Proposed treatment algorithm for diffuse-TGCT of large joints to be discussed in a multidisciplinary soft tissue tumours team. Treatment proposal should balance between disease severity and potential treatment morbidity and should be individually tailored for each patient. Wait and see and conservative treatment are considered similar, but should include a (2-)yearly MR imaging for follow-up to evaluate possible progressive disease (T1- and T2-weighted fast spin echo, possibly other fluid sensitive sequences, and preferably a scan after administration of contrast). Excision for functional improvement and joint preservation should be proposed in symptomatic patients. An open synovectomy could be preferred above an arthroscopic synovectomy in extra-articular disease (**chapter 7**), to reduce the risk of recurrence. External beam radiation therapy can only be advised in recurrent or severe diffuse cases and might be succeeded by targeted therapy in the near future. If arthroplasty is anticipated, radiotherapy should not be considered lightly. As the preferred dosage of radiotherapy is unknown, a moderate dose is recommended. Since targeted therapy trials are ongoing, no specific targeted therapy is advised. The timing and duration of (neo)adjuvant targeted therapy around surgery should be subject of future research.


diffuse-TGCT
no symptoms
debilitating symptoms/ progressive disease
joint destruction
no joint destruction
endoprosthetic reconstruction
TGCT severity: mild diffuse
TGCT severity: severe diffuse
wait and see
arthroscopic synovectomy
1 or 2 staged open synovectomy
targeted therapy
(symptomatic) residual or <1 year recurrent disease
≥1 year recurrent disease
little or no response
good response
external beam radiation therapy
1 or 2 staged open synovectomy
decrease dosage

Future treatment studies should combine current knowledge into new studies to improve treatment modalities. Recurrent disease, (short- and long-term) complications, health-related quality of life and joint function should be evaluated as outcome. Patients could be stratified by the TGCT severity classification (**chapter 4**), that may be improved by using biological differentiation using next generation sequencing or new MR imaging techniques. In a prospective cohort study, several different treatment groups could be evaluated and compared:

- Wait and see/conservative treatment in case of mild symptoms
- Surgical treatment (open versus arthroscopic resection, one versus two-staged synovectomy)
- Neoadjuvant targeted therapy + surgical treatment
- Surgical treatment + adjuvant targeted therapy
- Neoadjuvant external beam radiation + surgical treatment
- Surgical treatment + adjuvant external beam radiation

The intervention at group level could be implemented in stages, by use of the stepped wedge cluster design[46]. Best modality to monitor response of tumour activity is yet to be established. There might also be a role for dynamic contrast-enhanced MR imaging or fluorodeoxyglucose-positron emission tomography (FDG-PET), as TGCT shows high FDG update[64].

Evaluation of different treatment modalities, patient characteristics, disease severity and biological behaviour could result in a prediction model. This prediction model should predict individual risk profiles, that can then be linked to recommended treatment strategies and should take patient characteristics, affected joint, volume of disease, disease extent, performed treatment(s) and possibly histopathologic or genetic features into account.

3. Centralized treatment in a multidisciplinary team

The current trend in rare diseases is centralization of treatment that necessitates (highly) specialized expertise. Diffuse-TGCT treatment should sail along this trend. In addition, centralization of diffuse-TGCT treatment could be realized by creating more public awareness and easy available reliable information.

4. Patient-centred outcome measures

For future self-reported outcome evaluations in TGCT, the CAT method by use of the PROMIS item bank could be used. Preferably in the form of an easy accessible application on a mobile device. A new feature could be to not only link the application to the electronic patient dossier, but to also provide feedback to each individual patient personally, on how they are performing in the field of physical, mental and social health compared with themselves at specified time periods previously. As TGCT is known with recurrent disease developing years after initial surgical treatment, patients are more likely to continue completing questionnaires if they are short and simple.

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