Tenosynovial Giant Cell Tumour

From active surveillance to surgery and systemic therapy

Geert Spierenburg

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Dr. F.G.M. Verspoor
Dr. K van Langevelde

Voor mijn lieve en inspirerende moeder

Ans van der Hulst

18 februari 1958 – 4 mei 2022

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Chapter 1

General introduction and outline of thesis

Background

Tenosynovial giant cell tumour (TGCT) is a rare, proliferative lesion affecting joints throughout the body (1). TGCT is located intra- and/or juxta-articular, usually involving a single joint (2). Although it is a benign neoplasm, TGCT can behave locally aggressively and can have a detrimental effect on the quality of life (3-5). The most recent "World Health Organization (WHO) Classification of Tumours: Soft Tissue and Bone Tumours" categorises TGCT as a family of lesions originating from the synovium of joints, bursae, and tendon sheaths (6). TGCT comprises two main subtypes: Localised-type TGCT (L-TGCT) and Diffuse-type TGCT (D-TGCT). In the past, other denominators were commonly used, such as Giant Cell Tumour of Tendon Sheath (GCT-TS) for L-TGCT and Pigmented Villonodular Synovitis (PVNS) for D-TGCT, but in 2013 the WHO established the overarching name TGCT (7). Although the subtypes are different clinical entities, they are unified under one name due to their common pathogenesis and morphology (8).

Pathogenesis

The first record of TGCT dates back to 1852, described as 'cancer of tendon sheath' by Chassaignac (9). It was then considered a malignant entity. In 1941, Jaffe et al. suggested a reactive or inflammatory process as the origin of this condition. They introduced a unifying concept for localised and diffuse forms, comparable to the current WHO classification (10). The pathogenesis of TGCT was the subject of debate in the following years, in which several studies described chromosomal translocations indicating a neoplastic process (11, 12). In 2006, West et al. discovered that translocations of the Colony Stimulating Factor-1 (CSF1) lead to the proliferation of neoplastic cells (autocrine loop) expressing high levels of CSF1, causing accumulation of non-neoplastic macrophage lineage cells (paracrine loop), expressing the CSF1 receptor (CSF1R) on their surface (13). Several translocation partners for CSF1 have been identified (14-16). The pathogenesis and histopathology will be discussed in further detail in Chapter 8.

Epidemiology

TGCT is considered an orphan disease with an estimated annual incidence of 30-39 cases per million for L-TGCT and 5-8 cases per million for D-TGCT (17). L-TGCT mainly affects the digits of the hands and feet, and the incidence rates of L-TGCT affecting digits are estimated at 29 per million person-years and 10 per million person-years for

L-TGCT located in extremities. Around 2012, the prevalence was estimated at 44 per 100.000 persons for L-TGCT and 12 per 100.000 persons for D-TGCT in Denmark (18). TGCT has a female predilection, as females comprise around 60% of the patient population in both subtypes (17, 18). Also, it affects relatively young patients since it is typically diagnosed between the ages of 40 and 60 years, but it can occur at any age, even in children (19). While L-TGCT is more common, most TGCT arises in soft tissue near tendon sheaths of interphalangeal joints (20). The knee is the most affected joint in the extremities by both L-TGCT and D-TGCT (46% and 64%, respectively), followed by the hand and wrist for L-TGCT and the hip joint for D-TGCT (17, 18).

Clinical presentation

Since TGCT involves joints throughout the body, most patients report symptoms affecting their physical functioning (21). Common symptoms include pain, swelling, limited range of motion, instability, giving way and catching. Since these symptoms are nonspecific and doctors are unfamiliar with TGCT because of its rarity, diagnosis is often delayed (22). Although L-TGCT and D-TGCT belong to the same family of lesions, they are two different clinical entities (6). L-TGCT is characterised by a single nodular lesion often presenting as painless soft-tissue masses without joint dysfunction. D-TGCT, on the other hand, behaves locally more aggressively, leading to chronic joint pain often paired with secondary osteoarthritis (23, 24). D-TGCT, especially, can significantly impact the quality of life in a relatively young and active population (17, 25). Despite TGCT being a benign disease, there are incidental reports of D-TGCT (M-TGCT) malignant transformations, making this entity extremely rare (26, 27).

Diagnostics

Conventional radiography is the first option for patients with joint-related complaints to diagnose osteoarticular causes. Although osteoarthritic changes may be present, radiographs of TGCT are often normal. Osteochondral destruction is mainly seen in joints with limited volume and joint space, resulting in pressure erosions (24). Magnetic resonance imaging (MRI) is the modality of choice to diagnose TGCT (28). MRI is meaningful in the distinction between the subtypes of TGCT. L-TGCT presents as a single nodular lesion located intra- or extra-articular (23). D-TGCT is characterised by diffuse synovial thickening with intra- and/or extra-articular lesions. D-TGCT is often associated with joint effusion (2, 23). Hemosiderin deposits found in the tumour causes

artefacts on gradient echo sequences on MRI, causing typical blooming effects due to low signal intensity (23).

Macroscopically, TGCT presents as a brown-yellow tissue due to the hemosiderin, with L-TGCT usually as a small, well circumscribed single lesion and D-TGCT usually as larger, multi-nodular and villous lesion (7).

The definitive diagnosis of TGCT is obtained through histological analysis via excisional biopsies, arthroscopic biopsies, or core needle biopsies. TGCT falls into the category of fibrohistiocytic tumours, comprising mononuclear cells, multinucleated giant cells, foamy macrophages, inflammatory cells and siderophages (6). Inflammatory factors are found in the joint fluid. However, obtaining histology is not necessarily required as the characteristics of TGCT on MRI are often distinctive (23).

Treatment

Surgery remains the mainstay of treatment for TGCT (1, 29, 30). Achieving complete macroscopic resection is regarded the primary goal. For L-TGCT this can often be accomplished through arthroscopy or an open marginal excision with low recurrence rates (31, 32). Due to the extensive growth of D-TGCT, radical tumour resection may be challenging to accomplish or may result in iatrogenic morbidity. Treated D-TGCT is therefore associated with recurrence rates up to 55% (30, 33). The effect of tumour debulking on clinical outcome, given the high recurrence rates and continuing complaints, remains questionable.

Furthermore, consensus regarding the optimal surgical technique to remove the tumour is lacking (34). Tumour resection may be removed by open surgery or through arthroscopic synovectomy (31, 35). Arthroscopic synovectomy may be suited for D-TGCT located intra-articular, while open surgery provides better access to extra-articular invasion. Furthermore, when D-TGCT is localised at the anterior and posterior side of the knee, surgery can be performed in two tempi, addressing one side at a time, or one-stage (36). Joint replacement may be indicated for patients with degenerative changes, addressing joint pain and malalignment. However, even after joint replacement, recurrence rates are high (37, 38). Amputation is only seldom considered as a last resort for patients with remaining complaints or function impairment after prior treatments (39).

Radiotherapy is sometimes used as (neo)adjuvant therapy to reduce recurrence rates for D-TGCT. Radiotherapy consists of external beam radiotherapy or radiosynovectomy

(40-42). Data regarding the effect of radiotherapy is scarce and of low quality (41). Additionally, the use of radiotherapy is controversial since TGCT is a benign disease affecting a relatively young patient group. Radiotherapy may cause joint stiffness or even (although rare) secondary malignant transformation in the long term (43, 44).

For patients not amenable to surgery or when surgery is related to high morbidity, systemic therapy can be considered. The use of systemic treatment was first reported in 2008, and, since then, have been widely investigated (45). Systemic treatment mainly consists of targeted CSF1R inhibitors and can lead to tumour shrinkage, as well as symptomatic and functional improvement (46-50). However, systemic therapies also cause adverse effects, which are less tolerated in a non-malignant disease. To date, only one pharmaceutical, pexidartinib, is accepted by the Food and Drugs Authority for treating TGCT (51). Yet, due to an unfavourable risk-benefit ratio, the European Medicines Agency refused to authorise pexidartinib (52).

Since surgery is historically the mainstay of treatment, little is known regarding the natural course of TGCT. However, surgery results in high recurrence rates and often little improvement in quality of life. Therefore, active surveillance may be indicated for asymptomatic patients or patients in which surgical treatment would be associated with significant morbidity. The effect of a wait-and-see approach has not been researched to date. Physical therapy is suggested to positively affect the mental wellbeing of patients, but also improve function, although there is no data to support this yet.

Aim of thesis

Tenosynovial Giant Cell Tumour can be a debilitating disease for a relatively young patient population (3, 4, 25). Although there is a vast armamentarium of treatment modalities, disease recurrence is common, and many patients do not achieve curation, especially in D-TGCT (33). D-TGCT's low incidence makes it challenging to gather large datasets, and as a result, literature is relatively scarce (17, 18). This thesis mainly focuses on knowledge gaps in the treatment of D-TGCT. Several global collaborations were set up with tertiary sarcoma centres worldwide to collect substantial datasets. Also, this thesis includes the first prospective disease registry for D-TGCT.

This thesis aims to visualise the journey that D-TGCT patients experience from the onset of symptoms to diagnosis and treatment. Treatment ranges from wait-and-see to surgery and systemic therapy. The goal was to create more insight into several treatment strategies and better understand their effects on patients perspectives and tumour outcomes.

Outline of thesis

In **Chapter 2**, the first prospective disease registry for D-TGCT was conducted to describe the experience of care of sarcoma centres from Europe and the United States for a two-year observational follow-up period (53). The goal was to improve the understanding of patients' pathways, treatment patterns, health outcomes and health economics.

As mentioned above, MRI is the modality of choice to diagnose D-TGCT in the knee and is used for pre-operative mapping. Furthermore, MRIs are necessary for follow-up after surgery and assessing systemic therapy treatment response. Since reading MRIs can be difficult, we provided a systematic approach in **Chapter 3** in which specific imaging findings and localisations, differential diagnoses mimicking D-TGCT, potential pitfalls, and tumour responses after systemic therapies are described. We also set a first step in automated volumetric quantification of D-TGCT, which we propose as the next step.

Most D-TGCT patients are treated by surgery or systemic therapy to reduce symptoms and prevent secondary osteoarthritis. Sometimes active surveillance is indicated since TGCT is a non-malignant disease, but studies regarding a wait-and-see approach are lacking. **Chapter 4** is the first study that describes the natural course of disease in D-TGCT and evaluates active surveillance as a treatment strategy.

In the following three chapters, different surgical treatments are studied.

In **Chapter 5**, we evaluated the multidisciplinary treatment of patients with TGCT in the foot and ankle by presenting the largest series by combining the data of two sarcoma centres from the Netherlands and the United Kingdom. Although this thesis mainly focuses on D-TGCT, we also included L-TGCT since the foot and ankle are more often affected by L-TGCT (54).
Chapter 6 evaluated the surgical management of D-TGCT patients treated between 2000 and 2020 in one specialised sarcoma centre and analysed the effect of (in)complete resections on radiological and clinical outcomes.
D-TGCTs intra- and extra-articular expansion about the knee often necessitates an anterior and posterior surgical approach to facilitate an extensive synovectomy (55-57). In **Chapter 7**, consensus is formed on whether two-sided synovectomies should be performed in one or two stages. For this study, we combined data from several sarcoma centres worldwide.

In **Chapter 8**, we reviewed disease mechanisms and potential drug targets of D-TGCT. Also, the safety and efficacy of different systemic therapies were evaluated. One of the most used and studied systemic therapies is nilotinib. In **Chapter 9**, we report the long-

term outcomes of nilotinib in patients with advanced D-TGCT treated within a phase 2 prospective international study (49).
A summary of this thesis is provided in **Chapter 10**. And finally, conclusions, implications and future perspectives are discussed in **Chapter 11**.

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Chapter 2

The diffuse-type tenosynovial giant cell tumour (D-TGCT) patient journey: a prospective multicentre study

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Abstract

Background

Tenosynovial giant cell tumour (TGCT) is a rare, locally aggressive neoplasm arising from the synovium of joints, bursae, and tendon sheaths affecting small and large joints. It represents a wide spectrum ranging from minimally symptomatic to massively debilitating. Most findings to date are mainly from small, retrospective case series, and thus the morbidity and actual impact of this rare disease remain to be elucidated. This study prospectively explores the management of TGCT in tertiary sarcoma centres.

Methods

The TGCT Observational Platform Project registry was a multinational, multicentre, prospective observational study involving 12 tertiary sarcoma centres in 7 European countries, and 2 US sites. This study enrolled for 2 years all consecutive ≥ 18 years old patients, with histologically diagnosed primary or recurrent cases of diffuse-type TGCT. Patient demographic and clinical characteristics were collected at baseline and every 6 months for 24 months. Quality of life questionnaires (PROMIS-PF and EQ-5D) were also administered at the same time points. Here we report baseline patient characteristics.

Results

166 patients were enrolled between November 2016 and March 2019. Baseline characteristics were: mean age 44 years (mean age at disease onset: 39 years), 139/166 (83.7%) had prior treatment, 71/166 patients (42.8%) had ≥ 1 recurrence after treatment of their primary tumour, 76/136 (55.9%) visited a medical specialist ≥ 5 times, 66/116 (56.9%) missed work in the 24 months prior to baseline, and 17/166 (11.6%) changed employment status or retired prematurely due to disease burden. Prior treatment consisted of surgery (i.e., arthroscopic, open synovectomy) (128/166; 77.1%) and systemic treatments (52/166; 31.3%) with imatinib (19/52; 36.5%) or pexidartinib (27/52; 51.9%). Treatment strategies at baseline visits consisted mainly of watchful waiting (81/166; 48.8%), surgery (41/166; 24.7%), or targeted systemic therapy (37/166; 22.3%). Patients indicated for treatment reported more impairment compared to patients indicated for watchful waiting: worst stiffness NRS 5.16/3.44, worst pain NRS 6.13/5.03, PROMIS-PF 39.48/43.85, and EQ-5D VAS 66.54/71.85.

Conclusion

This study confirms that diffuse-type TGCT can highly impact quality of life. A prospective observational registry in rare disease is feasible and can be a tool to collect curated-population reflective data in orphan diseases.

Name of registry: Tenosynovial Giant Cell Tumours (TGCT) Observational Platform Project (TOPP).

Trial registration number: NCT02948088.
Date of registration: 10 October 2016.
URL of Trial registry record: https://clinicaltrials.gov/ct2/show/NCT02948088?term=NCT02948088&draw=

Introduction

Tenosynovial giant cell tumour (TGCT) is a rare, locally aggressive mesenchymal neoplasm arising from the synovium of joints, bursae, and tendon sheaths and affects both small and large joints (1). Two main subtypes of TGCT are defined based on clinical and radiological characteristics: localised- and diffuse-type TGCT (L-TGCT and D-TGCT). The malignant version of TGCT is extremely rare (2). From the molecular point of view, both subtypes usually share the presence of a fusion involving the colony stimulating factor (CSF) gene, which drives tumour growth (3, 4). Although both subtypes share a common pathophysiology, they represent a wide spectrum of clinical entities, making TGCT behaviour complex and hard to predict (5). Clinical disease spectrum ranges from mildly symptomatic to extremely debilitating, where patients present with symptoms like pain, stiffness, swelling, and limitation in range of motion (6). Further characterisation of disease severity has been made to identify cases as mild localised, severe localised, moderate diffuse, or severe diffuse (7). Uniform magnetic resonance (MR) descriptions are of utmost significance for clinical and research purposes. The classification of clear MR criteria is challenging, due to the rarity of the tumour and small number of heterogeneous cases, variety of joints involved, different disease severity as well as several treatment modalities. To date, MR imaging (MRI) has shown to be the best distinguishing method for evaluation of TGCT. The proposed TGCT severity classification informs physicians and patients on disease extent and risk for recurrence after surgical treatment. Definition of the most severe subgroup attributes to a universal identification of eligible patients for systemic therapy or trials for novel agents (7).

Although less prevalent, D-TGCT is an aggressive multi-lobulated lesion located intra- and/or extra-articular, affecting various joints in the body (mainly the knee) and having a detrimental effect on quality of life (QoL) (8-11). Incidence rate of D-TGCT is estimated at 5 per million person-years (8). Due to non-specific symptoms and the rarity of this disease, a proper diagnosis can sometimes take many years, which in turn may severely delay optimal treatment and care for these patients, resulting in them facing a higher risk of excessive, inadequate, or under treatment (8, 12). Once diagnosed, treatment options include mostly surgical intervention. However, recently tyrosine kinase inhibitors (TKIs) that target the CSF1 receptor (CSF1R) have been used for treatment in cases where surgery is not an option (3, 13-18).

As the predominant epidemiologic understanding of D-TGCT to date comes mainly from small, retrospective studies that traditionally focused on oncological outcomes, questions to elaborate the true morbidity and actual impact on QoL, both the disease and its various treatment options remains to be elucidated (1, 19). Given this context, there is a need for

a better understanding of the natural history of this tumour to understand the burden of D-TGCT from a patient perspective and of the treatment landscape beyond a single institution. Additionally, there is the need to explore the current management of TGCT, particularly of the diffuse type (including functional details measured pre- and post-treatment) to describe the spectrum of indications, challenges, and the actual impact on patient QoL and ability to work.

To this end, the first multinational, multicentre, prospective, non-interventional, observational disease registry study, named TGCT Observational Platform Project (TOPP), was launched in November 2016, involving hospitals and tertiary sarcoma centres from Europe (EU) and the United States (US). All patients included in the study were to be followed up with for a minimum of 2 years. Herein, we report on patient demographics and clinical characteristics at the time when patients were entered into the registry (baseline). This includes main disease characteristics, treatment patterns, and outcomes of the D-TGCT patient population from varying geographical regions to better understand the breadth of the patient journey. In addition, we aimed at identifying and describing factors influencing treatment decision making, in the absence of consensus treatment guidelines.

Material and Methods

Study design and participants

This global multicentre, prospective sponsored study included all consecutive patients from 12 tertiary sarcoma centres in 7 EU countries from 2016 to 2018. Two sites in the US enrolled patients from 2017 to 2019. Patients were enrolled during a 2-year period with prospective follow-up over 24 months. Participating sites were selected based of their expertise in treatment of TGCT.

Eligible patients were 18 years or older, with a primary or recurrent D-TGCT. TGCT had to be histologically confirmed and assessed as diffuse-type based on MRI or clinical presentation if this was missing. D-TGCT is often characterised by a multi-nodular tumour on MRI. The institutional review board or ethics board provided approval in each centre, and written informed consent was obtained from each patient who participated in this study.

Primary diagnosis was defined as patients who were awaiting treatment or were treated and showed no evidence of local progression at baseline. Recurrent disease was defined as tumour recurrence after complete resection or progression of residual tumour. Therapy-

naïve patients received no therapy prior to baseline and were consequently admitted as primary diagnosed patients. Disease severity was in line with the TGCT severity classification by Mastboom et al., with severe D-TGCT classified as intra- and extra-articular involvement with involvement of one or more ligaments or muscular/tendinous tissue observed on MRI (7).

Patient demographics, complete TGCT-related history, and current status, including radiologic assessments and health resources used in the past 24 months, were collected at baseline. Baseline visits occurred at the outpatient clinic of either the department of orthopaedic surgery or the Oncology department. Baseline data on TGCT-related patient-reported outcomes (PRO) for pain, stiffness, swelling, and limitations in range of motion were collected and followed every year thereafter through electronic data capture. The patient-reported outcome measurements (PROMs) were administered at baseline consisting of the mean brief pain inventory (BPI), mean worst pain and stiffness numerical rating scale (NRS), the Patient-Reported Outcome Measurement Information System Physical Functioning® (PROMIS-PF), and the EuroQoL 5D (EQ-5D) (Appendix). Admission status at baseline was categorised into patients with a primary diagnosis or recurrent disease.

Statistical analysis

Continuous data were described using either means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables were summarised as number of observations and percentages (%) of the observations in each category. Percentages do not include the missing category and are calculated over the number of subjects with available (non-missing) data. The whole analysis was descriptive only. Statistical analysis was performed using the Statistical Analysis System (SAS©) Version 9.4 under Microsoft Windows Operating System. Because D-TGCT is an orphan disease, no formal sample size consideration has been performed, as recruitment of patients within the scheduled 2-year period was expected to be difficult.

Results

Between November 2016 and March 2019, 166 patients from the EU and US were enrolled in the TOPP registry. Description of baseline patient demographics and clinical characteristics are provided in Table 1. The mean age at diagnosis was 39.0 years (range, 14.4–75.6; SD ± 14.42) and median time from diagnosis until TOPP entry point was 29.7 months (IQR, 9.5–80.0). TGCT had a female predilection (n = 102; 61.4%), and the knee joint was predominantly affected (n = 112; 68.5%). Other involved locations were the

ankle (n = 19; 11.4%), the hip (n = 12; 7.2%), the shoulder (n = 8; 4.8%), the foot (n = 5, 3.0%), the elbow (n = 3, 1.8%), the hand (n = 3, 1.8%), and the temporomandibular joint (n = 1; 0.6%). Ninety-five patients (57.2%) were primary diagnosed cases, and 71 patients (42.8%) had at least one recurrence prior to baseline, occurring after any treatment of their primary tumour.

Table 1. Demographic and clinical characteristics of patients included in the TOPP study at baseline

Features	n = 166 (%)
Mean age [years] at diagnosis ± SD	39.0 ± 14.42
Mean age [years] at baseline ± SD	44.0 ± 14.12
Female, n (%)	102 (61.4)
Level of education (n = 143)	
University (bachelor or higher)	63 (44.1)
Time [months] since diagnosis, median (Q1, Q3)	29.7 (9.5 – 80.0)
Localization, n (%)	
Knee	112 (68.5)
Ankle	19 (11.4)
Hip	12 (7.2)
Shoulder	8 (4.8)
Foot	5 (3.0)
Elbow	3 (1.8)
Wrist	3 (1.8)
Hand	3 (1.8)
Temporomandibular	1 (0.6)
Therapy prior to baseline, n (%)	139 (83.7)
Recurrent disease, n (%)	71 (42.8)
1 recurrence	37 (52.9)
2 recurrence	15 (21.4)
3 recurrence	18 (25.7)

Q1, quarter 1; Q3, quarter 3; SD, standard deviation; TGCT, tenosynovial giant cell tumour; TOPP, TGCT Observation Platform Project.

Diagnostic pathway

A median of 16.9 months (IQR, 4.0–44.0) elapsed from onset of symptoms until diagnosis of TGCT (Table 2). Most commonly, MRIs requested closest to baseline of TOPP were for postoperative follow-up (n = 56; 40.0%). Of all MRIs, D-TGCT was generally located both intra- and extra-articular (n = 90/147; 61.2%) with involvement of ligaments (n = 88/134; 65.7%), and tendons and muscles (n = 99/141; 70.2%), classifying half of the patients (n = 83) with severe D-TGCT at baseline (Table 2). If assessable, severe D-TGCT was

observed in the knee, ankle, hip, and other locations in 51.5% (n = 51/99), 55.6% (n = 5/9), 58.8% (n = 10/17) and 77.2% (n = 17/22) of the cases, respectively.

Table 2. Diagnostic pathway (%)

Time [months] from onset symptoms until diagnosis, median (Q1, Q3)	**16.9 (4.0 – 44.0)**
Information on MRI	
Any closest* to BL MRI, n (%)	157 (94.6)
Indication of MRI closest to BL, n (%)	
Primary diagnosis	36 (25.7)
Pre-surgery	16 (11.4)
Regular postoperative follow-up	56 (40.0)
Follow-up due to complaints	32 (22.9)
Missing	17
Characteristics of MRI, n (%)	
Both intra- and extra-articular (n = 147)	90 (61.2)
Extra-articular tendon/muscle involvement (n = 141)	99 (70.2)
Ligament involvement (n = 134)	88 (65.7)
TGCT severity, n (%)	
Moderate diffuse	64 (38.6)
Severe diffuse	83 (50.0)
Not assessable	19 (11.4)
Information on biopsy	
Any biopsy prior BL[a] (restricted to the 95 patients with primary diagnosis), n (%)	86 (90.5)
Excisional biopsy	32 (41.6)
Core needle biopsy	14 (18.2)
Arthroscopic biopsy	11 (14.3)
Surgery for suspected cancer diagnosis	10 (13.0)
Fine needle aspiration biopsy	6 (7.8)
Other	9 (11.7)
Missing	9

**Defined as MRI with nearest date to Baseline visit date, with the date of MRI either before or equal to the Baseline visit date or — if no treatment yet performed — at the latest 30 days after the Baseline visit date. [a]Percentage calculation can sum to > 100% because patients can fall in more than one category. BL, baseline; MRI, magnetic resonance imaging; Q1, quarter 1; Q3, quarter 3; TGCT, tenosynovial giant cell tumour.*

Sixty-nine patients (41.6%) were classified severe D-TGCT even after treatment, exemplifying the continued severity of the disease. Histological confirmation was primarily obtained after excisional biopsy (n = 32; 41.6%), however several non-excisional biopsy techniques were also performed in other patients (e.g., core needle biopsy, arthroscopic biopsy, or fine needle aspiration). In 13%, TGCT diagnosis was based on surgical histology from samples obtained during procedure undertaken for suspicion of a malignancy (Table 2).

Treatments received prior to baseline of TOPP

Of 166 patients who entered the TOPP study, 139 (83.7%) had already been exposed to a TGCT-related treatment, whereas only 27/166 patients (16.3%) were treatment-naïve (Table 1). Ninety-five patients (57.2%) were primary diagnosed cases, and 71 patients (42.8%) had at least one recurrence prior to baseline, occurring after any treatment of their primary tumour (Table 3).

Of 57 patients treated with surgery at the time of initial diagnosis, 30 (31.6%) had been treated arthroscopically. At the time of relapse, 71 (100%) patients had a re-operation, and in this case the surgical approach was open synovectomy in 49 (69.0%) and arthroscopic in 33 (46.5%). Five patients (3.9%) had received a (tumour) prosthesis secondary to TGCT in four cases due to a recurrent tumour. Fifty-two patients (31.3%) received systemic treatment; in 39.4% (28/71) this was indicated in recurrent cases and was still ongoing in 34.6% (18/52) at baseline. Thirty-two of 52 cases (62.7%) were indicated for systemic therapies because of locally advanced TGCT, 9.8% (5/52) as neo-adjuvant, 7.8% (4/52) for maintenance, and 7.8% (4/52) for palliative therapy. Eleven patients (21.2%) received systemic therapies as first treatment for TGCT. TKIs imatinib (off-label) or pexidartinib (in research setting) were most frequently administered as latest treatment prior to baseline (46/47; 97.9%) (Table 3). Radiation therapy, comprising external beam radiotherapy and radiosynoviorthesis with 90Yttrium, was administered in 15/166 (9%) and mostly performed as adjuvant therapy after surgery in refractory cases (10/15; 66.7%) (Table 3). Eighty-eight (53%) of all cases had received prior and concomitant therapies for TGCT-related symptoms.

Table 3. TGCT-related therapies prior to baseline, N (%)

	Tumour status		
	Primary diagnosis (n = 95)	**Recurrent diseases (n = 71)**	**Total (n = 166)**
Any surgery prior to baseline	57 (60.0)	71 (100)	128 (77.1)
Type of surgery prior to BL (if any)[a]			
Arthroscopic synovectomy	30 (31.6)	33 (46.5)	63 (49.2)
One-stage synovectomy	22 (23.2)	42 (59.2)	64 (50.0)
Two-stage synovectomy	6 (6.3)	7 (9.6)	13 (10.2)
(Tumour) prosthesis	1 (1.1)	4 (5.6)	5 (3.9)
Any systemic treatment prior BL	24 (25.3)	28 (39.4)	52 (31.3)
Type of last systemic treatment prior BL (if any)			
Tyrosine kinase inhibitors	22 (91.7)	25 (89.3)	47 (90.4)
Monoclonal antibodies	1 (4.2)	3 (10.7)	4 (7.7)
Other	1 (4.2)	-	1 (1.9)
Duration [days] until BL, median (Q1, Q3)	307.00 (120.00 – 421.00)	186.00 (88.00 – 345.00)	236.00 (118.00 – 366.00)
Ongoing	11 (45.8)	7 (25.0)	18 (34.6)
Possible side effects	11 (45.8)	19 (67.8)	30 (58.8)
Any radiation therapy	5 (5.3)	10 (14.1)	15 (9.0)
Type of radiation therapy prior to BL (if any)			
Radiotherapy	2 (40.0)	4 (40.0)	6 (40.0)
^{90}Yttrium	3 (60.0)	6 (60.0)	9 (60.0)
No prior therapy	27 (28.4)	-	27 (16.3)
Prior & concomitant therapies for TGCT-related symptoms	50 (52.6)	38 (53.5)	88 (53.0)

[a]Sum of all therapies can be more than total because a patient could have received ≥ 1 therapies. BL, baseline; Q1, quarter 1; Q3, quarter 3; TGCT, tenosynovial giant cell tumour.

Treatment strategies at time of TOPP study entry

Treatment strategies at baseline visits of TOPP consisted of watchful waiting (n = 81/166; 48.8%), surgery only (n = 41/166; 24.7%), or targeted systemic therapy only (n = 37/166; 22.3%). A multimodality approach was administered in 7/166 (4.2%) of cases, comprising different therapy combinations (e.g., surgery, targeted systemic therapies, and/or radiation therapy) (Additonal file 1).

A conservative monitoring approach at baseline was primarily decided on for patients who received only surgery before baseline (n = 47/81; 58.0%) (Table 4). Most MRIs were conducted as regular postoperative follow-up (n = 43/75; 57.3%), and this group comprised

the lowest percentage of severe cases (n = 38/81; 46.9%). Non-invasive interventions were common in this group; 26.2% of the patients received rehabilitation (n = 17), and patients in need of physical therapy (n = 23, 28.4%) had a median of 18 (range, 4.0–200.0) sessions.

Table 4. Patients' presentation and reported outcomes at baseline by treatment strategy, N (%)

	Wait & See (n = 81)	**Surgery only (n = 41)**	**Systemic only (n = 37)**
Mean age [years] ± SD	44.3 ± 15.17	41.8 ± 14.94	47.7 ± 10.44
Time since diagnosis primary tumour [months] median (Q1, Q3)	34.3 (13.8 – 77.9)	6.7 (1.2 – 59.8)	32.1 (18.2 – 89.6)
Treatment before baseline			
Therapy-naïve	11 (13.6)	16 (39.0)	
Surgery only	47 (58.0)	20 (48.8)	7 (18.9)
Systemic only	2 (2.5)	-	9 (24.3)
Multimodal treatment	21 (25.9)	5 (12.2)	21 (56.8)
Admission status			
Primary diagnosis	47 (58.0)	27 (65.9)	19 (51.4)
Recurrent diseases	34 (42.0)	14 (34.1)	18 (48.6)
Indication MRI closest to baseline			
Primary diagnosis	7 (9.3)	23 (57.5)	4 (11.4)
Pre-surgery	5 (6.7)	8 (20.0)	2 (5.7)
Regular postoperative follow-up	43 (57.3)	6 (15.0)	7 (20.0)
Follow-up due to complaints	15 (20.0)	2 (5.0)	13 (37.1)
Severity			
Moderate	34 (42.0)	15 (36.6)	12 (32.4)
Severe	38 (46.9)	20 (48.8)	21 (56.8)
Not assessable	9 (11.1)	6 (14.6)	4 (10.8)
In last 24 months prior to baseline			
Any rehabilitation	17 (26.2)	5 (13.2)	4 (12.5)
Specialist visits*, median (range)	5.0 (1.0 – 70.0)	3.0 (10 – 27.0)	12 (2.0 – 65.0)
Physical therapy sessions*, median (range)	18.0 (4.0 – 200.0)	11.0 (1.0 – 100.0)	11.5 (3.0 – 90.0)
Symptoms			
Pain	56 (69.1)	37 (90.2)	32 (86.5)
Stiffness	36 (44.4)	27 (65.9)	23 (62.2)
Swelling	44 (54.3)	34 (82.9)	19 (51.4)
Limited range of motion	39 (48.1)	31 (75.6)	30 (81.1)
≥ 3 symptoms	31 (38.3)	28 (68.3)	22 (59.5)

	Wait & See (n = 81)	Surgery only (n = 41)	Systemic only (n = 37)
Analgesics use	8 (9.9)	5 (12.2)	9 (24.3)
Worst stiffness NRS mean ± SD (n = 144)	3.4 ± 2.57	5.2 ± 3.14	5.3 ± 2.55
Worst pain NRS mean ± SD (n = 81)	5.0 ± 2.41	6.5 ± 2.27	5.8 ± 1.97
Pain severity score median (Q1, Q3) (n = 147)	2.25 (0.75 – 4.00)	4.25 (1.50 – 6.25)	4.25 (1.50 – 5.50)
Pain interference score median (Q1, Q3) (n = 146)	1.57 (0.14 – 4.00)	3.00 (1.14 – 5.57)	3.00 (0.57 – 5.57)
PROMIS-PF median (Q1, Q3) (n = 142)	44.43 (37.30 – 49.29)	39.54 (34.95 – 44.42)	39.98 (34.79 – 43.69)
EQ-5D Index score median (Q1, Q3) (n = 153)	0.84 (0.67 – 0.89)	0.80 (0.53 – 0.84)	0.74 (0.48 – 0.84)
EQ-5D VAS median (Q1, Q3) (n = 154)	79.0 (60.0 – 85.0)	69.0 (60.0 – 80.0)	70.0 (50.0 – 75.0)

**Based on patients that had any. EQ-5D, EuroQol 5D; MRI, magnetic resonance imaging; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System; PROMIS-PF, Patient-Reported Outcome Measurement Information System Physical Functioning®; Q1, quarter 1; Q3, quarter 3; SD, standard deviation; VAS, visual analog scale.*

Patients indicated for surgery in this population were most recently diagnosed with TGCT. A median of 6.7 (IQR, 1.2–59.8) months elapsed from TGCT diagnosis until baseline, and 65.9% (n = 27) had a primary diagnosis, of which 16/41 (39.0%) were therapy-naïve at baseline. Furthermore, MRIs closest to baseline were primarily indicated to diagnose TGCT (n = 23; 57.5%) (Table 4).

Twenty-one (56.8%) of the patients indicated for targeted systemic therapies at TOPP baseline already had received multimodality treatment before baseline. None of these patients were therapy-naïve at baseline, and just 7 (18.9%) patients had only surgery before. MRIs were predominantly obtained due to progressive complaints (n = 13; 37.1%), and in this patient group the highest percentage of recurrent (n = 18; 48.6%) and severe D-TGCT (n = 21; 56.8%) was observed. These patients visited medical specialists at a median of 12 times (range, 2.0–65.0) in the 24 months prior to baseline. Patients indicated for systemic therapies had a median age of 48.0 years (range 20.0–73.0). In addition, analgesics were most used by these patients (n = 9; 23.3%) and mean worst stiffness and pain NRS scores of 5.3 (SD ± 2.55) and 5.8 (SD ± 1.97), respectively, were reported. Physical functioning was limited with a median PROMIS-PF score of 39.98, and the lowest QoL scores were reported with an EQ-5D index score of 0.74 and visual analogue scale (VAS) score of 70.0. At baseline, 33 patients (89.2%) had a current systemic therapy, of which 18 (54.5%) were

started before. All current systemic therapies consisted of TKIs imatinib (n = 14; 42.4%) and pexidartinib (n = 19; 57.6%).

Only 11 patients did not report complaints due to TGCT at baseline, resulting in 93.4% of patients with at least one complaint. Patients indicated for treatment reported TGCT-related symptoms (e.g., pain, stiffness, swelling, and limited range of motion) more frequently compared to those with a wait-and-see policy (Table 4), except for swelling, which was least experienced by patients treated with systemic therapies (51.4%), and 68.3% indicated for surgery at baseline suffered from 3 or more TGCT-related symptoms. Both patient groups indicated for surgery and systemic therapies reported higher pain severity (4.25) and interference scores (3.00) compared to patients indicated for watchful waiting (2.25; 1.57). In addition, both treatment groups reported lower PROMIS-PF scores (39.54 and 39.98, respectively), EQ-5D index scores (0.80 and 0.74, respectively) and EQ-5D VAS scores (69.0 and 70.0, respectively).

Health economics related to the TOPP cohort

Thirty-three patients (23.9%) required at least 5 visits from disease onset, before reaching a diagnosis of TGCT.

Table 5. Health economics prior to baseline, N (%)

Any referral / specialists visits prior to diagnosis (n = 138)	135 (97.8)
≥ 5	33 (23.9)
24 months prior to baseline	
≥ 5 GP visits (n = 132)	21 (15.9)
≥ 5 specialists visits (n = 136)	76 (55.9)
≥ 10 PT sessions (n = 141)	36 (25.5)
Rehabilitation (n = 140)	26 (18.6)
Duration [days], median (range)	15.0 (1.0 – 120.0)
Hospitalization related to TGCT	151 (91.0)
≥ 5 hospitalizations	15 (9.9)
Duration [days], median (range)	3.0 (1.0 – 184.0)
Changed employment status from full-employment due to TGCT (n = 146)	17 (11.6)
Part-time employed	5 (3.4)
Unemployed	9 (6.2)
Retired	3 (2.1)

Work missed in 24 months prior to baseline (n = 116)	66 (56.9)
If work missed, number of [days], median (range)	25.0 (1.0 – 75.0)
Domestic help required at baseline (n = 162)	26 (16.0)

GP, general practitioner; PT, physical therapy; TGCT, tenosynovial giant cell tumour.

In addition, 76 patients (55.9%) consulted a medical specialist 5 times or more in the 24 months prior to baseline. Thirty-six patients (25.5%) had more than 10 physical therapy sessions in the 24 months prior to baseline. Hospitalisation and rehabilitation were required in 91.0% (151/166) and 18.6% (26/140), respectively, with a median of 3.0 (range, 1.0–184.0) and 15.0 (range, 1.0–120.0) days, respectively. Fifteen (9.9%) patients were hospitalised 5 or more times. Sixty-six patients (56.9%) missed work due to their TGCT in the 2 years prior to baseline, with a median of 25.0 days (range, 1.0–75.0). More importantly, of 146 patients who were employed, 17 (11.6%) were forced to change their employment status or even retire prematurely due to disease burden. Domestic help was necessary in 26 cases (16.0%).

Discussion

TOPP represents the largest prospective, international, multicentre disease registry for D-TGCT, being able to include 166 patients in slightly more than 2 years and shows that conducting collaborative observational studies for a rare tumour is feasible. Current literature is largely focused on the oncological outcomes of this often-chronic disease (13, 15, 17, 20-24). Baseline data derived from this registry help to describe a preliminary understanding of the D-TGCT patient journey and treatment decisions around disease onset and diagnosis of D-TGCT patients. We believe that such study design can guide collection of high-quality data for other orphan diseases.

The present study confirmed that TGCT has its onset in a relatively young, educated, and working patient population with a female predilection (8, 9). Time between onset of symptoms until diagnosis averaged more than a year, and in this time interval several medical specialists were frequently visited. An under- or overestimation could be introduced due to a recall bias. Nonspecific clinical signs and symptoms in TGCT patients often mimicked other mono-articular pathologies, resulting in frequent consultation of various healthcare professionals (e.g., physical therapists, rheumatologists, and sports doctors) and lag time in diagnosis (Figures. 1, 2) (25). MRI was the non-invasive gold standard

to diagnose TGCT type and distinguish between the localised and diffuse subtypes (26, 27). In addition, this modality was frequently utilised for postoperative surveillance for recurrence, evaluation of worsening complaints (e.g., distinguishing degenerative arthritic symptoms or internal derangement of the joint), or pre-surgical planning (Table 2). Definitive diagnosis was predominantly obtained by histological confirmation through different forms of biopsies (28, 29). In 10 cases, TGCT was coincidentally diagnosed after surgery for an initial suspicion of cancer. Disease mimicking and unfamiliarity could possibly introduce such misdiagnoses, with potential major consequences for a patient.

The primary form of care for TGCT is complete surgical removal of abnormal tissue, performed arthroscopically, open or combined, often requiring multiple incisions to access the disease thoroughly. However, there is a high risk for recurrence, especially in D-TGCT, due to invasive growth both in and outside the joint (12, 16, 21, 30). Synovectomies are generally relatively invasive, with a high recurrence rate and repetitive surgery causing significant impairment (21). Multimodality treatments (e.g., external beam radiotherapy and radiosynoviorthesis) have been performed in an attempt to reduce the recurrence rate in D-TGCT, leading to varied reported outcomes (22-24). In addition to surgery, several CSF1R inhibitors including TKIs showed promising results in tumour volume decrease and reduction of debilitating symptoms (13, 15, 17, 18, 31). Of the TKIs, pexidartinib is an FDA-approved systemic therapy, recently added as a category 1 recommendation for the treatment of adult patients with symptomatic TGCT/pigmented villonodular synovitis (PVNS) associated with severe morbidity or functional limitations that is not amenable to improvement with surgery.

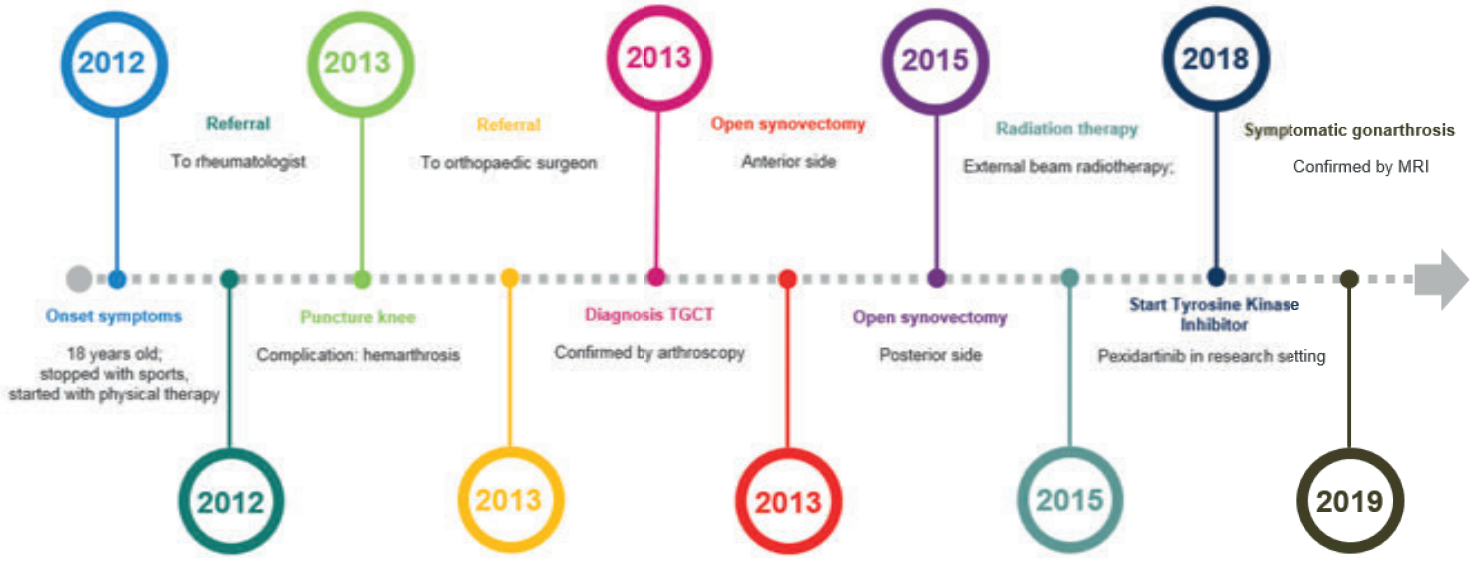

Figure 1

A typical timeline of D-TGCT in a single TOPP patient. The disease had its onset in an 18-year-old patient who was forced to stop exercising and in need of physical therapy due to D-TGCT-related complaints. Several recurrences occurred despite multimodality treatment, leading to secondary gonarthrosis at the age of 25

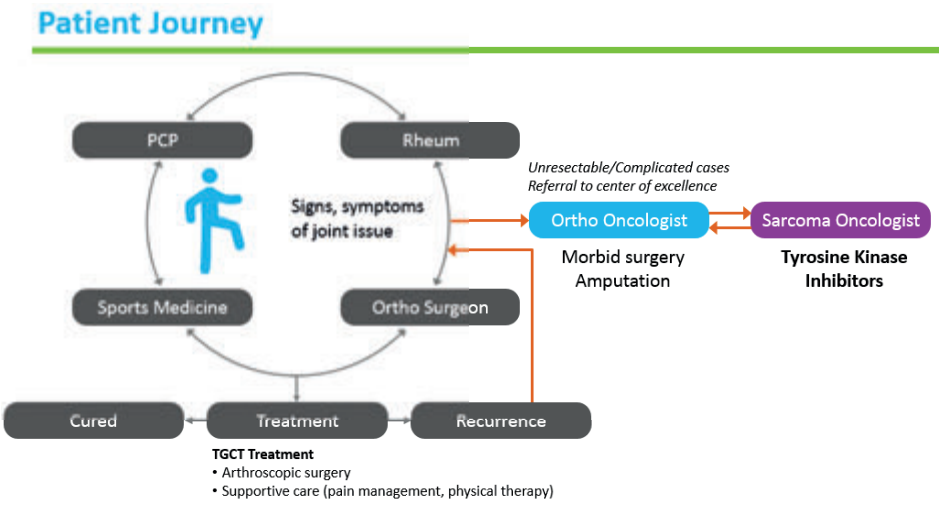

Figure 2
This figure represents the general patient journey of patients with D-TGCT. Non-specific symptoms and disease unawareness results in several visits to different healthcare practitioners and unnecessary or excessive treatment in first and second line before referral to an orthopaedic or sarcoma oncologist

Our results confirm that surgery was the mainstay of treatment (75%), which is consistent with other studies (12, 21, 30). Furthermore, all patients with recurrent D-TGCT disease had surgery, often combined with other treatment modalities (Figure 3). Synovectomies were mostly performed open. To date, literature reported conflicting results regarding different surgical techniques, not favouring one over another (20, 32, 33). However, we hypothesise that open surgery may allow for better overview of tumour, located intra- and extra-articular, with extension to surrounding tissues, possibly resulting in more complete removal of disease burden. Almost a third of the patients received systemic therapies, mainly TKIs such as pexidartinib (in research setting) and imatinib (off label)—a relatively high percentage, possibly due to a selection bias since sarcoma centres participating in TOPP were also involved in clinical studies on TGCT. Use of TKIs was mostly found indicated in locally advanced refractory cases, illustrating this modality being considered a last resort for patients who are not amenable for surgery (Figure 2). An individual well-thought-out treatment decision made by a multidisciplinary team of medical specialists is therefore needed regarding both surgical and systemic treatment options with such rates of response, local recurrence, complications, and side effects.

Given the lack of understanding of this disease, the incidence of TGCT may be underestimated as disease awareness increases and diagnostic tools improve (10). Diagnostic delay results in multiple visits to different health care practitioners (e.g., general practitioner, physiotherapist, sports medicine doctor, rheumatologist) and unnecessary or

excessive treatments (e.g., use of painkillers or diagnostic arthroscopies) in the first and second line before referral to an orthopaedic or sarcoma oncologist (12, 34). If treated inadequately, aggressive D-TGCT can become a chronic illness affecting an otherwise young, healthy patient population, leading to a significantly decreased QoL and concurrent high social costs (e.g., sick leave, medical costs) (Figure 1) (10, 35).

Current literature lacks treatment guidelines and does not present relevant clinical findings that support clinical decision making. Creating insight on such important factors can be of great value in optimising treatment strategies. Different treatment strategies were selected at baseline of TOPP, predominantly watchful waiting, surgery, or systemic therapies. The number and type of follow-up visits were not controlled, as they were influenced by patient and physician concerns. Systemic therapies were predominantly indicated for older patients with recurrent and severe D-TGCT despite their having received multimodality treatment before. This patient group reported the highest decrease in QoL and experienced a major limitation in physical functioning. The use of systemic therapies in the setting of relapsed D-TGCT might be justified in an attempt to avoid chronic disability (13, 15, 17). Local experience and availability of TKIs during TOPP possibly influenced the choice for treatment in the tertiary reference centres, with a preference for surgery followed by TKI. Primary or refractory cases are predominantly treated at doctors' preference. Improved disease-specific patient education, multidisciplinary discussion, and shared decision making would enable better treatment selection for each patient.

At baseline of TOPP, patients with a wait-and-see policy reported fewer TGCT-related symptoms, less frequent use of painkillers, and higher QoL, advocating that the lack of symptoms may be the driving force for choosing a more conservative approach. We therefore considered PRO to be important influencers in shared treatment decision making, which is consistent with the increasing role of patient-based care in chronic diseases, especially in a benign disease such as TGCT (36).

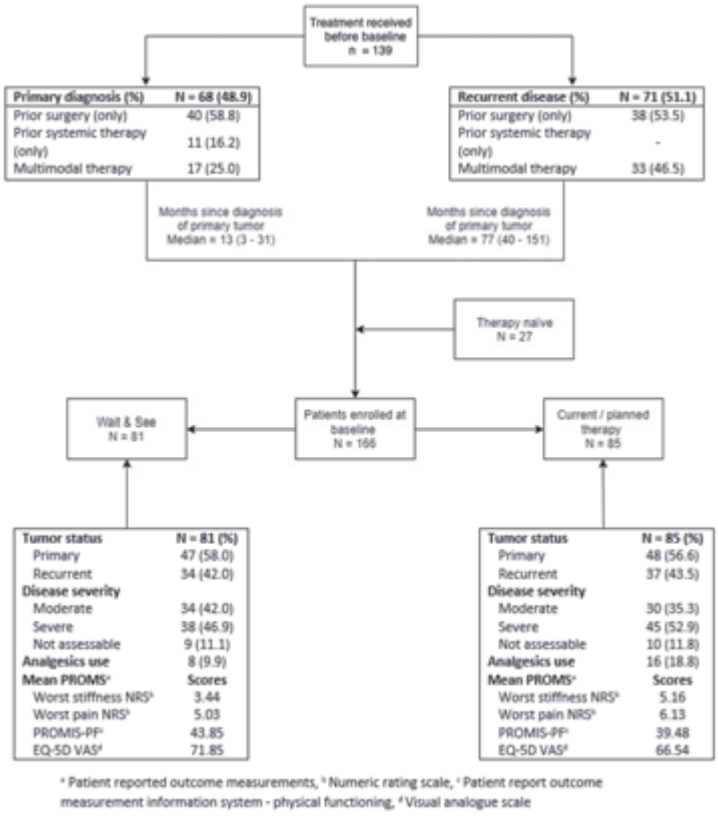

Figure 3

This flowchart gives a schematic overview of the treatment types patients received prior to TOPP, according to tumour status: primary diagnosis or recurrent disease. In addition, the cohort is stratified into 2 patient groups according to treatment plan at baseline: watchful waiting and indicated treatment at baseline. Possibly important factors in treatment decision making are shown per subgroup

The aim of TOPP is to provide insight on disease burden including healthcare utilisation, treatment landscape, and current management of TGCT in the tertiary sarcoma centre setting. In 2 years prior to baseline, medical professionals were often consulted, a fourth of the patients needed multiple physical therapy sessions, and medical specialists were frequently visited by more than half of the patients (Table 5). Hospitalisation and, to a lesser degree, rehabilitation were common with varying duration. Like the study by Burton et al., this suggests that TGCT causes a high health economic burden. In a like manner, this suggests that D-TGCT increases social costs (35). In the population studied, illness often caused work absence, intermittently more than 5 weeks of work in total in 2 years' time (Table 5). Additionally, several patients were forced to change their employment status from full-time to part-time, some had to become unemployed, while some even had to enter early retirement, all due to D-TGCT. The demand for domestic help illustrates the

impairment in activities of daily living. Worsening of D-TGCT over time will potentially increase the interference of the disease with work and the healthcare utilisation. However, since this study only reports data captured at baseline, we are not able to analyse such a change over a period of time.

While designed to report on epidemiologic data on D-TGCT, the TOPP study is exposed to potential selection bias, (i.e., underreferral of less severe cases to tertiary sarcoma centres). In addition, patients referred to such sarcoma centres are generally more impaired by D-TGCT, and the lack of patients treated in non-specialised centres could give an overestimation of the disease burden and healthcare utilisation. To avoid selection of patients and thus violation of the "real-life" principle, no explicit non-eligibility criteria were defined. In addition, as data about medical history that were not considered essential or were difficult to remember were collected at baseline, an underreporting of data might have occurred.

The present findings from baseline and 2 years prior to study entry provide new insights into patient management before arriving in a tertiary sarcoma centre. They strongly suggest that D-TGCT has its onset in a relatively young and working population but whose D-TGCT diagnosis is often delayed, most likely due to disease unfamiliarity or misdiagnosis. Evaluation of patient groups stratified by treatment received prior to study entry and at baseline in particular surgery and/or systemic therapy illustrate significant continued burden of disease. This is compounded by health economics and PRO data. Choice of treatment in the study population was mostly based on admission status, clinical experience, and PRO. Synovectomies were the mainstay of treatment, whereas TKIs were mostly restricted to severe and refractory cases, while a wait-and-see policy was applied for patients with less severe symptomatology. Within the context of these findings, developing multidisciplinary guidelines for the treatment of primary and refractory cases is of the utmost importance. Final results from the completed study will build upon these preliminary yet foundational understandings of the typical D-TGCT patient journey profile in this rare disease.

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Appendix

Tenosynovial Giant Cell Tumour Observational Platform Project (TOPP)

This is a multinational, multicentre, prospective, non-interventional observational disease registry. The sites will be specialised sites that treat TGCT regularly; no referral sites will be used, located in Austria, France, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the United States of America.

Country	Patients (n = 166)
Austria	8 (4.8%)
France	4 (2.4%)
Germany	13 (7.8%)
Italy	40 (24.1%)
The Netherlands	60 (36.1%)
Spain	8 (4.8%)
United Kingdom	3 (1.8%)
United States	30 (18.1%)

Participating centres

Department of Orthopaedics and Trauma, Medical University of Graz, Graz, Austria
Centre Hospitalier Universitaire de Nantes, Nantes, France
West deutschen Tumorzentrum, Essen, Germany
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy
Radboud University Medical Center, Nijmegen, The Netherlands
Leiden University Medical Center, Leiden, The Netherlands
University Castilla-La Mancha, Talavera de la Reina, Toledo, Spain
Hospital Universitario Virgen del Rocio, Sevilla, Spain
Oxford University Hospitals, Oxford, United Kingdom
UCLA Health, UCLA Medical Center, Santa Monica, US
Memorial Sloan Kettering Cancer Center, New York, US

Patient-reported outcome measurements

TGCT-related patient-reported outcomes (PROs) collected at baseline were pain, stiffness, swelling, and limited range of motion. Relevant patient-reported outcome measurements (PROMs) administered at baseline consisted of the mean brief pain inventory (BPI), mean worst pain and stiffness numerical rating scale (NRS), Patient-Reported Outcome Measurement Information System Physical Functioning® (PROMIS-PF), and EuroQol 5D (EQ-5D). The BPI assesses the severity and interference of pain on a scale from 0

(not severe/no interference) to 10 (severe/complete interference) (37). The worst pain and stiffness were scored on an NRS, requiring the patient to rate their worst pain and stiffness from 0 (nothing) to 10 (worst) in the last 24 hours. The PROMIS-PF evaluates physical, mental, and social health relevant to the affected limb region (upper/lower) with a score of 50 as mean in a US reference population (38). The EQ-5D is a simple generic instrument and it is defined in terms of 5 dimensions: mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression. The values or utilities are indicated on a scale where 0 corresponds to death and 1 corresponds to perfect health, with negative values also being possible. The second part of the EQ-5D consists of a vertical 20-cm, 0–100 visual analogue scale (VAS), where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. The respondent marks a point on the scale to reflect their overall health on the day of the interview (39).

Chapter 3

MRI of diffuse-type TGCT in the knee: a guide for diagnosis and treatment response assessment.

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Abstract

Tenosynovial giant cell tumour (TGCT) is a rare soft-tissue tumour originating from synovial lining of joints, bursae and tendon sheaths. The tumour comprises two subtypes: the localised-type (L-TGCT) is characterised by a single, well-defined lesion, whereas the diffuse-type (D-TGCT) consists of multiple lesions without clear margins. D-TGCT was previously known as pigmented villonodular synovitis. Although benign, TGCT can behave locally aggressive, especially the diffuse-type. Magnetic resonance imaging (MRI) is the modality of choice to diagnose TGCT and discriminate between subtypes. MRI can also provide a preoperative map before synovectomy, the mainstay of treatment. Finally, since the arrival of colony-stimulating factor 1-receptor inhibitors, a novel systemic therapy for D-TGCT patients with relapsed or inoperable disease, MRI is key in assessing treatment response. As recurrence after treatment of D-TGCT occurs more often than in L-TGCT, follow-up imaging plays an important role in D-TGCT. Reading follow-up MRIs of these diffuse synovial tumours may be a daunting task. Therefore, this educational review focuses on MRI findings in D-TGCT of the knee, which represents the most involved joint site (approximately 70% of patients). We aim to provide a systematic approach to assess the knee synovial recesses, highlight D-TGCT imaging findings, and combine these into a structured report. In addition, differential diagnoses mimicking D-TGCT, potential pitfalls and evaluation of tumour response following systemic therapies are discussed. Finally, we propose automated volumetric quantification of D-TGCT as the next step in quantitative treatment response assessment as an alternative to current radiological assessment criteria.

Introduction

Tenosynovial giant cell tumour (TGCT) is a fibro-histiocytic soft-tissue tumour that involves anatomical structures covered by a synovial membrane (joints, bursae and tendon sheaths). It can also affect extra-synovial locations, such as subcutaneous and intramuscular lesions (1). Common symptoms are pain, swelling, stiffness, and limited function, leading to decreased quality of life (2).

TGCT can be classified according to its site (intra- and extra-articular) and growth pattern (3). In the 2013 World Health Organisation classification of soft tissue and bone tumours, localised-type (L-TGCT) and diffuse-type (D-TGCT) replaced the terminology "giant cell tumour of the tendon sheath" and "pigmented villonodular synovitis", respectively (1). There is no clear histological distinction between both subtypes, therefore, diagnosis is based on radiological diagnosis and clinical presentation (4). TGCT is a rare neoplasm with incidence rates of 45 and 5 per million person-years for L-TGCT and D-TGCT, respectively. TGCT has a female predilection (♀:♂; 2:1) and affects a relatively young patient group mainly aged between 30 and 50 years, although it can occur at any age (5, 6).

L-TGCT occurs in an extra-articular location in 90% of cases, involving tendon sheaths of the volar aspect of fingers (85%), followed by foot and knee locations (15%) (7). These tumours primarily present as painless soft-tissue masses without joint dysfunction. The diffuse type originates predominantly in the intra-articular space of large joints such as the knee (70%) followed by the hip (15%) but often extends extra-articular (5). The extra-articular D-TGCT form is mostly a secondary extension of intra-articular disease (8). D-TGCT tends to present with chronic joint pain and swelling, often with progressive secondary osteoarthritis (2, 9). D-TGCT represents a monoarticular disease, which means that in case of polyarticular involvement with similar MRI appearance, other diagnoses should be considered, such as gout, haemophilic or amyloid arthropathy.

TGCT subtypes share a common underlying pathogenesis, mainly related to a Colony-Stimulating Factor 1 (CSF1) translocation resulting in CSF1 overexpression. CSF1 overexpression causes an increase in neoplastic cells by binding to CSF1-receptors (CSF1R) and accumulating CSF1R presenting cells (10). Histologically, TGCT shows an infiltrative growth pattern and comprises mononuclear cells, multinuclear osteoclast-like giant cells, macrophages and stromal hyalinisation. Also, hemosiderin depositions are frequently observed (1).

MRI is the imaging modality of choice for diagnosing and evaluating disease severity (11). It gives insight into areas that are not amenable for arthroscopic evaluation. Thereby, MRI

can provide a preoperative map of D-TGCT localisations to evaluate common blind spots before open synovectomy (8). Achieving complete resection can be challenging, especially in extensive tumour growth. Incomplete resections are associated with a higher chance of tumour relapse (12, 13). Other treatment modalities such as radiosynoviorthesis or external beam radiotherapy have been used to reduce relapse rates. However, evidence regarding the efficacy of these treatments is scarce (14, 15). Furthermore, the role of radiotherapy for TGCT remains controversial because it may result in complications such as osteoarthritis in a young patient population (13). With the arrival of CSF1R-inhibitors, a novel systemic therapy for D-TGCT patients not amenable to surgery, MRI is essential to select and follow-up on target lesions (16, 17).

In this educational review, we demonstrate the imaging features of D-TGCT and highlight blind spots and potential pitfalls on MRI.

Imaging features of D-TGCT

Radiography

Conventional radiography provides a first modality to assess osteoarticular complaints of the knee. Radiographs of the knee in D-TGCT are often normal, although features of osteoarthritis may be present, such as osteophytes, joint space narrowing and subchondral sclerosis. Pressure erosions may occur on both articular joint surfaces in advanced stages, especially in joints with limited volume and joint space, such as the ankle, hip and shoulder (9). In the knee, erosions have been described on radiographs in up to 30% of patients (18).

The presence of (peri)articular soft-tissue calcifications pleads against the diagnosis of D-TGCT and differential diagnoses such as gout or synovial chondromatosis should be considered (19).

Ultrasound

Ultrasound is not part of the standard diagnostic workup of D-TGCT; however, it can be helpful in performing image-guided biopsies (20). Appearance of D-TGCT has been described as hypoechoic irregular synovial thickening along with heterogeneous joint effusion and hyperemia, although these findings are non-specific and may be found in other types of diffuse synovitis (21). In addition, ultrasound does not provide the necessary information and correct evaluation of the areas that should be carefully scrutinised and reported when evaluating D-TGCT.

MRI

MRI is the modality of choice to diagnose D-TGCT. The scanning protocol applied at our tertiary referral centre for bone and soft tissue tumours (3 Tesla, Ingenia, Philips, Eindhoven, The Netherlands) is shown in Appendix: Table 1. A gradient-echo sequence may be beneficial for detecting hemosiderin related to tumour bleeding. Intravenous gadolinium contrast aids in tumour detection and is helpful for follow-up after synovectomy. TGCT can present with variable MRI appearances given its heterogeneous histological composition and the variety in growth patterns (intra- and/or extra-articular) (3).

D-TGCT findings include irregular synovial thickening (> 5 mm), typically described as "frond-like" with villous or nodular morphology (3). This synovial proliferation tends to engulf associated reactive joint effusion resulting in multiloculated thick-walled trapped cystic masses, especially seen in the subgastrocnemius synovial recesses and Baker's cysts (18).

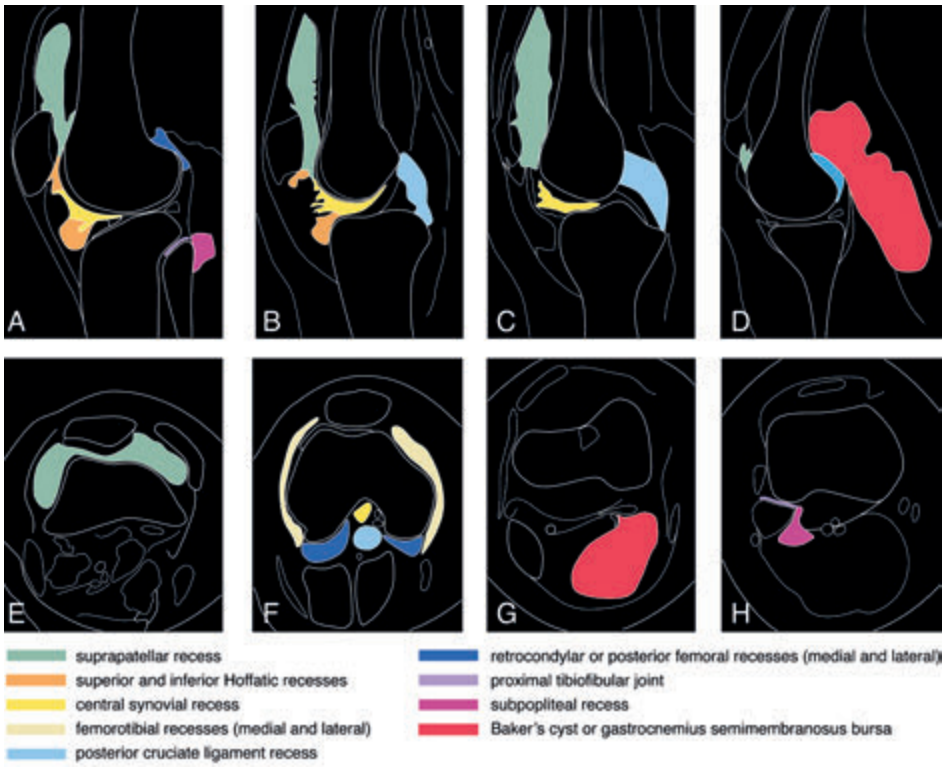

Figure 1

Schematic overview of synovial recesses in the knee. a–d Sagittal drawings from lateral (a) to medial (d). e–h axial drawings from superior (e) to inferior (h)

D-TGCT intra-articular forms are likely to spread diffusely, developing a multicompartmental growth pattern involving at least two contiguous intra-articular synovial recesses. In the knee, several recesses may be involved, as illustrated in the detailed description of Figure 1.

D-TGCT's extra-articular growth pattern mainly occurs secondary to intra-articular extension through transcapsular fenestrations (8). Mastboom et al. defined extra-articular extension as TGCT involvement outside the synovial lining of the joint. Furthermore, cartilage invasion, cortical bone erosions, muscular/tendinous, ligament and neurovascular involvement were proposed as parameters that determine the severity of D-TGCT (22). In the knee, tibial nerve encasement is rare but may be symptomatic. D-TGCT may extend into femoral and tibial medullary tunnels in patients with anterior cruciate ligament (ACL) reconstruction.

D-TGCT signal intensity is heterogeneous. T1-weighted imaging (T1-WI) shows a hypointense to iso-intense signal, whereas fluid-sensitive sequences show a hyperintense signal with foci of low signal intensity corresponding to hemosiderin in the tumour (Figure 2). D-TGCT is prone to bleeding (bleeding is more common than in L-TGCT), and therefore hemarthrosis is a common finding expressed as low signal intensity on both T1-WI and fluid-sensitive sequences. Haemorrhage constitutes a classic D-TGCT imaging hallmark mostly detected as blooming on gradient echo (GRE) images. This imaging feature has been described as pathognomonic to suggest TGCT diagnosis, but its absence does not exclude TGCT (23). Blooming is a paramagnetic susceptibility artefact secondary to hemosiderin deposition defined as enlargement and disproportionately lower signal intensity of blood deposits on GRE images compared to spin-echo (SE) sequences (Figure 3). Scout GRE acquisitions should be employed cautiously in the search for blooming owing to high false-negative rates (23). Diffusion-weighted images (DWI) can be deceptive because TGCT (both localised and diffuse subtypes) depict intrinsically low apparent diffusion coefficient (ADC) values due to hemosiderin deposits (24). D-TGCT shows avid heterogeneous enhancement. From dynamic post-contrast imaging (perfusion), a time-intensity curve can be obtained showing rapid early enhancement with a plateau phase (Figure 2) (25).

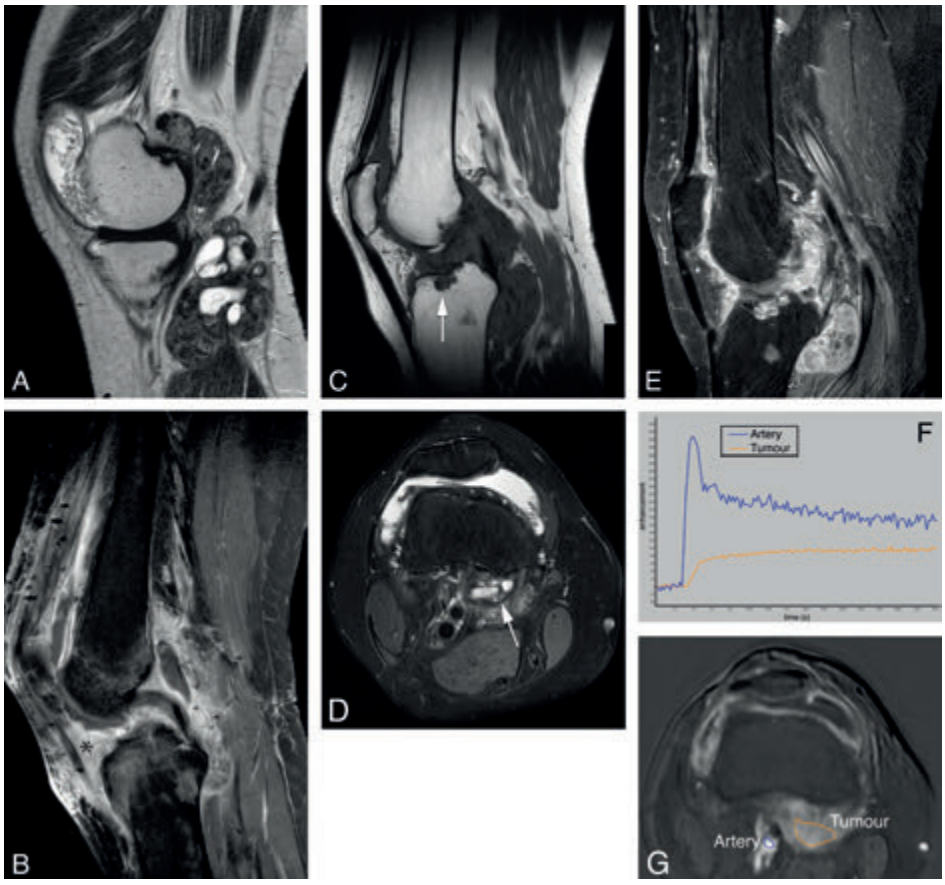

Figure 2

A case of D-TGCT demonstrating pre and post synovectomy findings on MRI. a Sagittal T2 weighted image shows multilobular posterior tumour with low signal intensity, and adjacent cyst-like components present within tumour in the popliteal cyst. Anterior, in the medial gutter of the suprapatellar recess smaller synovial proliferations are present. b Sagittal T1 SPIR post contrast performed 3 months after anterior and posterior synovectomy shows surgical clips with metal artefact anterior and posterior in the soft tissues, thickening of the quadriceps tendon, subcutaneous oedema and marked enhancement in Hoffa's fatpad (asterisk) and along the posterior cortex of the tibia (subpopliteal recess). This mass-like enhancement can be post operative but residual tumour cannot be excluded at this time. MRI performed 3 years post synovectomy: c Sagittal T1 shows a bone erosion centrally in the tibial plateau (arrow). Furthermore, soft tissue masses posteriorly in the knee are present containing foci of low signal intensity. d Axial PD SPAIR shows a typical location of a lesion containing cystic components at the medial retrocondylar recess (arrow). e Sagittal T1 SPIR post contrast demonstrates enhancement of tumour within the tibia plateau erosion and of the posterior mass lesions. Note that Hoffa's fat pad shows normalisation of fatty signal intensity except for a rim of tumour enhancement in the central synovial recess and inferior infrapatellar recess. f, g Time intensity curve of the tumour based on the region of interest (orange line) of the lesion demonstrated in d, showing early enhancement within 10 s after the artery (blue line) followed by a plateau phase (type III curve suggestive of a benign lesion)

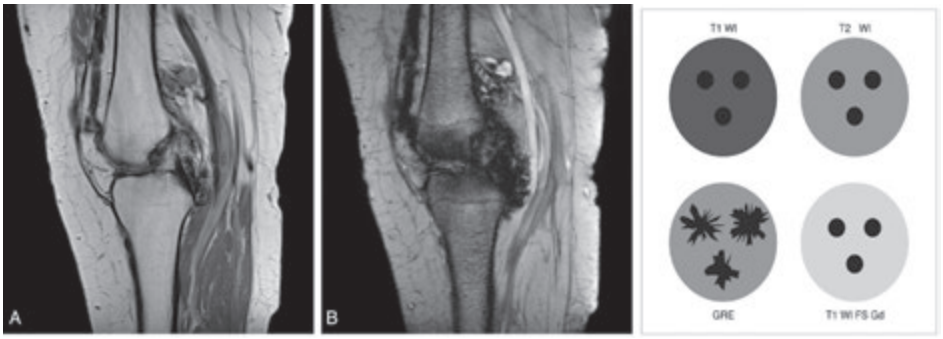

Figure 3
Blooming artefact. a Sagittal PD-weighted MR image of the knee in a patient with D-TGCT demonstrates multiple low signal intensity synovial lesions posterior to the PCL, along the posterior cortex of the femoral metaphysis and in the collapsed suprapatellar recess. b Sagittal T2- gradient echo weighted MR image of the knee showing blooming artefact: the low signal intensity synovial lesions containing hemosiderin increase in size and are ill defined, appearing as cloud-like dark areas. c Schematic illustration of hemosiderin signal intensities on gradient echo (GRE) weighted sequences versus T1- and T2-weighted sequences. Gradient echo images show increased size of the hemosiderin foci with irregular margins, this is called "blooming"

Areas of intralesional fat with high signal intensity on T1-WI related to deposition of lipid-laden macrophages (xanthoma cells) are a classic feature of D-TGCT, however, this finding is uncommon [3, 23]. This feature may represent entrapped fronds of perisynovial fat or subsynovial fat metaplasia as a reactive process to chronic TGCT, similar to lipoma arborescens in rheumatoid or psoriatic arthritis.

Differential diagnoses

Gout tophi can present as both intra- and extra-articular or peri-articular nodules. Typical locations such as the subcutaneous fat or within the distal quadriceps or proximal patellar tendon can help distinguish gout from D-TGCT (26). Gout and amyloidosis are soft-tissue masses appearing hypointense on T2 sequences, which can be intra-articular, mimicking TGCT (Figure 4) (27). Radiographs may be helpful to assess soft tissue calcifications, and dual-energy computed tomography (CT) may be performed to prove the presence of monosodium urate crystals in gout (28).

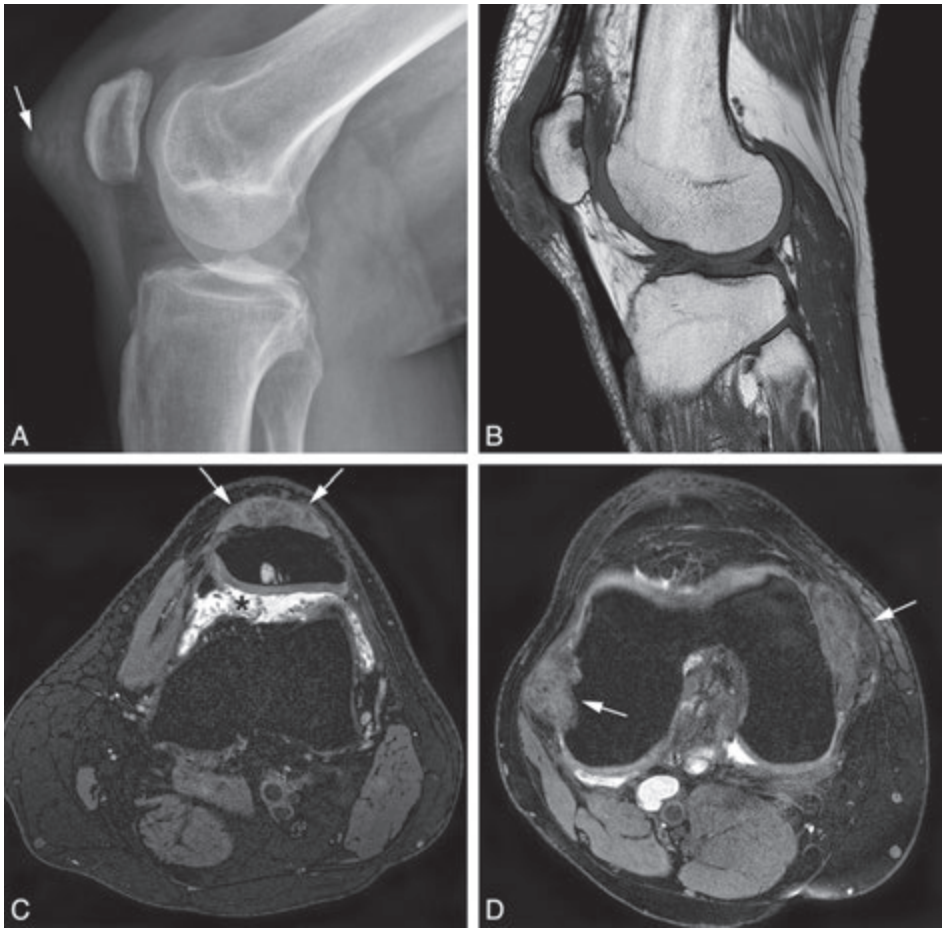

Figure 4

Differential diagnosis: gout in the knee. a Lateral radiograph demonstrates marked pre-patellar soft tissue swelling containing increased density and several ill-defined calcifications (arrow). b Sagittal T1 shows a prepatellar, low signal intensity oval shaped soft tissue mass and a subchondral cyst in the patella. c Axial T2 FS confirms the prepatellar, low signal intensity mass invading the quadriceps tendon (arrows) and shows joint effusion containing multiple small synovial proliferations in the suprapatellar recess (asterisk). Aspiration of joint fluid with crystals confirmed the diagnosis of gout. d Axial T2 FS demonstrates low signal intensity soft tissue lesions in keeping with gout tophi deep to the collateral ligaments, causing erosion of the medial and lateral femoral condyles (arrows)

Synovial chondromatosis can present either as multiple round bodies similar in size and shape with a "snowstorm" or "cobblestone" pattern and a variable degree of calcification (85% is calcified) or coalesce into multiple intra-articular synovial masses (Figure 5). The presence of calcification or metaplastic cartilage excludes the diagnosis of TGCT (19).

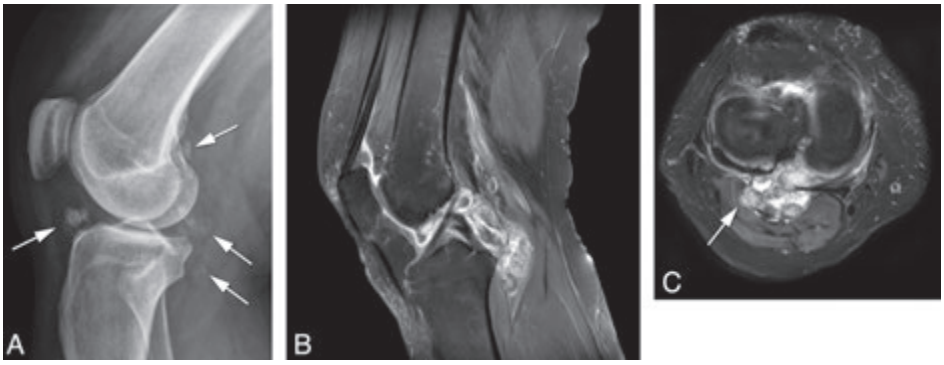

Figure 5
Differential diagnosis: synovial chondromatosis in the knee. a Lateral radiograph illustrating multiple punctiform masses in the soft tissues of the knee containing speckled calcifications (arrows). These calcifications are present in Hoffa and posterior in the knee. b Sagittal T1 SPIR post contrast showing rim enhancement of the synovial lesions, which contain low signal intensity foci corresponding to the calcifications on X-ray. Only minimal joint effusion is present surrounding the cruciate ligaments with rim enhancement. c Axial T2 DIXON shows posterior extracapsular extension into the lateral head of gastrocnemius muscle (arrow)

Lipoma arborescens is a chronic, slow-growing, intra-articular condition of benign nature, characterised by villous proliferation of the synovium with replacement of subsynovial connective tissue by mature fat cells. It may be misdiagnosed as TGCT if encountered on fat-suppressed fluid-sensitive sequences and not correlated with a native T1-weighted sequence. However, its feathery subsynovial fat deposition appearance on axial MR images is characteristic (Figure 6) (29). The classic location is the suprapatellar recess of the knee joint. In most cases, lipoma arborescens does not extend to other recesses, except when it develops in patients with chronic synovitis, such as in rheumatoid or psoriatic arthritis.

Synovial haemangioma may cause repetitive spontaneous hemarthrosis within a joint and thereby mimic D-TGCT clinically. However, the MRI appearance with a "bag of worms" caused by serpentine vascular channels and the presence of interspersed fat in a haemangioma may be helpful to distinguish the two entities. In addition, the enhancement pattern differs and a dynamic post contrast sequence can be used to determine slow-flow versus high-flow vascularity in the synovial haemangioma (30). Resection is the treatment of choice.

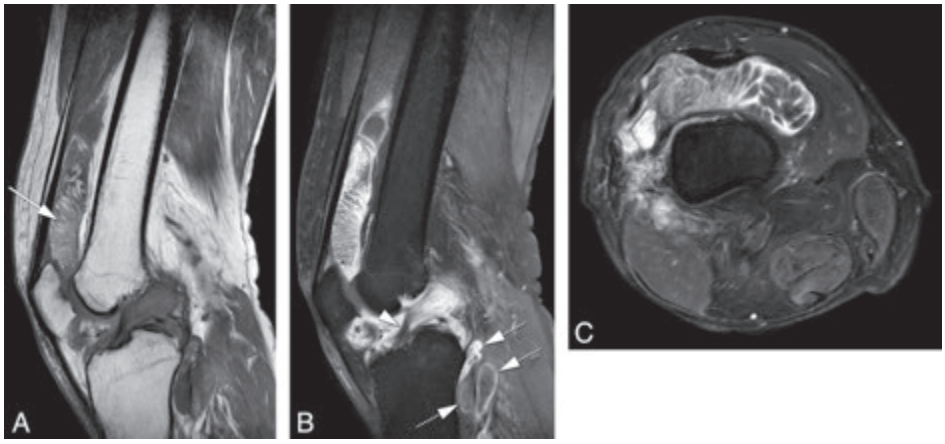

Figure 6
Differential diagnosis: lipoma arborescens. a Sagittal T1 demonstrates a hyperintense soft tissue mass in the suprapatellar recess, containing multiple villous proliferations (arrow). b Sagittal T1 SPIR post contrast shows the signal of the villi is suppressed and rim enhancement is present. In addition, there is mucoid degeneration of the anterior cruciate ligament and enhancing synovitis in the central synovial recess (arrowhead), superior and inferior infrapatellar recesses (asterisks), PCL and subpopliteal recess (arrows). c Axial T2 DIXON confirms fat suppression of the villi in the suprapatellar recess. These findings are in keeping with a lipoma arborescens, which is not a true neoplasm but rather a reactive process associated with rheumatoid or psoriatic arthritis or osteoarthritis

Haemophilic arthropathy may mimic D-TGCT due to widespread hemosiderin depositions and often severe secondary osteoarthritis; however, the clinical history is usually straightforward and fatty components are absent due to a lack of foam cells (18).

Treatment assessment in the knee

Pre- and postoperative MRI findings

Surgery is the mainstay of TGCT treatment, performed either open or arthroscopically (31). L-TGCT resection is relatively straightforward, with low recurrence rates (4–30%) controlled by re-excision (32). On the other hand, D-TGCT is a locally aggressive process with a high recurrence rate of around 40–60% (12, 33). MRI is fundamental to assess D-TGCT intra- and extra-articular extension and can help avoid incomplete resections.

The knee joint intracapsular space is composed of multiple and interconnected synovial recesses, some of which are rarely apparent on MRI of a healthy, non-affected knee (34). D-TGCT is characteristically found in certain areas showing a reproducible distribution pattern similar to loose bodies (35). Therefore, D-TGCT lesions can be identified on MRI due to reactive joint effusion making synovial recesses apparent and due to signal intensity contrast between tumour and fluid.

The same MRI protocol should be used for pre-and post-treatment assessment (as described in Appendix Table 1). Assessment of joint recesses may be done first in the sagittal plane (comparing T1-WI with T1-WI fat-suppressed (FS) gadolinium (Gd) side-to-side for anatomy and enhancement of lesions). Secondly, side-to-side comparison of axial fluid sensitive sequences (we use T2 DIXON) and T1-WI FS Gd images helps distinguish tumour from (rim-)enhancing synovial fluid or cyst-like components. Coronal images add value for assessment of erosions and femorotibial chondropathy

The following areas should be carefully scrutinised and reported (Figure 1):

The anterior compartment:

1. The suprapatellar recess is localised between the prefemoral and suprapatellar fat pads. It is the most distensible synovial recess, often containing hemosiderin deposits along its posterior synovial surface and nodular proliferations surrounded by joint fluid. Simultaneous assessment of T1-weighted images and fluid-sensitive sequences in axial and sagittal planes is crucial. The prefemoral fat has well-defined rounded margins, but not infrequently; it acquires dendritic borders protruding into the suprapatellar pouch resulting in TGCT overestimation due to taking fat-suppressed adipose tissue for TGCT.
   The medial and lateral parapatellar gutters are key areas to assess on axial images because D-TGCT is frequently trapped here.
2. The infrapatellar synovial recess is divided into the superior and inferior recesses, orientated vertically and horizontally, respectively, including the localisation of tumour underneath the anterior horns of the menisci and the intermeniscal ligament.
3. The involvement of pre-patellar and infra-patellar bursae in D-TGCT is rare and should urge the investigation of other entities such as gout.

The posterior compartment has a limited distensible capacity defined by the posterior femoral capsule:

1. The subgastrocnemius synovial recesses, also referred to as retrocondylar or posterior femoral recesses, are localised underneath the gastrocnemius head insertions (35). These areas present as fat signal intensity triangles with concave margins on sagittal T1-weighted images. Subgastrocnemius collapsed reactive synovitis without intervening effusion results in D-TGCT overestimation. Replacement of fat by low signal intensity tissue is in keeping with hemosiderin. Ganglion cysts at the medial or lateral gastrocnemius origins may be indistinguishable from tumour, because D-TGCT tends to show multiloculated thick-walled cystic masses (36). The cleft-

like morphology and presence of hemosiderin point towards D-TGCT, where it is prone to develop extra-articular extension encasing the gastrocnemious tendons.

2. The PCL recess is located between the PCL and the posterior joint capsule. It usually harbours fibrofatty tissue with thin enhancing septa, which can be misdiagnosed as TGCT on fat-suppressed sequences (23). The inspection of T1-weighted images and the absence of mass effect (posterior femoral capsule bulging) confirms its nature. This location is typical for extra-capsular D-TGCT popliteal extension due to perforating vessels on the posterior femoral capsule (37).
3. The subpopliteus synovial recess encases the popliteus tendon. It is connected to the popliteal hiatus between the posterosuperior and anteroinferior popliteomeniscal fascicles. It extends behind the posterior horn of the lateral meniscus to sit underneath the popliteus muscle belly in contact with the posterior aspect of the tibia. The subpopliteal recess represents a continuum with the proximal tibiofibular joint in approximately 10% of patients (38).
4. The Baker's or popliteal cyst is also known as the medial gastrocnemius—semimembranosus bursa. Baker's cyst D-TGCT involvement is considered intra-articular extension because of the communication with the knee joint synovial lining. Due to its dependent location and ball-valve communication mechanism, a Baker's cyst can harbour multi-cystic proliferations with or without involvement of another compartment. The medial gastrocnemius-semimembranosus tendon cross-over may mimic haemorrhage deposition, but its anti-gravitational site and axial tracking differentiate it from hemosiderin deposition.
5. Some bursae, such as the semimembranosus-tibial collateral ligament bursa (semimembranosus bursa) and pes anserinus are not connected to the knee joint and are atypical locations for D-TGCT.

The middle compartment is a tight area where distension is limited.

1. The central synovial recess is situated in front of the ACL.
2. The intercruciate space is challenging to assess on MRI, as D-TGCT is generally underestimated in this area due to the similar low signal intensity compared to the cruciate ligaments. Intra-articular pericruciate ganglion cysts should be differentiated from tumour. Bone erosions caused by the tumour in the intercondylar notch can be undercalled as cystic change at the insertion of the cruciate ligaments, which is a common finding on normal knee MRIs (39). Bone erosions in D-TGCT typically contain enhancing tumour tissue (Figure 2C, E).
3. The femorotibial synovial recesses, both medial and lateral, are occupied in severe D-TGCT cases when tumour volume generally exceeds 80–100 cc. These areas are prone to develop cortical erosions as they are virtually not distensible.

MRI is the modality of choice to assess residual D-TGCT after synovectomy and for postoperative follow-up. Common postoperative changes include skin thickening, fat stranding or inflammation in Hoffa (in the area of arthroscopy portal entrances), subcutaneous and intramuscular oedema with susceptibility artefacts secondary to surgical clips (Figure 2B). Joint effusion may be reduced due to drainage. Diffuse synovial thickening is equivocal for D-TGCT residual disease within the first six months because of associated reactive synovitis (40). Growing enhancing solid and nodular synovial thickening should raise the suspicion of disease recurrence (Figure 2B, E).

Systemic therapy response evaluation

With the arrival of systemic therapies targeting CSF1/CSF1R in D-TGCT patients not regarded amenable to surgery, MRI is required to objectively assess treatment response (16, 17, 41). Quantification of change in tumour volume is the main feature to evaluate the response of these agents. To date, Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 is the most frequently used tool to detect a change in tumour size by calculating the sum of the longest diameters for all target lesions. In addition, a modification of RECIST (m-RECIST) can be applied, adding a short axis measurement for target lesions, offering higher accuracy (17). However, the irregular tumour shape, absence of nodular lesions, asymmetrical growth, variable enhancement after contrast, and lack of clear tumour margins make it challenging to apply linear measurements (42).

Peterfy et al. developed a semiquantitative, joint-specific, visual tumour volume score (TVS) for D-TGCT. This score was developed analogous to and based on arthritis visual scores used in clinical trials. TVS expresses tumour volume as a percentage of the estimated volume of the maximally distended normal synovial cavity of the involved joint. TVS can incorporate all tumour regions and defines tumour size relative to the joint size (42). However, since TVS is a semiquantitative tool, clinicians have to estimate the percentage of tumour volume, limiting its reproducibility. In addition, TVS has not been validated as a method for response assessment yet. Therefore, there is an urgent need for an automated tool measuring D-TGCT tumour volume on MRI.

Aside from changes in tumour size, other specific MRI findings following CSF1R inhibitors have been described in pilot studies. These findings include a decrease in signal intensity on fluid-sensitive sequences with a reduction of capsular distension and joint effusion and an increase in hemosiderin deposition (43). Decreased enhancement seems to be an equivocal parameter. These imaging features appear to correlate well with clinical improvements, such as pain reduction (Figure 7) (44).

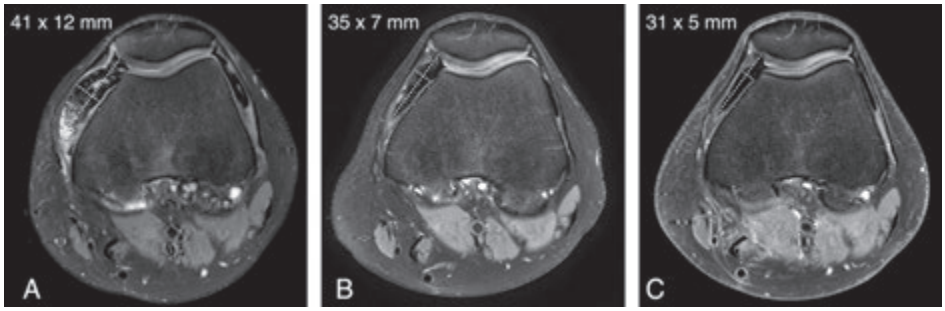

Figure 7
MRI findings after treatment of D-TGCT with a CSF1R inhibitor. a Axial PD SPAIR images in a patient with intra-articular D-TGCT. Baseline image showing a target lesion (two axial diameters measured according to modified RECIST, dotted lines) in the medial suprapatellar recess. Note a smaller similar lesion in the lateral suprapatellar recess. b After 8 weeks on CSF1R-inhibitor therapy, the tumour showed a significant decrease in size and signal intensity. Joint effusion was resolved (not shown). The patient experienced improvement in symptoms of pain and swelling. c After 36 weeks, residual low signal intensity hemosiderin "scars" remained both in the medial and lateral suprapatellar recesses

Of note, patients may experience complete symptomatic relief even in the setting of what appears to be an incomplete response based on imaging (43). So-called hemosiderin scars remain as a low signal intensity rim lining the synovium after therapy, without corresponding clinical complaints. It has been suggested to use "complete response" in case of residual hemosiderin scars with a short axis < 5 mm, however this approach needs further study (42).

Future directions: 3D segmentation

Following the limitations of the current response criteria, volumetric quantification techniques integrated with Artificial Intelligence (especially deep learning) methods may help measure tumour change. However, developing such an automated quantification method is challenging due to irregular growth and heterogeneous signal intensity of TGCT (42).

We performed a first step towards objective volumetric quantification of D-TGCT by segmenting 3D tumour volume in 40 treatment-naïve patients with D-TGCT. All imaging data were anonymised, and informed consent was waived by the institutional review board (G19.127). Measuring tumour volume was done in Brainlab (Elements), an application that is commonly used for preoperative planning of bone and soft-tissue tumours.

For 3D segmentation, a sagittal T1 spectral inversion recovery (SPIR) Gd and an axial T2 DIXON (water only) scan were utilised. In addition to the total volume, the volumes in the anterior and posterior compartments of the knee were calculated separately. The mean total volume was 44 cm3 (range 3.2–208.8 cm3). The mean volume located in the anterior compartment was 21 cm3 (range 0.0–205.8 cm3) and in the posterior compartment 23 cm3 (range 0.0–172.9 cm3). Examples of volumetric segmentation in three different patients are shown in Figure 8.

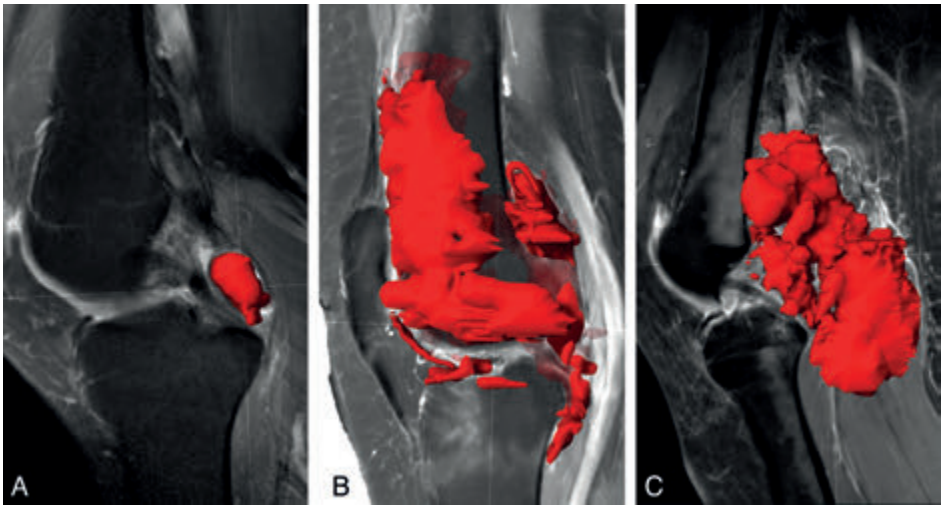

Figure 8
Volumetric segmentations of D-TGCT performed with Brainlab software on sagittal T1 SPIR-weighted sequences post gadolinium. a Tumour is segmented in the PCL recess (volume shown in red). Volume: 3.8 cm3. b Tumour segmentation in anterior, middle and posterior compartments. Volume: 86.2 cm3. c Tumour segmentation of a case with marked posterior disease, present in the PCL recess, subgastrocnemius synovial recesses, Baker's cyst, and extending extra-articular in the popliteal fossa. Volume: 91.9 cm3
We showed that 3D MR segmentation allows to objectively quantify the tumour burden of TGCT and provides a quick visual assessment of TGCT lesion distribution throughout the knee. However, since 3D segmentation of TGCT is time-consuming and operator-dependent, future steps will focus on automating this process.

Conclusions

MRI is the modality of choice in diagnosing D-TGCT, providing preoperative mapping and assessment of response to systemic therapies. However, due to its irregular shape, extensive growth and low signal intensity, D-TGCT disease extent can be challenging for the radiologist. We highlighted imaging characteristics of D-TGCT affecting the knee and provided a structured report template (Table 1). In addition, pitfalls such as mimickers of D-TGCT were addressed, and evaluation of tumour response following new systemic therapies. Finally, we demonstrated a first step towards objective 3D volume quantification

of D-TGCT. Automated quantification of tumour load to assess treatment response will become more important as systemic medical therapies evolve quickly.

Table 1 D-TGCT Knee MRI structured report template

ITEMS	FINDINGS
1- Shape	Well-circumscribed nodules *and /or* diffuse villous synovial thickening
2- Site	
2a. Intra-articular	Anterior compartment (suprapatellar, Hoffatic recess) Middle compartment (central, femorotibial, intercruciate recesses) Posterior compartment (retrocondylar, PCL, subpopliteus, Baker's cyst)
2b. Extra-articular	Posterior transcapsular extension to popliteal fossa Cartilage and bone invasion (chondropathy and/or pressure erosions) Muscular-tendinous involvement (invasion or encasement > 180°) Ligament involvement (invasion or encasement > 180°) Neurovascular bundle involvement (> 180° encasement of the tibial nerve and/ or popliteal artery/veins)
3- Signal Intensity	T1-WI: (hypo- / isointense) and (homogeneous / heterogeneous) T2-WI FS: (hypo- / iso- / hyperintense) and (homogeneous / heterogeneous) T1-WI FS Gd: enhancement (absent / present) and (homogeneous or heterogeneous) GRE: blooming (absent / present)
4- Size	Bidimensional measurements [RECIST 1.1: long axis of target lesions, modified RECIST: long and short axis of target lesions] Volumetric tumour burden (Tumour Volume Score)
5- Secondary findings (complications)	Joint Effusion (>10 mm anteroposterior in the suprapatellar pouch) Reactive synovitis (sometimes fatty metaplasia, hyperintense on T1-WI) Secondary osteoarthritis / Chondromalacia
CONCLUSION	
Subtype (growth pattern)	Diffuse-type TGCT (≥ 2 synovial recesses)
Extension	Intra-articular and/or extra-articular
Severity	Mild-Moderate [< 1 extra-articular structure involvement (ligaments, muscles, tendons)] / Severe (≥ 1)
Complications	Secondary osteoarthritis (mild, moderate, severe)

PCL Posterior cruciate ligament; WI Weighted imaging; FS Fat-suppressed; Gd Gadolinium; GRE Gradient echo; RECIST Response evaluation criteria in solid tumours

Abbreviations

ACL: Anterior cruciate ligament
ADC: Apparent diffusion coefficient
Ax: Axial
Cor: Coronal
CSF1: Colony-stimulating factor 1
CSF1R: Colony-stimulating factor 1-receptor
CT: Computed tomography
D-TGCT: Diffuse-type tenosynovial giant cell tumour
DWI: Diffusion-weighted images
FFE: Fast field echo
FOV: Field-of-view
FS: Fat-suppressed
Gd: Gadolinium
GRE: Gradient echo
IR: Inversion recovery
L-TGCT: Localised-type tenosynovial giant cell tumour
m-RECIST: Modification of RECIST
MRI: Magnetic Resonance Imaging
MST: Multi-stack
PCL: Posterior cruciate ligament
PD: Proton density
RECIST: Response evaluation criteria in solid tumours
Sag: Sagittal
SE: Spin-echo
SP(A)IR: Spectral (adiabatic) recovery
TFE: Turbo field echo
TGCT: Tenosynovial giant cell tumour
TSE: Turbo spin echo
TVS: Tumour volume score
WI: Weighted imaging

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Appendix

Table 1. MRI protocol for D-TGCT of the knee.

Scan	Name	Technique	FOV	Thickness (mm)	Slices	Scan time
1	Survey Ax	T1FFE				0:10
2	Survey MST	T1FFE				0:50
3	T1 Sag	TSE	220x180	3,0	50	3:30
4	PD SPAIR Sag	TSE	220x180	3,0	50	4:13
5	PD Cor	TSE	220x180	3,0	50	2:45
6	T2 DIXON Ax	TSE	180x180	4,0	40	2:51
7	T1W FFE Sag #	FFE	220x180	3,00	50	4:30
Administer contrast agent during dynamic scan: 0,2 ml Clariscan per kg body weight						
8	Dynamic + T1 map *	3D T1 TFE	250	5,0 – 10,0	9	5:09
9	T1 SPIR Gd Sag	TSE	220x220	3,0	50	3:54
10	T1 SPIR Gd Ax	TSE	180x180	4,0	40	1:55

Parameters shown are for a 3 Tesla Ingenia MRI scanner, Philips, Eindhoven, The Netherlands.
FOV Field-of-view; Ax Axial; FFE Fast Field Echo; MST multi-stack; Sag Sagittal; TSE Turbo Spin Echo; SP(A)IR Spectral (Adiabatic) Inversion Recovery; PD Proton Density; Cor Coronal; Gd Gadolinium; TFE Turbo Field Echo
** Addition of a dynamic sequence post-contrast is optional.*
 # Gradient echo sequence for assessment of blooming artifact.

Chapter 4

Active surveillance of diffuse-type tenosynovial giant cell tumours: a retrospective, multicentre cohort study

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Abstract

Background

Diffuse-type tenosynovial giant cell tumour (D-TGCT) is a mono-articular, soft-tissue tumour. Although it can behave locally aggressively, D-TGCT is a non-malignant disease. This is the first study describing the natural course of D-TGCT and evaluating active surveillance as possible treatment strategy.

Methods

This retrospective, multicentre study included therapy naïve patients with D-TGCT from eight sarcoma centres worldwide between 2000 and 2019. Patients initially managed by active surveillance following their first consultation were eligible. Data regarding the radiological and clinical course and subsequent treatments were collected.

Results

Sixty-one patients with primary D-TGCT were initially managed by active surveillance. Fifty-nine patients had an MRI performed around first consultation: D-TGCT was located intra-articular in most patients (n = 56; 95%) and extra-articular in 14 cases (24%). At baseline, osteoarthritis was observed in 13 patients (22%) on MRI. Most of the patients' reported symptoms: pain (n = 43; 70%), swelling (n = 33; 54%). Eight patients (13%) were asymptomatic.

Follow-up data were available for 58 patients; the median follow-up was 28 months. Twenty-one patients (36%) had radiological progression after 21 months (median). Eight of 45 patients (18%) without osteoarthritis at baseline developed osteoarthritis during follow-up. Thirty-seven patients (64%) did not clinically deteriorate during follow-up. Finally, eighteen patients (31%) required a subsequent treatment.

Conclusion

Active surveillance can be considered adequate for selected therapy naïve D-TGCT patients. Although follow-up data was limited, almost two-thirds of the patients remained progression-free, and 69% did not need treatment during the follow-up period. However, one-fifth of patients developed secondary osteoarthritis. Prospective studies on active surveillance are warranted.

Introduction

Tenosynovial giant cell tumour (TGCT) is a rare, mono-articular, proliferative disease (1). Although this is generally a non-malignant disease, TGCT can behave locally aggressively, especially the diffuse-subtype (D-TGCT) (1, 2). D-TGCT has an incidence rate of around five to eight per million person-years and affects mainly large joints, particularly the knee (3, 4). The clinical spectrum ranges from an indolent, asymptomatic tumour to infiltrative growth causing joint degeneration. The most frequently reported symptoms: pain, stiffness, swelling and limited function can significantly impair quality of life in a relatively young population (5-7). MRI is the main imaging modality to diagnose D-TGCT and evaluate the tumour extent (8). It is suggested that this synovial proliferation is driven by colony-stimulating factor 1 (CSF1) translocations, causing CSF1 overexpression (9). This leads, among other things, to the attraction of non-neoplastic macrophages with CSF1-receptors (CSF1R) (10).

Preferably, patients are referred to (oncological) orthopaedic surgeons in sarcoma centres experienced in treating rare soft-tissue tumours (11). Current guidelines suggest that surgery is the most conventional treatment modality (12). More invasive interventions, such as joint arthroplasty for secondary osteoarthritis, are sometimes indicated (13). However, surgery continues to be associated with high recurrence rates for D-TGCT (14). Repetitive or invasive surgery is associated with surgery-related morbidity. For multiple recurrent or more extreme cases, radiotherapy has occasionally been performed in some centres, consisting of external beam radiotherapy or radiosynoviorthesis (15, 16). Nonetheless, evidence regarding radiotherapy for D-TGCT is of low quality, and evident results regarding the benefits and (long-term) toxicity are lacking (16, 17). The limitations of the abovementioned treatments led to the development of new therapeutic modalities. Systemic treatments targeting CSF1R have shown good radiological and clinical outcomes (18, 19). Still, the risk-benefit ratio and side effect profile of these CSF1R inhibitors is questionable in a non-life-threatening disease. Furthermore, their long-term efficacy and toxicity is not available for most of agents approved or in clinical trials and and whether these CSF1R inhibitors also target the neoplastic TGCT cells directly remains unknown (20).

To date little is known about D-TGCT's natural course (21). Since D-TGCT is benign, active surveillance may be a valid option for asymptomatic patients, patients with a mild disease pattern or when surgical or systemic treatments might be associated with major morbidity or unacceptable risk of adverse events (22). This study aimed to describe the characteristics of patients initially treated by active surveillance and the effect of active surveillance on the radiological and clinical disease course.

Materials and Methods

This international, multicentre, retrospective cohort study includes eight sarcoma centres from the Netherlands, the United States of America, Italy, and Canada. Therapy naïve patients with diffuse-type TGCT in any joint initially managed by active surveillance between 2000 and 2019 were eligible for inclusion. Exclusion criteria were a radiological or clinical diagnosis of localised TGCT or patients that received a TGCT-related treatment before the first consultation in one of the participating sarcoma centres. Patients who underwent an excisional biopsy without the intention to completely remove all tumour or underwent a diagnostic arthroscopy were included.

Primary objective of this study was to describe the natural course of D-TGCT and whether patients can be treated safely by active surveillance.

All data were retrospectively collected following routine follow-ups of patients with D-TGCT managed by active surveillance. No standardised follow-up scheme was followed due to the study's retrospective design. No minimum length of follow-up was required because there was not always an indication for prolonged follow-up for patients who clinically improved without undergoing treatment. Data were extracted from patient medical records and pseudonymised before transferring to the principal investigator. The following data were collected at the first consultation: patient demographics, tumour extent on MRI (intra- and/or extra-articular localisation, bone/ligament/muscle/neurovascular involvement, and osteoarthritis), TGCT related symptoms (pain, swelling, stiffness, limited function) when reported in patient files, the need of pain medication and walking aids. The following data were collected during follow-up: radiological progression, degenerative change compared to baseline situation, clinical improvement/deterioration, and subsequent treatments. Radiological progression was defined as an increase in tumour size measured on MRI. Degenerative change was defined as the onset of osteoarthritis observed to MRI compared to baseline. Clinical change (improvement/stable/deterioration) was based on the change of the severity of symptoms reported by patients. This study was performed according to the Declaration of Helsinki and was approved by the institutional review board of the Leiden University Medical Center.

Continuous data were described by medians and ranges, and categorical data by the number of observations and percentages (%). Rates were calculated for the available data in individual categories. Chi-square, Mann-Whitney U, or unpaired t-test were performed to compare independent variables between patients receiving treatment or not. A Kaplan-Meier analysis was performed to analyse the progression-free survival from the first consultation till progression. No formal sample size calculation was performed. Due to

the low incidence rate of D-TGCT all eligible patients were included. IBM Statistical Package for Social Statistics 25 (Chicago, IL, USA) was used for analysis.

Results

Between January 2000 and December 2019, sixty-one D-TGCT patients without prior treatment at one of the participating sarcoma centres which were managed by active surveillance. The mean age was 46 years, and almost two-thirds were female (Table 1). The majority of patients were recruited in the Netherlands and had their primary consultation in one of the sarcoma centres between 2015 and 2019 (n = 36; 59%). The knee was the most affected joint (79%), followed by the hip (10%) and ankle (7%). TGCT was histologically confirmed in 33 patients (54%), while other patients had the diagnosis based on their radiological and clinical presentation (Table 1).

Table 1. Patient demographics of therapy naïve D-TGCT patients managed by active surveillance

Features	**N = 61**
Mean age at first consultation, years (SD)	46 (±16.2)
Gender (%)	
Female	37 (61)
Male	24 (39)
Patients per country (%)	
Netherlands	33 (54)
United States of America	14 (23)
Italy	10 (16)
Canada	4 (7)
Date first consultation (%)	
2000-2004	2 (3)
2005-2009	3 (5)
2010-2014	20 (33)
2015-2019	36 (59)
Affected joint (%)	
Knee	48 (79)
Hip	6 (10)
Ankle	4 (7)
Shoulder	1 (2)
Elbow	1 (2)
Foot	1 (2)
Histologically confirmed (%)	
Yes	33 (54)
No	24 (39)
Unknown	4 (7)

SD Standard deviation

Fifty-nine patients had an MRI performed at a median of one month around the first consultation. The tumour was located intra-articular in almost all patients (95%), while extra-articular D-TGCT was only present in a quarter of this cohort (Table 2). Furthermore, the involvement of ligaments, muscle/tendons, and bone were common, but none of the patients had neurovascular involvement. Osteoarthritis was observed in thirteen patients and was treated conservatively. While eight patients (13%) were asymptomatic, most patients experienced symptoms, particularly pain and swelling (Table 2). Twelve patients (21%) chronically used analgesics, mainly non-steroidal anti-inflammatory drugs (NSAIDs).

Table 2. Radiological and clinical presentation at first consultation of D-TGCT patients managed by active surveillance.

Features	
MRI performed around first consultation	N = 59
Months before or after baseline, median (IQR)	1 (0 – 2)
Tumour extent* (%)	
Intra-articular	56 (95)
Extra-articular	14 (24)
Ligament involvement	18 (31)
Muscle/tendon involvement	12 (20)
Bone involvement	10 (17)
Neurovascular involvement	-
Osteoarthritis	13 (22)
Symptoms at first consultation* (%)	N = 61
Pain	43 (70)
Swelling	33 (54)
Stiffness	9 (15)
Limited function	8 (13)
None	8 (13)
Chronic analgesics (%)	N=60
Acetaminophen	1 (2)
NSAIDs	10 (17)
Opioids	-
Other	1 (2)

** The sum of observations can be more than total; IQR Interquartile range; NSAID Non-steroidal anti-inflammatory drugs*

Follow-up data was missing for three patients and the median follow-up was 28 months (range 3–262 months). During active surveillance, 21 patients (36%) had radiological progression after a median of 21 months (Table 3). The median progression-free survival time was 49 months (Figure 1). Of 45 patients without osteoarthritis at the first consultation, eight (18%) developed radiological signs of joint degeneration. Clinically, 21 patients (37%) deteriorated, while most patients remained stable (n = 25; 43%)

or improved (n = 12; 21%) under active surveillance. Eighteen patients required a TGCT-related treatment after a median of 21 months, mainly (n = 14; 78%) consisting of surgery.

Table 3. Follow-up of D-TGCT patients managed by active surveillance

Features	N = 58
Median follow-up, months (IQR)	28 (14 – 61)
Radiological progression (%)	
Yes	21 (36)
No	32 (55)
Unknown	5 (9)
Months till radiological progression, median (IQR)	21 (10 – 45)
Developed osteoarthritis on MRI ¶ (%)	N = 45
Yes	8 (18)
No	34 (76)
Unknown	3 (7)
Clinical change (%)	
Worsened	21 (36)
Stable	25 (43)
Improved	12 (21)
Months till clinical worsening, median (IQR)	16 (10 – 31)
Months till clinical improvement, median (IQR)	9 (6 – 13)
Indication for TGCT-related treatment? (%)	
No	40 (69)
Yes	18 (31)
Synovectomy	14
Systemic therapy	1
Prosthesis	2
Amputation	1
Months to treatment, median (IQR)	21 (13-39)

IQR Interquartile range; ¶ Of patients not having osteoarthritis at baseline

Subgroup analyses

Baseline characteristics such as age, gender, tumour extent or symptoms did not significantly differ between patients who underwent a TGCT-related treatment and those who remained on active surveillance (Table 4). However, radiological progression and clinical deterioration were significantly more frequent for patients undergoing treatment (Table 4). Also, the median follow-up was significantly longer for patients receiving treatment, which may be attributed to the fact that they required more frequent visits and longer follow-up after their treatment. The median months to treatment was 21 months (interquartile range 13–19 months).

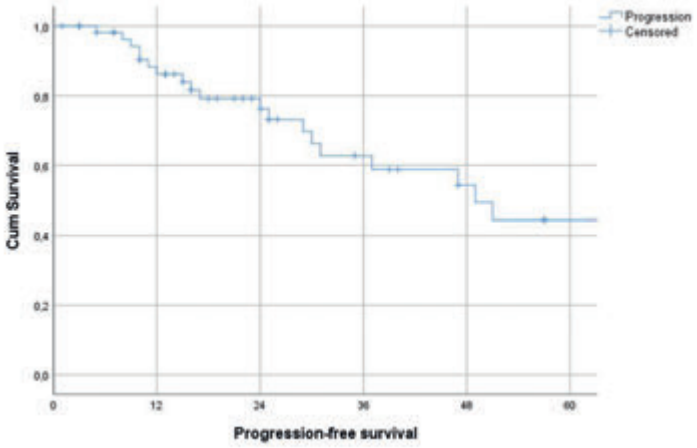

Figure 1. Progression-free survival of D-TGCT patients managed by active surveillance.

Table 4. Stratification of D-TGCT patients receiving treatment after active surveillance.

Features	No treatment N = 40	Received treatment N = 18	P-value
Mean age, years (SD)	47 (±17)	43 (±16)	0.380
Gender			
Female	24	12	0.628
Male	16	6	
Tumour extent			
Intra-articular			
Yes	36	17	0.577
No	4	1	
Extra-articular			
Yes	8	6	0.272
No	32	12	
Osteoarthritis	9	4	0.981
Yes	31	14	
No			
Symptoms			
Pain			
Yes	28	13	0.863
No	12	5	
Swelling			
Yes	23	10	0.890
No	17	8	
None	5	2	

Features	No treatment N = 40	Received treatment N = 18	P-value
Radiological progression			
Yes	9	12	0.004
No	26	6	
Degenerative change	N = 28	N = 14	
Yes	4	4	0.266
No	24	10	
Clinical change			
Worsened	5	16	<0.0001
Stable/Improved	35	2	
Median follow-up, months (IQR)	23 (13 – 49)	58 (22 – 93)	0.017

Discussion

Most patients with diffuse-type TGCT are treated by surgery, but due to the extensive tumour growth, surgery may result in iatrogenic morbidity. Some patients are managed with active surveillance since D-TGCT occasionally may have an indolent course of disease (22). However, data regarding the natural course of disease and outcomes with active surveillance are lacking (21). This study is the first to retrospectively analyse outcomes of treatment-naïve patients with D-TGCT initially managed by active surveillance in tertiary referral centres. Around a third of the patients in this cohort showed radiological progression (36%) and required treatment (31%) during follow-up. The majority of patients remained on active surveillance policy with an acceptable clinical complaint profile or did not require longer follow-up because they improved while being on active surveillance.

Radiologically, almost all patients had tumours located intra-articularly, while extra-articular localisation and involvement of other tissues were less common. Although thirteen patients already had osteoarthritis present and diagnosed at the first consultation, a conservative approach was still indicated. Clinically, only eight patients did not experience any TGCT-related symptoms at the first consultation. In the other cases (87%), patients did have TGCT-related symptoms, mainly pain and/or swelling, but this did not initially result in an indication for active treatment. Possibly the symptoms did not interfere with daily activities, but unfortunately, we could not measure the severity of symptoms by patient-reported outcomes measurements (PROMs) due to the retrospective design. Chronic analgesics were used in twelve patients (21%), mainly NSAIDs. NSAIDs are reported to significantly improve physical functioning while having a relatively safe toxicity profile (23). There was no opioid use in this cohort.

During the surveillance of therapy naïve D-TGCT patients, most had no radiological progression (55%). No MRI was performed in five patients during follow-up; therefore, it remains unknown whether they had radiological progression. Median progression-free survival was 49 months, comparable to cohorts in which patients were treated (12). Comparatively to our results, radiologic stability was also seen in 76% of patients at 25 weeks in the placebo arm of the ENLIVEN trial (18). Although follow-up was limited in both studies, most patients remained free of disease progression. Of the 45 patients who did not have osteoarthritis at baseline, eight (18%) developed this during follow-up, of which half (n = 4, 9%) underwent surgical treatment. Thirty-seven patients (63%) clinically remained stable or even improved despite not undergoing treatment. For a disease that is localised and nonlife-threatening, the decision to treat TGCT should preferably focus on possible clinical improvement and not solely on tumour removal. Surgery can result in joint stiffness and surgery-related complications, while systemic therapy may cause significant adverse effects.

When therapy naïve patients visit a tertiary sarcoma centre's outpatient clinic, active surveillance may be considered as first-line treatment for asymptomatic and mildly symptomatic patients (12). TGCT can behave indolent (even in the setting of diffuse presentations), and as our results demonstrate, radiological and/or clinical progression does not occur in the majority of patients. For symptomatic patients, active surveillance can be considered when surgery would be associated with a high risk of iatrogenic morbidity due to the extensive tumour growth or specific tumour localisation, when then the risks of systemic therapies do not outweigh the benefits or when symptoms are acceptable and do not interfere with their daily lives. The decision for active surveillance needs to be discussed in a multidisciplinary tumour board with experience with this rare tumour and the final treatment decision should be made through shared-decision making (12, 24). If active surveillance is chosen as a treatment approach, the authors broadly agree that the follow-up scheme needs to be individualised and depends on the affected joint, growth into surrounding tissues, bone and cartilage involvement, and severity of symptoms. Based on our experience, we advise that patients should undergo an MRI scan at baseline and an additional scan if they clinically deteriorate. In cases where D-TGCT remains stable in the first years, patients may be advised to return only on indication and not require longer routine follow-up. Furthermore, active surveillance includes conservative treatments such as physical therapy and the use of analgesics such as NSAIDs (25). Physicians need to explain that deciding to active surveillance may lead to the development of secondary osteoarthritis, and must also realise that a conservative treatment approach may lead to uncertainty and anxiety in some patients (26).

After the initial surveillance period, 31% of the patients underwent treatment. Surgery was most common, underlining surgery as the index treatment of choice. Two patients received a joint arthroplasty due to osteoarthritis, which was already present around the first consultation but progressed under active surveillance. One patient underwent amputation of the forefoot after first having a histologically proven Non-Hodgkins lymphoma of the foot treated by radiotherapy, later followed by a histologically proven D-TGCT of the foot. This patient was asymptomatic for approximately eight years until symptoms increased. Only one patient received anti-CSFR1 systemic treatment, which may result from systemic therapies not being widely available during the dates of inclusion for this retrospective study. Pexidartinib is approved by the Food and Drugs Authorization in the United States of America (USA) (27). However, it is not available outside of USA and for risks of serious and potentially fatal liver injury pexidartinib might be prescribed only to patients without liver comorbidities under a Risk Evaluation and Mitigation Strategy (REMS) safety program. Until now, no systemic agent is yet approved for TGCT by the European Medicines Agency, not even pexidartinib due to its uncertain risk-benefit ratio (28). Other experimental systemic therapies are under investigation and are now used when, surgical removal of D-TGCT is associated with major morbidity (12, 19, 29).

Limitations

At first, only therapy naïve patients managed by active surveillance and who did not undergo another treatment initially were included in this study. Since these patients were all retrospectively included, this has likely introduced selection bias by selecting patients that probably had less severe presentations of D-TGCT and experienced mild symptoms and resulting in a lower generalizability. This may have also led to the inclusion of more female patients compared to other cohorts. Although we are aware of this major limitation, this study aimed to describe the presentation of this subset of patients at the first consultation and the course of disease under active surveillance in patients eligible for this approach.

Secondly, TGCT was not histologically confirmed in all patients due to a conservative approach. Although TGCT is often diagnosed by its radiological and clinical presentation, especially differentiating between the localised- and diffuse-type, this may have introduced false positive diagnoses. As all patients were diagnosed and treated by experienced multidisciplinary teams in tertiary sarcoma centres this possible risk for misdiagnosis is regarded limited.

Thirdly, this study had a limited median follow-up, which makes it difficult to assess the long-term effect of active surveillance. For example, perhaps more patients will experience radiological progression and/or clinical deterioration and require treatment. Contrarily,

if patients remain radiologically and clinically stable, they are pragmatically often told to return only when D-TGCT related symptoms increase, resulting in a lack of long-term follow-up data.

Finally, due to the study's retrospective design, no centralised assessments were used for scoring radiological progression, degenerative change, or PROMs were scored based on patient's medical records and are potentially biased by inconsistent documentation by physicians. Therefore, future prospective studies should include validated radiological and clinical assessments.

Conclusion

Active surveillance can be considered an acceptable and safe approach for a large subgroup of therapy naïve D-TGCT patients. Almost two-thirds of the patients remained progression-free, most did not undergo active treatment, and some patients even improved under active surveillance. Furthermore, the median progression-free survival is comparable to cohorts in which patients were treated. On the other hand, one-third of the patients eventually did get treatment and one-fifth developed secondary osteoarthritis. The decision for active surveillance must be made by shared-decision making and requires an individualised follow-up scheme.

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Chapter 5

Management of tenosynovial giant cell tumour of the foot and ankle

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Abstract

Background

Tenosynovial giant cell tumour (TGCT) is one of the most common soft-tissue tumours of the foot and ankle and can behave in a locally aggressive manner. Tumour control can be difficult, despite the various methods of treatment available. Since treatment guidelines are lacking, the aim of this study was to review the multidisciplinary management by presenting the largest series of TGCT of the foot and ankle to date from two specialised sarcoma centres.

Methods

The Oxford Tumour Registry and the Leiden University Medical Centre Sarcoma Registry were retrospectively reviewed for patients with histologically proven foot and ankle TGCT diagnosed between January 2002 and August 2019.

Results

A total of 84 patients were included. There were 39 men and 45 women with a mean age at primary treatment of 38.3 years (9 to 72). The median follow-up was 46.5 months (interquartile range (IQR) 21.3 to 82.3). Localised-type TGCT (n = 15) predominantly affected forefoot, whereas diffuse-type TGCT (D-TGCT) (n = 9) tended to panarticular involvement. TGCT was not included in the radiological differential diagnosis in 20% (n = 15/75).

Most patients had open rather than arthroscopic surgery (76 vs 17). The highest recurrence rates were seen with D-TGCT (61%; n = 23/38), panarticular involvement (83%; n = 5/8), and after arthroscopy (47%; n = 8/17). Three (4%) fusions were carried out for osteochondral destruction by D-TGCT. There were 14 (16%) patients with D-TGCT who underwent systemic treatment, mostly in refractory cases (79%; n = 11). TGCT initially decreased or stabilised in 12 patients (86%), but progressed in five (36%) during follow-up; all five underwent subsequent surgery. Side effects were reported in 12 patients (86%).

Conclusion

We recommend open surgical excision as the primary treatment for TGCT of the foot and ankle, particularly in patients with D-TGCT with extra-articular involvement. Severe osteochondral destruction may justify salvage procedures, although these are not often undertaken. Systemic treatment is indicated for unresectable or refractory cases. However, side effects are commonly experienced, and relapses may occur once treatment has ceased.

Introduction

Tenosynovial giant cell tumour (TGCT), formerly known as pigmented villonodular synovitis (PVNS) or giant cell tumour of tendon sheath (GCT-TS), is a rare neoplasm which affects joints, tendon sheaths, and bursae (1). It is one of the most common soft-tissue tumours of the foot and ankle (2). Despite being a benign tumour, TGCT can be locally aggressive. This may have a serious impact on function and quality of life in the relatively young population it affects, most of whom are in the fourth and fifth decades of life (3, 4). Nonspecific symptoms, such as pain, swelling, stiffness, and limited range of motion, often lead to diagnostic delay (5).

TGCT consists of two subtypes with different clinical and radiological presentations, localised-type (L-TGCT) and diffuse-type (D-TGCT) (1). L-TGCT describes a solitary intra- or extra-articular nodule (Figures 1a and 1b), mainly around the digits, while D-TGCT is characterised by extensive intra-articular disease, frequently with extra-articular spread (Figures 2a and 2b), commonly within large joints (1, 4). The diagnosis and distinction between the two subtypes are primarily made by MRI. On MRI, TGCT is often characterised by synovial proliferation, joint effusion, and haemosiderin deposits. D-TGCT arising in smaller capacity joints, such as the foot and ankle, is associated with bony involvement probably due to increased joint pressure (6).

The standard first-line treatment is surgical excision, carried out either open or arthroscopically. Reported recurrence rates vary between 12% for L-TGCT and 44% for D-TGCT for all joints (7, 8). Repeated and invasive surgery may result in iatrogenic morbidity. Salvage procedures, such as arthrodesis, (tumour) prosthesis, or amputation, are a last resort in cases of severe osteochondral destruction. To lessen recurrence rates, (neo)adjuvant external beam radiation therapy and radiosynoviorthesis can be considered, but their benefit is not validated for foot and ankle disease as only small series have been reported in the literature (9). Radiotherapy is also related to adverse events such as fibrosis, joint stiffness, skin necrosis, and an increased risk for radiation-induced sarcoma (10, 11).

A progressive understanding of TGCT pathogenesis has shown that TGCT is driven by the deregulated expression of colony-stimulating factor (CSF), leading to an increase in neoplastic cells and the additional recruitment of inflammatory cells (12). Recent studies show promising results for different CSF1 receptor (CSF1R) antagonists, either tyrosine kinase inhibitors (TKI) (e.g. imatinib, nilotinib, and pexidartinib) or CSF1R antibodies (e.g. cabiralizumab, emactuzumab) (13-16). CSF1R antagonists have strong activity against the CSF pathway but can cause side effects ranging from the more common adverse events (e.g. nausea, fatigue, and fluid retention) to serious adverse events (e.g. hepatotoxicity) (15).

Figure 1. Localised-type TGCT

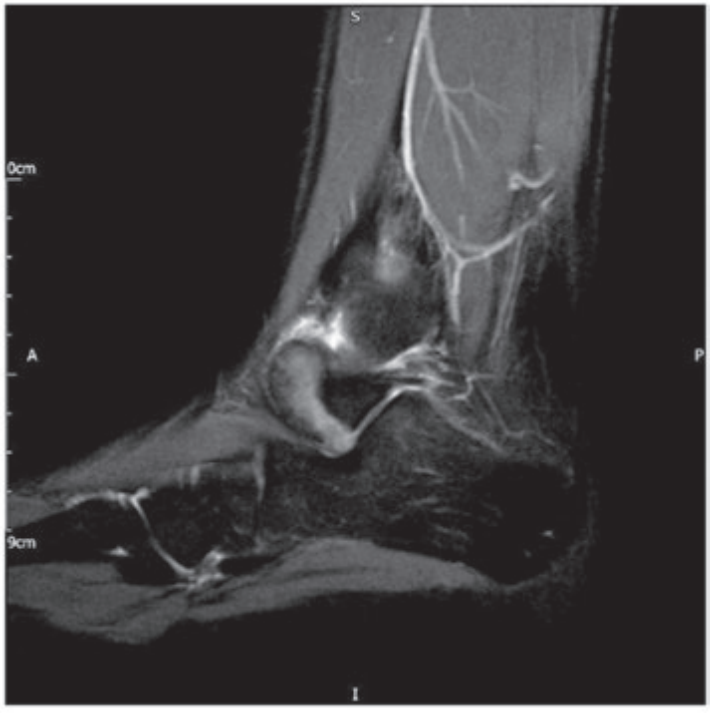

Figure 1a: Sagittal T2 MRI image showing a well-circumscribed lesion in the subtalar joint, presenting localised-type TGCT.

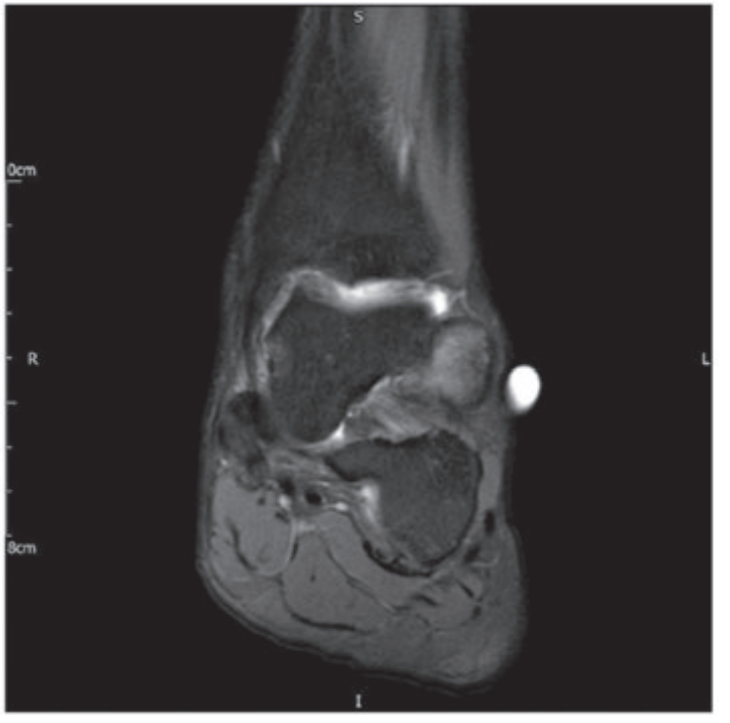

Figure 1b: Coronal T2 MRI images showing a well-circumscribed lesion in the subtalar joint, presenting localised-type TGCT. The white spot indicates the location where the patient experiences most complaints

Figure 2. Diffuse-type TGCT

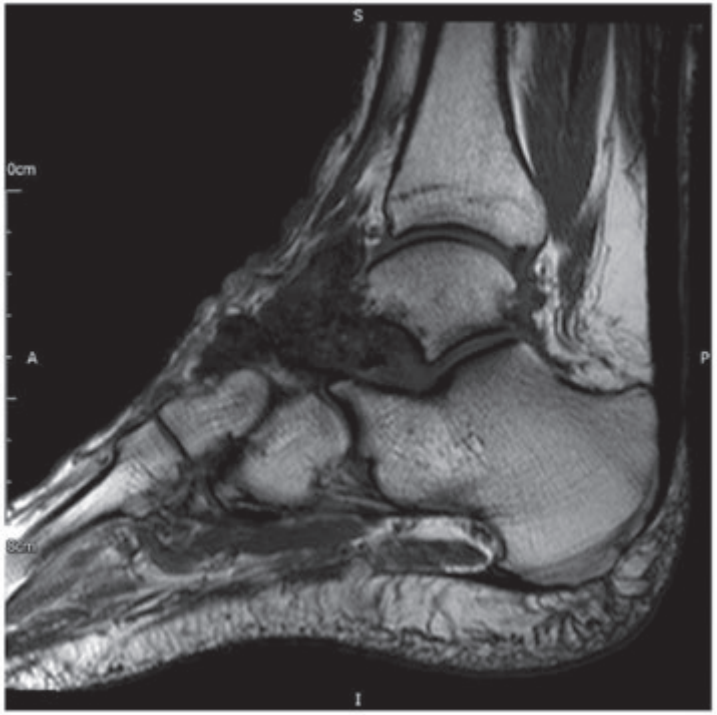

Figure 2a: Sagittal T1 MRI scan showing diffuse-type TGCT, affecting the ankle joint. Characteristic TGCT blooming effect is seen, attributed to scattered areas of low signal intensity, which is typical for iron deposition.

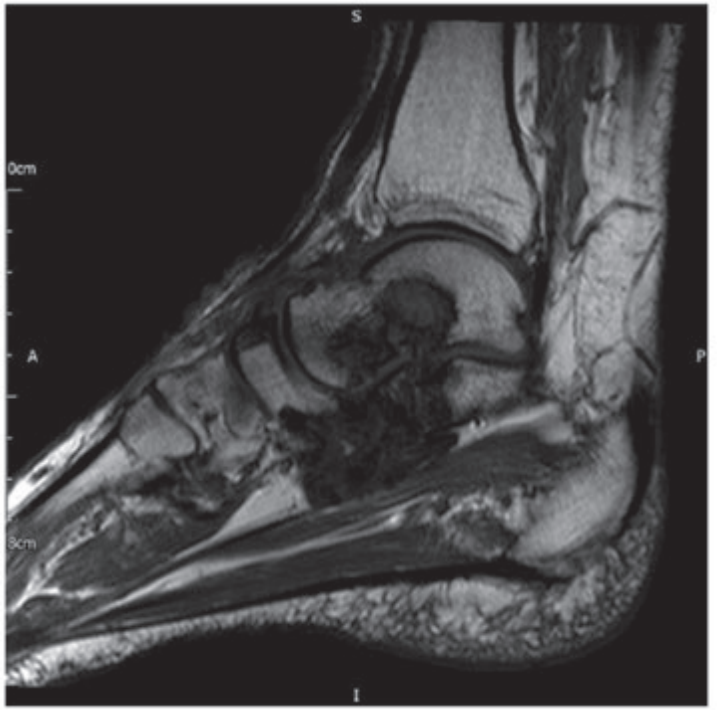

Figure 2b: Sagittal T1 MRI scan showing diffuse-type TGCT, affecting the subtalar joint. Characteristic TGCT blooming effect is seen, attributed to scattered areas of low signal intensity, which is typical for iron deposition.

Although a wide range of treatment methods are available, tumour control can be hard to achieve in a number of patients, and therefore there is a need for consensus treatment guidelines. To our knowledge, the current literature lacks a large series of foot and ankle TGCT, and the effect of different systemic treatments on foot and ankle TGCT has not been described in a single study (9). This study aims to provide treatment guidance by retrospectively reviewing the multidisciplinary management of TGCT by foot and ankle surgeons, oncological orthopaedic surgeons, and sarcoma oncologists in two specialised sarcoma centres. We present the largest series to date of TGCT affecting the foot and ankle.

Material and Methods

The Oxford Tumour Registry and Leiden University Medical Centre (LUMC) Sarcoma Registry were retrospectively reviewed to identify cases of TGCT affecting the foot and ankle between January 2002 and August 2019. Approval was given by the Committee for Medical Ethics (CME) of Leiden University Medical Center (LUMC) (G19.127). A total of 84 patients were included in the study, all with histologically confirmed TGCT in the foot and/or ankle.

The age of the patients at the time of presentation to hospital, their sex, joint affected, histology, clinical features, operative intervention, adjuvant use of systemic treatments, and recurrent events were recorded. The foot and ankle were subdivided into three anatomical regions; the hindfoot, midfoot, and forefoot. The hindfoot consisted of the talus and calcaneus, including the ankle joint; the midfoot of the cuboid, navicular, and cuneiform bones; and the forefoot of the metatarsals and phalanges. The ankle was subdivided into four anatomical areas: anterior, posterior, anterior and posterior, and syndesmosis. When three or more joints were involved, the anatomical location was referred to as panarticular. Recurrence was defined as the presence of new tumour after macroscopic surgical removal. Disease progression was defined as radiological progression or clinical worsening on systemic therapies.

If the diagnosis was uncertain, ultrasound- or CT-guided biopsies were undertaken prior to treatment. TGCTs found incidentally were listed as separate surgical interventions because the incisions and approaches used were based on the planned procedure. Arthroscopy was classified as ‘single portal’ meaning anterior arthroscopy or ‘dual portal’, where anterior and posterior portals were used. Arthroscopy and ankle and subtalar fusions were carried out by foot and ankle surgeons, and the other procedures by sarcoma surgeons. Systemic treatment was administered by oncologists after multidisciplinary team consultation and

as part of a clinical trial. Specific drugs were used in active clinical trials at the specific time indicated. The clinical trials did not all take place simultaneously.

Descriptive analyses were performed in this study. Continuous data were described by means and ranges or medians and interquartile ranges (IQR), and categorical data by the number of observations and percentages. Percentages were calculated for individual categories, excluding missing data.

Results

A summary of the patients' demographic data is given in Table 1, and the anatomical locations affected shown in Table 2. There were 84 patients with a slight female predominance (n = 45; 54%) . The mean age of patients at primary treatment was 38.3 years (9 to 72), and their median follow-up 46.5 months (IQR 21.3 to 82.3). A total of 44 patients had L-TGCT (52%): 40 (48%) had D-TGCT. The forefoot was predominantly affected by L-TGCT (n = 15). Panarticular involvement only occurred in patients with D-TGCT (n = 9).

Table 1. Summary of demographic patient data

Features	**n = 84**
Mean age at presentation [years] (range)	38.3 (9 – 72)
Gender (%)	
Male	39 (46)
Female	45 (54)
Median follow-up [months] (IQR)	46.5 (21.3 – 82.3)
TGCT disease type (%)	
Localised	44 (52)
Diffuse	40 (48)

IQR Interquartile range, TGCT Tenosynovial Giant Cell Tumour

Table 2. Anatomical locations affected by TGCT

Location*	Localised	Diffuse
Pan-articular		9
Hindfoot		
Ankle (whole)	6	14
Anterior only	6	2
Posterior only	1	1
Syndesmosis only	1	2
Sinus Tarsi	4	3
Subtalar joint	4	4
Peroneal tendons		4
Tibialis posterior	3	
Lateral malleolus	1	
EDL		1
Midfoot		
Os cuboid	1	
Cuneonavicular joint	1	
TMTJs		1
1st & 2nd	3	
5th	1	
Forefoot		
MTPJs		3
2nd	2	
3rd	4	
4th & 5th	2	1
FDL		2
1st and 2nd	2	
FHL	1	2
EDL		1
2nd toe	1	
5th toe	1	
5th PIPJ	1	
1st webspace	1	

TMTJ tarsometatarsal joint, MTPJ metatarsalphalangeal joint, FDL flexor digitorum longus, FHL flexor hallucis longus, EDL extensor digitorum longus, PIPJ Proximal interphalangeal joint
**The sum of all affected locations can be more than the included 84 cases since TGCT can affect multiple locations.*

Preoperative imaging

Three patients did not have an MRI before surgical intervention as TGCT was an incidental finding (Table 3). Of the remaining 81 cases, 75 had available accompanying radiology reports. A total of 60 patients had MRI reports that included TGCT (or PVNS) as the main differential diagnosis. The remaining 15 patients (20%) had differential diagnoses that included soft tissue mass (n = 3), ganglion (n = 3), synovial sarcoma (n = 2), vascular lesion, possible malignancy, osteoarthritis with associated tenosynovitis, old haematoma, fibromatosis, synovial haemangioma, or no lesion identified.

Table 3. Surgical interventions, complications and recurrence

Features	Localised	Diffuse
Any type of surgery	44	38
> 1 surgery	3	14
Surgical intervention*		
Open synovectomy	37	39
Arthroscopy		
Single (anterior) portal	6	5
Dual portal	1	5
(Subsequent) ankle fusion		2
(Subsequent) subtalar fusion		1
Partial amputation toe		1
Found incidentally	4	
Triple fusion for Charcot foot reconstruction	1	
Subtalar joint fusion	1	
Tarsometatarsal joint fusion	1	
Debridement of an osteophyte	1	
Complications	5	4
Achilles tendinopathy	2	
Paraesthesia excision scar	1	1
Sensibility loss medial aspect foot	1	
Complex regional pain syndrome		1
Post-operative wound infection		1
Prolonged ankle stiffness	1	
Luxation peroneal tendon		1
Recurrence	4	23
Median duration till recurrence [months] (IQR)	84.5 (23.8 – 174.0)	25 (13.0 – 39.5)

IQR Interquartile range
**Sum of all interventions can be more than total since multiple procedures per patients could be performed*

Surgical management

Surgical excision was most commonly carried out open regardless of the subtype: dual portal arthroscopy was predominantly used for cases of D-TGCT (Table 3). Eight patients (10%) underwent three or more operative interventions, seven of whom had D-TGCT. L-TGCT was incidentally found four times (9%) (Table 3). Two patients did not undergo any surgical intervention, and were treated systemically.

Recurrences occurred in 23 patients with D-TGCT (n = 23/38; 61%) and four (n = 4/44; 9%) with L-TGCT, after a median of 25 (IQR 13.0 to 39.5) and 84.5 (IQR 23.8 to 174.0) months, respectively. Of these, 18 D-TGCT recurrences (78%) were managed with subsequent surgery or systemic treatment, and the rest by active surveillance.

Three recurrences of L-TGCT were treated by further surgical resection: the remaining patient did not require further surgery.

After 17 arthroscopic synovectomies, TGCT recurred on eight occasions (47%; localised n = 1/6, 17%; diffuse n = 7/11, 64%). After 76 open excisions, TGCT recurred on 27 occasions (36%; localised n = 4/37, 11%; diffuse n = 23/39, 59%). Based on anatomical location, panarticular TGCT recurred most frequently (diffuse n = 5/8; 63%), followed by TGCT in the hindfoot (n = 16/47, 34%; localised n = 2/23, 9%; diffuse n = 14/24, 58%), forefoot (n = 5/20, 25%; localised n = 0/14, 0%; diffuse n = 5/6, 83%), and midfoot (n = 1/7, 14%; localised n = 1/6, 17%; diffuse n = 0/1, 0%).

Two patients had no recurrence but underwent arthroscopic ankle fusion for osteoarthritis. Radiological imaging showed complete fusion at four and eight months after surgery with good clinical outcomes. One patient underwent a subtalar fusion after two recurrences, but the joints were only partially fused one year after surgery. One further patient will be undergoing an ankle arthrodesis.

Nine complications occurred after 97 TGCT related surgeries (9%), of which seven (n = 7/76; 9%) followed open synovectomy and two (n = 2/17; 12%) after arthroscopy (Table 3). One patient required reconstruction of a luxating peroneal tendon.

Systemic therapies

Overall, 14 (16%) patients received systemic treatment for D-TGCT, consisting of imatinib, nilotinib, pexidartinib, or cabiralizumab. All except one patient received one type of CSF1R antagonist. The sole patient switched to pexidartinib after TGCT progressed on imatinib. The mean age of this patient group was 41.1 years (25 to 62), and there was an equal sex distribution. A summary of these patients and their radiological response are given in Table 4.

CSF1R antagonists were indicated in 11 patients (79%) for recurrences or persistent symptoms after previous surgery. Two patients received imatinib as primary treatment because surgery was associated with a high risk of iatrogenic morbidity: one patient was given it as a neoadjuvant prior to surgery. The dose and duration of therapy varied, depending on clinical response and adverse events. Nilotinib was given as a neoadjuvant prior to surgery in study design for the maximum length of one year.

Imatinib

Eight patients (57%) received imatinib. Tumour volume decreased radiologically in four cases, stabilised in two and progressed in two. Six patients had a good clinical response: one

patient reported an increase in pain, and data for one patient was missing. Common adverse events were nausea, vomiting, and fatigue: one patient reported no adverse events at all. Four patients continued to receive imatinib at time of data collection: it was stopped after clinical improvement in three cases, and stopped in one patient as TGCT had progressed.

Nilotinib

Four patients (29%) received nilotinib. Tumour volume decreased in one patient and stabilised in three patients. However, in one case TGCT progressed one year after initial stabilisation. All patients responded to treatment, but pain persisted in one patient. Adverse events reported more than once with nilotinib were fatigue, headache, rash, and itch; one patient reported no adverse events. Nilotinib was stopped after 12 months as per protocol and was used as neoadjuvant prior to surgery in three patients.

Pexidartinib

Two patients received Pexidartinib, one after disease progression on imatinib. In both cases, D-TGCT stabilised. Both patients initially improved clinically, but in one patient symptoms progressed after three months. Both patients experienced hair discolouration, and one patient developed elevated liver enzymes. Worsening symptoms led to the cessation of pexidartinb in one case, and the other patient stopped it after the D-TGCT clinically improved.

Cabiralizumab

One patient received cabiralizumab which was stopped after five months. The tumour did not progress but the patient experienced no clinical improvement and suffered unacceptable itching and periorbital oedema.

TGCT progressed in five patients, in two after systemic treatment was stopped (Table 4; ID 1, 2) and in three who were still on systemic treatment (Table 4: ID 5, 8, 10). All five patients with progression went on to have further surgery. Four patients without progression were recommended to have surgery for osteochondral destruction or removal of the residual tumour—the patients were referred to other hospitals for this operation and therefore became lost to follow-up. Of the remaining patients, two are continuing to be treated with imatinib (Table 4; ID 4, 7) and three patients are being managed with watchful waiting. One of these patients has been lost to follow-up as their care has been transferred elsewhere (Table 4; ID 3).

Table 4. Summary of Dt-TGCT patients receiving CSF1R antagonists

ID	Age/ gender	Indication for CSF1R antagonist	CSF1R antagonist	Therapy length	Response tumour volume	Clinical response	Side-effects	Indication to stop	Progression
1	F / 59	Recurrence after surgery	Imatinib	Unknown	Decreased	Unknown	Yes	Stable TGCT	Yes
2	M / 62	Neo-adjuvant therapy prior to surgery	Imatinib	4 months and ongoing	Stabilised	Pain increased under Imatinib	None recorded	n/a	Yes
3	F / 55	Persistent pain despite 3 debridements	Imatinib	9 months	Decreased	Pain decreased	Yes	Stable TGCT	Lost to follow-up
4	M / 49	Recurrence after surgery	Imatinib	13 months and ongoing	Decreased	Pain decreased	Yes	n/a	No
5	M / 30	Recurrence after surgery	Imatinib	7 months and ongoing	Increased	Mild symptomatic improvement	Yes	n/a	Yes
6	F / 54	Surgery associated with high risk of morbidity	Imatinib	12 months	Decreased	Symptomatic improvement	Yes	Stable TGCT	No
7	F / 38	Surgery associated with high risk of morbidity	Imatinib	108 months and ongoing	Stabilised	Symptomatic improvement	Yes	n/a	No
8	F / 35	Recurrence after surgery	Imatinib	27 months	Increased	Symptomatic improvement	Yes	Tumour progressed	Yes
	F / 37	Progression while on Imatinib	Pexidartinib	12 months	Stabilised	Symptomatic worsening	Yes	Symptoms progressed	Yes
9	M / 33	Symptomatic residual after surgery	Nilotinib	9 months	Stabilised	Pain persisted	Yes	Neo-adjuvant before surgery	No
10	M / 27	Recurrence after surgery	Nilotinib	12 months	Stabilised	Symptomatic improvement	Yes	Neo-adjuvant before surgery	Yes
11	F / 38	Recurrence after surgery	Nilotinib	12 months	Stabilised	Pain decreased	Yes	Neo-adjuvant before surgery	No
12	M / 28	Recurrence after surgery and radiosynoviorthesis	Nilotinib	12 months	Decreased	Symptoms disappeared	None reported	Reduction TGCT	No
13	M / 47	Persistent complaints after surgery	Pexidartinib	12 months	Stabilised	Pain and swelling decreased	Yes	Stable TGCT	No
14	M / 25	Recurrence after surgery	Cabiralizumab	5 months	Stabilised	No clinical response	Yes	No clinical response and side-effects	Lost to follow-up

CSF1R Colony-stimulating factor 1 receptor, TGCT Tenosynovial giant cell tumour

Discussion

TGCT, although rare, is one of the most common soft-tissue tumours of the foot and ankle along with haemangioma, superficial fibromatosis, and schwannoma.2 Achieving tumour control is often difficult, despite the various modalities of treatment (17). Treatment guidelines are currently lacking. To the best of our knowledge, we present the largest series of patients with TGCT of the foot and ankle to date, and include the effect of different systemic therapies (9).

This study confirms that TGCT in the foot and ankle affects mostly a young, active, working population. The distribution between L-TGCT and D-TGCT is almost equal, which is unexpected given the documented incidences of 39 and 4 per million person-years, respectively (4). Mild cases of L-TGCT in the digits are not routinely treated in specialised sarcoma centres such as the Oxford University Hospitals or the Leiden University Medical Centre. This can result in underestimation of the incidence of L-TGCT.

Although not all MRIs were reported by specialised musculoskeletal radiologists, since some were carried out before referral to a specialised sarcoma centre, the initial differential diagnosis on MRI did not contain TGCT in a fifth of our cases. The differential diagnosis ranges from benign ganglion to malignant sarcoma, underlining the nonspecific clinical and radiological presentation of TGCT and a lack of disease awareness within the radiological community. This can cause diagnostic delay and unnecessary treatment (18). A correlation between the anatomical location involved in the foot and ankle and the different subtypes is seen on MRI. D-TGCT is exclusively related to panarticular involvement and most cases with involvement of the whole ankle, findings that are consistent with its locally aggressive behaviour.1 The mid- and forefoot are particularly affected by L-TGCT, as reported by Cevik et al (19).

Most patients undergo surgery, predominantly open. In line with previous research, our results show a higher recurrence rate in D-TGCT than in L-TGCT (7, 8). Recurrences occur considerably earlier in D-TGCT than in L-TGCT, with a median of 25 and 84.5 months, respectively. Several studies have compared open surgical excision to arthroscopic resection, but neither technique has been shown to be better than the other to date. Only small series of TGCT of the foot and ankle have been reported (9, 20). Our study shows a higher rate of recurrence after arthroscopic synovectomy than open synovectomy, regardless of subtype. After evaluating the largest known dataset of L-TGCT patients, Mastboom et al7 concluded that initial arthroscopy is a risk factor for recurrent disease. The use of arthroscopic surgery for D-TGCT is questioned by some, because of its limited range and extra-articular access. A combined approach may reduce the limitations of both

techniques, but more research is needed to establish this (21). Besides surgical technique, higher recurrence rates are related to site, the highest rate being in the hindfoot. Due to the complex anatomy of the hindfoot, radical resection is often impossible in cases of extensive disease, especially if undertaken arthroscopically. In this study, the margins of excision were not further analysed since synovectomy for D-TGCT is essentially an intralaesional resection.

According to Nishida et al,6 bony lesions occur in 58% of patients with TGCT of the foot and ankle and may require arthrodesis. In our cohort, only three patients (4%) had joint fusion surgery, all after synovectomy, for osteochondral destruction by invasive growth of D-TGCT in the hindfoot. Joints completely fused within eight months of surgery had a good clinical outcome: only one patient had a partial fusion of the subtalar joint. This small number of salvage procedures suggests that arthrodesis is used as a last resort, as it may limit joint movements and decrease gait efficiency, thereby restricting a young and active patient in their daily life (22). There were no cases of total ankle arthroplasty for TGCT in our cohort.

Repeated surgery may cause unacceptable iatrogenic morbidity, and therefore systemic targeted treatment is considered for recurrent or progressive disease (17). In addition, patients who have not previously undergone systemic treatment might qualify for this treatment if complete tumour excision is considered impossible due to the extent of the tumour. In our cohort, only patients with D-TGCT qualified for systemic treatment, of whom three patients were therapy-naïve. CSFR1 antagonists imatinib, nilotinib, pexidartinib, and cabiralizumab were given, often as part of clinical trials for TGCT (13-15). Our results suggest that CSFR1 antagonists can have potential benefit for patients with refractory D-TGCT whose disease is not amenable to surgery as most of these patients had good clinical responses. However, progression can still occur on, or after, stopping drug treatment. Besides, adverse events are common, and serious systemic adverse events have been reported after treatment of a local and non-malignant disease (15).

Based on our results, current literature, and the experience of two specialised sarcoma centres, we propose an algorithm for the multidisciplinary treatment of symptomatic TGCT affecting the foot and ankle (Figure 3) (23). Watchful waiting can be used for patients experiencing minimal or mild symptoms if no joint destruction is anticipated. Arthroscopy is recommended in cases of L-TGCT, where a small intra-articular nodule can be removed with relative ease. For extra-articular L-TGCT and D-TGCT, we suggest open synovectomy, in order to have a better view of the tumour and better access for its removal. Revision surgery is indicated for patients with recurrent TGCT, as long as this does not cause greater iatrogenic morbidity or additional joint damage.20 CSF1R antagonists

are indicated for tumours not amenable to surgery: this results in stabilisation of the disease and relief of symptoms in most patients (17). Although most systemic treatment is still administered as part of a clinical trial and is not yet widely available, it should be considered when accessible. To date, only pexidartinib is FDA-approved in the USA, but other systemic treatments have shown encouraging results (13-16, 24). Radiotherapy can be considered in severe cases of TGCT or in patients who are not eligible for systemic treatment (25). It may, however, cause serious complications such as skin necrosis, joint stiffness, and even an increased risk of malignant radiation-induced sarcoma.10,11 The authors believe that the risk of malignant change after radiotherapy needs very careful consideration in such cases given the benign nature of TGCT.

The authors acknowledge the limitations of this study due to its retrospective design. Data are drawn from just two specialised sarcoma centres, which can result in an overestimation of the number of severe D-TGCT cases and limits generalizability. Due to its retrospective design, standardised description of symptoms, complications or side effects are lacking and data were occasionally missing. Also, data on a heterogeneous group of CSF1R antagonists (either TKIs or antibodies) are presented, with a small number of patients per treatment and subsequent additional treatments. Therefore, the effect of specific CSF1R antagonists cannot be truly assessed. It is, however, the largest cohort study of its kind, describing the pragmatic management of an unusual condition that poses many challenges to the clinician. We believe that systemic treatment for TGCT of the foot and ankle needs more research for patients who are not amenable to surgery.

Although L-TGCT can be treated by surgery alone, we recommend a multidisciplinary treatment for patients with severe L-TGCT and all cases of symptomatic D-TGCT of the foot and ankle. This should involve surgeons (both foot/ankle and sarcoma surgeons), and medical and clinical oncologists in a tertiary referral unit. The results of further trials looking at other CSF1R antagonists are awaited. D-TGCT in the foot and ankle is associated with a high risk of recurrence, significant morbidity, and a need for revision surgery. CSF1R antagonists may be a useful adjunct in the management of patients with refractory disease if well tolerated.

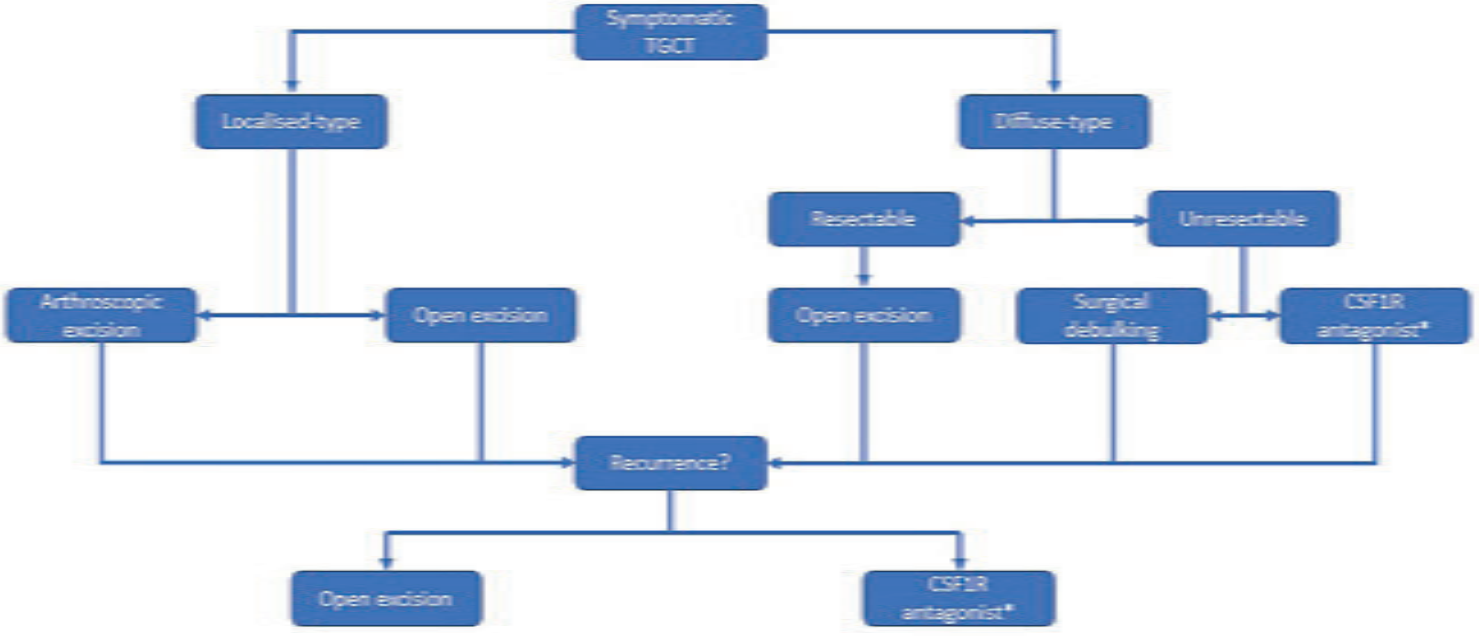

Figure 3. Multidisciplinary treatment pathway for symptomatic TGCT in the foot and ankle.
The authors do not advocate radiotherapy, due to lack of reported outcomes of radiotherapy in the foot and ankle. Radiotherapy may lead to unacceptable adverse events.
**CSF1R antagonists are not widely available yet. To date, only Pexidartinib is FDA approved in the USA, and other systemic therapies have shown encouraging results*

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Chapter 6

Surgical management of 144 TGCT patients in a single institution: a 20-year cohort study

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Abstract

Background

Surgery is the mainstay of treatment for tenosynovial giant cell tumours (TGCTs). However, achieving a cure through surgery alone remains challenging, especially for the diffuse-type (D-TGCT).

Methods

Our goal was to describe the surgical management of patients with D-TGCT related to large joints, treated between 2000 and 2020. We analysed the effect of (in)complete resections and the presence of postoperative tumour (POT) on magnetic resonance imaging (MRI) on radiological and clinical outcomes.

Results

A total of 144 patients underwent open surgery for D-TGCT, of which 58 (40%) had treatment before. The median follow-up was 65 months. One hundred twenty-five patients underwent isolated open surgeries, in which 25 (20%) patients' D-TGCT was intentionally removed incompletely. POT presence on the first postoperative MRI was observed in 64%. Both incomplete resections and POT presence were associated with higher rates of radiological progression (73% vs. 44%; Kaplan–Meier [KM] analysis $p = 0.021$) and 59% versus 7%; KM analysis $p < 0.001$), respectively. Furthermore, patients with POT presence clinically worsened more often than patients without having POT (49% vs. 24%; KM analysis $p = 0.003$).

Conclusions

D-TGCT is often resected incompletely and tumour presence is commonly observed on the first postoperative MRI, resulting in worse radiological and clinical outcomes. Therefore, surgeons should try to remove D-TGCT in toto and consider other multimodal therapeutic strategies.

Introduction

Tenosynovial giant cell tumour (TGCT) is a rare neoplasm originating from the synovium of joints, bursae, and tendon sheaths (1). Genomic rearrangement causes overexpression of colony-stimulating factor 1 (CSF1), leading to tumourigenesis (1, 2). Common symptoms are pain, swelling, stiffness, and limited range of motion (3). Although TGCT rarely metastasises and is not life-threatening, the advanced disease may significantly burden the quality of life in a relatively young patient population (4-6).

TGCT comprises two subtypes: localised-type TGCT (L-TGCT) and diffuse-type TGCT (D-TGCT), previously known as giant cell tumour of the tendon sheath and pigmented villonodular synovitis, respectively (1). L-TGCT is the most common subtype, mainly located in digits of hands and feet (7). D-TGCT predominantly affects the knee (8). Both subtypes are histologically identical but behave differently and are considered separate clinical entities (9). Subtypes are distinguished by clinical and radiological patterns, where magnetic resonance imaging (MRI) is the most discriminating imaging technique (10). L-TGCT is characterised by a small lesion, mainly located intra-articular, behaving less aggressively. D-TGCT is multilobulated, often located intra- and extra-articular and infiltrating into surrounding tissues, regularly leading to joint destruction (1).

Complete excision is the gold standard, performed either by arthroscopy or open (11). However, complete macroscopic resection can be challenging and relapse rates can be high, especially in D-TGCT (8, 12). Repeated surgery may lead to iatrogenic joint morbidity, necessitating additional nonsurgical treatments. CSF1 receptor (CSF1R) inhibitors show considerable efficacy for patients with inoperable or relapsing D-TGCT, but to date, the use of CSF1R inhibitors may be limited because of their safety profile (13-16). Therefore, surgery remains the mainstay of treatment. We report the largest cohort of surgically treated D-TGCT patients in one sarcoma centre with a relatively long follow-up. Although Palmerini et al. found incomplete macroscopic resection a risk factor for higher relapse rates, this finding was no longer significant after multivariate analysis (17). Our primary aim was to analyse the effects of the surgical intention (complete/incomplete resection) and postoperative tumour (POT) presence on radiological and clinical outcomes.

Material and Methods

Study design and participants

This study was a retrospective, observational, monocentric cohort study. Consecutive patients with D-TGCT related to the larger joints, who underwent primary surgery

between 2000 and 2020 in one sarcoma centre, were eligible for inclusion. Larger joints were defined as all joints proximal to metatarsophalangeal and metacarpophalangeal joints. TGCT was histologically confirmed in all patients by dedicated bone and soft tissue tumour pathologists.

Patients were categorised by tumour status when referred to our centre (i.e., therapy-naïve or relapsing TGCT) because patients with relapsing D-TGCT have higher risks of new relapses following surgery, as reported in the literature (8, 17). Relapsing D-TGCT at baseline was defined as progressive residual or recurrent tumour after treatment elsewhere before referral to our centre. Diagnostic arthroscopies or "whoops" procedures were not classified as TGCT treatments because they were not intentionally performed to treat TGCT. Furthermore, outcomes were stratified by the preoperative intention of the surgeons. The intention for complete resection was defined as macroscopic removal of all intra- and extra-articular lesions, while incomplete resection was defined as intentionally leaving lesions behind.

Most patients were seen by an oncological orthopaedic surgeon at first consultation in our centre. Cases of mild or severe D-TGCT, following the classification proposed by Mastboom et al., were discussed by a multidisciplinary tumour board (MDTB) to determine the optimal treatment approach if indicated (18). The preoperative surgical intentions were analysed per surgeon. Patients were seen for up to 6 weeks to evaluate their postoperative recovery, after which an MRI was protocolised approximately around 6 months after surgery in most cases. The main reason to perform an MRI is to determine the presence of POT. MRIs were deliberately not performed within the first few months after surgery because these scans are often distorted by postoperative changes making it challenging to discriminate between TGCT tissue or reactive synovitis. In some cases, MRIs were performed later or not for varying reasons, such as patients declining to undergo an MRI for financial or other personal reasons. POT presence on the first postoperative MRI comprised residual and recurrent tumours because it was not possible to discriminate between the two. Since TGCT is a non-metastasising disease, long-term follow-up may depend on the clinical presentation and additional MRIs were mainly performed when patients clinically deteriorated and occasionally to set patients at rest. This study was situated in a specialised sarcoma centre and is part of centralised sarcoma care.

Data

Demographic characteristics, TGCT presentation, treatment characteristics, and follow-up data were collected from patient records. Total follow-up concerned time from surgery until the moment of data collection. For two-stage synovectomies, defined as two synovectomies performed on different sides of a joint within 6 months, the date of

the last surgery was taken as the start of follow-up. The first postoperative MRIs were assessed on POT after surgery (interquartile range [IQR] 4–12 months). Radiological progression during follow-up was defined as considerable progression of tumour on MRI. The postoperative radiological status and progression rates were assessed for patients that underwent isolated open synovectomies. Also, clinical deterioration was measured for these patients, defined as a return to the outpatient clinic with symptomatic worsening of the affected joint after postoperative recovery. Data were collected after approval of the institutional review committee and according to the Declaration of Helsinki.

Statistical analysis

Continuous data were described using means and standard deviations or medians and IQR. Categorical variables were summarised as the number of observations and percentages. Progression-free survival (PFS) was analysed for patients undergoing solely open synovectomies using Kaplan–Meier (KM) survival method. IBM Statistical Package for Social Statistics 25 was used for analysis.

Results

Between 2000 and 2020, 144 patients with D-TGCT underwent surgery as primary treatment at our centre with a mean age of 39 years. The knee (72%) was the most affected joint. For 86 patients (60%), surgery at our centre was their first TGCT-related treatment, while 58 patients (40%) underwent surgery for relapsing TGCT, primarily treated elsewhere (Table 1). Removal of D-TGCT was solely performed open. More invasive surgeries such as joint arthroplasty, (tumour)endoprostheses, or even amputation were performed occasionally, mainly in relapsing patients (n = 9/10; 90%). (Neo)adjuvant radiotherapy was applied in seven cases (5%) (Figure 1).

Table 1. Patient demographics

Features	n = 144 (%)
Mean age at surgery (years; ±SD[a])	38.5 ± 13.6
Gender	
Female	85 (59.0)
Male	59 (41.0)
Affected joint	
Shoulder	2 (1.4)
Elbow	3 (2.1)
Wrist	7 (4.9)
Hip	11 (7.6)
Knee	104 (72.2)
Ankle	12 (8.3)
Foot	4 (2.8)
Other	1 (0.7)
Tumour status at moment of surgery	
Primary tumour	86 (59.7)
Relapsing tumour	58 (40.3)

[a]*SD Standard deviation*

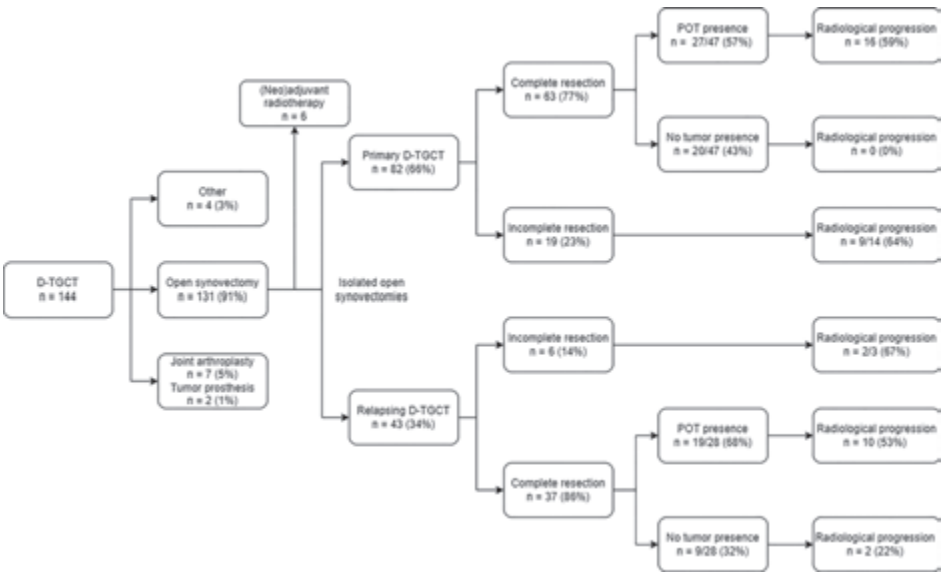


Figure 1: Flowchart of D-TGCT patients surgically treated between 2000 and 2020. D-TGCT, diffuse-type tenosynovial giant cell tumours;
One-hundred twenty-five patients (87%) were treated by isolated open synovectomies of which 100 surgeries (80%) were intended to remove all tumours macroscopically (Table 2). D-TGCT located around the knee was intentionally left behind more often than tumours affecting other joints. The surgeon performing most TGCT-related surgeries completely removed TGCT more frequently than other surgeons (Table 2). Furthermore, relapsing D-TGCT was more commonly removed in toto compared to primary tumours (Figure 1).

Table 2. Follow-up of Diffuse-type TGCT treated solely by open synovectomy[a]

Features	Planned complete resection n = 100	Planned incomplete resection n = 25	Total n = 125
Joints			
Knee	72 (78.2)	20 (21.8)	n = 92 (100)
Other joints	28 (84.8)	5 (15.2)	n = 33 (100)
Surgeons			
Surgeon 1	77 (87.5)	13 (12.5)	N = 90 (100)
Remaining surgeons	23 (66.7)	12 (33.3)	N = 35 (100)
Median follow-up [months] after surgery (IQR[b]; Q1 – Q3)	63.0 (33.3-91.3)	94.0 (42.0-103.0)	64.0 (35.5 – 95.5)
Radiological status during follow-up			
Total follow-up; ≥1 MRI	N = 85	N = 22	N = 107
Stable	48 (56.5)	6 (27.3)	54 (50.5)
Deterioration	37 (43.5)	16 (72.7)	53 (49.5)
Clinical status during follow-up	N = 100	N = 25	N = 125
Stable	67 (67.0)	13 (52.0)	80 (64.0)
Deteriorated	33 (33.0)	12 (48.0)	45 (36.0)

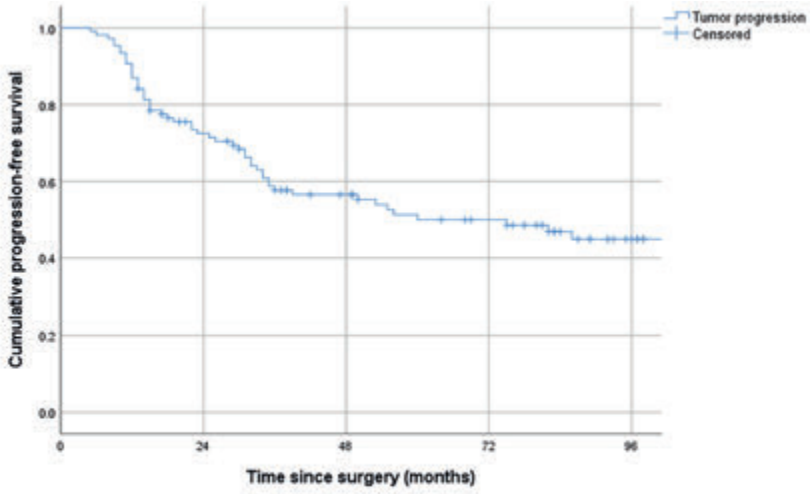
*[a]TGCT Tenosynovial Giant Cell Tumour; [b]IQR Interquartile range; [c]MRI Magnetic Resonance Imaging; [d]Confidence interval *Patients that underwent open synovectomies without any adjuvant treatment*

The median follow-up was 64 months (IQR Q1–Q3; 36–96), whereas patients with incomplete resections were followed considerably longer than patients with complete resections (Table 2). Ninety-eight D-TGCT patients (78%) had a postoperative MRI performed after a median of 6 months, of which 29 patients (30%) showed no tumour and 63 (64%) showed POT presence. Six patients (6%) already had newly emerged lesions on the first MRI performed after surgery (range 6-13 months) compared to the preoperative MRI (Table 3). Fifty-three of 107 patients (50%) with ≥1 MRI during follow-up had considerable radiological progression (Figure 2), occurring more often in patients with incomplete resections (73% vs. 44%; KM analysis logrank: $p = 0.021$) (Table 2; Figure 3). In addition, patients with POT presence on the first postoperative MRI had significantly higher chances of relapses compared to patients with no POT presence (59% vs. 7%; KM analysis logrank: $p < 0.001$) (Table 3; Figure 4). The 5-years PFS rate of patients with POT presence on the first MRI was 33% (95% confidence interval; 19%–46%).

Table 3. Follow-up of Diffuse-type TGCT treated solely by open synovectomy[a]

Features	Therapy-naïve n = 82 (%)	Relapsing n = 43 (%)	Total n = 125 (%)
Median follow-up [months] after surgery (IQR[b]; Q1 – Q3)	63.5 (36.5-95.3)	67.0 (33.0-96.0)	64.0 (35.5 – 95.5)
Radiological status during follow-up			
Median time till 1st postoperative MRI [months] (IQR[b]; Q1-Q3)	6.0 (4.0 – 11.0)	6.0 (4.0-13.0)	6.0 (4.0-12.0)
1st MRI postoperative; available MRIs[c]*	n = 63 (76.8)	n = 35 (81.4)	n = 98 (78.4)
No tumour	20 (31.7)	9 (25.7)	29 (29.6)
Tumour presence	41 (65.1)	22 (62.9)	63 (64.3)
Significant tumour progression	2 (3.2)	4 (11.4)	6 (6.1)
Total follow-up; ≥1 MRI	n = 68 (82.9)	n = 39 (90.7)	n = 107 (85.6)
Stable	37 (54.4)	17 (43.6)	54 (50.5)
Deterioration	31 (45.6)	22 (56.4)	53 (49.5)
Relapses per tumour status on 1st MRI postoperative			
No tumour	n = 20	n = 9	n = 29
No relapse	20 (100)	7 (77.8)	27 (93.1)
Relapse	0 (0)	2 (22.2)	2 (6.9)
Residual tumour	n = 41	n = 22	n = 63
No relapse	16 (39.0)	10 (45.5)	26 (41.3)
Relapse	25 (61.0)	12 (55.5)	37 (58.7)
Clinical status during follow-up	n = 82 (100)	n = 43 (100)	n = 125
Stable	54 (65.9)	26 (60.5)	80 (64.0)
Deteriorated	28 (34.1)	17 (39.5)	45 (36.0)

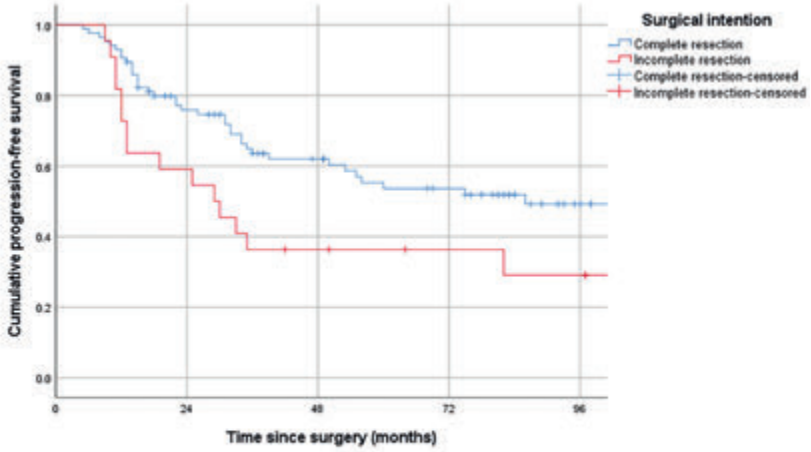
*[a]TGCT Tenosynovial Giant Cell Tumour; [b]IQR Interquartile range; [c]MRI Magnetic Resonance Imaging; [d]Confidence interval *Patients that underwent open synovectomies without any adjuvant treatment*



Years since surgery	0	2	4	6	8
Number at risk	107	71	47	36	17

Figure 2

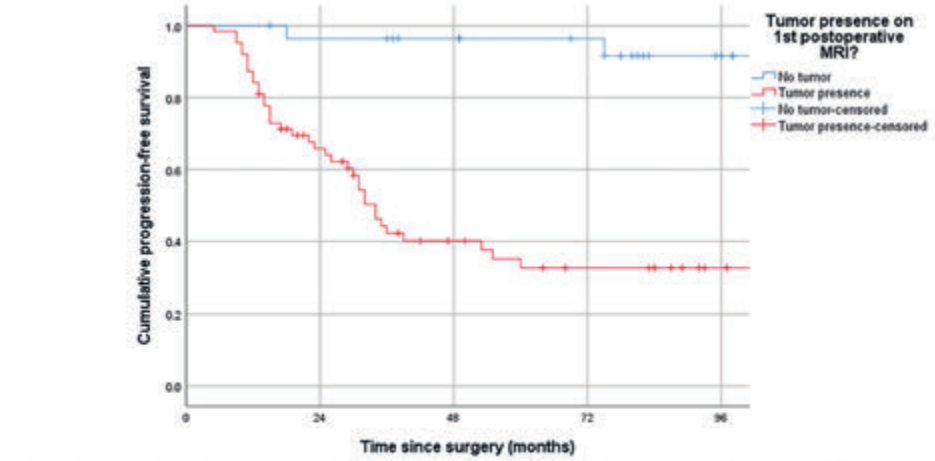
Progression-free survival curve and survival table of D-TGCT patients with ≥1 MRI (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumours; MRI, magnetic resonance imaging.



Years since surgery	0	2	4	6	8
Number at risk					
Complete	85	62	40	30	13
Incomplete	22	13	7	5	4

Figure 3

Progression-free survival curves and survival table of D-TGCT patients, stratified on preoperative surgical intention (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumours.

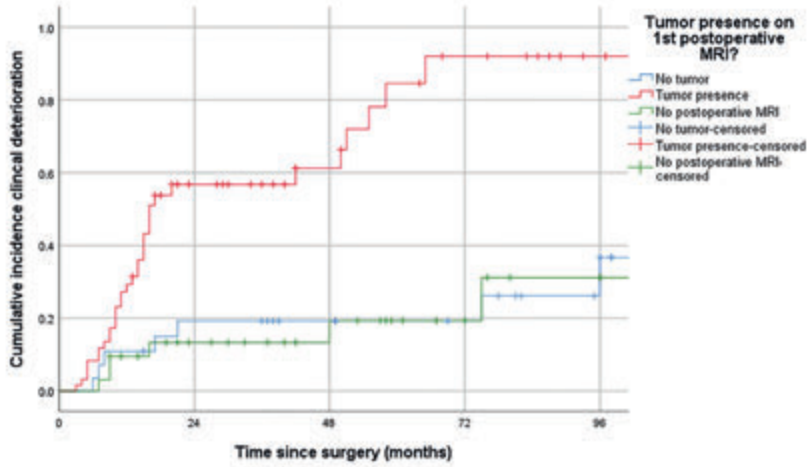


Years since surgery	0	2	4	6	8
Number at risk					
No tumor	29	27	24	20	12
Tumor presence	63	36	17	11	4

Figure 4

Progression-free survival curves and survival table of D-TGCT patients, stratified on tumour presence of first postoperative MRI (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumours; MRI, magnetic resonance imaging.

Besides radiological progression, D-TGCT clinically deteriorated in 47 of 125 patients (38%) treated by isolated open synovectomies, of which in 23 cases (49%) before radiological progression was observed. POT located extra-articular resulted less often in clinical deterioration compared to D-TGCT located intra-articular with or without extra-articular involvement (n = 8/21; 38% vs. n = 33/59; 56%). Further analysis of clinically deteriorated patients showed that 10/47 patients (21%) had no radiological progression. Contrastingly, radiological progression did not lead to clinical worsening in 16/60 patients (27%). Also, patients with POT presence on the first postoperative MRI clinically worsened more often than patients with no POT on MRI or patients without an MRI performed (49% vs. 24% vs. 21%; KM logrank: p = 0.003) (Figure 5).



Years since surgery	0	2	4	6	8
Number at risk					
No tumor	29	23	19	15	10
Tumor presence	63	30	20	12	5
No MRI	33	23	17	10	6

Figure 5

Cumulative incidence curves and survival table of D-TGCT patients that clinically worsened, stratified on first postoperative MRI status (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumours; MRI, magnetic resonance imaging.

Complications

Complications occurred relatively frequently in all patients treated by surgery (n = 22; 15%). Superficial wound infection was most common, all cured with oral antibiotics (Table 4). Septic arthritis occurred twice in the knee, necessitating arthroscopic lavage and intravenous antibiotics. Impaired wound healing only occurred after posterior synovectomies of the knee but required no further treatment in any of these patients. Joint stiffness occurred twice: after total knee arthroplasty and after open synovectomy of the knee.

Table 4. Surgery related complications

Features	Diffuse-type n = 144 (%)
Complications	**22 (15.3)**
Superficial wound infection	6 (27.3)
Deep infection	3 (13.6)
Wound healing problems	2 (9.1)
Hemorrhage	2 (9.1)
Joint stiffness	2 (9.1)
Nerve damage	2 (9.1)
Thrombosis	1 (4.5)
Other	4 (18.1)

Discussion

Surgery remains the mainstay of treatment for TGCT, predominantly performed open. However, achieving a cure even in experienced surgical hands remains challenging, especially for D-TGCT. It is widely acknowledged that complete resection can be difficult or undesirable in some cases due to the extensive tumour growth in and outside the joint. The goal of this study is to describe the surgical experience of a high-volume sarcoma centre with long follow-ups. This is the largest single-centre cohort of surgically treated patients with D-TGCT to date, introducing homogeneity in treatments and follow-up. Our hospital is one of few centres where sarcoma care is centralised, leading to higher patient adherence (19). As a result, we were able to describe a relatively long-term follow-up with a considerable number of MRIs performed postoperatively. This study showed that although surgeons may choose to debulk or partially resect TGCT, incomplete resections are associated with worse radiological and clinical outcomes. Also, if the tumour is present on the first postoperative MRI, patients tend to have higher chances of radiological progression and clinical deterioration. Although we are one of the most experienced centres treating TGCT worldwide and demonstrated that experienced surgeons tend to result in POT less often, POT is still common overall. This finding highlights that D-TGCT remains a challenging entity to treat surgically.

A recent meta-analysis concluded that arthroscopic surgical management of D-TGCT is associated with a higher risk of recurrence compared to an open approach, but no prospective study has investigated this yet (20, 21). In our institution, surgeons prefer to perform TGCT-related surgeries open, to have a good overview and access, especially tumours located around joint borders or extra-articular. Since no arthroscopies were performed, we could not compare the outcome between different techniques. Despite all surgeries being performed open, surgeons chose to remove D-TGCT not in toto in a fifth of the cases. Reasons for incomplete resections can be lesions that are asymptomatic

or require aggressive surgery, implying considerable postoperative morbidity that may interfere with the patients' functional outcome and quality of life. Surgeons attempted to completely resect D-TGCT treated elsewhere before more often than primary tumours (Figure 1). Regardless of the intention to resect all tumours macroscopically, POT was regularly observed on the first postoperative MRI. A possible explanation is that the diffuse type lacks well-defined borders and it is difficult to perform a radical resection. Our study showed that both incomplete resections and POT observed on the first postoperative MRI are associated with worse radiological and clinical outcomes. Considering the TGCT pathogenesis, remaining tumour cells will continue to produce CSF1, resulting in an increase in neoplastic cells and recruitment of nonneoplastic cells (2, 22). Therefore, this study underlines the importance of performing adequate excisions by experienced surgeons, preferably in a multidisciplinary setting. Furthermore, patients should be followed more extensively if POT is observed on the first postoperative MRI despite the intention to remove the D-TGCT in toto. Although these can be recognised as intuitive findings, we suggest that surgeons should carefully decide whether debulking or incomplete resections are indeed indicated, considering the associated negative outcomes. Alternatively, other therapeutic strategies can be proposed. We believe that such treatment decisions are best made in multidisciplinary teams within sarcoma centres with experience in TGCT care.

Neoadjuvant therapies could be considered for preoperative downstaging of the tumour to facilitate a (more) complete excision in advanced TGCT. Neoadjuvant therapies could consist of CSF1R inhibitors or antibodies, but evidence regarding neoadjuvant therapies in TGCT is scarce. Gelderblom et al. reported that a secondary resection following nilotinib treatment did not affect PFS (14). Other CSF1R inhibitors are not investigated as neoadjuvant therapy to date. CSF1R inhibitors may be indicated as a stand-alone treatment for patients not amenable to surgery. Recent studies showed promising results of CSF1R inhibitors, and new therapies are in the pipeline (15, 16, 23, 24). The role of adjuvant radiotherapy in TGCT treatment, consisting of external beam radiotherapy (EBRT) or radiosynoviortheses, remains controversial. Mollon et al. claimed that perioperative EBRT might reduce recurrence rates in D-TGCT, but the level of evidence was low (25). During this 20 years cohort, our MDTB indicated radiotherapy in only a few cases, and thus the actual treatment effect could not be determined. Radiotherapy may result in disproportionate complications such as early-onset osteoarthritis, avascular necrosis, skin problems, and even radiation-induced sarcomas, which is unacceptable in a nonmalignant disease in a young patient population (25, 26).

During total follow-up, D-TGCT radiologically progressed in 50% of the patients. However, this may be under- or overestimations since these rates were based on patients who underwent ≥1 MRI during follow-up. This also applies to observed POT presence.

Besides the first postoperative MRI, additional MRIs are mainly performed when patients are symptomatic or when joint destruction is expected. Since patients without residual tumour or progression are expected to be symptomatic less often, MRIs are presumably performed less frequently potentially causing bias. Contrarily, patients could also have an asymptomatic tumour (growth), which would not be observed if no MRI was made. To date, it is unclear when radiological progression coincides with clinical deterioration and vice versa. This study showed that the clinical situation deteriorated in several TGCT patients, even without considerable radiological progression on MRI. In these cases, other causes than tumour progression may lead to a symptomatic worsening of TGCT, such as joint destruction, joint effusion, or synovitis flare-up. Additionally, radiological tumour progression on MRI did not lead to clinical deterioration in a substantial number of D-TGCT patients. It remains unclear whether or when treatment is required for these patients and we believe shared decision-making is essential in such cases. TGCT is often treated aggressively due to its conceivably destructive behaviour, resulting in irreversible joint damage in the longer term. However, data about the natural course of TGCT is lacking. In the placebo group of the ENLIVEN trial, TGCT remained stable at 78%. 16 POT diagnosed by MRI in our study may therefore be regarded as residual more than the recurrent disease. The exact underlying molecular mechanism for disease progression is unknown (9, 22, 27). Identifying patients with a higher risk of relapse or joint destruction would be a tremendous breakthrough in TGCT treatment. However, at this moment, we feel that an experienced MDTB in a high-volume centre is the best approach to recognising patients at risk (28).

Finally, surgery-related complication rates were moderately high for D-TGCT but similar to other studies (8, 29). Most complications were not severe and required no or noninvasive treatment. Delayed wound healing happened solely after posterior synovectomies of the knee. Orthopaedic surgeons should be aware of this, and postoperative posterior wound inspection must be done carefully.

Limitations

The retrospective study design resulted in not having an MRI performed on all patients and some missing data. MRIs were mainly performed around 6 months postoperatively and additional MRIs when patients become symptomatic due to this benign character of TGCT. Since no strict follow-up protocol was followed, MRIs were performed at different intervals and not at fixed moments, which can be considered a major limitation. Additionally, the assessment of scans was performed in clinical practice without predefined (response) criteria, such as RECIST or tumour volume score. Predefined MRI (response) criteria should be applied to obtain better tumour quantification in future studies. In future studies, scans can be performed sooner after surgery to determine whether POT is residual

or recurrent. However, it might not be possible to discriminate between postoperative changes and residual lesions. Still, a single-centre cohort introduces homogeneity in imaging data, treatment, and follow-up policies, and available data were collected more trustworthy than in a multicentre study. Conversely, the generalizability of a single-centre study is limited.

Second, one may suggest that during 20 years, a change in the treatment landscape has taken place. However, surgical treatment of TGCT did not fundamentally change in the last 2 decades (21, 30).

Finally, clinical deterioration of patients was not measured by validated patient-reported outcome measurements but based on patients' medical records.

Conclusion

After more than 20 years of experience in a high-volume sarcoma centre, it remains challenging to control D-TGCT by surgery alone. As our results demonstrate, incomplete tumour removal is common, leading to worse radiological and clinical outcomes. Our study underlines the importance of adequate surgical resections and if this is not possible, we believe that alternate multimodal treatment strategies should be considered.

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Chapter 7

One-stage synovectomies result in improved short-term outcomes compared to two-stage synovectomies of diffuse-type tenosynovial giant cell tumour (D-TGCT) of the knee: a multicentre, retrospective, cohort study

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Abstract

Diffuse-type tenosynovial giant cell tumours' (D-TGCTs) intra- and extra-articular expansion about the knee often necessitates an anterior and posterior surgical approach to facilitate an extensive synovectomy. There is no consensus on whether two-sided synovectomies should be performed in one or two stages. This retrospective study included 191 D-TGCT patients from nine sarcoma centres worldwide to compare the postoperative short-term outcomes between both treatments. Secondary outcomes were rates of radiological progression and subsequent treatments. Between 2000 and 2020, 117 patients underwent one-stage and 74 patients underwent two-stage synovectomies. The maximum range of motion achieved within one year postoperatively was similar (flexion 123–120°, $p = 0.109$; extension 0°, $p = 0.093$). Patients undergoing two-stage synovectomies stayed longer in the hospital (6 vs. 4 days, $p < 0.0001$). Complications occurred more often after two-stage synovectomies, although this was not statistically different (36% vs. 24%, $p = 0.095$). Patients treated with two-stage synovectomies exhibited more radiological progression and required subsequent treatments more often than patients treated with one-stage synovectomies (52% vs. 37%, $p = 0.036$) (54% vs. 34%, $p = 0.007$). In conclusion, D-TGCT of the knee requiring two-side synovectomies should be treated by one-stage synovectomies if feasible, since patients achieve a similar range of motion, do not have more complications, but stay for a shorter time in the hospital.

Introduction

Tenosynovial giant cell tumours (TGCTs) are typically monoarticular diseases, emerging from the synovial lining of joints, bursae, and tendon sheaths (1). The tumour is composed of neoplastic and reactive components, both driven by CSF1 overexpression (2). TGCTs comprise two main subtypes: localised-type (L-TGCTs) and diffuse-type TGCTs (D-TGCTs). Both subtypes are histologically identical and are distinguished by their differing radiological pattern and clinical behaviour (1). Malignant TGCTs are considered a third subtype; however, this is only incidentally reported (3).

D-TGCTs behave locally more aggressively, and disease control is more challenging compared to L-TGCTs (1, 4-6). This study focuses on patients with D-TGCTs. The incidence rate of D-TGCTs is estimated to be 5 to 8 per million person years, and has its onset in a relatively young population, mostly between 30 and 50 years of age (7, 8). D-TGCTs affect large joints, in particular the knee. Common symptoms are pain, swelling, stiffness, and limited function; therefore, D-TGCTs can significantly impair patients' quality of life (9, 10). These unspecific symptoms often lead to diagnostic delays (11). Diagnosis is made through MRI and histological confirmation. D-TGCTs are characterised by a multilobulated lesion (>5 cm) with indistinct borders on MRI, and can be located both intra- and extra-articularly (12). Additionally, its locally aggressive behaviour can result in joint deterioration caused by inflammatory conditions and infiltrative growth.

To date, surgery is regarded as the backbone of treatment to relieve symptoms and prevent joint deterioration (13). Surgery by means of synovectomy aims to remove all tumours macroscopically to increase the chance of favourable outcomes (14, 15). However, achieving complete resection may result in iatrogenic morbidity if neurovascular structures are involved or because D-TGCTs' extensive growth necessitates large incisions and surgical exposures. Synovectomies for D-TGCTs are associated with recurrence free-survival of 40% at 10 years (5, 15, 16). The elucidation of the CSF1R driver mechanism led to the use of new therapeutic modalities, such as CSF1R inhibitors (17-19). CSF1R inhibitors are indicated for patients not amenable to surgery but have only limited availability to date. While the US Food and Drug Administration approved one CSF1R inhibitor, pexidartinib (Daiichi Sankyo, Tokyo, Japan), for D-TGCTs, the European Medicines Agency and Health Canada declined market authorisation due to an unfavourable risk–benefit ratio (20). Therefore, extensive synovectomies still remain a mainstay of treatment. Nevertheless, a consensus regarding the optimal surgical approach has not been reached (13). A recent meta-analysis by Chandra et al. estimated a 1.56 increased risk of recurrence after arthroscopic surgical management of D-TGCTs of the knee compared to an open approach (21). Furthermore, D-TGCTs in the knee often requires incisions from the

anterior and posterior sides to remove all intra- and extra-articular diseases. It remains undecided whether operating on the anterior and posterior sides should be performed in one or two stages (22-24). One-stage synovectomies are arguably less invasive for patients, as undergoing only one surgery requires one recovery period. Hypothetically, a one-stage synovectomy could result in impaired postoperative recovery and increased complications risk with simultaneous wounds on two sides of the knee. This study aims to compare the short-term outcomes of one- versus two-stage synovectomies of the anterior and posterior sides performed for D-TGCTs of the knee. A multicentre collaboration was initiated to bundle the experiences and data of several sarcoma centres worldwide.

Materials and Methods

In this international, multicentre, retrospective observational cohort study, patients that had a synovectomy of the anterior and posterior side of the knee for D-TGCTs between January 2000 and June 2021 were eligible. All consecutive patients were included from nine specialised sarcoma centres in the Netherlands, United States, Australia, and Canada.

All patients had histologically confirmed TGCTs located in the knee. Additionally, they underwent a two-sided synovectomy of the knee performed in one or two stages. In a one-stage synovectomy, the anterior and posterior sides of the knee were operated on during the same surgery. A two-stage synovectomy was defined as two separate surgeries, one addressing the anterior side and the other the posterior side. The separate surgeries must have been performed within six months to be defined as a two-stage synovectomy. The order of approach (i.e., first anterior or first posterior) or the surgical technique (open or arthroscopic) were not exclusion criteria.

Two-Sided Synovectomy for D-TGCTs of the Knee

D-TGCTs in the knee are often located throughout the joint due to their multicompartmental growth pattern (12). Common locations on the anterior side are the patellar recesses, the medial and lateral gutter, Hoffa's fat pad, and the anterior cruciate ligament. Posterior, D-TGCTs are typically located beneath the gastrocnemius insertions and intercondylar recesses, around the posterior cruciate ligament, and in the Baker's cyst around the hamstring tendons. Extra-articular locations often occur with extensive intra-articular growth.

Total synovectomy of the ventral side comprises removal of the synovium, often including the entire capsule and the suprapatellar bursa (Figure 1A). In addition, all tumour around the patella, along the femur, Hoffa's fat pad, in the posterolateral and posteromedial spaces, and surrounding the anterior cruciate ligament should be removed (Figure 1B).

Bone erosions are often located in the notch, around the femoral origin of the medial collateral ligament and the posterior tibial plateau (Figure 1C,D). Parts of the posterior recesses can be accessed through the ventral approach, but a separate posterior exposure is commonly required.

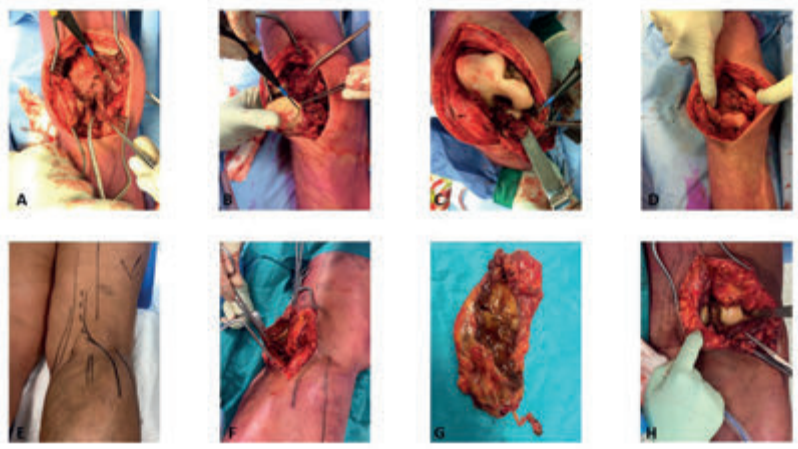

Figure 1
Two-sided synovectomy of the knee. An anterior synovectomy for D-TGCT about the knee is illustrated in figures (A–D). A posterior synovectomy for D-TGCT about the knee, in which also a Bakers' cyst is also removed, is illustrated in figures (E–H).

For the posterior approach, a lazy S-shaped incision is made before dissecting the popliteal fascia (Figure 1E). Commonly, the involvement of the hamstring tendons coincides with tumour located in a Baker's cyst (Figure 1F,G). After deeper dissection and retraction of the gastrocnemius muscle, posterior tumour in the subgastrocnemius recess appears (Figure 1H). Additional necessary approaches can be made medial to the semimembranosus, between the semimembranosus and the popliteal vessel and tibial nerve, and between the popliteal vessels and peroneal nerve for tibial–fibular joint involvement. The popliteal artery, tibial, peroneal, and sural nerves, and the small saphenous vein are at risk during this approach.

During a one-stage synovectomy, patients are turned from a prone to a supine position or vice versa intraoperatively.

Data

All data were retrospectively collected from patient medical records and pseudonymised before transferring to the principal investigators. The following data were collected: patient demographics, prior treatments, preoperative clinical presentation, date(s) and type(s)

of surgical interventions, length of hospital stay counting from the day of surgery till the day of discharge, postoperative range of motion up to one year, the need of walking aids, surgery-related complications, radiological progression, and subsequent treatments. For two-stage synovectomies, the length of hospital stay and surgical duration of the two separate surgeries were added together. In addition, radiological progression was measured from the date of the second intervention to the date of progression for two-stage synovectomies to avoid immortal time bias.

The primary aim of this study was to compare short-term outcomes between one- and two-stage synovectomies, such as surgical duration, length of hospital stay, postoperative range of motion within the first year after surgery, and complications. Secondary outcomes were radiological progression, clinical improvement, and the need for subsequent treatments.

This study was performed according to the Declaration of Helsinki and was approved by the Institutional Review Board from the Leiden University Medical Center.

Statistical Analysis

Continuous data were described by medians and ranges, and categorical data by the number of observations and percentages (%). Rates were calculated for the available data in individual categories. For all data, patients were stratified by undergoing a one- or two-stage synovectomy. Chi-square, Mann–Whitney U, or Kruskal–Wallis tests were performed to compare independent variables between the groups.

Finally, we performed subgroup analyses comparing only open one-stage and two-stage synovectomies. Due to the low incidence of TGCTs, no formal sample size calculation was performed, and all patients that fulfilled the inclusion criteria were included. IBM Statistical Package for Social Statistics 25 (Chicago, IL, USA) was used for analysis.

Results

Between January 2000 and June 2021, 191 consecutive patients underwent a one- or two-stage synovectomy of the anterior and posterior side of the knee for D-TGCTs. Of these 191 patients, 117 underwent a one-stage synovectomy and 74 a two-stage synovectomy. No significant differences were found between age, gender, and admission status (i.e., therapy naïve or prior treatment) between the two subgroups (Table 1). However, the participating sarcoma centres differed in their preferences for performing one- or two-stage synovectomies. Three sarcoma centres performed only one-stage synovectomies,

one centre performed only two-stage synovectomies, and both methods were used in the remaining centres (Table 1).

Table 1. D-TGCT patient baseline characteristics

Features	One-stage synovectomy N = 117	Two-stage synovectomy N = 74	P-value
Age, median (range)	39 (14-74)	37 (14-65)	0.717
Gender			0.460
Male	57	32	
Female	60	42	
Centres			<0.0001
LUMC	20	19	
RUMC	17	19	
MSH	31	-	
AUMC	6	17	
MAYO	11	6	
MCW	15	-	
RPAH	-	12	
UCD	10	-	
UCLA	7	1	
Prior treatments*	N=113	N=73	0.548
None	54	39	
Yes	59	34	
Synovectomy	56	33	
Systemic therapy	4	1	
RSO	2	4	
EBR	-	2	
Unknown	4	-	

**Sum of observations can be more than the total number of individual patients; RSO Radiosynoviorthesis, EBR External Beam Radiotherapy*

Of the 191 patients, 10 underwent a second one- or two-stage synovectomy, totaling 201 interventions. These interventions were comprised of 126 one-stage and 75 two-stage synovectomies. The preoperative range of motion, including a flexion of 120 degrees and no extension lag, was equal, and the surgeries in both groups were performed around the same period (Table 2). The one-stage synovectomies were performed either completely open, completely arthroscopic, or with both techniques combined. Conversely, most two-stage synovectomies were performed solely open, and a combined technique was only used in a few cases ($p < 0.0001$). The median interval between the first and second intervention of two-stage synovectomies was 2 months (range 0–6 months). The length of hospital stay was longer for patients undergoing a two-stage synovectomy (sum of two admissions) ($p < 0.0001$) (Table 2). Postoperative knee flexion motion measured across multiple time points postoperatively was equal at 3, 6 and 12 months postoperatively, and the maximum range

of motion reached within the first year after treatment was not different between the two groups (Figure 2, Table 2). Complications occurred more often in the patients undergoing a two-stage synovectomy (p = 0.095), although this was not statistically significant. In both groups, superficial wound infections and wound healing problems were the most common complications. Three deep wound infections occurred after two-stage synovectomies. Six patients required walking aids at six months postoperatively, consisting of elbow crutches and canes. Four of these six patients underwent a one-stage synovectomy (2%), and the others a two-stage synovectomy (3%). At one year, only two patients still used a cane, one from each group.

Table 2. Surgery characteristics of all interventions

Features	**One-stage synovectomy N=126**	**Two-stage synovectomy N=75**	**P-value**
Preoperative range of motion, degrees, median (range)	N=108	N=45	
Flexion	120 (30-150)	120 (90-140)	0.630
Extension	0 (0-20†)	0 (0-15†)	0.830
Median year of surgery (range)	2015 (2002-2021)	2013 (2002–2020)	0.020
Surgical technique	N=123	N=75	<0.0001
Open	58 (47%)	67 (89%)	
Combined[a]	51 (42%)	8 (11%)	
Arthroscopic	14 (11%)	-	
Length of hospital stay, days, Median (range)[b]	N=124 4 (1-13)	N=71 6 (3-26)	<0.0001
Maximum range of motion PO, degrees, median (range)	N=114	N=49	
Flexion	123 (75 – 145)	120 (95-140)	0.109
Extension	0 (0-30†)	0 (0-10†)	0.073
Complications*	N=123	N=72	
Yes	29 (24%)	27 (36%)	0.095
Wound healing problems	10	9	
Superficial wound infection	8	12	
Deep wound infection	-	3	
Joint stiffness	1	2	
Hemarthrosis	3	3	
Neurovascular damage	3	2	
Thrombosis	1	-	
Other	9	1	

[a]Combined comprises arthroscopic synovectomy of the anterior side and open synovectomy of the posterior side; [b]For two-stage synovectomy the sum of both surgeries is calculated [c]PO Postoperative
*†The number of degrees equals the degrees of extension lag *Sum of observations can be more than the total number of individual patients*

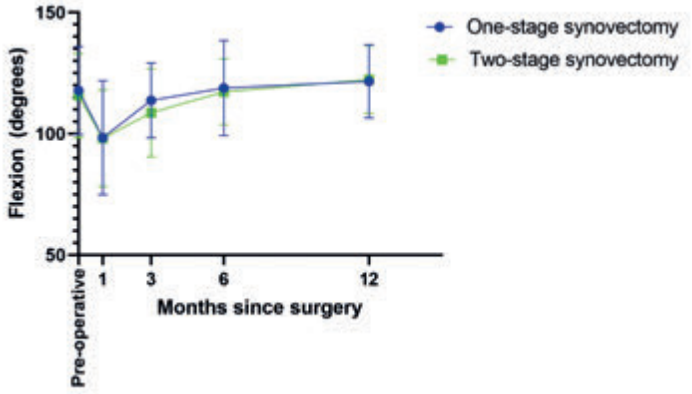

Figure 2
Course of the postoperative flexion range.

Median follow-up for patients undergoing a one-stage or two-stage synovectomy was 45 and 59 months, respectively (p = 0.047) (Table 3). The progression rate for patients undergoing a one-stage synovectomy was 37%, and the progression rate was 52% for the two-stage group (p = 0.036). However, this finding was no longer significant after performing a Kaplan–Meier analysis (log-rank test p = 0.080) (Figure 3). Additionally, patients undergoing a two-stage synovectomy required subsequent treatments significantly more often than after a one-stage synovectomy (54% vs. 34%; p = 0.007). Patients were mainly retreated by a repeat synovectomy (Table 3).

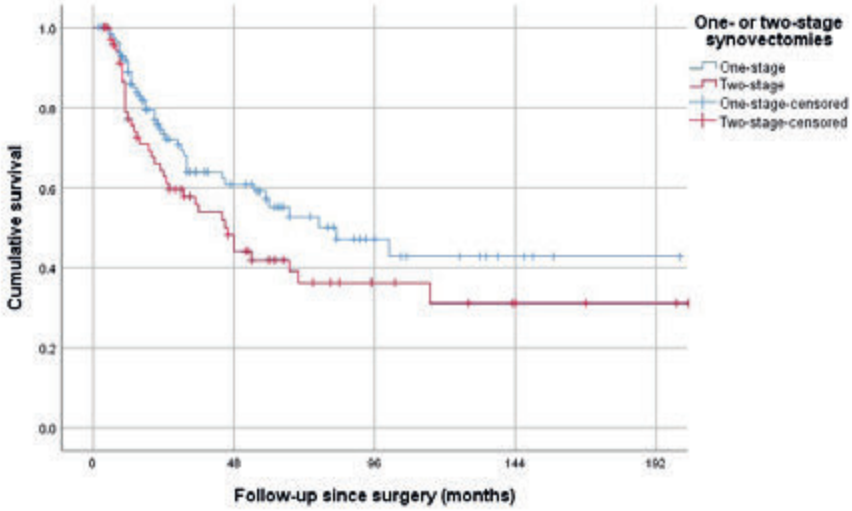

Figure 3
Postoperative progression-free survival; Kaplan–Meier analysis.

Table 3. Postoperative course

Features	One-stage synovectomy N=117	Two-stage synovectomy N=74	P-value
Median follow-up, months (range)	45 (1-200)	59 (3-203)	0.047
Radiological progression	N = 115	N=73	
Yes	42 (37%)	38 (52%)	0.036
Months till radiological progression, median (range)	18 (5-101)	17.5 (6-115)	
New treatment after synovectomy	N=117	N=74	
No	77	34	
Yes*	40	40	0.007
Synovectomy	21	17	
EBR	11	11	
RSO	-	3	
Systemic	6	3	
(Tumour)prosthesis	4	8	
Tumour status at final follow-up†	N=77	N=34	
No evidence of disease	53	19	
Alive with disease, watchful waiting	18	10	
Alive with disease, (planned) treatment	5	1	
Dead of other disease	1	-	

**Sum of observations can be more than total number of individual patients; EBR External Beam Radiotherapy; RSO Radiosynoviorthesis; † For patients not undergoing a subsequent treatment after a one- or two-stage synovectomy*

At six months and one year postoperatively, pain and swelling were the symptoms that most frequently improved compared to the preoperative status. While stiffness commonly improved in patients undergoing one-stage synovectomies (34% at one year postoperatively), it only improved in three patients at six months (7%) and in one at one year (2%) of the patients undergoing a two-stage synovectomy (Figure 4).

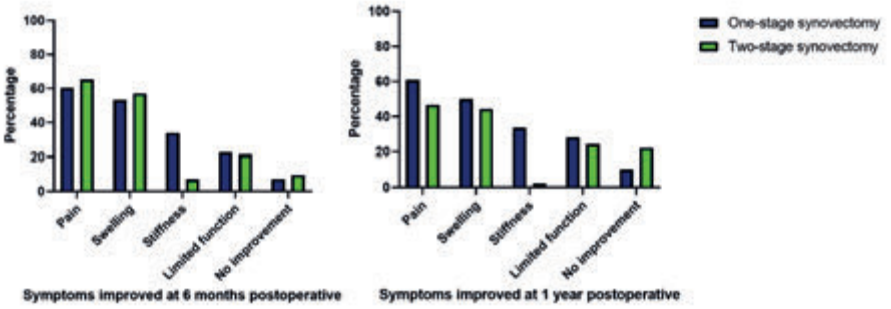

Figure 4
Symptoms improved at six months and one year postoperatively.

Subgroup Analyses

After comparing only open one-stage and two-stage synovectomies, patients achieved a similar range of motion within the first year after surgery (flexion 125–120°, p = 0.126; extension 0°, p = 0.253), and the median length of hospital stay was equal (6 days); however, the distribution was significantly longer for patients undergoing two-stage synovectomies (p = 0.008) (Supplementary Table S2). Additionally, complications occurred more frequently following a two-stage procedure, although this finding was not significant (36% vs. 22%, p = 0.069) (Supplementary Table S2).

Discussion

There is a need for new therapeutic modalities, which are in development; meanwhile, surgery remains the standard treatment for TGCTs. A complete (anterior and posterior) synovectomy is often indicated in diffuse-type TGCTs of the knee, but consensus regarding the ideal surgical procedure is lacking (13, 25). This is the first multicentre study with a large cohort comparing the short-term outcomes of one- and two-stage synovectomies of the anterior and posterior sides of the knee (23-25). Patients undergoing one-stage synovectomies achieved an equal range of motion postoperatively, but stayed shorter in the hospital and had fewer complications. Thus, one-stage synovectomies are preferred over two-stage synovectomies if feasible.

While most previous studies focused on different techniques used during two-sided synovectomies (open or arthroscopic), this study is the first to compare the effect of one or two stages (22-25). Since simultaneous surgery on the anterior and posterior side of the knee is more invasive for patients, this can lead to discouraging surgeons from performing a one-stage synovectomy in some cases. Although prolonged rehabilitation may not be desirable in some cases (e.g., elderly patients), the typical population affected by D-TGCTs is relatively young, as also shown by this cohort and in accordance with the literature (7, 8). Younger patients can cope better with invasive procedures in general (26). Patients undergoing one-stage synovectomies had an equal range of motion at 3, 6 and 12 months and achieved the same range of motion within the first year after surgery compared to patients undergoing two-stage synovectomies (median flexion 123 degrees with full extension). In conclusion, patients undergoing one-stage synovectomies do not have an impaired recovery and achieve the range of motion required to perform activities of daily living (27).

On the other hand, for two-stage synovectomies, the range of motion was measured after the second intervention, and the median interval of 2 months between the first and second

surgery was not taken into account. In this period, patients are still recovering from the first intervention, resulting in prolonged rehabilitation for patients undergoing a two-stage synovectomy. Besides more extended rehabilitation, patients undergoing two-stage synovectomies also had to stay longer in the hospital due to two separate interventions. The length of admission was not affected by the invasiveness of one-stage synovectomies. Repeated admissions for surgery and longer lengths of hospital stay have a negative impact on TGCT-related medical costs (10). Additionally, prolonged rehabilitation results in a longer return to work time and daily activities such as sports.

Approaching the anterior and posterior sides of the knee surgically simultaneously did not result in higher complication rates following one-stage synovectomies. Contrariwise, two-stage synovectomies led to higher complication rates following two separate interventions, although not significantly. Compared to the study of Mastboom et al., the total complication rate in this cohort was relatively high (28% vs. 12%) (5). Selection bias may have been introduced since only patients were included with D-TGCTs located on the anterior and posterior side of the knee, resulting in a cohort with more severe presentations and requiring more invasive surgeries.

Radiological progression, a secondary outcome, occurred more frequently after two-stage synovectomies, although this finding was not significant after a Kaplan–Meier analysis. In addition, patients undergoing a two-stage synovectomy required repeated treatments more often. However, local surveillance and treatment regimens may have biased these results, since local recurrences are not always symptomatic and do not require treatment in every case.

Limitations

Since patients were not randomised to either one- or two-stage synovectomies, some biases may have been introduced. First, sarcoma centres significantly differed in performing one- or two-stage synovectomies. Some centres performed only one approach, which could introduce information bias toward this approach. Secondly, bias is possible by surgeons or patients who prefer one of the two interventions. Finally, indication bias might have been introduced by sarcoma centres performing both procedures. Complete arthroscopic approaches were only performed in one-stage synovectomies, which could suggest that this treatment group included less severe cases. When looked at in more detail, no considerable differences were found per centre between the disease status at the time of surgery (primary or recurrent disease) for patients undergoing one- or two-stage synovectomies (Supplementary Table S1). Unfortunately, no more data were available to assess disease severity based on tumour size, tumour localisation, or patient-reported

outcome measurements. Nonetheless, results regarding the short-term outcomes were not different after analysing subgroups of patients treated by solely open procedures.

The authors agree that removing D-TGCTs arthroscopically is technically challenging and requires a lot of training to achieve complete tumour resection (28). Thus, removing extensive D-TGCTs located anterior and posterior arthroscopically should only be performed by sarcoma centres with skilled arthroscopists.

Due to the retrospective multicentre study design, no standardised follow-up schemes were followed. This may have resulted in different rates of radiological progression and indications for subsequent treatments per centre, since local recurrences can be asymptomatic and do not always necessitate treatment.

Finally, no prospective data were collected due to the retrospective design. Therefore, no validated classification criteria could have been compared, such as tumour volume score used to measure radiological progression or patient-reported outcome measurements to quantify the health-related quality of life.

A randomised controlled trial will minimise the risk of these biases, and validated measurements can be integrated. Although this would be the ideal study design to compare both approaches, performing a prospective trial for a rare disease such as D-TGCT is challenging but not impossible (11, 19).

Conclusion

A synovectomy of the anterior and posterior sides of the knee is often required to remove all advanced D-TGCTs macroscopically. This retrospective multicentre study showed that one-stage synovectomies do not result in impaired rehabilitation compared to two-stage synovectomies. Additionally, patients undergoing a one-stage synovectomy had a shorter length of hospital stay and no more complications than patients undergoing two-stage synovectomies.

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Appendix

Supplementary table 1. One- vs two-stage synovectomies per centre.

Centres	One-stage	Two-stage
LUMC	20	19
Previous treatment (%)	13 (59)	8 (42)
Median Follow-up, months (range)	18 (10-123)	62 (3-194)
RUMC	17	19
Previous treatment (%)	11 (58)	11 (58)
Median Follow-up, months (range)	86 (6-200)	95 (9-199)
MSH	31	
Previous treatment (%)	18 (58)	-
Median Follow-up, months (range)	57 (12-157)	
AUMC	6	17
Previous treatment (%)	2 (33)	9 (53)
Median Follow-up, months (range)	11 (2-62)	39 (4-203)
MAYO	11	6
Previous treatment (%)	8 (73)	4 (67)
Median Follow-up, months (range)	45 (10-137)	32 (6-52)
MCW	15	
Previous treatment (%)	3 (20)	-
Median Follow-up, months (range)	54 (4-84)	
RPAH		12
Previous treatment (%)	-	1 (8)
Median Follow-up, months (range)		62 (4-104)
UCD	10	
Previous treatment (%)	4 (40)	-
Median Follow-up, months (range)	16 (1-35)	
UCLA	7	1
Previous treatment (%)	4 (57)	(100)
Median Follow-up, months (range)	49 (23-159)	58
Total	117	74
Previous treatment (%)	59 (50)	34 (46)
Median Follow-up, months (range)	45 (1-200)	59 (3-203)

Supplementary table 2. Outcomes for open one- and two-stage synovectomies in particular.

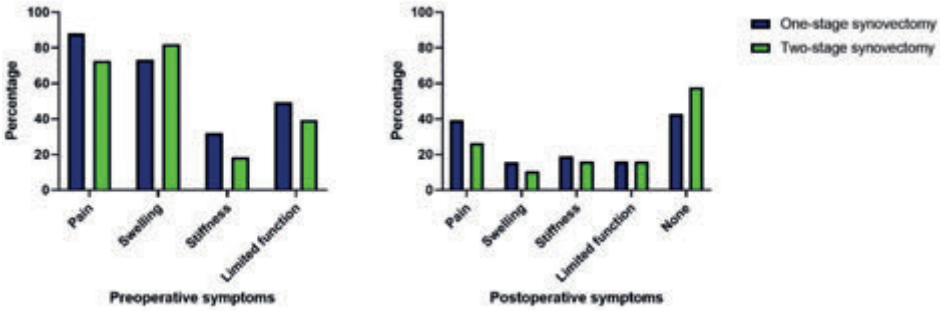
Features	One-stage synovectomy open N = 58	Two-stage synovectomy open N = 67	P-value
Length of hospital stay, days, median (range)[b]	N=56 6 (1-13)	N=63 6 (3-26)	0.008
Maximum range of motion, degrees, median (range)	N=51	N=46	
Flexion	125 (70-145)	120 (45-140)	0.126
Extension	0 (0-20†)	0 (0-10†)	0.253
Complications	N=58	N=64	
Yes	13 (22%)	23 (36%)	0.069
No	45 (78%)	41 (64%)	
Radiological progression	N=57	N=66	
Yes	23 (40%)	31 (47%)	0.371
No	34 (60%)	35 (53%)	

†The number of degrees equals the degrees of extension lag

Supplementary table 3. Outcomes per different techniques performed for one-stage synovectomies.

Features	Complete open approach N=58	Combined approach N=51	Complete arthroscopic approach N=14	P-value
Length of hospital stay, days, median (range)[b]	N=56 6 (1-13)	N=53 3 (1-8)	N=53 1 (1-4)	<0.0001
Maximum range of motion, degrees, median (range)	N=51	N=46	N=42	
Flexion	125 (70-145)	120 (90-140)	127.5 (90-140)	0.654
Extension	0 (0-20†)	3 (0-30†)	0 (0-15†)	0.092
Complications	N=58	N=50	N=12	0.009
Yes	13 (22%)	14 (28%)	-	
No	45 (78%)	36 (72%)	12 (100%)	
Radiological progression	N=57	N=51	N=12	0.069
Yes	23 (40%)	17 (33%)	5 (42%)	
No	34 (60%)	34 (67%)	7 (58%)	

†The number of degrees equals the degrees of extension lag



Supplementary figure 1. Pre- and postoperative symptoms of patients undergoing a one- or two-stage synovectomy and no subsequent treatment

Chapter 8

Tenosynovial giant cell tumours (TGCT): molecular biology, drug targets and non-surgical pharmacological approaches

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Abstract

Background

Tenosynovial giant cell tumour (TGCT) is a mono-articular, benign or locally aggressive and often debilitating neoplasm. Systemic therapies are becoming part of the multimodal armamentarium when surgery alone will not confer improvements. Since TGCT is characterised by colony-stimulating factor-1 (CSF1) rearrangements, the most studied molecular pathway is the CSF1 and CSF1 receptor (CSF1R) axis. Inhibiting CSF1-CSF1R interaction often yields considerable radiological and clinical responses; however, adverse events may cause treatment discontinuation because of an unfavourable risk-benefit ratio in benign disease. Only Pexidartinib is approved by the US FDA; however, the European Medicines Agency has not approved it due to a uncertain risk-benefit ratio. Thus, there is a need for safer and effective therapies.

Areas covered

Light is shed on disease mechanisms and potential drug targets. The safety and efficacy of different systemic therapies are evaluated.

Expert opinion

The CSF1-CSF1R axis is the principal drug target; however, the effect of CSF1R inhibition on angiogenesis and the role of macrophages, which are essential in the postoperative course, needs further elucidation. Systemic therapies have a promising role in treating mainly diffuse-type, TGCT patients who are not expected to clinically improve from surgery. Future drug development should focus on targeting neoplastic TGCT cells.

Introduction

Tenosynovial giant cell tumour (TGCT) is a monoarticular, proliferative lesion located in and around joints throughout the body (1). According to the most recent 'World Health Organization Classification of Tumours: Soft tissue and Bone Tumours,' TGCT comprises a family of lesions originating from the synovium of joints, bursae, and tendon sheaths (2). TGCT consists of two main subtypes: Localised-type TGCT (L-TGCT) and Diffuse-type TGCT (D-TGCT), previously referred to as Giant Cell Tumour of Tendon Sheath and Pigmented Villonodular Synovitis (PVNS), respectively (3). Although varieties of names have been used in the past, both subtypes are now unified under one denomination, sharing common pathogenesis and morphology (4, 5).

Epidemiology

TGCT is considered an orphan disease, with reported incidence rates ranging from 30–39 and 5–8 per million person-years for L-TGCT and D-TGCT, respectively (6, 7). There is a female predilection (♂:♀ ratio 1:1.5) and both subtypes affect a relatively young population. TGCT is mainly diagnosed between 40 and 60 years; nevertheless, it can occur at all ages, even in children (8). L-TGCT is primarily located in the digits of the hand and feet (85%), while D-TGCT is more involved in the large joints, especially the knee (9).

Clinical presentation

L-TGCT and D-TGCT behave differently and are categorised as separate clinical entities. Common experienced symptoms are pain, swelling, stiffness and limited range of motion. Other functional signs are instability, giving way and joint blockage (10). However, these nonspecific presentations can lead to a delay in diagnosis and visits to various medical professionals (11). Additionally, a decrease in quality of life (QoL) and interference with daily activities, leading to work loss and requiring domestic help, are often reported. TGCT's associated burden on QoL and healthcare emphasize the need for an adequate treatment strategy (12-14).

Diagnostics

Magnetic Resonance Imaging (MRI) is the state of art imaging technique for TGCT and demonstrates the extent of the disease, presence of joint effusion, and secondary degenerative changes. L-TGCT is characterised by a focal, well-demarcated lesion, whereas D-TGCT is classified as more than one, multilobulated lesions with synovial thickening, villous projections and hemosiderin depositions, often extending both intra- and extra-articular (15). Additionally, the diffuse-type is often associated with bone erosions, cartilage loss and osteophyte formation. In more progressive stages this leads to secondary

osteoarthritis (16). Histological confirmation of the diagnosis is mainly obtained by either excisional biopsies, arthroscopic biopsies or core needle biopsies (11). However, since often no clear histological distinction can be made between the two main subtypes, L-TGCT and D-TGCT are mainly differentiated by a radiological distribution of tumour within the joint and clinical characteristics.

Pathogenesis

The pathogenesis of TGCT has been the subject of debate for a long period. In 1941, Jaffe et al. suggested that TGCT had a reactive or inflammatory origin (17). Several decades later, cytogenic studies revealed numerical and structural chromosomal alterations, indicating a clonal, neoplastic process (18, 19). In 2006, the main view regarding the pathogenesis changed after West et al. demonstrated the presence of recurrent translocations in several TGCT patients. These translocations involve region 1p11-13, on which the colony-stimulator factor 1 (CSF1) gene is located (20). CSF1, also known as macrophage colony-stimulating factor (M-CSF), regulates survival, proliferation, differentiation and function of macrophages and their precursors by binding to its receptor (CSF1R) (21, 22). Most cells in TGCT express CSF1R, while CSF1 (the ligand of CSF1R) is only present in a low percentage of cells (2–16%). These neoplastic TGCT cells produce elevated levels of CSF1 as a result of the translocation, leading to an increase in more neoplastic cells (autocrine loop) and an accumulation of non-neoplastic CSF1R-expressing cells of the macrophage lineage (paracrine loop). This is referred to as the landscape effect (20). The most common translocation partner of CSF1 is collagen type VI alpha-3 (COL6A3), located on chromosome 2p37 resulting in t(1;2)(p13;p37) (23, 24). However, recent studies showed that this fusion is only present in a subset of patients. Also, they showed the involvement of other fusion partners leading to additional underlying mechanisms for CSF1 upregulation (24-27). More specific, novel fusions result in the deletion of CSF1 exon 9, a negative regulator of CSF1 expression, and truncation of 3'-UTR region may account for CSF1 overexpression in more cases instead of overexpression of full-length CSF1 via promoter swapping (28, 29). Also, CBL (Cas-Br-Murine ecotropic retroviral transforming sequence) mutations are present in more than a third of TGCT cases, although not mutually exclusive to CSF1 fusions (28, 29). CBL is a multifunctional protein that associates with receptor tyrosine kinases and could be the driver event in some cases where CSF1 rearrangements are not present (29). A consensus regarding the effect of different fusions or truncations and levels of CSF1 overexpression and the role of CBL mutations on clinical behaviour is still lacking (30-32).

The gene expression profile of TGCT is consistent with apoptosis resistance, inflammation, and matrix degradation, leading to ongoing proliferation and joint destruction. Genes

highly overexpressed include CD53, ALOX5AP, SPP1, MMPs 1 and 9 (33). Contrarily, tumour suppressor genes, such as TP53, are downregulated (33).

Histopathology

TGCT belongs to the so-called fibrohistiocytic tumours according to the 5th edition of the World Health Organization Classification of Tumours and the tumour microenvironment contains a heterogeneous cell population (2). Tumours are composed of a variable proportion of mononuclear cells, multinucleated (osteoclast-like) giant cells, foamy macrophages (xanthoma cells), inflammatory cells, and siderophages (hemosiderin-laden macrophages), with stromal hyalinisation (Figure 1) (34-36). Two principle cell types are described, in variable proportion, within the mononuclear cell compartment: small histiocyte-like cells with round to oval nuclei often represent the main cellular component. In addition, larger epithelioid cells with abundant cytoplasm and larger nuclei are seen (Figure 1) (2).To date, it remains unknown from which lineage these cells are derived. Immunohistochemically, the larger mononuclear cells express clusterin, podoplanin and to lesser extent desmin, highlighting dendritic processes (2, 37). The smaller histiocyte-like cells are positive for CD68, CD163 and CD45 (38). Although osteoclast-like giant cells are the most distinctive histological feature of TGCT, giant cells may be sparse or absent (39). In the joint fluid, various inflammatory factors are present, such as Interleukine-1β (IL-1β) and Tumour necrosis factor-α (TNF-α), indicating the presence of a highly inflammatory microenvironment within joints affected by TGCT (Figure 2) (40). Besides the two main subtypes, malignant TGCT is incidentally reported. This aggressive subtype has a high potential for metastasis, mainly in pulmonary and regional lymph nodes (41). Besides the typical TGCT histology, malignant TGCT displays increased mitotic activity, including atypical mitoses, necrosis, enlarged nuclei with nucleoli, spindling of mononucleated cells, and myxoid change (2). The malignant TGCT cells are suggested to be derived from clusterin-positive large mononuclear cells (42). The etiology of malignant TGCT is not well understood.

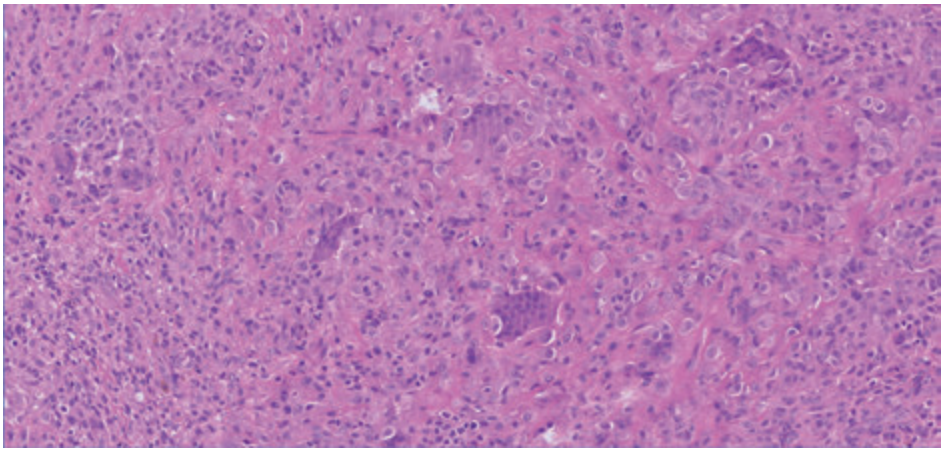

Figure 1. TGCT H&E stained tissue section showing characteristic histologic features such as small histiocyte-like cells with oval nuclei, larger epithelioid cells of which some contain hemosiderin depositions, multinucleated osteo-clast like giant cells, and stromal hyalinisation.

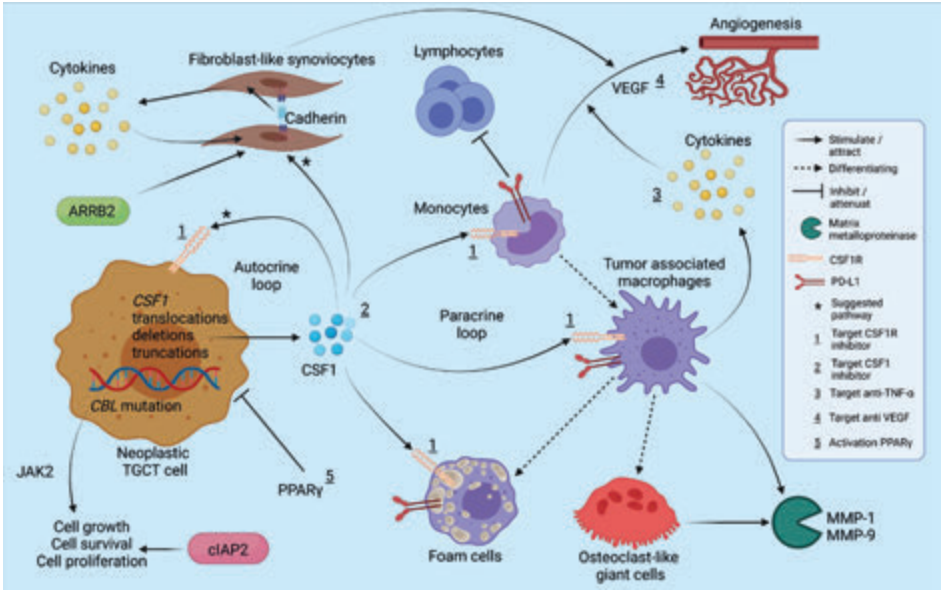

Figure 2. Simplified overview of pathways involved in TGCT chromosomal aberrations of the CSF1 gene lead to an overexpression of CSF1. Elevated levels of CSF1 are suggested to cause an increase in neoplastic TGCT cells (autocrine loop) and accumulate CSF1R presenting cells of the macrophage lineage (paracrine loop). CSF1 is also suggested to be involved with the proliferation of FLS. Monocytes/macrophages can differentiate into osteoclast-like giant cells and foam cells. Monocytes can produce VEGF resulting in angiogenesis and expressing PD-L1, leading to attenuation of lymphocytes. VEGF can also be induced by hypoxic stress by FLS amongst others. Macrophage produced cytokines can strengthen the effect of VEGF. Cadherin-11 can stimulate FLS to produce cytokines, while the cytokines can stimulate FLS through a positive loop. Additionally, the effect of proteins ARRB2, cIAP2, PPARγ and targets over several drugs are depicted. Created with BioRender.com.

Current gold-standard treatments

Complete excision of TGCT is the primary choice of treatment (43). L-TGCT is often removed relatively easily by either arthroscopy or open surgery, depending on the localisation, with a recurrence rate around 10% (44, 45). Contrarily, adequate removal of D-TGCT can be challenging due to the localisation in- and outside the joint and the non-clear-cut boundaries of the tumour. Additionally, D-TGCT has high recurrence rates and often requires re-excision (46, 47). Relapse-free survival rate is estimated at 40% at 10 years (46). The optimal surgical technique remains to be elucidated (48). Some specialists claim that open surgery leads to better overview and access, especially in widespread lesions. On the other hand, open surgery may lead to more iatrogenic morbidity, especially in patients having relapses.

The high rate of recurrences in D-TGCT underlines the demand for (neo)adjuvant or new stand-alone treatment approaches (47). Radiotherapy, consisting of radiosynoviorthesis (RSO) with the injection of intra-articular radioactive isotopes and external beam radiotherapy (EBR), is occasionally performed (49-51). Only a few studies are available with low-level evidence for both types of radiotherapy. Mixed results have been reported regarding the efficacy of RSO, but this is also associated with serious complications such as skin necrosis (52-54). A meta-analysis by Mollon et al. suggested that surgery combined with EBR leads to a reduced recurrence rate, but they also concluded that large long-term prospective multicentre studies are required to confirm these findings (55). Long-term findings are important since EBR is associated with radiation-induced malignancies, especially in a relatively younger patient population. This is regarded as an unacceptable outcome in a benign or intermediate disease (56).

In 2008, Blay et al. were the first to report the effect of the drug imatinib (or imatinib mesylate) in a patient with TGCT, leading to complete remission (57). This implied a promising role for targeted therapies in TGCT, especially for patients not amenable to surgery. The interest in systemic therapies is increasing more recently, leading to the development and clinical testing of new and available drugs, providing enlargement of the current therapeutic armamentarium.

Cell line models

Patient-derived tumour cell lines are essential to investigate molecular mechanisms of TGCT pathogenesis and develop novel therapeutic strategies. Recently, a new cell line was established from TGCT tissue (58). Complimentary use of a culture can be helpful in in

vitro studies to gain new insights and increase drug screening reliability (58). In addition, Tang et al. established the use of patient-derived tumour TGCT xenografts for drug validation in ex vivo models (59).

Potential therapeutic targets

Systemic therapies provide a new avenue for patients with inoperable TGCT and are sometimes considered as a last resort (49). Various underlying molecular pathways have been explored as new therapeutic strategies (Table 1) (Figure 2).

Table 1. (Potential) TGCT drug targets

Molecular target	Biological target	Related drugs applied in TGCT
CSF1-CSF1R axis	Tumour cell proliferation and monocyte/ macrophage survival, proliferation and differentiation	Imatinib, nilotinib, pexidartinib*, vimseltinib, lacnotuzumab, emactuzumab, cabiralizumab
JAK2	Cytokine activity	No
cIAP2	Cell apoptosis	No
B-Arrestin2	Cell survival, apoptosis, migration and proliferation of FLS	No
PPARγ	Tumour cell proliferation, invasion, differentiation and apoptosis	Zaltoprofen
TNF-α	Inflammatory conditions and monocyte, macrophage, osteoclast proliferation and differentiation	Infliximab, etanercept
VEGF	Angiogenesis	Bevacizumab
RANKL	Differentiation and activation of osteoclasts	No
PD-L1	Regulation of immune response on tumour cells	No
Cadherin-11	Cytokine and metalloproteinase production and migration and invasion of FLS	No

**Only drug with US FDA approval for TGCT, FLS Fibroblast-like synoviocytes*

Therapeutic targets related to tumour cells

Colony stimulating factor 1

Since the discovery of CSF1 overexpression in TGCT patients, the CSF1-CSF1R axis has been the most studied target (60). Where in some patients genomic alterations cause overexpression of CSF1 in the neoplastic cells, in other patients, the origin of elevated levels of CSF1 and CSF1R remains unclear (20, 26, 28). Nonetheless, targeting the CSF1-

CSF1R signalling pathway is suggested to have an anti-tumoural effect by blockade of CSF1R. Different approaches to CSF1R blockade have been investigated, such as CSF1R antibodies and tyrosine kinase inhibitors (TKIs) (27).

Janus-kinase-2

Tsuda et al. found that CBL mutations in TGCT prolong the phosphorylation of tyrosine kinase Janus-Kinase-2 (JAK2), leading to enhanced cell proliferation (28). They also found that CBL mutations are associated with increased JAK2 expression and worse disease outcomes. Therefore, the authors suggest inhibiting JAK2 as a possible new therapeutic strategy. However, the CBL mutation is not mutually exclusive to CSF1 fusions (28, 29). In cases with the presence of CSF1 rearrangements and CBL mutations, combined treatment might be reasonable.

Cellular inhibitor of apoptosis 2

Cellular inhibitor of apoptosis 2 (cIAP2) is an anti-apoptotic protein, and deregulation of this protein is associated with tumour development and progress (61). Levels of cIAP2 are significantly higher in D-TGCT compared to the localised-type. Besides, overexpression of cIAP2 is related to ligament, cartilage and bone erosion, and tumour relapses (62). Since high levels of cIAP2 in TGCT patients were associated with poor prognosis, cIAP2 gene may have a promising role in prognosis prediction and targeted therapy in D-TGCT (62).

β-Arrestin2

β-Arrestin2 (ARRB2) is associated with cell survival, apoptosis, migration, and proliferation in several tumour types. ARRB2 is also highly expressed in TGCT, leading to increased cell proliferation and inhibition of apoptosis through activation of the PI3K-Akt pathway (63). Cao et al. observed that knockdown of ARRB2 inhibited cell proliferation and increased apoptosis of FLS. They concluded that ARRB2 could be a potential molecular target in TGCT treatment (63).

Proliferator-activated receptor gamma

Proliferator-activated receptor gamma (PPARγ) is a member of the nuclear receptor super family of transcription factors. It is expressed in high levels in adipose tissue and monocyte-derived macrophages and stimulates adipocyte and macrophage differentiation (64). Ligand activation of PPARγ in monocytes/macrophages inhibits inflammatory mediator and cytokine production. Also, PPARγ is expressed in a variety of cancer cells and specific ligands can induce growth inhibition and apoptosis (65).

Therapeutic targets related to reactive myeloid cells

Tumour necrosis factor-α

Analysis of the gene expression pattern of TGCT showed elevated levels of macrophages and proinflammatory cytokines, such as TNF-α (33). Proinflammatory cytokines drive inflammation, which is associated with joint destruction (66). In addition, the synergistic paracrine loop between TNF-α and CSF1 contributes to monocyte, macrophage, and osteoclast proliferation and differentiation, resulting in tumourigenesis. TNF-α blockade is assumed to antagonise the inflammatory process predominantly (67).

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) promotes endothelial cell proliferation and new blood vessel formation. Angiogenesis is crucial for tumour development. In addition, CSF1 can activate multiple cell signaling pathways leading to VEGF production. VEGF inhibition is associated with reducing tumour growth by blocking angiogenesis and, therefore, could be a potential target (68).

Receptor-activator of nuclear factor kappa-B ligand

Receptor-activator of nuclear factor kappa-B ligand (RANKL) is a cytokine involved in differentiation and activation of osteoclasts, causing bone resorption (69). The monoclonal antibody denosumab successfully inhibits RANKL in various diseases, such as giant cell tumours of the bone (70). Yamagishi et al. showed RANKL expression in several soft tissue tumours, for instance, TGCT (69). RANKL expression can be induced by proinflammatory cytokines, such as TNF-α and interleukins, among others (71). Although RANKL levels were lower compared to giant cell tumours of the bone, there may be a role for RANKL antibody treatment to inhibit giant cells, although this has not yet been under study (69, 72). However, multinucleated cells such as osteoclast-like giant cells from synovial tumours might represent a different entity than bone tumour-derived multinucleated cells, which may result in different efficacy of RANKL blockage. Additionally, since RANKL antibody treatment targets giant cells and not underlying mechanisms of pathogenesis in TGCT, such as the CSF1-CSF1R axis, this strategy remains uncertain.

Programmed cell death ligand 1

Programmed cell death ligand 1 (PD-L1) regulates immune responses by attenuating lymphocyte activation and stimulating tumour growth. PD-L1 was highly positive in 53% of CSF1-activated TGCT cases, expressed on mononuclear cells, multinucleated giant cells, and foam cells (73). In addition, a positive correlation was found between PD-L1 expression and larger tumour sizes. Based on their findings, Zheng et al. suggested that anti-PD-L1 immunotherapy in combination with other molecular targeted therapy

may possibly improve outcomes of anti-tumour therapy in patients with CSF1/CSF1R signalling (73). Nonetheless, PD-L1 immunohistochemistry expression can be variable and thus the value of PD-L1 is questionable (74).

Cadherin-11

Cadherin-11 mediates adhesion between FLS and contributes to the formation of the synovium lining layer. Additionally, cadherin-11 can stimulate FLS to produce inflammatory cytokines and MMP (40). Meanwhile, cytokines IL-1β and TNF-α in the joint fluid can increase cadherin-11 expression through the PI3K-Akt pathway, eventually promoting proliferation, migration, and invasion of FLS through a positive feedback loop. This underlying molecular mechanism can cause joint destruction, relapses, or even metastasis and, therefore, may be used as a prognostic molecular marker for D-TGCT. Finally, cadherin-11 inhibition could present a new promising treatment strategy by weakening the migration and invasion of FLS (40, 64, 65).

Systemic therapies

In the last decade, the safety and efficacy of several drugs regarding TGCT have been investigated (Table 2) (Figure 2). The systemic therapies are categorised by drugs targeting the CSF1-CSF1R axis and other therapeutics and published peer-reviewed data is separated from studies whose results are awaited. Furthermore, studies are presented in chronological order of publication.

Table 2. Systemic treatment studies

Authors	Year	Drug	Class	Therapeutic target	Administration	Company	Funded by company	Type of study	Patients
Blay et al.(57)	2008	Imatinib	TKI	CSF1R	Oral	Novartis	Yes	Case-report	1
Cassier et al.(75)	2012	Imatinib	TKI	CSF1R	Oral	Novartis	No	Retrospective cohort	29*
Stacchiotti et al.(76)	2013	Imatinib	TKI	CSF1R	Oral	Novartis	No	Case-report	2
Verspoor et al.(77)	2019	Imatinib	TKI	CSF1R	Oral	Novartis	No	Retrospective cohort	62*
Mastboom et al.(78)	2020	Imatinib	TKI	CSF1R	Oral	Novartis	No	Retrospective cohort	25
Cassier et al.(79)	2015	Emactuzumab	CSF1R AB	CSF1R	Intravenous	Roche	Yes	Phase I	29
Cassier et al.(80)	2020	Emactuzumab	CSF1R AB	CSF1R	Intravenous	Roche	Yes	Phase I	63*
Gelderblom et al.(81)	2018	Nilotinib	TKI	CSF1R	Oral	Novartis	Yes	Phase II	56
Tap et al.(82)	2015	Pexidartinib	TKI	CSF1R	Oral	Daichii-Sankyo	Yes	Phase I/II	41 + 23
Tap et al.(83)	2019	Pexidartinib	TKI	CSF1R	Oral	Daichii-Sankyo	Yes	Phase III	120 (59 placebo)
Gelderblom et al.(84)	2020	Pexidartinib	TKI	CSF1R	Oral	Daichii-Sankyo	Yes	Retrospective cohort	130*
Cheng et al.(85)†	2015	Lacnotuzumab	CSF1 AB	CSF1	Intravenous	Novartis	Yes	Phase II, abstract	5
Sankhala et al.(86)†	2017	Cabiralizumab	CSF1R AB	CSF1R	Intravenous	Five Prime therapeutics	Yes	Phase I/II, abstract	22
Smith et al.(87)†	2021	Vimseltinib	TKI	CSF1R	Oral	Dicephera	Yes	Phase I/II, abstract	3
Gelderblom et al.(88)†	2021	Vimseltinib	TKI	CSF1R	Oral	Dicephera	Yes	Phase I/II, abstract	68*
Kroot et al.(89)	2005	Infliximab	Anti-TNF-α	TNF-α	Intra-articular	Unknown	Unknown	Case-report	1
Fiocco et al.(90)	2006	Etanercept	Anti-TNF-α	TNF-α	Intra-articular	Unknown	Unknown	Case-report	2
Fiocco et al.(67)	2010	Etanercept	Anti-TNF-α	TNF-α	Intra-articular	Unknown	Unknown	Case-series	4
Nissen et al.(91)	2014	Bevacizumab	VEGF AB	VEGF	Intra-articular	Roche	No	Case-report	1
Takeuchi et al.(92)†	2019	Zaltoprofen	NSAID	PPARγ	Oral	Nippon Chemiphar	No	Phase II, abstract	10

*TNF Tumour necrosis factor, TKI Tyrosine Kinase Inhibitor, VEGF vascular endothelial growth factor, AB antibody, CSF1 Colony-stimulating factor 1, CSF1R Colony-stimulating factor 1 receptor NSAID non-steroidal anti-inflammatory drug PPARγ Proliferator-activated receptor gamma *included patients that were involved in a prior study † studies representing preliminary result*

CSF1-CSF1R targeted therapies

Imatinib

Imatinib is an inhibitor of a few tyrosine kinases, including Abelson proto-oncogene (Abl), breakpoint cluster region-Abl (Bcr-Abl) complex, c-Kit proto-oncogene (KIT), platelet-derived growth factor receptor (PDGFR) and CSF1R (75). Before imatinib was applied in TGCT, this oncogene-targeted therapy was already indicated for patients with chronic myeloid leukemia and gastrointestinal stromal tumours (57). The effect of imatinib on TGCT was first evaluated in one patient, in which complete remission was observed five months after initiation (57). After treatment interruption, TGCT relapsed both clinically and radiologically, but diminished again after treatment was resumed. After successful treatment of this single patient, a retrospective study reported the effect of imatinib in 29 patients with advanced or metastatic D-TGCT (57, 75). Imatinib is an oral drug, dosed at 400 mg daily. Imatinib led to an objective response rate (ORR) of 20% according to Response Evaluation Criteria in Solid Tumours (RECIST) and symptomatic/functional improvement in 74% of patients. Although a substantial activity against D-TGCT was observed, the effect was less when compared with GIST and dermatofibrosarcoma protuberans, probably due to a lower activity against CSF1-driven chemotaxis (75). Six patients had to stop due to toxicity (of which three had grade 3 or 4 toxicities), and four without any apparent medical reason (75).

Subsequently, the same study group described the long-term efficacy of imatinib on the initial 29 patients and 33 additional patients. In this cohort, 31% had radiological response and 78% had clinical improvement. A drop-off rate of 59% within a year suggested an unfavourable efficacy/toxicity balance, with grade 3–4 toxicities occurring in 11%. All four patients with metastatic TGCT progressed rapidly on imatinib (77).

Another research group observed partial response in 32% after imatinib use, consistent with the previous reports. Additionally, this study showed a significant decrease in the maximum standardised uptake value (SUV-max) on PET-CT after imatinib. However, 80% of the patients discontinued treatment with imatinib for poor response or intended surgery (78).

Finally, Stachiotti et al. showed anti-tumour activity following imatinib in two patients resistant to prior nilotinib. They assumed that targeted agents with similar profiles could induce different clinical results. However, further research is required (76).

Emactuzumab

Emactuzumab is a recombinant, humanised monoclonal Immunoglobulin 1 (IgG1) antibody directed against CSF1R (93). In a phase I trial, Cassier et al. determined the safety, tolerability, and clinical activity of emactuzumab in 28 patients (79). After a median

follow-up of 12 months, 86% of the patients showed an objective response, of which 2 achieved complete response; one patient had a relapse. The most frequent adverse events were facial edema, asthenia, pruritus, and rash. Five serious adverse events were reported, of which three were grade 3, including lupus erythematosus twice. Overall, emactuzumab was well tolerated, but 20% of patients dropped out due to adverse events. Eight patients who were resistant to either imatinib or nilotinib or both before achieved objective tumour response. The authors hypothesised that the difference in activity between imatinib, nilotinib and emactuzumab could be attributed to the fact that imatinib and nilotinib are no strong inhibitors of CSF1R.

The same research group performed a subsequent study, including 63 patients, to evaluate the long-term clinical benefit and safety (80). The best ORR of 71% was observed, and responses were durable at one- and two years at 70% and 64%, respectively. Stable disease was achieved in 98%, which changed to 93% at one- and two-year follow-up. In addition, a significant improvement in the EQ-5D-3 L QoL and WOMAC was observed. Reported AEs were comparable with the previous study. Nine patients (14%) withdrew from the study due to AEs. Finally, a reduction in tumour-associated CD68/CD163-positive and CSF1R-positive cells was shown. Durable responses were seen despite a relatively short treatment duration, which can be interpreted as an advantage.

A third study estimated the optimal biological dose (OBD) based on the previous phase I study. They recommended an OBD of 1000 mg intravenously every two weeks. Dosing flexibility is possible by dosing emactuzumab once every three weeks (94).

Nilotinib

Nilotinib was the first drug whose efficacy and safety was investigated in an open-label, phase II trial for non-resectable D-TGCT (81). Nilotinib inhibits tyrosine kinases Abl, KIT, PDGFR and CSF1R. Patients received 400 mg orally twice daily until treatment discontinuation or completion of 1 year of treatment. Of 51 evaluable patients, 49 (96%) were progression-free at 12 weeks and 46 (90%) at 24 weeks. After one year of treatment, the best objective response was partial response achieved in three patients (6%) and stable disease in 46 (90%). In total, ten (20%) patients had had disease progression during the 1-year study period. Six patients discontinued nilotinib due to disease progression; five patients due to toxicities. Headache, nausea, increased alanine aminotransferase (ALT) concentrations, fatigue and asthenia, were the most common AEs. Nine grade 3 AEs occurred, including hepatic disorders and toxicodermia. Post-hoc analysis showed progression-free survival in 57% at 48 months. However, secondary resection and nilotinib treatment duration had no additional effect on progression-free survival, although selection biases of patients for surgery are probable.

Pexidartinib

Pexidartinib is a novel TGCT targeting drug, the first drug approved by the US Food and Drug Administration (FDA) (95). It was derived from other TKIs, and showed more potential in blocking CSF1R dependent cells and limited cross-reactivity with other kinases. Besides strong selective activity against CSF1R, it also inhibits KIT and fmls-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) (82). In a phase I study by Tap et al., 41 patients were enrolled in various dose-escalation cohorts. 27% had at least one drug-related adverse event of grade 3 or higher, including anaemia, increase in aspartate aminotransferase level (AST), and decrease in lymphocytes. The maximum tolerated dose was set at 1000 mg per day taken orally. In the phase II extension study, 23 patients with D-TGCT were enrolled. Frequently experienced AEs were hair colour change, fatigue, nausea, dysgeusia, and periorbital oedema. Eight patients had grade 3 or higher AEs, including elevated levels of liver enzymes. Two patients discontinued treatment because of AEs. Disease control was observed in 19 (83%) patients, of which 12 had a partial response. Only one patient with metastatic TGCT had disease progression after a stable period of eight months.

The same study group performed a phase III, randomised, mutational, double-blind, then an open-label trial with pexidartinib (83). One hundred twenty patients were randomly assigned to pexidartinib (n = 61) or placebo (n = 59) treatment. At 25 weeks, the ORR in the pexidartinib group was 39% according to RECIST and 56% by tumour volume score (TVS) compared to 0% in the placebo group for both measurements. In addition, clinical outcomes were significantly improved in the pexidartinib group compared to the placebo group. However, 98% of the patients in the pexidartinib group experienced AEs. Grade 3–4 AEs occurred in 44% and mainly consisted of increased levels of AST, ALT, alkaline phosphatase (AP) and hypertension. Eight patients (13%) discontinued treatment with pexidartinib due to AEs, of which seven were liver-related (including hepatotoxicity and hyperbilirubinaemia requiring liver dialysis procedures). Subsequently, 30 patients from the placebo group were assigned to a crossover group with 800 mg pexidartinib a day. Of this group, 30% had RECIST response, and 57% had TVS response at week 25. Patients in this group experienced fewer liver enzyme elevations and no bilirubin increases or signs of drug-induced cholestatic hepatotoxicity.

Finally, the same study group described the long-term outcomes of pexidartinib by pooling analysis encompassing the three pexidartinib-treated TGCT cohorts described above (84). One hundred thirty patients received pexidartinib for a median duration of 19 months at data cutoff. With a median follow-up of 39 months, the RECIST ORR was 60%, the TVS ORR was 65%. Tumour response often occurred within six months after treatment but occurred even more after long-term pexidartinib treatment. The median treatment duration was 19 months. A total of 16 (12%) patients progressed on therapy or after

treatment discontinuation. 127 (98%) patients experienced one or more treatment-related AEs; 57 patients (44%) had grade 3 or higher treatment-related AEs of which fourteen had treatment-related serious AEs. 119 (92%) patients had aminotransferase elevations, predominantly AST and ALT. Four (3%) patients experienced mixed or cholestatic hepatotoxicity, which started within eight weeks of the first treatment and was reversible.

Because of the risk of hepatotoxicity, frequent monitoring of liver function is needed to help balance the benefit-to-risk. Since long-term safety data did not show late-emerging or cumulative toxicities, monitoring is especially required in the first two months. In the EU the European Medicines Agency (EMA) refused market authorization due to uncertainties on the risk-benefit ratio. In the US, pexidartinib was FDA approved and available through the risk evaluation management system (REMS) program, which ensures appropriate monitoring (96, 97).

Preliminary results of CSF1-CSF1R targeted therapies

Lacnotuzumab

Lacnotuzumab (MCS110) is a monoclonal antibody against CSF1. Preliminary results of lacnotuzumab in TGCT patients in a phase Ib/II study were presented during a congress (85). Five patients were treated with a single dose of 10 mg/kg intravenously. Lacnotuzumab was well tolerated with no drug-related AEs. Four weeks after dose administration, the tumour volume by MRI was reduced by 40%. Improvement in clinical symptoms and pharmacodynamics effects were also observed. Results of study extension, with multiple-dose administration and a goal of tumour ablation, are awaited.

Cabiralizumab

In 2017, preliminary results of a phase I/II study of cabiralizumab were presented (86). Cabiralizumab is a monoclonal antibody that inhibits the interaction of CSF1 and IL-34 ligands with their shared receptor CSF1R. Cabiralizumab was intravenously administered in 22 patients with inoperable D-TGCT every two weeks for six months in different dosages. Positive functional status improvements by Ogilvie-Harris scores (combination of pain, synovitis, range of motion and functional capacity on a scale of 0–12) were noted in objective responders (from 2 to 7). Most reported AEs were creatine kinase elevations, rash and other skin disorders, fatigue and oedema; 10 grade 3 AEs were reported. Updated results are awaited.

Vimseltinib

Vimseltinib is a selective, orally administered inhibitor of CSF1R. In contrast to small-molecule inhibitors of CSF1R, this drug is designed to be selective not affecting closely related kinases KIT, FLT3, PDGFRA, PDGFRB, and the rest of the kinome (87). This

selectivity potentially leads to a more optimal CSF1R suppression. It is currently being evaluated in a phase I/II clinical study for the treatment of TGCT. The first three TGCT patients, included in the phase I trial, showed rapid, preliminary anti-tumour activity by three cycles with deepening response over time. Vimseltinib was generally well tolerated in these patients, although the authors concluded it was too premature to draw safety conclusions on this limited data set (87).

Results of the first 68 patients included in this phase I/II clinical study were recently presented at the European Society for Medical Oncology congress 2021 (88). The majority of common treatment-emergent AEs were grade 2 or lower; most common grade 3 or 4 AEs were increased levels of creatine phosphokinase in blood. Two serious AEs were reported, consisting of metabolic encephalopathy and vaginal haemorrhage and three (4%) patients discontinued treatment due to treatment-emergent AEs. The median duration of treatment in the phase 1 cohort was 10.1 months and a high ORR of 50% according to RECIST was observed. In the phase II cohort, an ORR of 42% was seen in evaluable patients. The study is still ongoing with continuing follow-up evaluation and a randomised, placebo-controlled, phase III trial evaluating the effect vimseltinib is started (MOTION-study).

Other therapeutics

Tumour necrosis factor-α blockage

Three studies have reported the effect of TNF-α blockade treatment, with only seven patients in total receiving this treatment (67, 89, 90). Off-label intra-articular infliximab injection was administered in one patient and etanercept in six. Improvement in knee function, regression in synovial stromal fibrosis and vasculogenesis, reduction of cellularity and synovial fluid and decreased thickness were observed. On the other hand, no decrement in CSF1 protein of mRNA expression nor synovial tumour shrinkage was seen after infliximab administration. TNF-α blockade treatment affects the reactive component of TGCT but less likely the neoplastic cells. Although Fiocco et al. considered anti-TNF-α antibody injections as a possible neoadjuvant treatment before synovectomy, they concluded that TNF-α blockade alone does not seem to lead to stable remission of D-TGCT and is ineffective in blocking CSF1 secretion (67).

Bevacizumab

Among other activators such as hypoxic stress, CSF1 is also reported to induce angiogenesis via vascular endothelial growth factor (VEGF) expression in monocytes, essential for tumourigenesis (68, 98). Bevacizumab is a humanised monoclonal VEGF antibody and thus inhibits angiogenesis. Nissen et al. investigated the effect of intra-articular injections with bevacizumab as adjuvant therapy after arthroscopic synovectomy in one patient with relapsing D-TGCT located in the knee (91). During follow-up, complete response was

observed, and the patient reported no symptoms nor adverse events (AEs). However, dosage and number of injections and total follow-up duration were not described. Additionally, the effect of synovectomy prior to bevacizumab is unknown. To our knowledge, this is the only report regarding bevacizumab applied for TGCT.

Preliminary results of other therapeutics

Zaltoprofen

Based on the approaches with zaltoprofen in rheumatoid arthritis and targeted therapy activating PPARγ in other types of cancer, the anti-tumour effect of zaltoprofen was investigated on primary cultured TGCT cells (92). Zaltoprofen, a non-steroidal anti-inflammatory drug (NSAID), was found to inhibit cell proliferation via activation of PPARγ. Subsequently, a pilot study of zaltoprofen in D-TGCT affecting the knee and ankle joints was conducted, including ten patients. Oral zaltoprofen was given daily for 48 weeks or until disease progression. At 48 weeks, eight patients had stable disease, and one patient showed progressive disease at 72 weeks. Zaltoprofen was well-tolerated. With the results of this pilot study, a study protocol of a double-blind phase II study of zaltoprofen for D-TGCT and unresectable L-TGCT was published. Results are awaited.

Conclusion

To date, the preferred choice of treatment for TGCT remains surgical excision. However, there is a need for other therapeutic strategies in patients where local tumour control cannot be achieved and (repeated) surgery is associated with iatrogenic morbidity. Furthermore, the role of (neo)adjuvant radiotherapy is disputed, because it is associated with unacceptable long-term side effects. A better understanding of the pathogenesis of TGCT led to opportunities for the development of medical therapies. In the last decade, new drug targets were discovered, and the efficacy and safety of several drugs have been studied. Currently, pexidartinib is the only drug approved for TGCT by the US FDA. Pexidartinib showed significant radiological and clinical efficacy, but also severe adverse events occurred, including hepatotoxicity. Therefore, active monitoring of liver functions is mandatory. Contrarily, the EMA refused marketing authorisation because it was unclear how long treatment effects would last and because of an unbalanced risk/benefit ratio. More recently, new treatments are under research and recent discoveries regarding new therapeutic targets are promising for the development of drugs with even better tolerability and higher efficacy.

Expert opinion

Several efforts have been made during the past years to augment the treatment armamentarium for TGCT, especially for patients with relapsing or inoperable D-TGCT. Also, for orphan diseases, such as TGCT, there is a need for tailored therapy. After the discovery of the presence of CSF1 translocations in TGCT, the CSF1-CSF1R axis became the main pathway to target. Imatinib was one of the first TKIs regularly used off-label (57). Nilotinib was assumed to have a favourable tolerability profile, especially concerning oedema. However, the radiological response was inferior to imatinib and a substantial number of patients discontinued treatment (95). With both drugs, more patients discontinued treatment without tumour progression than usually in oncology trials, which could be attributed to the nonmalignant character of TGCT and thus lower patient-acceptance rate of side-effects. Pexidartinib, another TKI, was designed to have higher selectivity against CSF1R, leading to better response (82). Nonetheless, rare but serious liver injuries occurred in patients on pexidartinib treatment, resulting in marketing authorisation refusal by the EMA. Of the reviewed therapeutic strategies, drugs targeting the CSF1/CSF1R axis showed potential in tumour size reduction and improving quality of life. However, most CSF1R inhibitors also target closely related tyrosine kinases next to CSF1, leading to off-target activity and causing an unfavourable risk-benefit ratio for a subset of patients (87). Also, the long-term efficacy of most of the CSF1R inhibitors is still unknown to date. The evidence regarding other therapeutic strategies is limited and therefore their efficacy cannot be accurately assessed. Currently, new drugs, such as vimseltinib, are being investigated, aiming to have less interference with other tyrosine kinases than CSF1R, resulting in a more favourable safety profile (87, 88) Secondly, the effect of intra-articular injections with CSF1R inhibitors is being studied, hoping to cause less systemic adverse events but having at least comparable local efficacy (99). Finally, blockage of other targets than CSF1 or overlapping pathways may provide new solutions in the future (28, 40, 62, 63, 92).

A limitation in all studies is the lack of an appropriate method to monitor the medical treatment effect on TGCT tumour growth. TGCT treatment response is predominantly scored by RECIST, which evaluates target lesions over time by one-dimensional criteria (maximum diameter), although TGCT has an irregular shape and no clear tumour margins. TVS was explicitly developed for TGCT for volumetric quantification of tumour in relation to the maximally distended synovial cavity and is mainly used for tumour assessment in the knee (82). Still, TVS is an unvalidated, semiquantitative scoring approach. This underlines the need for future approaches for volume measurement in TGCT.

Until now, only patients with inoperable D-TGCT or patients with expected morbidity of operative treatment qualified for TKI therapy, yet inoperable TGCT is not clearly defined. At present, multidisciplinary tumour boards are best capable of determining which patients should receive systemic treatment. Looking at the future, it would be a massive step in the tailored treatment of TGCT to identify predictive and/or prognostic markers to select patients who would benefit from specific drug agents.

Besides not knowing which patients will benefit the most, questions remain about treatment tendencies. Little is known about the optimal treatment duration or length of response. In pexidartinib, tumour response often occurred within six months after the first treatment, but even more tumour responses occurred after long-term treatment (84). However, in a relatively young population, chronic treatment is undesirable. Emactuzumab showed durable responses despite a relatively short treatment duration, which could also be an advantage for intermittent treatment. A study to evaluate discontinuation and re-treatment with systemic therapy in patients with TGCT is now open to inclusions (100). Finally, since complete response is not very common, perhaps studies should focus more on partial response, achieving a stable state of disease or improving QoL. Current systemic therapies target the CSF1/CSF1R axis and may not eliminate the neoplastic cells, making it impossible to achieve a true, complete response. Drug cessation is expected to result in a return of the reactive cells and subsequent lesion growth. Therefore, future studies should focus on targeting the neoplastic cell components.

Although systemic therapies are primarily used as a stand-alone treatment in patients with advanced TGCT, their role as (neo)adjuvant therapy and in an earlier stage of the disease is yet to be explored. Starting earlier with such treatment could prevent disease worsening and even secondary joint deterioration. In addition, these therapies may be used for surgical downstaging in inoperable cases or to decrease expected morbidity. However, post-hoc analysis showed no additional effect of surgery performed directly after nilotinib treatment(81). Secondly, the effect of CSF1R inhibition on angiogenesis and the role of macrophages, which are essential in the postoperative course, needs to be further elucidated (60). Besides the role as (neo)adjuvant therapy, the efficacy of CSF1R inhibitors combined with other therapies, such as anti-VEGF therapy, requires further investigation.

Medical treatment paved the way for those patients not amenable to surgery, despite the uncertainties regarding the optimal treatment. There is an unmet medical need for broader availability of TGCT related drugs, but drug approval can be challenging in rare diseases (101).

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Abbreviations

TGCT – Tenosyonvial giant cell tumour
CSF1 – Colony-stimulating factor 1
CSF1R – Colony-stimulating factor 1 receptor
D-TGCT – Diffuse-type tenosynovial giant cell tumour
L-TGCT – Localised-type tenosynovial giant cell tumour
PVNS – Pigmented villonodular synovitis
M-CSF – Macrophage colony-stimulating factor 1
COL6A3 – Collagen type VI alpha-3
CBL – Cas-Br-Murine ecotropic retroviral transforming sequence
ALOX5AP – Arachidonate 5-lipoxygenase–activating protein
SSP1 – Osteopontin
MMP – Matrix metalloproteinase
TP53 – Tumour suppressor protein p53
FLS – Fibroblast-like synoviocytes
IL-1β – Interleukine-1β
TNF-α – Tumour necrosis factor-α
MRI – Magnetic resonance imaging
QoL – Quality of life
RSO – Radiosynoviorthesis
EBR – External beam radiotherapy
Abl – Abelson proto-oncogene
Bcr-Abl – Breakpoint cluster region-Abl
KIT – c-Kit proto-oncogene
PDGFR – Platelet-derived growth factor receptor
TKI – Tyrosine kinase inhibitors
JAK2 – Janus-Kinase-2
PD-L1 – Programmed cell death ligand 1
RANKL – Receptor-activator of nuclear factor kappa-B ligand
cIAP2 – Cellular inhibitor of apoptosis 2
ARRB2 – β-Arrestin2
VEGF – Vascular endothelial growth factor
AE – Adverse events
GIST – Gastrointestinal stromal tumours
ORR – Objective response rate
RECIST – Response evaluation criteria in solid tumours
IgG1 – Immunoglobulin 1
OBD – Optimal biological dose

FDA – Food and Drug Administration
ALT – Alanine aminotransferase
FLT3-ITD – Fmls-like tyrosine kinase 3 internal tandem duplication
AST – Aspartate aminotransferase level
TVS – Tumour volume score
REMS – Risk evaluation management system
PPARγ – Proliferator-activated receptor gamma
NSAID – Non-steroidal anti-inflammatory drugs
EMA – European Medicines Agency

Chapter 9

Long-term follow-up of nilotinib in patients with advanced tenosynovial giant cell tumours

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Abstract

Background

Diffuse-type tenosynovial giant cell tumour (D-TGCT) is a non-malignant but locally aggressive tumour driven by overexpression of colony-stimulating factor-1 (CSF1). CSF1R inhibitors are potential therapeutic strategies for patients not amenable to surgery. We report here the long-term outcome of nilotinib in patients with advanced D-TGCT treated within a phase II prospective international study (ClinicalTrials.gov: NCT01261429).

Methods

Patients were enrolled between December 2010–September 2012 at 11 cancer centres. Eligible patients had histologically confirmed D-TGCT, not amenable to surgery. Patients received nilotinib until evidence of progression, toxicity or a maximum of one year. Long-term data were retrospectively collected after the completion of the phase II trial. Patients with nilotinib treatment ≥12 weeks and follow-up ≥12 months were included for long-term analysis.

Results

Forty-eight of 56 enrolled patients were included. Median treatment duration was 11 months; 31 (65%) patients completed the treatment protocol. After 102 months of follow-up (median; range 12–129), 25 patients (52%) had progression. The median progression-free survival (PFS) was 77 months. The five-year PFS rate was 53%. Fifteen patients (n = 15/46; 33%) experienced clinical worsening after 11 months (median). Twenty-seven patients (58%) received additional treatment, after which eleven patients (n = 11/27; 41%) had a second relapse. Nine patients required a subsequent treatment, primarily other CSF1R inhibitors (n = 6/9; 67%). No unfavourable long-term effects were observed.

Conclusion

This long-term analysis of nilotinib for advanced D-TGCT showed that about half of the patients had progression and underwent additional treatment after 8.5 years follow-up. Contrarily, several patients had ongoing disease control after limited treatment duration, demonstrating the mixed effect of nilotinib.

Introduction

Tenosynovial giant cell tumour (TGCT) is a rare, connective tissue tumour affecting the synovium of joints, bursae and tendon sheaths in a relatively young population (1, 2). TGCT consists of two main subtypes: localised-type (L-TGCT) and diffuse-type (D-TGCT), of which the diffuse variant can behave locally aggressive (3). Formerly the names giant cell tumour of tendon sheath and pigmented villonodular synovitis (PVNS) were used for these subtypes, respectively. Malignant TGCT is considered as the third subtype; however, this is extremely rare (4).

TGCT is predominantly driven by chromosomal aberrations involving colony-stimulating factor 1 (CSF1) gene, leading to an overexpression of CSF1 (5-7)]. CSF1 overexpression stimulates the growth and proliferation of neoplastic tumour cells and also accumulates cells of the macrophage lineage expressing CSF1 receptor (CSF1R) (6). There is no clear histological distinction between the two TGCT subtypes; they are predominantly distinguished by radiological and clinical presentation (8).

Complete surgical excision is the mainstay of treatment for TGCT, curing L-TGCT in 80–90% (9-11). For D-TGCT, complete resection is often not achievable or associated with morbid surgery due to the extensive villous tumour growth intra- and extra-articular (12, 13). Local relapses occur in more than 50%, and repeated surgery is usually necessitated (13). Both repeated surgery and mutilating surgery in advanced cases of TGCT can cause iatrogenic morbidity. For these cases, there is an unmet medical need for additional therapeutic strategies. Radiotherapy can be used as (neo)adjuvant treatment or stand-alone, but data regarding the efficacy of radiotherapy is limited and of low-level quality (14, 15). Additionally, radiotherapy is related to complications such as avascular necrosis, osteoarthritis and even radiation-induced malignancies, an important issue for a locally aggressive yet benign disease (14, 16-18).

More recently, novel drugs targeting CSF1R are being developed and the safety and efficacy are evaluated for patients with relapsing or inoperable D-TGCT (19-24). CSF1R-inhibiting drugs, consisting of CSF1R antibodies and tyrosine kinase inhibitors (TKI), have shown substantial clinical activity (25). A phase II clinical trial evaluating the effect of nilotinib in patients with locally advanced D-TGCT, was started in 2010 (ClinicalTrials.gov: NCT01261429) (23). Nilotinib is a phenylaminopyrimidine, inhibiting several tyrosine kinases, including ABL, KIT, platelet-derived growth factor receptors and CSF1R. Nilotinib is an approved drug for chronic myelogenous leukaemia (26). Nilotinib was found to have short-term anti-tumour activity, achieving disease control in more than 90% of patients with advanced D-TGCT (23).

The effect of CSF1R antagonists on TGCT has only been studied in the last decade. Therefore, data regarding their long-term efficacy is limited. Nevertheless, it is essential to know the long-term effects of CSF1R inhibitors because TGCT has its onset in a relatively young patient population. The present study is an extension of the previously published phase II clinical trial and the article reports the long-term outcomes of nilotinib in patients with advanced inoperable or relapsing D-TGCT (23).

Material and Methods

This study describes the long-term effect of nilotinib in patients with locally advanced D-TGCT. This is a long-term report of a multi-centre, open-label, single-arm, phase II trial, registered with ClinicalTrials.gov, number NCT01261429 (23, 27). Patients were enrolled at 11 cancer centres or hospitals in four countries (France, the Netherlands, Italy and Australia) between December 2010 and September 2012. A summary of this study and a comprehensive overview of the in- and exclusion criteria can be found in the appendix (supplementary Table 1). The study protocol of the phase II trial was approved by the local ethics committee at each site and is available online (23, 27). This study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Procedures

During the phase II trial, patients received oral nilotinib 400 mg twice per day until disease progression, intolerable toxicities, patient's decision to withdraw or completion of one-year treatment. Patients were followed up at fixed time points up to 12 months. Patients who were progression-free after one year of treatment could receive continuation of nilotinib as compassionate treatment. Radiological response was assessed by CT scan or MRI according to Response Evaluation Criteria in Solid Tumours 1.1. After one year of treatment, local teams classified tumours as operable or not operable.

As the study did not foresee a follow-up period after the end of the first year, the long-term effect of nilotinib was studied by retrospectively updating the investigator-assessed progression in October 2021. This long-term follow-up was performed at each site according to the local schedule. Data regarding progression following nilotinib treatment and subsequent therapies were retrospectively collected from patient medical records. This study primarily focused on patients receiving at least 12 weeks of nilotinib treatment (the primary endpoint in the phase II trial) and a follow-up of ≤12 months for long-term analysis.

Outcomes

The primary endpoint was the long-term progression-free survival (PFS). Secondary endpoints were duration of response, median time to progression, clinical worsening, nilotinib-related long-term adverse events, operability after nilotinib and types of subsequent therapies.

Statistical analysis

Continuous data were described using means and standard deviations (SD) or medians and interquartile ranges (IQR). Kaplan–Meier method was used to analyse PFS. The statistical analyses were performed in IBM Statistical Package for Social Statistics (SPSS) 25 (Chicago, IL, USA) was used for analysis. A swimmer plot was created using RStudio version 4.1.0 (RStudio Team, Boston, United States).

Results

During the phase II trial, 56 patients were enrolled. Data from all included patients were made available by the investigators from the recruiting institutions. Six patients (10.7%) discontinued treatment before the primary endpoint at 12 weeks and two patients (3.6%) had a follow-up ≤12 months and were not included in the long-term analysis. A total of 48 of 56 patients (85.7%) were included in this long-term analysis (Figure 1). Two of the eight patients not included for long-term analysis had progressive disease as the best objective response within 12 weeks of treatment. Of the 56 patients enrolled during the phase II trial, 29 patients (51.8%) had tumour progression and the median PFS was 77 (IQR 12.0–97.0) months.

The 48 patients included for the long-term analysis had a mean age of 37 years (SD ± 13.7) at nilotinib initiation. Before nilotinib initiation, three patients (6.3%) received imatinib, two patients (4.2%) had radiotherapy and 32 patients (66.7%) underwent surgery with a median of 24 months (IQR 11.0–50.0) before initiation with nilotinib. Table 1 presents the patient characteristics of the included patients.

Table 1. Baseline demographics and treatment characteristics

Features	N = 48
Age, years, mean	36.6 (13.7)
Sex	
Women	24 (50.0)
Men	24 (50.0)
Time since diagnosis, months, median	22 (4.0 – 86.0)
Primary tumour location	
Knee	23 (47.9)
Hip	6 (12.5)
Ankle	7 (12.5)
Foot	5 (10.4)
Ulna	1 (2.1)
Wrist	2 (4.2)
Hand	3 (6.3)
TMJ	1 (2.1)
Previous treatment with imatinib	3 (6.3)
Time since imatinib start, months, median	13.3 (5.1)
Previous treatment with radiotherapy	2 (4.2)
Time since radiotherapy, months, mean	48.5 (16.3)
Previous surgery	32 (66.7)
Time since last surgery, months, median	24 (11.0 – 50.0)
Duration of treatment, months, median	11 (8.0 – 12.0)
Treatment duration of 12 months (according to protocol)	25 (52.1)
Treatment duration >12 months (compassionate use after end of protocol)	6 (12.5)
Treatment duration <12 months	17 (35.4)
Time till treatment discontinuation, months, median	7 (4.5 – 8.5)
Reason treatment discontinuation	
Patient's refusal	5 (29.4)
Disease progression	4 (23.5)
Tumour resection	4 (23.5)
Toxicity	2 (11.8)
Investigators choice	1 (14.3)
Other	1 (14.3)
Best OR	
Partial response	3 (6.3)
Stable disease	45 (93.8)

Data are n (%), mean (standard deviation) or median (interquartile range)
OR Overall response; TMJ Temporomandibular joint

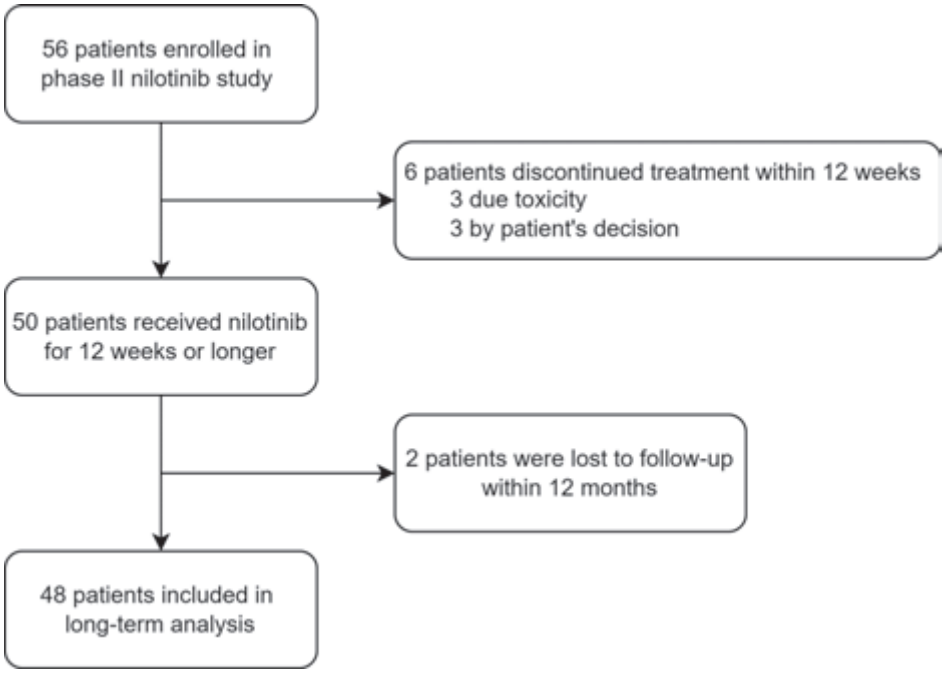


Figure 1. Flowchart of patients included for the long-term analysis.

For the 48 patients, median duration of nilotinib treatment was 11 months (IQR 8.0–12.0) and 31 patients (52.1%) completed 12 months of treatment according to the protocol (Table 1). Six patients continued nilotinib as a compassionate treatment after one year for 5–48 additional weeks (total treatment duration range 13–22 months). Seventeen patients (35.4%) discontinued treatment prematurely, primarily due to patients' refusal (n = 5), disease progression (n = 4), tumour resection (n = 4), toxicity (n = 2). Median time to treatment failure was seven months (IQR 4.5–8.5). Under nilotinib treatment, three patients (6.3%) achieved a partial response as best overall response and 45 patients (93.8%) achieved stabilization of disease. The four patients with on-treatment progression achieved stable disease as best overall response before progression, and then progressed 5–8 months after starting with nilotinib treatment.

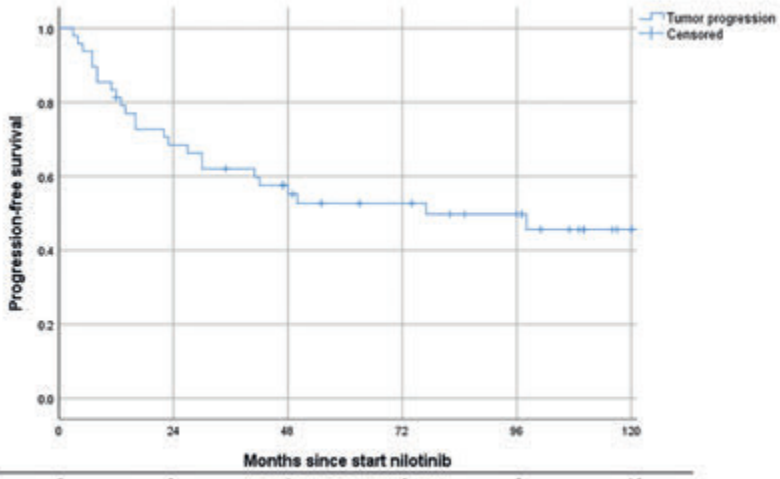
Long-term follow-up of TGCT

The median follow-up since nilotinib initiation was 102 months (8.5 years; IQR 65.0–111.8 months) (Table 2). Tumour progression was reported in 25 of 48 patients (52.1%), in 18 cases (72.0%) after nilotinib completion of which four patients received a subsequent treatment before progression. The three patients who achieved a partial response remained without tumour progression and their duration of response till the last moment of follow-up were 49, 63 and 110 months, respectively. Amongst the 25 patients who progressed, the median time until progression was 16 months (IQR 8.0–41.5). The median PFS was reached after 77 months (Figure 2). PFS rates at three, five and seven years were 62.0% (SD ± 13.9), 52.7% (SD ± 14.5) and 49.7% (SD ± 14.7), respectively (Figure 2). Nine of eleven patients (82%) who received nilotinib for approximately one year (11–12 months) and did not undergo a subsequent treatment remained progression-free after a median of 79 months. Furthermore, the five-year PFS rate from treatment discontinuation for patients completing treatment protocol and who did not have progression or clinically deteriorate under nilotinib was 71.5% (SD ± 19.4) (Figure 3). Fifteen patients (n = 15/46, for two patients this data was not available; 32.6%) experienced clinical worsening after a median of eleven months (n = 14; IQR 7.0–30.5) of which in seven cases (46.7%) under nilotinib treatment. No long-term adverse events were reported.

Table 2. Long term follow-up characteristics

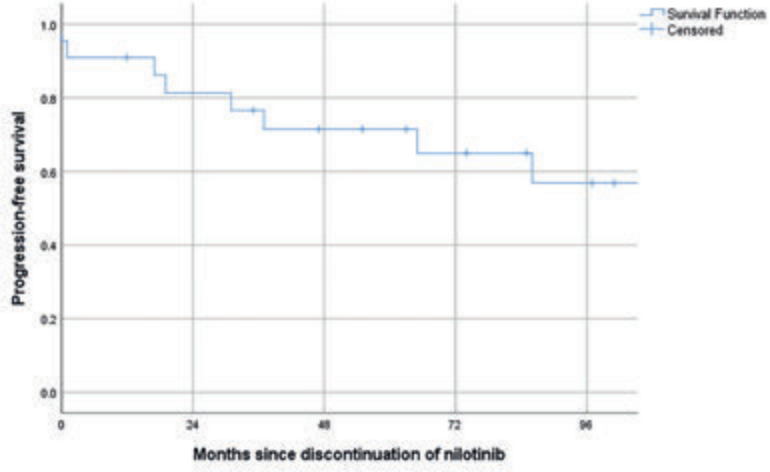
Features	N = 48
Total follow-up, median, months	102 (65.0 – 111.8)
Progression disease	**25 (52.1)**
Time to tumour progression, months, median	16 (8.0 – 41.5)
Under nilotinib	7 (28.0)
After nilotinib	18 (72.0)
Clinical worsening*	**15 (32.6)**
Time to clinical worsening, months, median	11 (7.0 – 30.5)
Under nilotinib	7 (46.7)
After nilotinib	8 (53.3)
Operable tumour after start nilotinib	31 (64.6)
Underwent surgery	17 (54.8)
First subsequent treatment after nilotinib	**27 (56.3)**
Synovectomy	19 (70.4)
Other CSF1R inhibitors	
Imatinib	4 (14.8)
Emactuzumab	2 (7.4)
Other	
Total knee arthroplasty	1 (3.7)
Embolization	1 (3.7)
Time to subsequent therapy*, months, median	6 (2.0 – 18.0)
Progression after subsequent therapy	**11 (22.9)**
Time to progression from subsequent therapy, months, mean	27 (27.7)
Second subsequent treatment after nilotinib	**9 (18.8)**
Synovectomy	2 (22.2)
Radiotherapy	1 (11.1)
Other CSF1R inhibitors	
Imatinib	1 (11.1)
Emactuzumab	3 (33.3)
Pexidartinib	1 (11.1)
Vimseltinib	1 (11.1)
Time from first subsequent therapy to second subsequent therapy, months, median	21 (5.5 – 61.5)

Data are n (%), mean (standard deviation) or median (interquartile range)
**For two patients this data was missing*



Years since nilotinib	0	2	4	6	8	10
Patients at risk	48	32	24	19	15	3

Figure 2. Progression-free survival since start of nilotinib (Kaplan–Meier analysis).

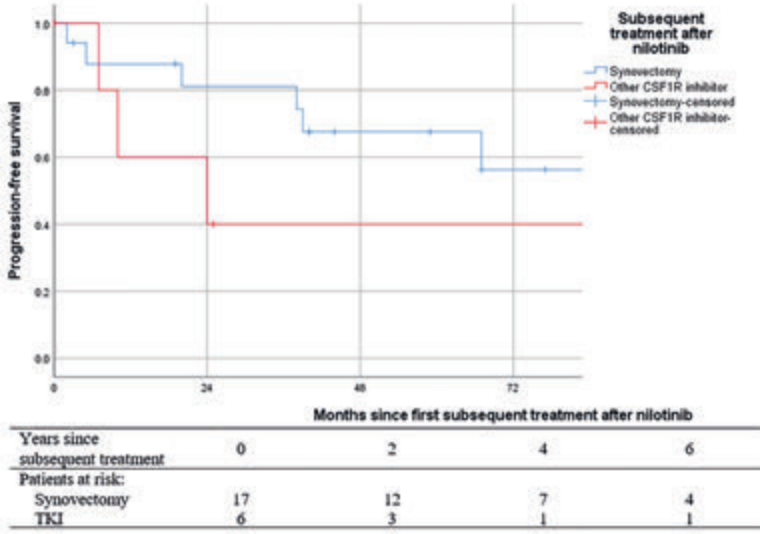


Years since treatment discontinuation	0	2	4	6	8
Patients at risk	22	17	13	10	7

Figure 3. Progression-free survival since discontinuation of nilotinib of patients completing treatment protocol and not having disease progression or clinical deterioration under nilotinib treatment (Kaplan–Meier analysis).

Subsequent therapies

D-TGCT was assessed as an operable tumour in 31 of 48 patients (64.6%) at the completion of the phase II trial (Table 2). Twenty-seven of 48 patients (58.3%) had subsequent therapy (median 6 months; IQR 2.0–18.0) after nilotinib cessation (Table 2). Patients mainly underwent synovectomies (n = 19/27; 70.4%) or received other CSF1R inhibitors (n = 6/27; 22.2%) as first subsequent treatment. Seventeen of the 31 patients (54.8%), who were assessed as operable (54.8%), underwent an additional synovectomy. In addition, nine of 23 patients (39.1%) having no tumour progression underwent a synovectomy following one-year nilotinib treatment. Six of 19 patients (31.6%) undergoing a synovectomy and 4 of 6 patients (66.7%) receiving another CSF1R inhibitor after nilotinib had tumour progression (Figure 4). TGCT progressed after a median of 17 months (range 7.0–84.0) following a second CSF1R inhibitor. In total, 11 of 27 patients (40.7%) were not cured after a subsequent therapy and nine (81.8%) had an additional treatment after 21 months (median; IQR 5.5–61.5). The majority received other CSF1R inhibitors (n = 6/9; 66.7%). A more extensive overview of the individual patients' TGCT course and related treatments can be found in Figure 5.



Years since subsequent treatment	0	2	4	6
Patients at risk:				
Synovectomy	17	12	7	4
TKI	6	3	1	1

Figure 4. Progression-free survival following the first subsequent treatment after nilotinib (Kaplan–Meier analysis).

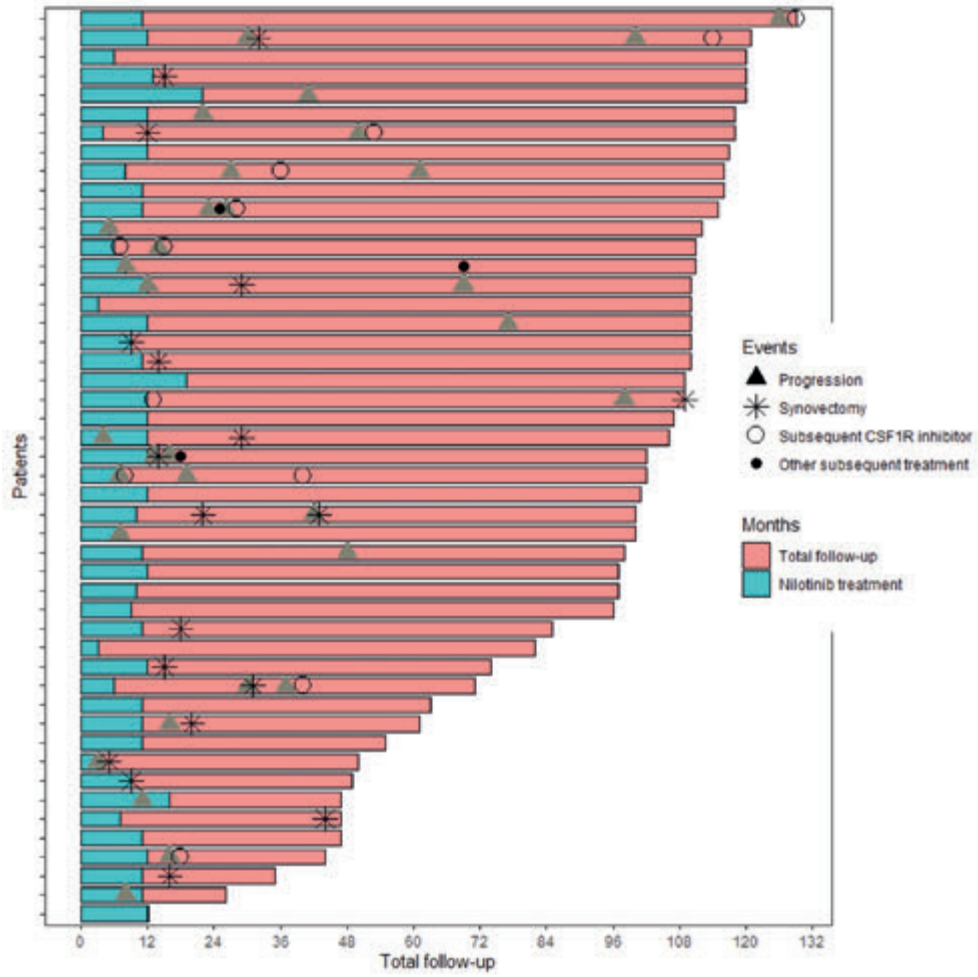


Figure 5. Swimmer plot showing the duration of nilotinib treatment and follow-up in individual patients with locally advanced D-TGCT included for long-term analysis.

Discussion

The interest in CSF1R inhibitors for TGCT is growing, offering new therapeutic possibilities for patients not amenable to surgery (28). TGCT has its onset in a relatively young patient population and is a non-malignant disease (2, 3). Therefore, patients will be followed for a long period, and it is of great importance to know the long-term effects of therapeutic strategies. This study evaluates the long-term efficacy of nilotinib in patients with progressive, advanced D-TGCT patients and, to our knowledge, contains the longest follow-up of TGCT treated with CSF1R inhibitors.

Nilotinib was the first TKI prospectively investigated in patients with advanced D-TGCT and provided a benchmark for alternative therapeutic strategies. As a result, a follow-up of more than eight years could be achieved to evaluate the long-term efficacy of nilotinib. Although most patients with progressive D-TGCT reached at least stabilisation of disease under nilotinib and a considerable amount of patients remained progression-free after a brief treatment duration, radiological tumour progression and clinical worsening frequently occurred after a relatively short period. Higher PFS rates were observed for patients completing treatment protocol and showing clinical benefit. Contrarily, half of the patients had subsequent therapies, demonstrating the mixed efficacy of nilotinib. Subsequent therapies after nilotinib mainly consisted of synovectomies and other CSF1R inhibitors. The relapse rates were lower in patients treated by surgery following nilotinib than would be expected from postoperative relapse rates reported in literature (13, 29). Although we cannot conclude that nilotinib followed by surgery improves PFS based on this small heterogeneous group and the lack of a control group, multi-modality treatment including a CSF1R inhibitor and synovectomy deserves further exploration. The proportion of patients who received another CSF1R inhibitor as subsequent treatment was relatively high, considering that CSF1R inhibitors are only available as part of trials outside the US.

Since the first report of the activity of CSF1R inhibitors in TGCT, several drugs have been developed and investigated (28). The long-term efficacy of several other TGCT-related drugs has been studied, comprising imatinib and pexidartinib (both TKIs) and emactuzumab (CSF1R antibody) reporting a median follow-up of 52 months, 39 months and 24 months, respectively (30-32). Better overall responses were observed for these CSF1R inhibitors, although patients receiving imatinib or pexidartinib discontinued treatment more often. However, an external comparison cannot be made, since these drugs were investigated in different designs and cohorts. Currently, only pexidartinib is approved in the US by the Food and Drug Administration (33). The European Medicines Agency has not approved medical treatment for TGCT to date due to the safety profiles (34). CSF1R inhibitors are associated with relatively high rates of adverse effects in relation to a young healthy population with, albeit cumbersome, benign disease. Nilotinib was assumed to have a more favourable tolerability profile than imatinib, causing less soft tissue and facial oedema (23, 35). During the phase II trial, 96% of the patients experienced treatment-related adverse events, of which six (11%) patients had at least one grade 3 treatment-related adverse events (23). Fourteen (25%) patients discontinued treatment for reasons other than disease progression or an operable tumour, including toxicity, investigator's choice and patient's withdrawal. In other studies, investigating the safety and efficacy of CSFR1 inhibitors, even complications such as liver failure are reported (36). In a non-life-threatening disease, it is essential to achieve a considerable benefit/risk ratio since patients are less willing to accept severe adverse effects. Especially, when complete response is not achieved and treatment

could be chronic. Reassuringly, no long-term adverse events were observed during follow-up in this study. Nilotinib's patent expires in 2023 in both the United States and the European Union, and could be a possible solution as a low-cost off-label drug (37).

More recently, new CSF1R inhibitors have been developed and investigated, such as cabiralizumab and vimseltinib (22, 38). Apparently, cabaralizumab is not developed further whereas vimseltinib is currently being explored in a phase III registration study (MOTION) (39). With the arrival of CSF1R inhibitors showing greater potential, the current role of nilotinib in TGCT treatment can be questioned. In addition to systemic therapies, the effect of intra-articular injections with CSF1R inhibitors is being studied, which are expected to cause less systemic adverse events but may be locally effective (40). The first results are awaited.

Future studies on TGCT should also focus on selecting the most favourable patients and an adequate treatment plan. There is an unmet need to identify patients who will benefit from these drugs, if CSF1R inhibitors applied as (neo)adjuvant therapy improve tumour control and if they are suitable for intermittent usage (41). Nilotinib seems less appropriate for intermittent use since only 6% achieved partial response and duration of response lasted for 15 months. On the other hand, many patients had ongoing disease control after treatment discontinuation. This suggests that TKI discontinuation in TGCT is not inevitably linked to progression, as seen in other diseases such as advanced gastrointestinal stromal tumours, possibly justifying treatment breaks (42). Because nilotinib's primary effect in TGCT is considered to target non-neoplastic cells, it is unlikely that treatment breaks promote resistance. Therefore, effective and well-tolerated CSF1R inhibitors could be given for longer durations. We encourage future studies to collect long-term data regarding different treatment durations, retreatment or alternative treatments.

This study contains several limitations. Although the nilotinib phase II study was a prospective trial, current data were retrospectively collected for this long-term study. This resulted in some missing data and follow-up regimes were performed according to local schedules. Secondly, radiological progression, clinical worsening and adverse events were not assessed by validated criteria such as RECIST, patient-reported outcome measurements or CTCAE because this was no longer performed after study completion. Additionally, the criteria such as radiological progression, clinical worsening and tumour operability were assessed by local teams and not centrally. This could possibly introduce assessment bias. However, these criteria were assessed by experts from reference sarcoma centres, which might decrease heterogeneity. Also, all expert centres provided their data and we were able to include all patients from the original study in the current analysis. Finally, since

this is a single-arm study, there is an inability to distinguish between treatment effect and natural behaviour of TGCT, which is not well understood to date.

In conclusion, this study reports nilotinib's long-term efficacy. Nilotinib showed mixed long-term efficacy regarding volumetric progression and clinical worsening for patients with advanced D-TGCT. Contrarily, several patients had ongoing disease control after a relatively short treatment duration, which could justify treatment breaks. In addition, no long-term adverse events were observed. However, with the arrival of CSF1R inhibitors showing greater potential, the current role of nilotinib in TGCT is questionable.

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Appendix

Supplementary Table 1. Summary of Nilotinib phase II trial by Gelderblom et al. 2018.

Study ID (NCT No.) / study title	Study design	Inclusion criteria	Exclusion criteria	Dose regimen, and patients	Outcomes
NCT02371369 Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial	Phase II, open-label, single-arm Including 11 centres from 4 countries Inclusion period: dec 2010 – sept 2012	≥ 18 years WHO performance status ≤ 2 Histologically confirmed TGCT Progressive/relapsing D-TGCT that was inoperable or resectable with mutilating surgery ≥1 measurable lesion according RECIST 1.1 Adequate liver, renal, hematological functions, normal potassium and magnesium levels, normal cardiac function	Previous treatment with imatinib (except patients with no disease progression under imatinib) Hypersensitivity to nilotinib Concomitant treatment with warfarin, anti-arrhythmic drugs, medication that prolongs the QT interval Medical products that induce or inhibit CYP3A4 activity Acute or chronic uncontrolled liver disease, severe renal disease, impaired cardiac function, hypertension, severe or uncontrolled concurrent medical disease Family history of long QT syndrome, unexplained syncope or sudden death	Nilotinib 400 mg twice per day One year of treatment 56 patients included	Primary endpoint: Progression free at 12 weeks Secondary endpoints: Progression free at 24 weeks, OR rate at 12 weeks, Progression free at 12 weeks according local investigator, Best OR during study, Duration of response, Progression free survival, Time to treatment failure, Inoperable tumour after nilotinib according local investigator, Concomitant treatment use. Association between Nilotinib levels and OR, Adverse events according CTCAE

RECIST Recist evaluation criteria in solid tumours; OR Objective response, defined as complete response or partial response according to RECIST; CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

Chapter 10

Thesis summary, general discussion and future perspectives

This thesis investigated the journey of patients with diffuse-type Tenosynovial Giant Cell Tumour (TGCT), ranging from the onset of symptoms to the multidisciplinary treatment. This final chapter summarises the results and conclusions and discusses future perspectives.

Thesis summary

The following chapters shed light on the intricacies of TGCT, especially the diffuse-type (D-TGCT), and the efforts to understand and manage this rare neoplasm. **Chapter 2** introduces the Tenosynovial Giant Cell Tumour Observational Platform Project (TOPP), the first prospective disease registry involving 176 patients from multiple sarcoma centres in Europe and the United States (1) .This study gained insight into the characteristics of D-TGCT by assessing the journey of these patients from disease onset to diagnosis, disease severity, treatment patterns, rate of recurrence and impact of the disease on patient-reported outcome measurements (PROMs). Also, the effect on health outcomes and economics was described. D-TGCT has its onset in a relatively young working population and may interfere highly with daily activities such as work (2). There is often a delay in diagnosis of multiple years and visits of several medical practitioners before receiving the proper diagnosis. With high recurrence rates and limited treatment options, the treatment of D-TGCT is complex and often based on the disease status and clinical expertise of the treating physician. Therefore, developing multidisciplinary guidelines is essential. Patients evaluated by multidisciplinary teams only sometimes require a change of treatment plan, as evidenced by the low rate of changing treatment strategy over the 2-year observational period (3).

As observed in Chapter 2, patients often experience a delay in diagnosis. Conventional radiographies often do not show abnormalities. Magnetic Resonance Imaging (MRI) is the imaging modality of choice to diagnose TGCT and evaluate disease severity (4, 5). **Chapter 3** describes the imaging characteristics of D-TGCT affecting the knee, including several differential diagnoses that can mimic D-TGCT. A structured report template is provided to scrutinise the knee's anterior, middle and posterior compartments and medial and lateral gutters (6). Also, the evaluation of tumour response on new systemic therapies is described. Finally, a first attempt was made at objective volumetric quantification of D-TGCT by 3D segmentation. Although this was a time-consuming and operator-dependent process, since all cases were segmented manually, automated volumetric quantification of tumour load will become more critical as systemic therapies evolve quickly (7).

Once D-TGCT is diagnosed, an adequate treatment plan is required. For symptomatic patients, surgery is still regarded the primary choice in treatment (8, 9). However, more information is needed about the natural course of D-TGCT and the effect of active

surveillance (10). **Chapter 4** analyses D-TGCT patients initially treated with active surveillance and its effect on the radiological and clinical course. This international, multicentre retrospective cohort included 61 therapy-naïve patients from eight sarcoma centres worldwide (11). During follow-up, 36% of the patients had radiological progression after a median of 21 months, and 18% of the patients who did not have osteoarthritis at baseline developed degenerative changes during follow-up. On the other hand, 64% did not clinically deteriorate, and only one third required subsequent treatment. Although follow-up time was limited and only a subset of the D-TGCT patients were included, active surveillance can be considered an acceptable initial approach for therapy-naïve patients. We recommend that active surveillance should only be initiated after MDT agreement and shared decision-making with the patient balancing clinical complaints and the risk of progression or joint degeneration.

The surgical treatment of TGCT was explored in more detail in the following three chapters.

Chapter 5 evaluates the management of TGCT in the foot and ankle, one of the most common soft-tissue tumours of the foot and ankle (12). It is the first large series describing multimodal treatment, including systemic therapies. This is the only chapter including treatment of localised-type TGCT (L-TGCT) since this type is common in the foot and ankle. Eighty-four patients were retrospectively included from two sarcoma centres in the Netherlands and the United Kingdom, of which 44 had L-TGCT and 40 D-TGCT (13). L-TGCT predominantly affects the forefoot, while D-TGCT involves more extensive areas of the foot and ankle. Where most L-TGCT cases can successfully be treated by surgery alone, recurrence rates were relatively high for D-TGCT (61%). Systemic therapies initially had good results in D-TGCT patients not amenable to surgery but progressed in 36% during follow-up, and patients often experienced significant side effects. We recommend that patients with D-TGCT or severe L-TGCT will benefit from multidisciplinary treatment involving specialised clinicians such as foot/ankle and sarcoma surgeons together with oncologists.

Although complete excision is regarded as the gold standard, this can be challenging due to D-TGCT's extensive growth. Sometimes, surgeons deliberately choose not to resect all tumourous tissue, or it may be impossible to remove all tumour since extensive surgeries are associated with iatrogenic morbidity. **Chapter 6** reports the largest cohort of surgically treated D-TGCT patients in one sarcoma centre. This study aimed to analyse the effect of surgical intention (complete/incomplete resection) and postoperative tumour presence on radiological and clinical outcomes. In 20 years, 144 patients with D-TGCT underwent surgery as primary treatment in one sarcoma centre, of which 125 were treated by isolated

open synovectomies (14). In 80%, surgeons intended to remove all tumour tissue. There was a median follow-up of 64 months. Both incomplete resections and the presence of postoperative remaining tumours were associated with significantly higher rates of radiological progression (p=0.021 and p=0.001, respectively). Furthermore, patients with postoperative tumour presence clinically worsened more frequently compared to patients without residual disease. Therefore, surgeons should aim for complete removal of D-TGCT balancing progressive disease and surgical sequelae. When complete removal of the tumour is not regarded feasible, one should consider other multimodal or neoadjuvant therapeutic strategies.

Chapter 7 is the last chapter investigating the surgical treatment of D-TGCT, especially the knee. D-TGCT is often located intra- and extra-articularly on both the anterior and posterior sides of the knee, requiring incisions from both sides (15-17). This study evaluated whether surgery on two sides of the knee should be performed in one or two stages and focused on postoperative short-term outcomes, such as achieved range of motion within one year after surgery, length of hospital stay and complications. In this international, multicentre, retrospective cohort study, 191 patients from nine sarcoma centres worldwide underwent a one- or two-stage synovectomy of the anterior and posterior side of the knee between 2000 and 2021 (18). Of these 191 patients, 117 underwent a one-stage synovectomy, and 74 a two-stage synovectomy. Patients undergoing a one-stage synovectomy did not experience impaired rehabilitation within one year after surgery, did not have more complications but had a shorter hospital stay (4 vs. 6 days, $p < 0.0001$). One stage synovectomy is therefore considered safe and efficient in the surgical treatment of TGCT about the knee.

After looking into surgical therapies in more detail, the last two chapters focus on systemic therapies. The interest in this treatment modality is growing, and they provide new options for patients not regarded amenable to surgery (7, 10).

Chapter 8 reviews disease mechanisms involved in TGCT, potential therapeutic targets and evaluates systemic therapies (19). The pathogenesis of TGCT is consistent apoptosis resistance, inflammation and matrix degradation. Although several pathways are involved in this pathogenesis, the most studied drug target is the Colony Stimulating Factor 1 (CSF1) – Colony Stimulating Factor 1 Receptor (CSF1R) axis due to the overexpression of CSF1 in TGCT patients. Different systemic therapies have been investigated, particularly CSF1-CSF1R targeted therapies, such as imatinib, emactuzumab, cabaralizumab, nilotinib, vimseltinib, and pexidartinib. Currently, only pexidartinib has been approved by the US Food and Drug Administration (20). The European Medicines Agency refused

market authorisation due to uncertainties on the risk-benefit ratio (21). Results are awaited of new therapies as there is an unmet need for broader availability of TGCT-related drugs.

Since CSF1R antagonists have only been studied in the last decade, data regarding their long-term efficacy still needs to be provided. Nevertheless, it is essential to know the long-term effects while TGCT has its onset in a young patient population. **Chapter 9** is the first study investigating the long-term effects of nilotinib in patients with advanced or relapsing D-TGCT. The study extends a previously conducted, multi-centre, open-label, single-arm, phase 2 clinical trial (ClinicalTrials.gov, NCT01261429) (22). Between 2010 and 2012, 56 patients were enrolled at 11 sarcoma centres. All patients received oral nilotinib twice daily until disease progression, intolerable toxicities, the patient's decision to withdraw or completion of one-year of treatment. This study analysed the long-term progression-free survival by retrospectively updating the investigator-assessed progression in 2021 (23). Of the 56 patients, 48 were included, with a median follow-up of 102 months. The median progression-free survival was 77 months, and the five-year progression-free survival was 53%. Twenty-seven (58%) received additional treatment. No unfavourable long-term effects were observed. This study demonstrated the mixed impact of nilotinib as several patients had ongoing disease control after limited treatment duration. In contrast, half of the patients had disease progression and required subsequent treatment.

General discussion & Future perspectives

Over the last two decades, the scientific interest in TGCT has been growing due to the druggable target CSF1R in TGCT (19). This led to a significant increase in research papers, and as a result, a consensus has been formed regarding treating L-TGCT (24). If symptomatic, this nodular tumour can be surgically removed with relatively low recurrence rates (25). However, treatment of D-TGCT remains open to discussion (10). Although D-TGCT is a benign tumour, it is likely to reoccur, can behave aggressively and can have a detrimental effect on the quality of life of young and active patients (26). Management of these non-malignant tumours can be complex, especially when they become chronic. Treatment may be required if patients experience symptoms, but not at any price. This thesis provided insight into the natural course of D-TGCT and the journey that patients undergo from disease onset into the diagnostic and heterogeneous treatment landscape. The goal was to create more disease awareness and to answer open questions regarding the optimal treatment strategy of D-TGCT.

In the past, a variety of names have been used for this family of lesions, such as pigmented villonodular synovitis, tenosynovial giant cell tumour of tendon sheath, synovial

xanthoma, synovial endothelioma, benign fibrous histiocytoma, amongst others (27). In 2013, the WHO established TGCT as an encompassing name, including the localised and diffuse subtypes (28). More recently, a group of sarcoma experts suggested changing the name of localised TGCT to nodular TGCT as it better reflects imaging and clinical findings (10). Besides, Tenosynovial Giant Cell Tumours also share the same abbreviation as Testicular Germ Cell Tumours (29). Continuously changing the nomenclature results in ambiguity, and it is recommended to be consistent in terminology to gain more awareness and disease familiarity (30). Furthermore, information regarding TGCT needs to be more accessible for health care practitioners and patients, and patient associations need to be promoted. This will lead to a decrease in diagnostic delays and referrals to the right healthcare professionals.

It is challenging to obtain substantial cohorts to address research questions for a rare disease with low incidence numbers, such as D-TGCT. This thesis set up multiple global collaborations between tertiary sarcoma centres to assemble meaningful research cohorts (2, 11, 13, 18). For example, the first prospective disease registry for D-TGCT (TGCT Observational Platform Project; TOPP) was conducted, and in this thesis, the first results of this prospective study were reported (2). Data was collected at set time points for two years. Setting up a prospective study for an orphan disease requires commitment, time, and often money, especially when a longer follow-up is desired. The downside of collaborations including only experienced tertiary sarcoma centres is that this possibly introduces selection bias by under-referral of less severe cases. On the other hand, the patient group with more severe or extensive tumour load is the most demanding in (surgical) management.

TOPP gave insight into the journey that D-TGCT patients undergo and showed that active surveillance is often regarded as the first treatment of choice, primarily for patients experiencing limited symptoms with subsequently less impact on their quality of life (2). This advocates that the disease burden drives shared treatment decision-making and that patient-based care is vital in this benign and often chronic disease. As a result, further research into the role of active surveillance in D-TGCT was performed in this thesis. In addition, TOPP demonstrated the demanding healthcare utilisation of D-TGCT, caused by multiple visits to physical therapists, medical specialists, hospitalisations, and rehabilitation, as well as social costs following work absence due to illness or even early retirement (2, 31).

Imaging

The clinical profile of D-TGCT is non-specific as is common in several joint diseases. MRI is the standard imaging modality to diagnose this disease as it shows characteristic imaging features (4, 32, 33). It is also helpful for preoperative mapping and assessment

of the response of systemic therapies (34, 35). MRI availability and quality are growing, making this modality more accessible. Assessing D-TGCT on MRI can be difficult, especially for those who do not often encounter this disease entity. Therefore, a structured report template is provided in this thesis (6). However, it is suggested that a dedicated (oncological) musculoskeletal radiologist should evaluate the MRIs due to the rarity and complexity of D-TGCT.

Other modalities, such as combinations of emission tomography and computed tomography, containing 18F-Flurodeoxyglucose positron emission tomography, computed tomography (18F-FDG-PET/CT) or bone single-photon emission computed tomography (SPECT/CT), have been reported to show distinctive features of D-TGCT, helpful in diagnosing (36, 37). However, their added value compared to MRI needs to be demonstrated, and these modalities are more complex, less available and have higher costs and radiation exposure.

With a growing interest in systemic therapies, MRIs are more frequently utilised to evaluate their effect. The response to systemic therapies is mainly assessed by quantification of tumour volume. The Response Evaluation Criteria in Solid Tumours (RECIST 1.1 or modified-RECIST) is a general tool used to detect changes in tumour size (34). However, D-TGCT's irregular shape, asymmetrical growth and lack of clear margins make RECIST unsuitable. More recently, Peterfy et al. developed a specific D-TGCT tool called tumour volume score (TVS) (35). TVS defines the tumour size relative to the joint size. It's a semiquantitative tool, and as clinicians have to estimate the percentage of tumour volume, it will introduce intra- and inter-observer variability.

Additionally, TVS still needs to be validated as a method for response assessment. This illustrates the need for automated volumetric quantification of D-TGCT on MRI. In this thesis, the first approach was made into 3D segmentation, allowing the quantification of the tumour volume objectively. Although 3D segmentation objectively measures the volume instead of estimating, the segmentations were performed manually and were thus operator-dependent. Automatic segmentation by deep learning has already been developed for knee synovitis (38). But developing automatic segmentation of D-TGCT has yet to be accomplished.

The severity of D-TGCT is not only based on tumour volume. Assessment of D-TGCT should also include other findings, such as inflammation, cartilage invasion, bone erosions, muscular, tendinous, ligament and neurovascular involvement (5). Finally, objective findings on MRI need to be correlated to PROMs, as a decrease in tumour volume does not always correspond to an improvement in PROMs and vice versa (14).

Treatment

The treatment armamentarium of D-TGCT is broad. Most patients are treated by surgery, as shown in TOPP, including different surgical approaches (3). D-TGCT is a heterogeneous tumour and ranges from a small intra-articular lesion to a widespread tumour located intra- and extra-articular (39). Specific surgical themes were addressed in this thesis to aid in treatment decision-making. Unfortunately, due to the retrospective character, these studies were performed without predefined radiological outcome measurements. In this thesis, we demonstrated that there is often residual tumour after surgery on MRI (14). Therefore, assessing radiographic outcomes in a standardised fashion can increase the reliability of future studies. On the other hand, the necessity of MRIs as part of standard follow-up is questionable. With a benign nature, QoL should be the main treatment goal and perhaps MRIs should only be performed on clinical indication.

When patient and surgeon decide that surgery is indicated, surgeons should pursue a complete macroscopic resection to achieve better outcomes in tumour control (14). Additionally, most tumours can be removed in one session without negatively impacting joint function, and patients have to rehabilitate only once (18). But if D-TGCT is located intra- and extra-articular, complete resection may not be feasible or may not be desirable, as extensive surgery can lead to joint damage or postoperative stiffness. In these cases, one should be cautious about planning only tumour debulking or primary irradical resection; and other treatment modalities should be considered.

An issue not addressed in this thesis is the choice of open or arthroscopic synovectomies. Although most surgeries were performed open in our studies, some experts allege for arthroscopic surgery (40-43). The advantages of arthroscopy are better visualisation of tumours, especially intra-articular, and hypothesised better functional outcomes. On the other hand, it can be challenging to access extra-articular tumour extend located in specific compartments and gutters, resulting in incomplete resection. Open surgery may provide a better overview and access to the tumour, but extensive open surgery can lead to iatrogenic morbidity. A meta-analysis by Chandra et al. estimated a 1.56 increased risk of recurrence after arthroscopic surgical management of D-TGCTs of the knee compared to an open approach (43). Contrarily, a recent case series showed promising results using posterior and trans-septal portals (44). Collaborations between oncological orthopaedic surgeons and skilled arthroscopic orthopaedic surgeons could improve oncological outcomes and can provide a solution when extensive open surgery is too morbid.

It remains difficult to determine which surgical approach provides the best outcomes due to the heterogeneity of D-TGCT disease extent and localisation, patient population and prior treatments. Therefore, individually tailored treatment is required. Besides surgery,

other modalities should be looked at, especially considering the high recurrence rates following surgery (9). Since D-TGCT is a non-life-threatening disease, a wait-and-see approach can be an option for patients whose current disease burden is acceptable and for whom surgical treatment could deteriorate complaints and does not outweigh the risk for progression (2, 3). Many patients do not clinically worsen during a follow-up of more than two years; some even improve and require no further treatment (11). Although active surveillance was only studied as primary treatment for patients included in this thesis, TOPP has demonstrated that this approach is also common and suitable for patients who underwent prior treatment (2). The majority remained on no treatment at the end of TOPP, although it is unknown if they remain without treatment after longer follow-up (3).

The role of radiotherapy as a stand-alone or (neo)adjuvant treatment remains disputed. Some studies have reported positive radiotherapy results, but their low-level quality limits these studies (45, 46). As D-TGCT is a non-malignant disease affecting a young patient population, the risk of radiation-induced malignant transformation is regarded unacceptable (47). Also, radiotherapy may cause complications such as fibrosis, joint stiffness or secondary osteoarthritis (48). However, the incidence of these adverse effects are considered very low, especially in low-dose radiation. Furthermore, these adverse effects have not been reported in more recent studies with a relatively long follow-up (49-51). With the development of systemic therapies, the role of radiotherapy seems to disappear into the background. Still, radiotherapy could be considered in selected cases such as patients who do not tolerate systemic therapies.

Since the first successful report of imatinib in a patient with D-TGCT, the interest in systemic therapies has grown rapidly (52, 53). It can provide an alternative treatment solution for patients not amenable to surgery. Several drugs have been developed and tested, where the majority of drugs focus on the inhibition of CSF1R, amongst others (19). Nevertheless, only one drug has been approved for the treatment of TGCT, namely pexidartinib, and this is only available in a couple of countries (20). In 2020, the European Medicines Agency refused market authorisation due to an unfavourable risk-benefit ratio(21). Only slight improvement in symptoms and joint function were observed, but hepatotoxicity occurred as adverse event in a few cases.(54) The Food and Drug Administration encountered this by mandating the risk evaluation management system (REMS) program (55). Furthermore, it was not clear how long the effect of pexidartinib lasted. Because systemic therapy developments for D-TGCT are relatively new, data regarding the long-term effects still need to become available in the near future. This is of utmost importance as D-TGCT affects a young patient population. A few studies, one of which is in this thesis, have shown that long-term tumour control can be achieved and that no new complications occur later on (23, 56-59). Approval of drugs for ultrarare

diseases can be challenging. When research organisations collaborate, it will be easier to set up randomised controlled trials, which may lead to accelerated drug approval (60, 61).

Most recently developed TGCT related drugs are tyrosine kinase inhibitors (TKIs). Pexidartinib was developed with stronger selective activity against CSF1R than prior TKIs. Although expected to result in fewer adverse events than non-selective CSF1R inhibitors, they still occurred (34). While D-TGCT is a benign disease, there is less urgency to eradicate the tumour and accept side effects against all costs compared to malignancies. Vimseltinib is a switch-control TKI designed explicitly with greater selectivity for CSF1R and not inhibiting closely related kinases, expected to cause less adverse events (62). The first results of a phase 1 and 2 study showed that vimseltinib was well tolerated and had a manageable safety profile (63). The results of a randomised, controlled phase 3 trial are still awaited (ClinicalTrials.gov, NCT05059262).

Intra-articular injections provide another pharmacotherapeutic option to enable high drug concentration at the tumour site while minimising systemic exposure and toxicity. Meaningful clinical improvement in function and quality of life were seen after 12 weeks in a pilot study where patients received a selective anti-CSF1R monoclonal antibody (64). The results of a phase 2 study are still awaited (ClinicalTrials.gov, NCT04731675). The local and systemic effect of administering a high dose of CSF1R inhibitor locally is not known yet.

Besides developing a drug with an optimal risk/benefit ratio, the usage of TGCT-related drugs needs to be further elucidated. There is still much unknown, such as the ideal length of treatment duration and the effect of intermittent treatment (56, 65, 66). Also, the effect of systemic therapy in combination with surgery requires further assessment (67). In cases with extensive tumour growth, systemic therapy might reduce tumour load so that complete resection can be performed resulting in better outcome of surgery. In contrast, in cases of incomplete resection, systemic therapies can target the residual disease and thus reduce the number and recurrences and elongate time to recurrence.

Recent translational research by IJzerdoorn et al. demonstrated that the neoplastic cells of TGCT lack an autocrine loop involving CSF1-CSF1R (68). This suggests that current CSF1-CSF1R inhibitors do not target the neoplastic cells but mainly affect bystander activated macrophages. However, the authors state that they cannot entirely exclude the possibility of CSF1R expression on neoplastic cells in rare cases. Additionally, they found expression of platelet-derived growth factor receptor (PDGFR) on neoplastic cells. Imatinib targets PDGFR and could, therefore, possibly target both the neoplastic cells

and bystander macrophages. Nonetheless, previous studies researching imatinib showed that several patients do not benefit from treatment with imatinib (56, 69).

Conclusion

The broad clinical spectrum of D-TGCT, varying from an asymptomatic indolent tumour to a locally aggressive tumour with high potential of recurrence, means that every patient's journey is unique. Treatments range from wait-and-see to surgery or systemic therapy (2). Treatment decisions are not necessarily right or wrong and should be individually tailored. Shared treatment decision-making is crucial to balance decreasing symptoms and improving function and quality of life on the one hand and obtaining tumour control and preventing/stopping further joint degeneration on the other hand. Due to the heterogeneity in clinical presentation, the multimodal treatment and conundrum in the order of treatment options, patients will benefit from care centralised in specialised sarcoma centres (70, 71).

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Chapter 11

Nederlandse samenvatting

Dit proefschrift onderzocht het traject van patiënten met de diffuse vorm van reusceltumour van de weke delen, ook wel tenosynoviale reusceltumour genoemd. De Engelse naam is Tenosynovial Giant Cell Tumour, afgekort als TGCT. Zowel de symptomen en de impact op de kwaliteit van leven van de ziekte als de multidisciplinaire behandeling zijn onderzocht. Dit hoofdstuk vat de resultaten en conclusies samen.

De volgende hoofdstukken belichten de complexiteit van TGCT, met name de diffuse vorm (D-TGCT), en de inspanningen die nodig zijn om inzicht te krijgen in deze zeldzame tumour en de behandeling hiervan. In hoofdstuk 2 wordt het Tenosynovial Giant Cell Tumour Observational Platform Project (TOPP) geïntroduceerd. Dit is het eerste prospectieve ziekteregister voor TGCT met 176 patiënten uit meerdere sarcomencentra in Europa en de Verenigde Staten. Dit onderzoek verkreeg inzicht in de kenmerken van D-TGCT door het beloop van deze patiënten te onderzoeken. Hierbij werd gekeken naar het beloop van het begin van de ziekte tot de diagnose, de ziektelast, behandelpatronen, recidiefkans en de impact van de ziekte op door de patiënt gerapporteerde uitkomsten (Patient reported outcome measurements; PROM's). D-TGCT komt voor bij een relatief jonge, werkende populatie en kan een sterke invloed hebben op dagelijkse activiteiten zoals werk. Het duurt vaak enkele jaren en verschillende bezoeken aan medisch specialisten voordat de diagnose wordt gesteld. Door de hoge recidiefkans en de beperkte behandelopties is de behandeling van D-TGCT complex en vaak gebaseerd op de ziekte-status van de patiënt en klinische expertise van de behandelend arts. Het is daarom essentieel om multidisciplinaire richtlijnen te ontwikkelen. Patiënten die beoordeeld zijn door een multidisciplinair team veranderen niet vaak van het eerder opgestelde behandelplan, zoals blijkt uit het lage wijzigingspercentage van de behandelstrategie gedurende de tweejarige observatieperiode.

Zoals geobserveerd in hoofdstuk 2, kan het soms lang duren voordat de definitieve diagnose wordt gesteld. Conventionele röntgenfoto's laten vaak geen afwijkingen zien. Magnetic Resonance Imaging (MRI) is de beeldvorming bij uitstek om TGCT te diagnosticeren en de ernst van de ziekte te evalueren. Hoofdstuk 3 beschrijft de kenmerken van beeldvorming van D-TGCT in de knie, inclusief verschillende differentiaaldiagnoses die D-TGCT kunnen imiteren. Er is een gestructureerd schema opgesteld om de voorste, middelste en achterste compartimenten van de knie en de mediale en laterale groeven te beoordelen. Ook wordt de evaluatie van tumorrespons op nieuwe systemische therapieën beschreven. Ten slotte werd er een eerste poging gedaan tot objectieve volumetrische kwantificatie van D-TGCT door middel van 3D-segmentatie. Dit proces was een tijdrovend en gebruiker afhankelijk proces was, omdat alle casussen handmatig werden gesegmenteerd. Desondanks zal geautomatiseerde volumetrische kwantificatie van het tumorvolume belangrijker worden naarmate systemische therapieën vaker toegepast zullen worden.

Zodra D-TGCT is gediagnosticeerd, is een adequaat behandelplan vereist. Voor symptomatische patiënten wordt chirurgie nog steeds beschouwd als de primaire keuze in behandeling. Er is echter meer informatie nodig over het natuurlijk verloop van D-TGCT en het effect van een 'active surveillance' beleid. Hoofdstuk 4 analyseert D-TGCT-patiënten die aanvankelijk een active surveillance beleid ondergingen en het effect daarvan op het radiologische en klinische verloop. Deze internationale, multicentre, retrospectieve cohortstudie omvatte 61 therapie-naïeve patiënten uit acht sarcomencentra wereldwijd. Tijdens de follow-up had 36% van de patiënten radiologische progressie na een mediane follow-up van 21 maanden. 18% van de patiënten die bij aanvang geen artrose hadden, ontwikkelden radiologische kenmerken passend bij slijtage tijdens follow-up. Aan de andere kant verslechterde 64% klinisch niet, en slechts één derde had een verdere behandeling nodig. Hoewel de follow-up tijd beperkt was en slechts een specifieke groep van de D-TGCT-patiënten werd opgenomen in deze studie, kan active surveillance worden beschouwd als een acceptabele initieel beleid voor therapie-naïeve patiënten. We adviseren om een active surveillance beleid alleen te starten na overleg binnen een multidisciplinair team en gedeelde besluitvorming met de patiënt, waarbij klinische klachten en het risico van progressie of gewrichtsdegeneratie worden afgewogen.

De chirurgische behandeling van TGCT werd nader onderzocht in de volgende drie hoofdstukken. Hoofdstuk 5 evalueert de behandeling van TGCT in de voet en enkel, een van de meest voorkomende weke delen tumoren van de voet en enkel. Het is de eerste grote serie die de multimodale behandeling beschrijft voor TGCT in de voet en enkel, inclusief systemische therapieën. Dit is het enige hoofdstuk dat ook de behandeling van de lokale vorm van TGCT (L-TGCT) omvat, aangezien dit type vaak voorkomt in de voet en enkel. Vierentachtig patiënten werden retrospectief geïncludeerd uit twee sarcomencentra in Nederland en het Verenigd Koninkrijk, waarvan 44 L-TGCT en 40 D-TGCT hadden. L-TGCT tast voornamelijk de voorvoet aan, terwijl D-TGCT meestal betrekking heeft op grotere delen van de voet en enkel. Terwijl chirurgie voor de meeste L-TGCT-patiënten een succesvolle behandeling was, waren de recidiefkansen voor D-TGCT na chirurgie relatief hoog (61%). Systemische therapieën hadden aanvankelijk goede resultaten bij D-TGCT-patiënten die niet geopereerd konden worden, maar in 36% vorderde de ziekte tijdens de follow-up en patiënten hadden vaak last van bijwerkingen. We denken daarom dat patiënten met D-TGCT of ernstige L-TGCT baat hebben bij een multidisciplinaire behandeling waarbij gespecialiseerde clinici zoals voet/enkel- en sarcoomchirurgen samen met oncologen betrokken zijn.

Hoewel complete resectie van de tumour wordt beschouwd als de gouden standaard, kan dit soms lastig zijn vanwege de uitgebreide groei van D-TGCT. Soms kiezen chirurgen er bewust voor om niet al het tumorweefsel te verwijderen, of is het niet mogelijk om

alle tumoren te verwijderen aangezien dergelijke uitgebreide operaties geassocieerd zijn met iatrogene morbiditeit. Hoofdstuk 6 bevat het grootste cohort van chirurgisch behandelde D-TGCT-patiënten in één sarcoomcentrum. Deze studie had als doel het effect van de chirurgische intentie (volledige/incomplete resectie) en postoperatieve tumoraanwezigheid op radiologische en klinische uitkomsten te analyseren. In een periode van 20 jaar ondergingen 144 patiënten met D-TGCT een operatie als primaire behandeling, waarvan 125 werden behandeld door alleen open synovectomieën. In 80% van de gevallen had de chirurg de intentie om al het tumorweefsel te verwijderen. Er was een mediane follow-up van 64 maanden. Zowel incomplete resecties als de aanwezigheid van tumour postoperatief waren geassocieerd met significant hogere percentages van radiologische progressie. Bovendien verslechterden patiënten met de aanwezigheid van tumour postoperatief klinisch vaker vergeleken met patiënten zonder resttumor. Chirurgen moeten daarom streven naar complete resectie van D-TGCT, waarbij er een balans moet worden gevonden tussen het voorkomen van progressie en de schade die uitgebreide chirurgie kan veroorzaken. Wanneer het niet haalbaar wordt geacht om de tumour volledig te verwijderen, moet men overwegen andere multimodale of (neo)adjuvante therapeutische strategieën te gebruiken.

Hoofdstuk 7 is het laatste hoofdstuk dat de chirurgische behandeling van D-TGCT onderzoekt en is gericht op de knie. D-TGCT bevindt zich vaak zowel intra- als extra-articulair aan zowel de voor- als achterkant van de knie. Hierdoor zijn er vaak excisies aan beide kanten van de knie nodig. Deze studie onderzocht of een synovectomie aan beide zijden van de knie in één of twee stadia moeten worden uitgevoerd. Het onderzoek richtte zich met name op de postoperatieve kort termijn uitkomsten, zoals de functie van de knie binnen één jaar na de operatie, de duur van het ziekenhuisverblijf en operatie gerelateerde complicaties. In deze internationale, multicentre, retrospectieve cohortstudie ondergingen 191 patiënten uit negen sarcomencentra wereldwijd een synovectomie van de voor- en achterkant van de knie in één of twee fasen tussen 2000 en 2021. Van deze 191 patiënten ondergingen 117 een synovectomie van de voor- en achterkant van de knie in één fase en 74 een synovectomie in twee fasen. Patiënten die een synovectomie van de knie in één fase ondergingen, ervaarden geen hinder in de revalidatie in het eerste jaar na de operatie, hadden niet meer complicaties en verbleven korter in het ziekenhuis. Een synovectomie van zowel de voor- als achterzijde van de knie in één fase wordt daarom als veilig en efficiënt beschouwd in de chirurgische behandeling van D-TGCT aan de knie.

Na het onderzoek naar chirurgische behandelingen richten de laatste twee hoofdstukken zich op systemische therapieën. Deze behandelopties bieden nieuwe kansen voor patiënten die niet in aanmerking komen voor chirurgie of geen chirurgie willen ondergaan en de interesse hierin neemt toe. Systemische therapieën kunnen in de toekomst mogelijk voor

een brede groep van D-TGCT-patiënten worden gebruikt, maar aanvullend onderzoek is noodzakelijk. Overexpressie van macrofaagkoloniestimulerende factor-1 (M-CSF of CSF1) is kenmerkend voor TGCT patiënten en de focus ligt daarom het meest op de Colony Stimulating Factor 1 (CSF1) - Colony Stimulating Factor 1 Receptor (CSF1R). Verschillende systemische therapieën zijn onderzocht, met name CSF1-CSF1R-gerichte therapieën, zoals imatinib, emactuzumab, cabiralizumab, nilotinib, vimseltinib en pexidartinib. Momenteel is alleen pexidartinib goedgekeurd door de Amerikaanse Food and Drug Administration. De European Medicines Agency heeft toelating tot de markt echter geweigerd vanwege onzekerheden over de risico-batenverhouding. Op korte termijn worden er resultaten van nieuwe therapieën verwacht aangezien er veel behoefte is aan een bredere beschikbaarheid van TGCT-gerelateerde geneesmiddelen.

Aangezien CSF1R-antagonisten pas in het laatste decennium worden gebruikt en zijn onderzocht, is de data met betrekking tot hun lange termijn effectiviteit nog beperkt. Desalniettemin is het essentieel om de lange termijn effecten te kennen aangezien TGCT met name optreedt bij een jonge patiëntenpopulatie. Hoofdstuk 9 is de eerste studie die de lange termijn effecten van nilotinib bij patiënten met gevorderde of recidiverende D-TGCT onderzoekt. Deze studie is een voortzetting van een eerder uitgevoerde multicentre, open-label, single-arm, fase 2 clinical trial. Tussen 2010 en 2012 werden 56 patiënten geïncludeerd bij 11 sarcomencentra. Alle patiënten kregen tweemaal daags nilotinib oraal totdat de ziekte verslechterde, er niet verdraagbare bijwerkingen optraden, de patiënt besloot te stoppen of de behandeling van een jaar was voldaan. De huidige studie analyseerde het aantal jaren dat de ziekte niet toenam op de lange termijn door de eerder verzamelde data in 2021 retrospectief bij te werken. Van de 56 patiënten was er van 48 patiënten lange termijn data beschikbaar, met een mediane follow-up van 102 maanden. De mediane progressievrije overleving was 77 maanden en de vijfjarige progressievrije overleving was 53%. Zevenentwintig (58%) patiënten kregen een aanvullende behandeling. Er werden geen nadelige lange termijn effecten geobserveerd. Deze studie toonde het ambivalente effect van nilotinib aan, aangezien bij verschillende patiënten de ziekte aanhoudend onder controle was na een beperkte behandelingsduur, terwijl de ziekte bij de helft van de patiënten vorderde en er een aanvullende behandeling nodig was.

Appendices

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Curriculum Vitae

Geert Spierenburg was born on October 9, 1992 in Zoeterwoude, The Netherlands, and is the youngest son of Ans van der Hulst and Ruud Spierenburg. In 2010, he graduated from the Stedelijk Gymnasium in Leiden, after which he began studying Lifestyle Informatics at the Vrije Universiteit Amsterdam. Although Geert enjoyed this innovative study, he was delighted when he was admitted to medical school at Leiden University the following year. Early in the bachelor's program, Geert was interested in orthopaedic surgery when educated about the musculoskeletal system. In 2015, he obtained his Bachelor of Science (BSc), after which he had to wait before starting his internships. During this waiting period, Geert performed his research internship in the oncological field of orthopaedic surgery at the Leiden University Medical Centre (LUMC), where he would later start his PhD career. Subsequently, Geert went to Austria following his passion for sports and obtained his ski-instructor certificate to give skiing lessons in Gerlos. His interest in orthopaedic surgery became clearer as he did multiple internships at the department of orthopaedic surgery in several hospitals. Additionally, he did an internship abroad in Suriname during his study. In 2018, he obtained his Master of Science (MSc) and started working as a non-training resident at the department of orthopaedic surgery at the LangeLand Hospital in Zoetermeer.

In 2019, he continued his career as a PhD candidate at the department of orthopaedic surgery in the LUMC under the guidance of Prof. Dr. M.A.J. van de Sande, Prof. Dr. A.J. Gelderblom, and Dr. L. van der Heijden. The results of this scientific journey are reported in this thesis. In the middle of his PhD, the COVID pandemic emerged, which made it challenging to collaborate with other hospitals worldwide and attend congresses. Nevertheless, global collaborations were set up and results were presented at several (inter)national conferences. He also contributed to the distribution of care for COVID patients throughout the region. Furthermore, he educated medical students clinically and scientifically during his PhD.

In 2023, he was admitted to the orthopaedic surgery residency, starting as a clinical resident in the surgical department at the Alrijne Hospital in Leiderdorp. In January 2025, he will continue his residency at the Reinier Haga Orthopaedic Centre (RHOC), LUMC, and Haaglanden Medical Center (HMC).