Tenosynovial giant cell tumour: from active surveillance to surgery and systemic therapy

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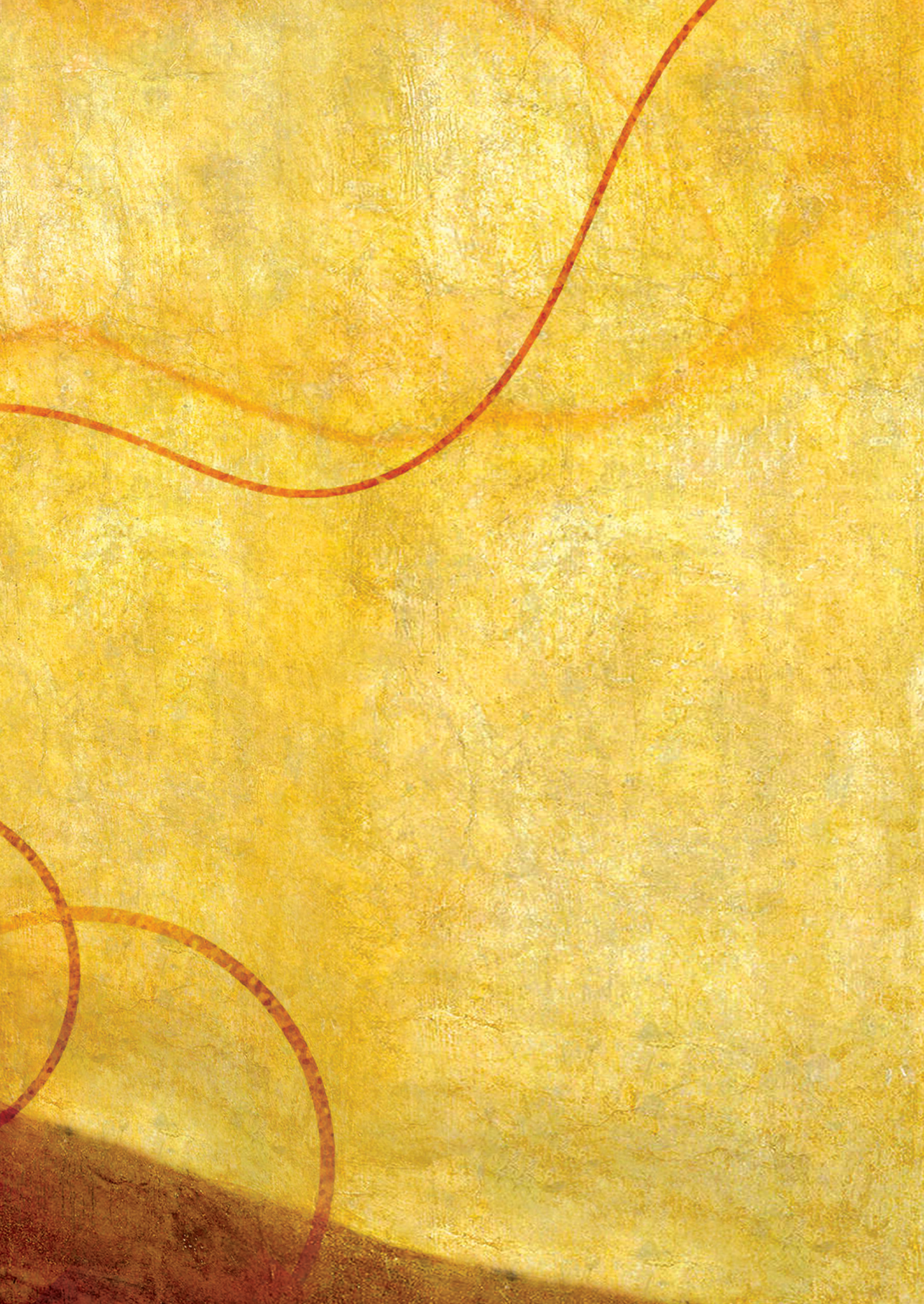

Chapter 5

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

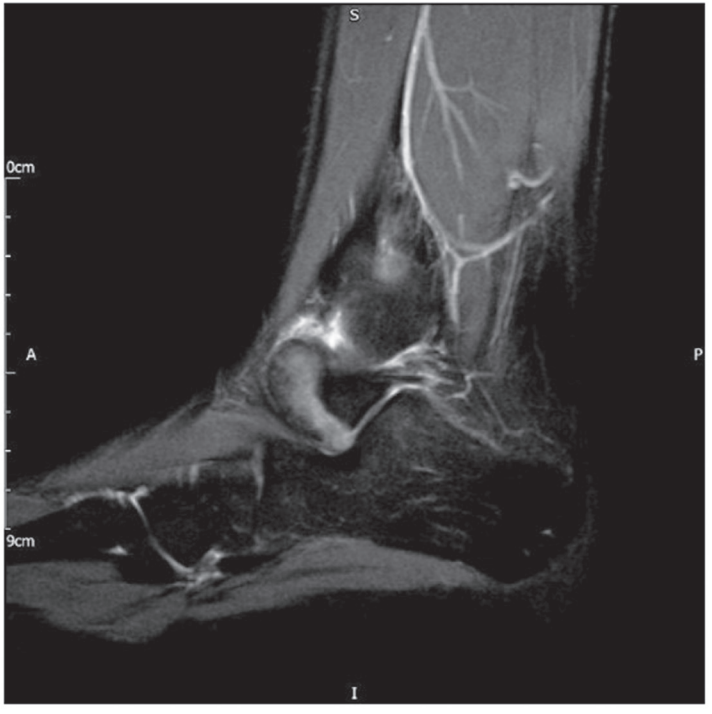

Figure 1a: Sagittal T2 MRI image showing a well-circumscribed lesion in the subtalar joint, presenting localised-type TGCT.

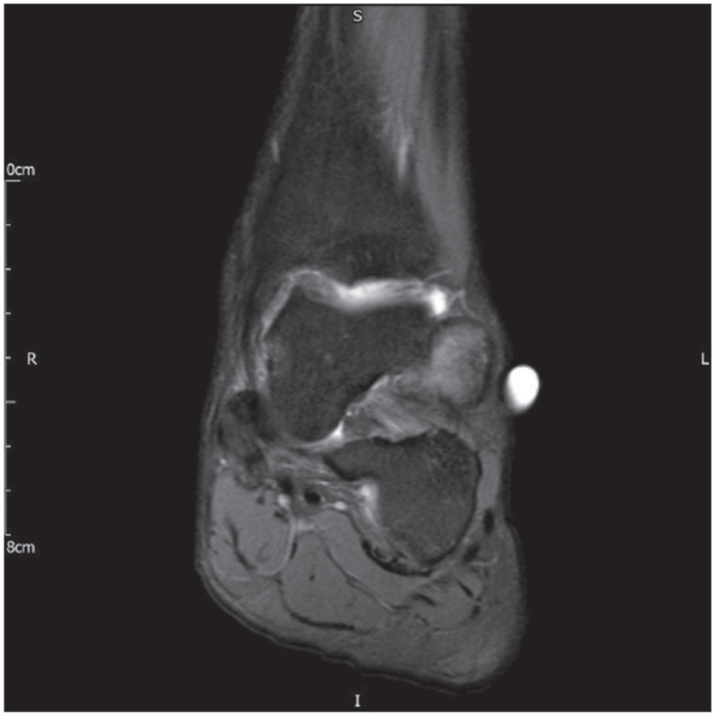

Figure 1b: Coronal T2 MRI images showing a well-circumscribed lesion in the subtalar joint, presenting localised-type TGCT. The white spot indicates the location where the patient experiences most complaints

Figure 2. Diffuse-type TGCT

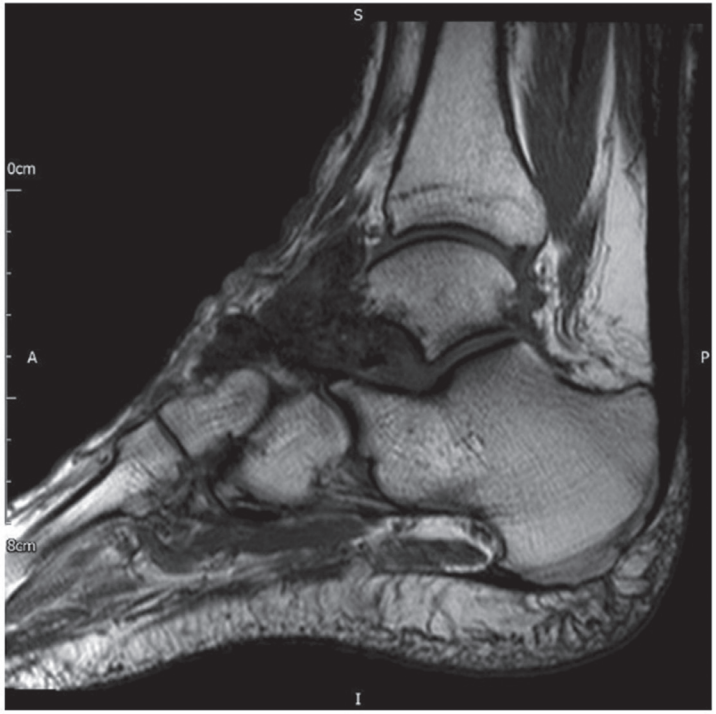

Figure 2a: Sagittal T1 MRI scan showing diffuse-type TGCT, affecting the ankle joint. Characteristic TGCT blooming effect is seen, attributed to scattered areas of low signal intensity, which is typical for iron deposition.

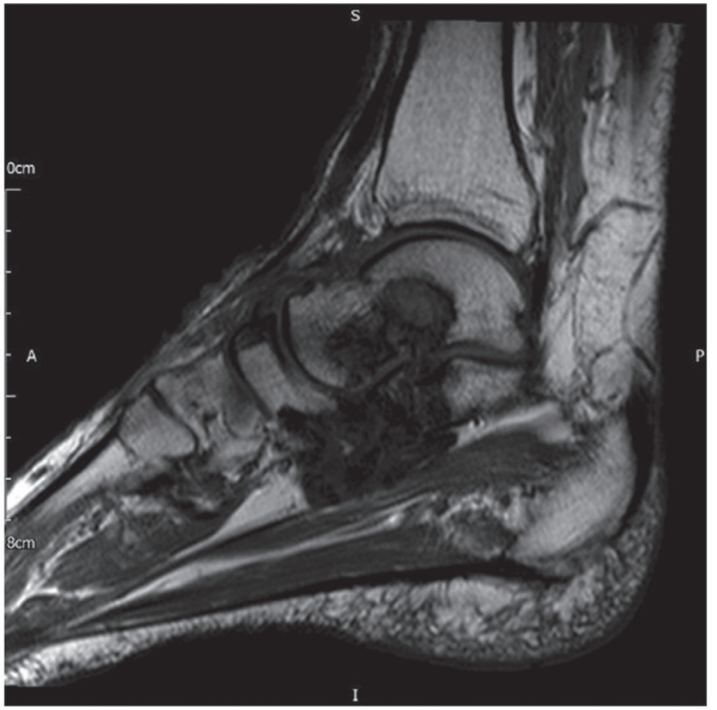

Figure 2b: Sagittal T1 MRI scan showing diffuse-type TGCT, affecting the subtalar joint. Characteristic TGCT blooming effect is seen, attributed to scattered areas of low signal intensity, which is typical for iron deposition.

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.

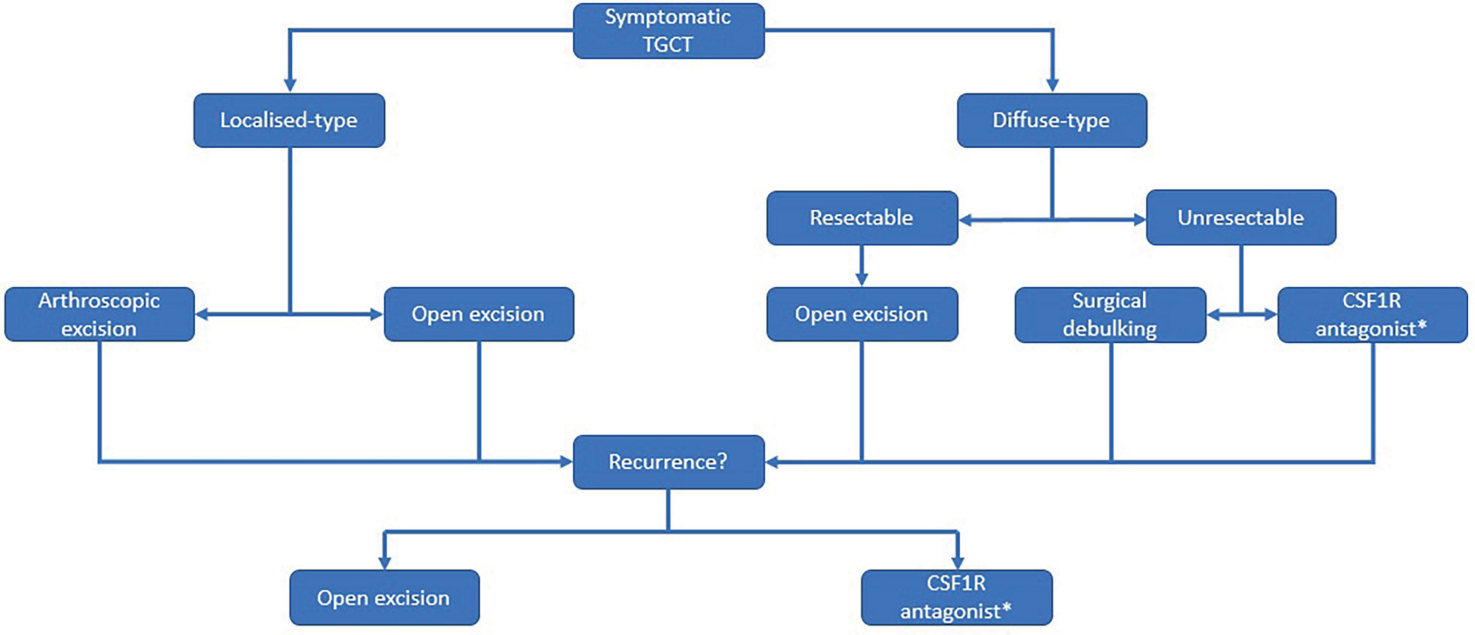

Figure 3. Multidisciplinary treatment pathway for symptomatic TGCT in the foot and ankle.
The authors do not advocate radiotherapy, due to lack of reported outcomes of radiotherapy in the foot and ankle. Radiotherapy may lead to unacceptable adverse events.
**CSF1R antagonists are not widely available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

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