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Active surveillance of diffuse-type tenosynovial giant cell tumors: A retrospective, multicenter cohort study

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A B S T R A C T

Background: Diffuse-type tenosynovial giant cell tumor (D-TGCT) is a mono-articular, soft-tissue tumor. 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, multicenter study included therapy naïve patients with D-TGCT from eight sarcoma centers 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.

1. Introduction

Tenosynovial giant cell tumor (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 tumor to infiltrative growth causing joint degeneration. The most frequently reported symptoms: pain, stiffness, swelling and limited function [5] can significantly impair quality of life in a relatively young population [6,7]. MRI is the main imaging modality to diagnose D-TGCT and evaluate the tumor extent [8]. It is suggested that this synovial proliferation is driven by colony-stimulating factor 1

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(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) orthopedic surgeons in sarcoma centers experienced in treating rare soft-tissue tumors [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 multiply recurrent or more extreme cases, radiotherapy has occasionally been performed in some centers, 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 [12]. 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.

2. Materials & methods

This international, multicenter, retrospective cohort study includes eight sarcoma centers 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 localized TGCT or patients that received a TGCT-related treatment before the first consultation in one of the participating sarcoma centers. Patients who underwent an excisional biopsy without the intention to completely remove all tumor 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 standardized 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 pseudonymized before transferring to the principal investigator. The following data were collected at the first consultation: patient demographics, tumor extent on MRI (intra- and/or extra-articular localization, 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 tumor 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 analyze 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.

3. Results

Between January 2000 and December 2019, sixty-one D-TGCT patients without prior treatment at one of the participating sarcoma centers 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 centers 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).

Fifty-nine patients had an MRI performed at a median of one month around the first consultation. The tumor 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,

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.

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)
Tumor extent[a] (%)	
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[a] (%)	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)

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

particularly pain and swelling (Table 2). Twelve patients (21 %) chronically used analgesics, mainly non-steroidal anti-inflammatory drugs (NSAIDs).

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 (Fig. 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.

3.1. Subgroup analyses

Baseline characteristics such as age, gender, tumor 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).

4. Discussion

Most patients with diffuse-type TGCT are treated by surgery, but due to the extensive tumor 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 analyze outcomes of treatment-naïve patients with D-TGCT initially managed by active surveillance in tertiary referral centers. 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 tumors located intra-articularly, while extra-articular localization 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 localized and nonlife-threatening, the decision to treat TGCT should preferably focus on possible clinical improvement and not solely on tumor 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 center'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),

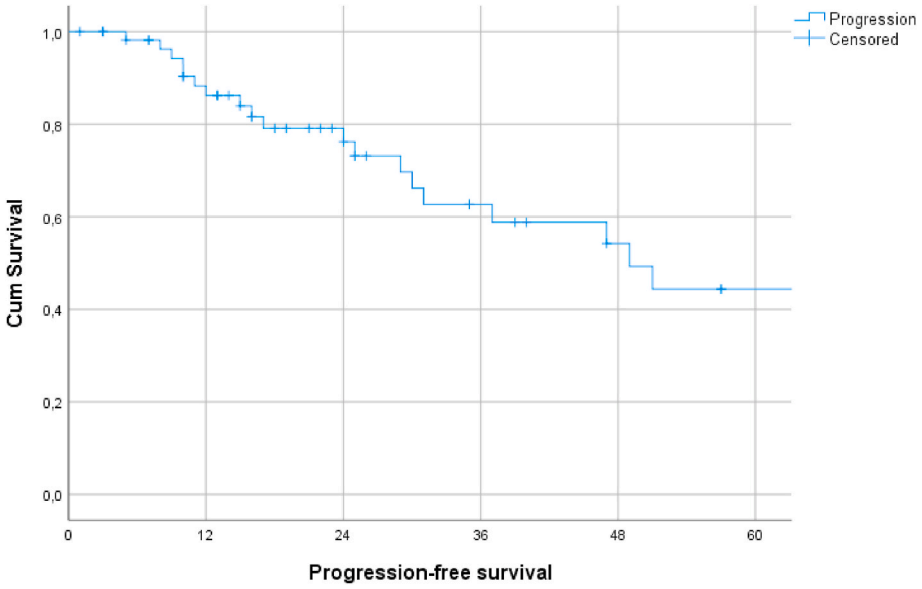

Fig. 1. Progression-free survival of D-TGCT patients managed by active surveillance.

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	
Tumor extent			
Intra-articular			
Yes	36	17	0.577
No	4	1	
Extra-articular			
Yes	8	6	0.272
No	32	12	
Osteoarthritis			
Yes	9	4	0.981
No	31	14	
Symptoms			
Pain			
Yes	28	13	0.863
No	12	5	
Swelling			
Yes	23	10	0.890
No	17	8	
None	5	2	
Radiological progression			
Yes	9	12	
No	26	6	0.004
Degenerative change	N = 28	N = 14	0.266
Yes	4	4	
No	24	10	
Clinical change			
Worsened	5	16	
Stable/Improved	35	2	<0.0001
Median follow-up, months (IQR)	23 (13–49)	58 (22–93)	0.017

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 tumor growth or specific tumor localization, 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 tumor board with experience with this rare tumor 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 individualized 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 realize 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) [28]. 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 [27]. 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].

4.1. 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 localized- and diffuse-type, this may have introduced false positive diagnoses. As all patients were diagnosed and treated by experienced multidisciplinary teams in tertiary sarcoma centers 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 centralized 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.

4.2. 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 individualized follow-up scheme.

Author contributions

Conceptualization, G.S., H.G., M.A.J.v.d.S. and L.v.d.H.; Methodology, G.S., M.A.J.v.d.S. and L.v.d.H.; Formal analysis, G.S.; Data curation, G.S., E.S., E.P, R.L R., S.W.T, J.S.W., P.C.F., F.G.M.V, M.T.H., N.M.B., B.H.W.B.S.; Writing—original draft, G.S., H.G., M.A.J.v.d.S. and L.v.d.H.; Writing—review & editing, E.S., E.P, R.L R., S.W.T, J.S.W., P.C.F., F.G.M.V, M.T.H., N.M.B., B.H.W.B.S.; Supervision: H.G., M.A.J.v.d.S. and L.v.d.H. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

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