Tenosynovial giant cell tumours

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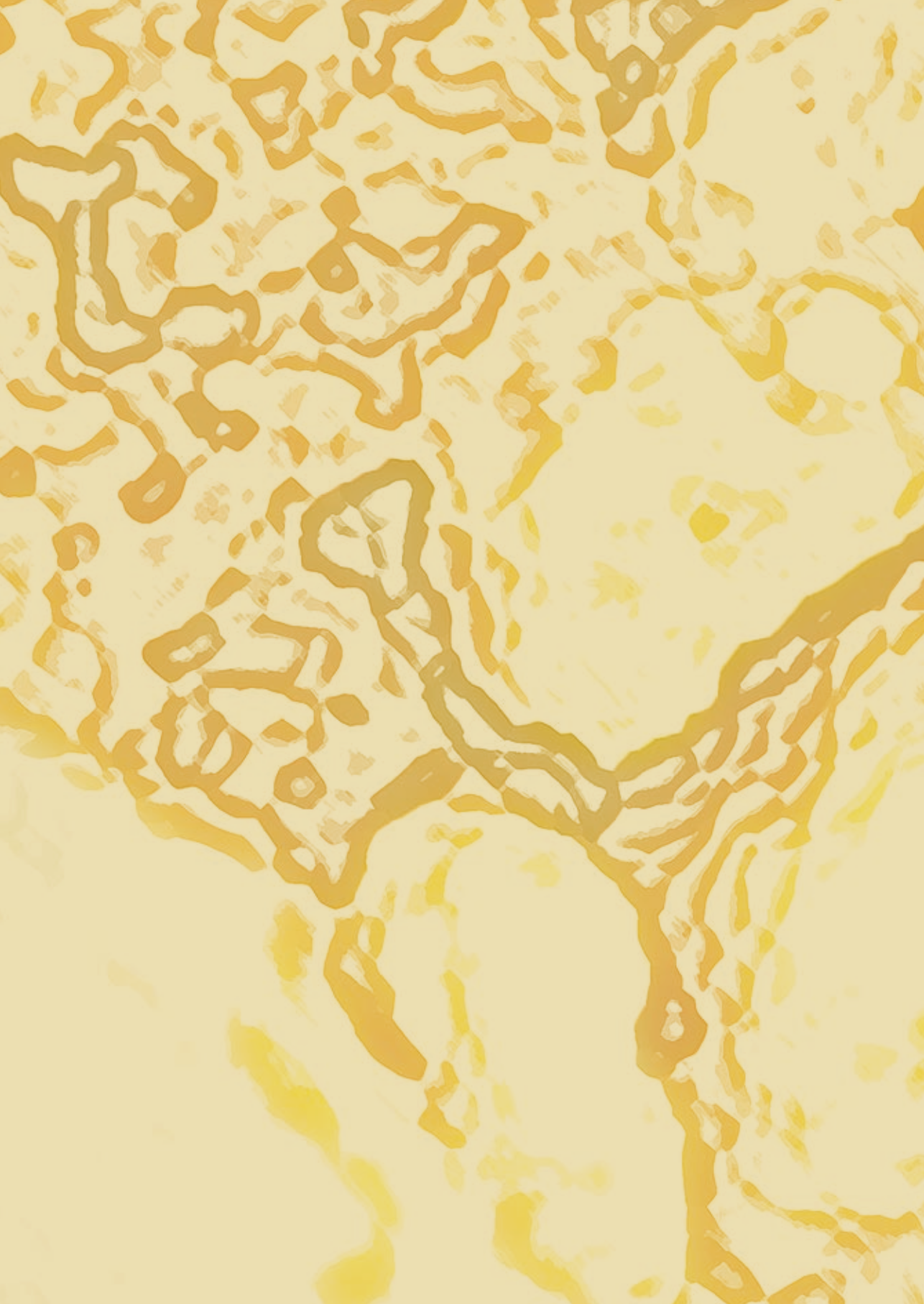

DIFFUSE

chapter eight

Outcome of surgical treatment for patients with diffuse-type Tenosynovial Giant Cell Tumours

Largest cohort of individual participant data meta-analysis of 31 international sarcoma centres

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Abstract

Objective

Diffuse-type Tenosynovial Giant Cell Tumour (TGCT) is a rare, locally aggressive and difficult to treat disease. An international multicentre-pooled retrospective study of individual patient data was developed to describe global treatment protocols, evaluate oncological outcome, complications and functional results. A secondary study aim was to identify risk factors for local recurrence after surgical treatment.

Methods

Patients treated in 31 sarcoma reference centres between 1990 and 2017, with histologically proven diffuse-TGCT of large joints were included. Of 1192 cases of diffuse-TGCT, 58% were female with a median age 35 years. 64% affected the knee and in 54% primary treatment was one-staged open synovectomy. Risk factors were tested in a univariate analysis and significant factors subsequently included for multivariate analysis, with first local recurrence after surgical treatment in a tertiary centre as the primary outcome.

Results

At a median follow-up of 54 (95%CI 50-58) months, recurrent disease developed in 44% of all surgically treated cases, with local recurrence free survival (RFS) at 3, 5, 10 years of 62%, 55% and 40%, respectively. The strongest risk factor for recurrent disease was prior recurrence (HR 3.5 95%CI 2.8-4.4, $p<0.001$) with a 5-year RFS of 64% in surgery naïve patients compared with 25% in patients operated for recurrent disease. Complications were noted in 12% of patients. Pain and swelling improved after surgical treatment(s) in 59% and 72% of patients respectively. In a subgroup analysis including only naïve cases affecting the knee, neither sex (male;female), age (≤35years;>35years), bone-involvement (present;absent), surgical technique (open;arthroscopic) nor tumour size (<5cm;≥5cm) yielded an association with the first local recurrence.

Conclusion

This largest international individual data study of patients with diffuse-TGCT, provides a comprehensive and up to date disease overview, evaluating the clinical profile and management of the disease. Since complete resection of diffuse-TGCT could be regarded as nearly impossible and recurrence rates are unacceptably high after both arthroscopy and open synovectomy in the knee, even in specialized centres, a multimodality approach in this disease, including adjuvant treatments, is warranted.

Introduction

In the most recent WHO classification (2013), giant cell tumour of the tendon sheath and pigmented villonodular synovitis (PVNS) were unified by one overarching term: tenosynovial giant cell tumours (TGCT). This rare, mono-articular disease arises from the synovial lining of joints, bursae or tendon sheaths in predominantly young adults[1, 2]. Excluding digits, TGCT is most commonly diagnosed around the knee and can be found in other weight bearing joints as well[1-4].

Two clinically and radiographically distinct subtypes of TGCT are defined with different natural courses of disease. The localized-type is defined as a well-circumscribed nodule. On the contrary, the diffuse-type is known as an ill-circumscribed, locally aggressive and invasive tumour (*figure 1, chapter 1, page 13*)[1, 2, 5]. Even though histopathology and genetics seem identical, the biological behaviour of both subtypes is incomparable and therefore necessitates separate evaluations, analyses and treatments. The current study focuses on diffuse-TGCT of large joints.

Macroscopically, diffuse-type TGCT involves a large part or even the complete synovial lining of a joint with either a typical villous pattern (intra-articular) or a multi-nodular appearance (extra-articular), including a diverse colour pattern, varying from white-yellow to brown-red areas. This subtype shows an infiltrative growth pattern. Definite diagnosis is established on microscopy by an admixture of mononuclear cells (histiocyte-like and larger cells) and multinucleated giant cells, lipid-laden foamy macrophages (also known as xanthoma cells), siderophages (macrophages including hemosiderin-depositions), stroma with lymphocytic infiltrate and some degree of collagenisation. Molecular analysis is generally not required to confirm the diagnosis.

Pain, (haemorrhagic) joint effusion, stiffness and limited range of motion are the main clinical complaints[6]. These non-specific symptoms frequently cause a delay in diagnosis[7]. The predominant standard of care is surgical resection of diffuse-TGCT, either arthroscopically or with an open resection or a combination of both, in order to: (1) reduce debilitating symptoms and joint destruction caused by the disease process; (2) improve limb function; and (3) minimize the risk of local recurrence. Clinical and oncological outcomes following surgery largely depend on multiple factors including preoperative diagnostic evaluation, the localization and extent of disease and possibly the choice of treatment modalities by orthopaedic surgeons[3, 5, 8-10]. Diffuse-

TGCT frequently causes significant morbidity due to the invasiveness of the surgical resection and the high rate of local recurrence (14-40% depending on surgical procedure and follow-up time), with deteriorated health-related quality of life[6, 8, 9, 11-14]. Therefore, treatment of diffuse-TGCT may include adjuvant or multimodality treatment such as external beam radiation therapy[10, 15, 16], radiation synovectomy with ^{90}Yttrium[17] or *CSF1* inhibitors, such as nilotinib, imatinib, pexidartinib, emactuzumab, cabrilazimab and MSC110[18-22]. Of note, so far none of these agents have been formally approved for use in the disease, and long-term efficacy is unknown.

The incidence of diffuse-TGCT of large joints is 4.1 per million person-years[4]. Therefore, the current literature mainly consists of relatively small, or larger but heterogeneous case-series. Risk-factors for recurrent disease in individual patients need to be identified by evaluating outcomes of different treatment strategies. Since (larger) randomized controlled trials on the role of surgery in TGCT are lacking, individual participant data meta-analysis is currently the highest achievable evidence. It offers advantages above a meta-analyses, including: (1) missing data can be accounted for at an individual patient level, (2) subgroup analyses can be performed (e.g. per affected joint) and (3) follow-up information can be updated[23]. Therefore, we aimed to collaborate with tertiary sarcoma centres across the globe to include individual patient data in this investigation.

The main aim of this international multicentre cohort study is to provide comprehensive and up to date insights on the surgical treatment and outcome for patients with diffuse-type TGCT. Oncologic results, complications and functional results are described. In addition, risk factors for local recurrence after surgical treatment are identified.

Methods

Recruitment and patient inclusion criteria

Patients of any age treated between January 1990 and December 2017 in one of 31 international sarcoma centres (supplementary material: participating international sarcoma reference centres, page 160) with histologically proven TGCT of large joints were retrospectively included. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints. Identification and collection of the patients was performed in the centres of origin and data were analysed from initial treatment at these tertiary centres. Data were encrypted and transferred to the international multicentre database at the Leiden University Medical Centre (LUMC), with patient collection ending as of May 2018.

Study parameters

Collected patient-, tumour- and treatment characteristics with corresponding definitions are shown in *appendix table 1 (chapter 7, page 158)*. The following characteristics were defined as core criteria: TGCT-type (localized-; diffuse-; unknown-type), admission status (therapy-naïve; 1st recurrence; 2nd recurrence; 3rd recurrence; etc.) date and type of initial treatment at a tertiary centre (arthroscopic synovectomy; one-staged synovectomy; two-staged synovectomy; synovectomy not specified; (tumour)prosthesis; amputation; wait and see); and first local recurrence after treatment (yes; no) in a tertiary centre. Complete data on these core criteria were necessary for reliable analyses.

Patient-, tumour- and treatment characteristics

Thirty-one specialized sarcoma centres spread throughout Europe, North America, Canada and Asia collaborated to provide a total of 1192 diffuse-TGCT cases (*table 1*). As per entry criteria, patients with localized-TGCT (N=941) and unknown type TGCT (N=36) were excluded.

Statistical analyses

The primary endpoint was local recurrence free survival (RFS) after initial treatment in a tertiary centre. Recurrent disease was defined as the presence of new disease after resection (and synovectomy) performed in a tertiary centre or progressive residual disease (as diagnosed by local investigators on repeated follow-up Magnetic Resonance (MR) imaging).

Table 1 Patient-, tumour- and treatment characteristics

Characteristics	Overall (%)
Total number	1192 (100)
Admission status (N=1192)	
Therapy naïve^	910 (76)
≥1 Surgery elsewhere^^	282 (24)
Sex (N=1192)	
Male	499 (42)
Female	693 (58)
Median age at initial treatment years (N=1122)	35
IQR	26-48
Localization (N=1192)	
Knee	758 (64)
Hip	124 (10)
Ankle	162 (14)
Foot*	63 (5)
Shoulder	15 (1)
Elbow	17 (1)
Wrist	25 (2)
Hand*	13 (1)
Other	15 (1)
Bone involvement (N=847)	
Present	259 (30)
Absent	588 (70)
Median duration of symptoms# months (N=744)	18
IQR	6-36
Type of surgical treatment at tertiary centre (N=1163)	
Arthroscopic synovectomy	159 (14)
One-staged open synovectomy	628 (54)
Two -staged open synovectomy##	187 (16)
(Tumour)prosthesis+,¥	63 (5)
Amputation¥	3 (0.3)
Wait and see$,¥	76 (7)
Synovectomy not specified	47 (4)
Median tumour size initial treatment in cm (N=701)	5.4
IQR	3.0-8.8
<5 cm	297 (42)
≥5 cm	404 (58)
Adjuvant therapy initial treatment (N=1033)	
External beam radiotherapy	58 (6)
^{90}Yttrium	60 (6)
Systemic/molecular targeted treatment	15 (1)
Other	11 (1)
None	889 (86)

IQR, Interquartile Range; ^Therapy-naïve or primary admission status at tertiary centre are considered similar; ^^≥1 Surgery elsewhere or recurrent admission status are considered similar; *Digits are excluded; #Symptoms were defined as either pain, swelling, stiffness or limited range of motion (table 7-8); ##A two-stage synovectomy is defined as two synovectomies within six months; +An arthrodesis is classified as (tumour)prosthesis; $Wait and see and conservative treatment are considered similar; ¥(Tumour)prosthesis, amputation or wait and see as initial treatment are excluded for risk and survival analyses.

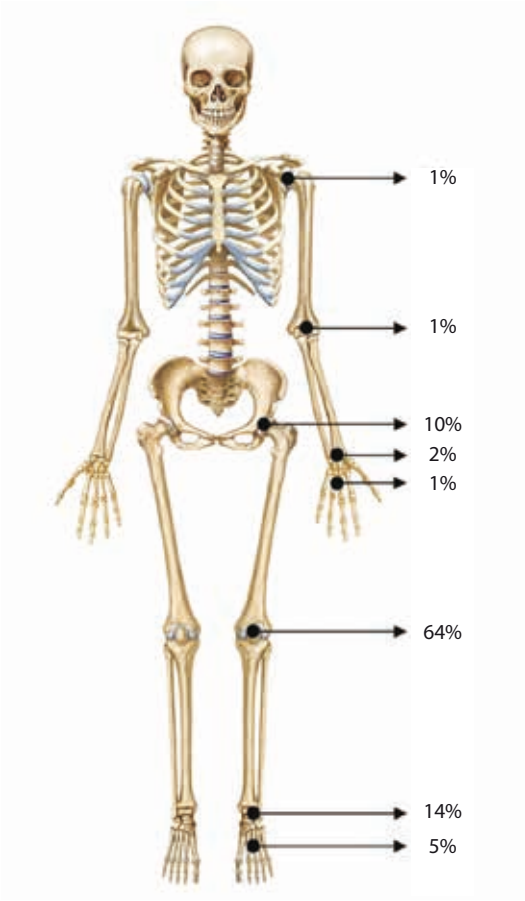


Figure 2 Skeleton showing localization of TGCT in 1192 diffuse-TGCT cases. 15 diffuse-TGCT cases were classified as 'other localization'

To investigate the effect of risk factors on the outcome, univariate analyses were performed and significant factors ($p<0.05$) were subsequently included into a multivariate analysis. Proposed risk factors were admission status (therapy-naïve versus recurrent disease), sex (male versus female), age (≤35 years versus >35 years), localization (knee versus hip versus foot/ankle versus upper extremity), bone-involvement (present versus absent), surgical technique (open versus arthroscopic) and tumour size (<5 cm versus ≥5cm). Patients with a wait and see policy or as initial treatment (tumour) prosthesis surgery or an amputation were excluded from statistical analysis (N=142).

Observed RFS probabilities at 3, 5, and 10 years were computed for all cases and subgroups based on admission status and localization.

For some patients exact survival information was not available (*appendix: proportion of data missing per variable*). In 34 out of 107 cases, we could recover the missing recurrence indicator: 9 patients had a second treatment and 25 patients had follow-up status 'alive with disease' and were classified as having recurrent disease. When the exact time of recurrence was not recorded, an approximation was applied where possible. When the date of surgery to treat a recurrence was known, this was used as the date of local recurrence instead (N=177). When this information was missing as well, the date of last recurrence was used as an upper bound (N=58). Otherwise the date of last recorded follow-up was used as an upper bound (N=69). When data on recurrence status or date of recurrence was missing and could not be recovered as described, patients were excluded for risk- and survival analyses (N=84).
Some centres did not record follow-up time for patients without recurrent disease. To prevent exclusion of these patients, we imputed their follow-up time (N=79). Multiple imputation technique was applied and 5 complete data sets were imputed using the R-package Amelia II[24]. Statistical analyses were conducted on all data sets and the results were then pooled following Rubin's rule[25].

As a consequence of the approximation of the time of recurrent disease by upper bounds in some cases, common survival methods (Kaplan-Meier estimate, logrank test) were substituted by methods that allow for interval censoring. Observed survival curves and probabilities were computed using non-parametric maximum likelihood estimates for interval censored data with the R-package interval[26]. P-values for the univariate analyses were calculated with the score test of Sun (1996)[27].
Covariates that were found to have a significant association with local recurrence free survival in the univariate analysis were included in a multivariate Cox regression analysis using the icenReg R-package, which allows for interval censored data[28].

All data were selected for completeness on core criteria (*appendix, chapter 7, page 158*). Statistical analyses were carried out using R version 3.4.1.

On purpose, an estimate of the median time to recurrence was not provided. Calculating such a median based on patients for whom a recurrence was recorded, would assume that all other patients could not experience a recurrence in the future. The extent of this so-called immortal time bias is unknown. For this reason, such an estimate will be an underestimation of the true time to recurrence.

Ethical consideration

This study is conducted according to the Declaration of Helsinki (October 2013) and approved by the institutional review board (CME) from the Leiden University Medical Center (LUMC) (May 4th, 2016; G16.015).

RESULTS

Oncologic outcome

In 966 patients with surgically treated diffuse-TGCT and complete survival data, 425 (44%) had a tumour recurrence following treatment. The recurrence free survival (RFS) continued to decrease with longer follow-up times (*table 2-3, figure 3*).

Univariate- and multivariate analyses for local recurrence

In univariate analysis of 966 patients with surgically treated diffuse-TGCT and complete core data, the risk factor admission status was found to be significantly associated with recurrence: 5-year RFS was 64% for therapy naïve patients (95% CI 60-68) compared to 25% for patients entering the tertiary hospital with recurrent disease (95% CI 19-31; p <0.001). This difference was confirmed by multivariate analysis (HR 3.5 95% CI 2.8-4.4, p<0.001).

After excluding patients admitted with recurrent disease, surgical technique was also positively associated with first local recurrence (*table 4*). This result was confirmed by cox regression analysis (HR 1.407; 95% CI 1.02-1.95, p=0.04). In a subgroup analysis of therapy naïve patients with diffuse-TGCT affecting the knee, surgical technique was not found to be associated with first local recurrence (p=0.113).

Observed recurrence free survival according to admission status and localization

Highest recurrence rates are report in TGCT affecting the knee; 43% after arthroscopic synovectomy and 37% after open synovectomy (*figure 4*). A progressively declining RFS was seen at 3, 5 and 10 years in a subgroup analysis of the knee, hip, foot/ankle and upper extremity locations in patients either admitted with therapy naïve TGCT or patients admitted with recurrent TGCT (*table 5*). After 10 years follow-up, patients with therapy naïve disease affecting the knee were found to have the lowest RFS rates of all sites (46%, 95% CI 39-54). All patients entering a tertiary hospital with recurrent disease exhibited very low RFS at 10 years (*figure 3a*).

Table 2 Oncologic outcome after surgical treatment of diffuse-TGCT of large joints of all patients primary treated at a tertiary centre

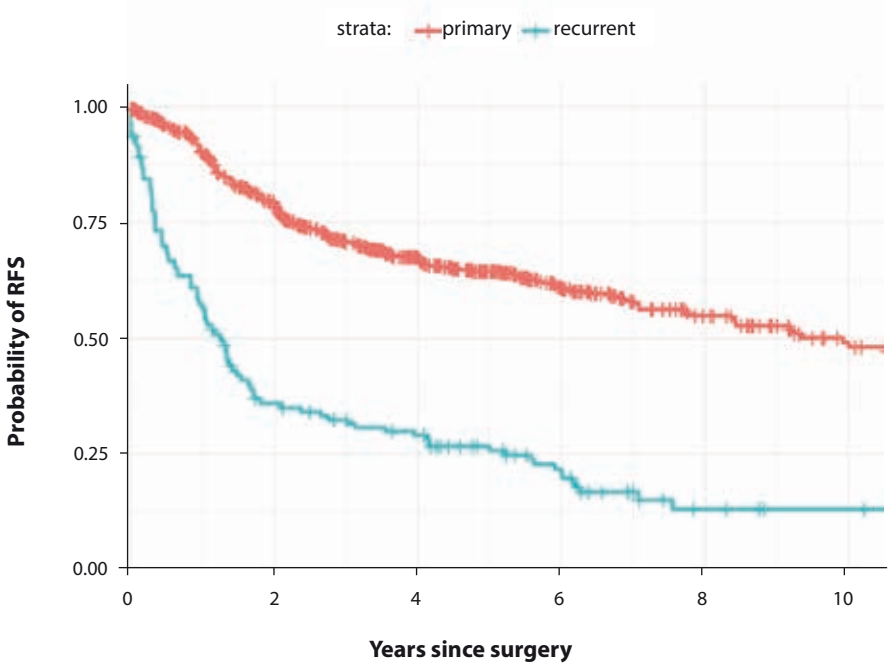
Characteristics	Overall (%)
First local recurrence after initial treatment at tertiary centre (N=966)	
Present	425 (44)
Absent	541 (56)
Total number of recurrences (N=425)	
1	267 (63)
2	85 (20)
≥3	73 (17)
Mean total number of surgeries (N=707)	2.0 (range 1-10)
Mean total number of surgeries in recurrent disease (N=425)	2.7 (1-10)
Median follow-up months (N=966)	54
95% CI	50-58
Status last follow-up (N=891)	
No evidence of disease	587 (66)
Alive with disease - wait and see	190 (21)
Alive with disease - awaiting treatment	31 (3)
Death of other disease	10 (1)
Lost to follow-up*	73 (8)

*Lost to follow-up was defined as follow-up less than 6 months or stratified during follow-up as lost to follow-up.

Table 3 Diffuse-TGCT recurrence free survival (RFS) all patients versus therapy naïve patients treated at tertiary centre

Year	N all	% RFS all (95%CI)	N therapy naïve	% RFS therapy naïve (95%CI)
3	474	62 (59-65)	372	70 (67-74)
5	297	55 (51-58)	227	64 (60-68)
10	89	40 (35-45)	70	50 (44-56)

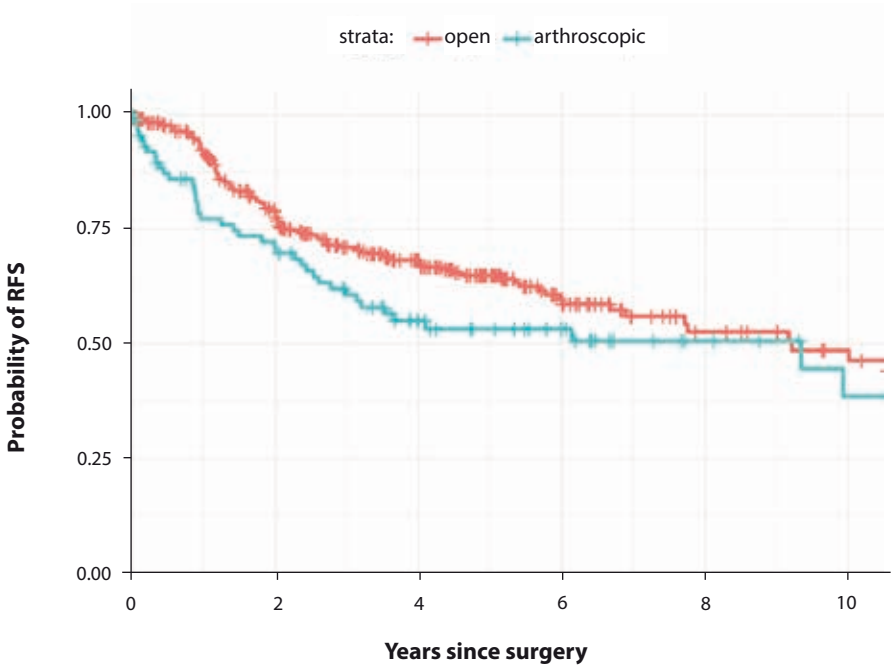
N is number of patients at risk for recurrent disease at 3, 5 and 10 years.



number at risk

primary	758	506	310	170	97	63
recurrent	208	128	88	53	30	18
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 3a Local recurrence free survival curve in diffuse-TGCT stratified for admission status (p<0.001). Time zero was date of initial resection at tertiary centre. Primary: patient with therapy-naïve disease initially treated at tertiary centre, recurrent: patient initially treated elsewhere.



number at risk

open	346	225	146	71	39	29
arthroscopic	99	65	40	25	13	8
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 3b Local recurrence free survival curve in patients with therapy naïve diffuse-TGCT affecting the knee stratified for surgical technique (p=0.11). Time zero was date of initial resection at tertiary centre. Open: open resection, arthroscopic: arthroscopic resection.

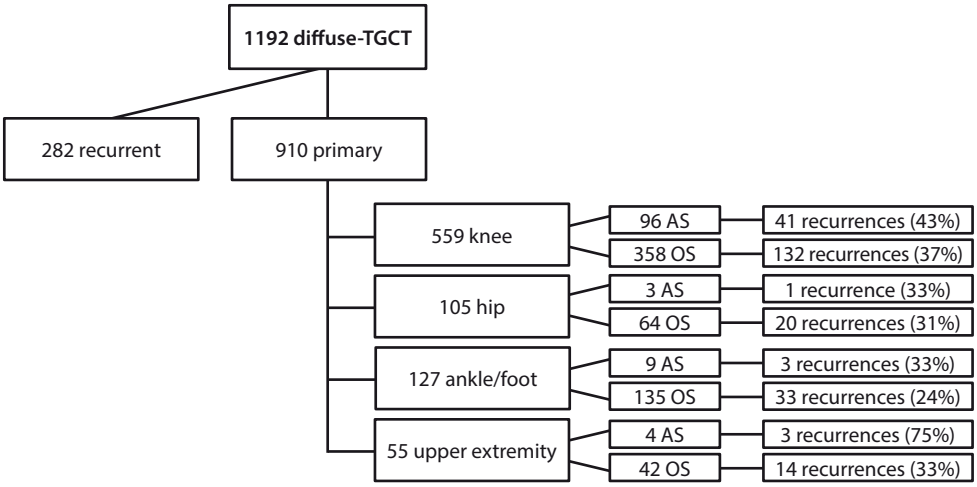


Figure 4 Flowchart of diffuse-TGCT patients with treatments and recurrences for each affected joint.
Primary: patient was first seen at tertiary centre with therapy-naïve disease, recurrent: patient initially treated elsewhere, AS: Arthroscopic synovectomy, OS: Open synovectomy. Treatments other than AS and OS were not included in this flowchart (e.g. (tumour)prosthesis, amputation, wait and see treatment).

Complications

A total of 105 (12%) complications occurred following surgical treatment of diffuse-TGCT (*table 6*). The majority of these complications developed after one- or two-staged open synovectomy (86/105; 82%). In comparison, 12 complications (11%) were reported following arthroscopic synovectomy.

Functional outcome

Prior to surgical treatment, the majority of patients had symptoms of pain (76%) and swelling (75%) (*table 7*). After surgical treatment, at final follow-up, these symptoms largely disappeared, although 37% and 24% of patients respectively were still symptomatic. Joint stiffness and limited range of motion were only present in 21% and 27% of cases, respectively, and these symptoms improved slightly after treatment (17% and 19% at final follow-up).

Table 4 Univariate analyses in 758 patients with therapy naïve diffuse-TGCT

Variable	N	%RFS at 5 years	95%CI	P value
Age				
≤35 years	391	64	59-70	0.94
>35 years	364	63	57-69	
Sex				
male	307	63	56-69	0.86
female	451	64	59-70	
Localization				
knee	471	61	56-66	0.10
hip	70	65	54-77	
foot/ankle	158	72	64-81	
upper extremity	59	59	44-74	
Size				
<5 cm	217	71	64-78	0.42
≥5 cm	295	64	58-71	
Bone involvement				
present	158	61	52-69	0.82
absent	425	64	58-69	
Surgical technique				
open	595	66	61-70	0.03
arthroscopic	120	54	44-64	

A mean of 578 (48%) patients with diffuse-TGCT had complete data on symptoms both prior to initial treatment and at final follow-up (*table 8*). The majority of patients experienced pain and swelling prior to initial treatment, of which 59% and 72% resolved after surgical treatment(s). Patients with initial complaints of stiffness and limited range of motion also improved after surgery (64% and 73%).

Table 5 Recurrence free survival probabilities at 3, 5, and 10 years for on type of TGCT, admission status and localization

Admission status	Localization	N+	% RFS at 3 years	95% CI	% RFS at 5 years	95% CI	% RFS at 10 years	95% CI
primary	knee	471	68	63-73	61	56-66	46	39-54
primary	hip	70	67	56-79	65	53-77	54	38-70
primary	foot/ankle	158	79	72-87	72	64-81	57	44-70
primary	upper extremity*	59	69	56-82	59	44-75	55	38-71
recurrent	knee	145	29	21-36	25	18-32	15	8-21
recurrent	hip	8	40	6-74	40	6-74	**	
recurrent	foot/ankle	39	43	27-59	24	10-38	18	4-33
recurrent	upper extremity*	16	25	3-47	25	3-47	15	0-33

+N: number at baseline (time point = 0), *Upper extremity including other localization, **10 years RFS and associated 95%CI of recurrent hip cases could not be estimated (due to lack of follow-up information). Primary: patient was first seen at tertiary centre with therapy-naïve disease Recurrent: patient initially treated elsewhere, 95%CI: 95% Confidence interval.

Table 6 Complications after surgical treatment at tertiary centre (N=906)

Complications after surgical treatment	N (%)
Superficial wound infection	15 (2)
Deep wound infection	10 (1)
Joint stiffness	32 (4)
Haemorrhage	7 (1)
Neurovascular damage	15 (2)
Thrombosis	1 (0.1)
Other+	25 (3)

+Other surgical complications after initial treatment included: joint luxation (hip), compartment syndrome, ligament incision during surgery, complex regional pain syndrome, tourniquet blistering, tendinitis. As osteoarthritis is either caused by extensive disease or by (multiple) treatments, it was not taken into account for complications.

Table 7 Symptoms prior to treatment and at final follow-up

Symptom	Pre-treatment	Final follow-up
Pain (PT 969, FF 630)	738 (76%)	233 (37%)
Swelling (PT 775, FF 627)	579 (75%)	149 (24%)
Joint stiffness (PT 759, FF 617)	161 (21%)	105 (17%)
Limited range of motion (PT 760, FF 624)	209 (27%)	118 (19%)
Chronic analgesic treatment* (FF 714)		92 (13%)

*Chronic analgesic treatment data was only available at final follow-up; PT, pre-treatment; FF, final follow-up

Table 8 Comparing symptoms diffuse-TGCT prior to treatment to last follow-up

	No pain last fu	Pain last fu	Total
No pain initially	118 (20%)	36 (6%)	154
Pain initially	255 (43%)	179 (31%)	434
	No swelling last fu	**Swelling last fu**	
No swelling initially	119 (20%)	13 (2%)	132
Swelling initially	328 (56%)	125 (22%)	453
	No stiffness last fu	**Stiffness last fu**	
No stiffness initially	383 (68%)	55 (10%)	438
Stiffness initially	82 (14%)	47 (8%)	129
	No limited range of motion last fu	**Limited range of motion last fu**	
No limited range of motion initially	337 (59%)	59 (10%)	396
Limited range of motion initially	128 (23%)	48 (8%)	176

Fu; follow-up

Local recurrence versus symptoms final follow-up

A higher percentage of patients with pain, swelling, stiffness and limited range of motion at final follow-up had recurrent disease (pain; 55% recurrence versus 45% no recurrence, swelling; 66% versus 34%, stiffness; 51% versus 49%, limited range of motion; 56% versus 44%).
More patients with recurrent disease 21% (64/300) used chronic analgesic treatment at last follow-up compared to patients 6% (24/388) without recurrent disease.

Surgical technique versus functional outcome at last follow-up

Surgical technique did not influence functional outcome at last follow-up (pain: 41% symptoms after AS versus 37% after OS, swelling: 29% versus 22%, stiffness: 13% versus 18%, limited range of motion: 16% versus 21%, chronic analgesic treatment: 18% versus 12%).

Chronic analgesic treatment versus complications

24% (16/67) of patients using chronic analgesic treatment had a complication, compared with 10% (50/482) of patients without a complication.

DISCUSSION

This international multicentre study offers new insights into the outcome of patients with the orphan and heterogeneous disease diffuse-type Tenosynovial Giant Cell Tumour (TGCT). The greatest strength of this dataset is that it represents the largest collection of surgically treated diffuse-TGCT patients in the scientific literature, including RFS estimates for the knee, hip, foot/ankle and upper extremity locations with long-term follow-up (>10 years). Oncologic results, complications and functional results after surgical treatment are evaluated.

Oncologic outcome diffuse-TGCT

The fundamental question of whether curative treatment is necessary, or should be attempted in non-lethal diffuse-TGCT often arises in literature. Debilitating symptoms and (progressive) joint destruction commonly result from untreated diffuse-TGCT but can also occur following treatment. At present, the choice of treatment is established by the preference of the patient, treating physician and might differ by treatment centre. Surgical treatment for the locally aggressive diffuse-TGCT is challenging, as pathologic tissue can be widely spread throughout the joint and may be technically difficult to access and remove. In extensive disease, less than radical or only partial resection could be preferred to improve symptoms with joint preservation in mind. However, higher rates of recurrence have been described after macroscopically incomplete resections[8, 29-31].

Some reports consider arthroscopic management of TGCT superior to open surgery, because of less morbidity and a shorter recovery period[32-36]. Standard arthroscopy of the knee using only anteromedial and anterolateral approaches however, does not allow surgical access to remove all areas where diseased tissue is likely to be present. Therefore Blanco et al. and Mollon et al. used multiple portals including posteromedial and posterolateral in arthroscopic synovectomy[37-39]. Chin et al. stated that knee arthroscopy alone is an inferior treatment for extra-articular TGCT[40]. Open synovectomy, either one- or two-staged, seems to be the preferred surgical approach to diffuse-TGCT in most centres, because of tumour visibility and reported lower short-term recurrence rates[11, 41, 42]. The disadvantage of a one- or two-staged open resection, could be deteriorated joint function accompanied with decreased patient health-related quality of life[13]. A systematic review showed lower recurrence rates for open synovectomy (average 14%, maximum 67%) compared to arthroscopic synovectomy (average 40%, maximum 92%) in diffuse-TGCT[11]. Patel et al. (N=214)

reported a statistically significant higher risk of recurrence in diffuse-type TGCT with arthroscopic compared to open synovectomy (83.3% vs 44.8%, RR = 1.86 95% CI 1.32–2.62, P = 0.0004)[9]. Palmerini et al. (N=206) did not find a difference in recurrence based on surgical technique for localized- and diffuse-TGCT combined[8].

A combined anterior arthroscopic- and posterior open synovectomy in the knee might be a viable option, but is only incidentally reported. Mollon et al. described the combined approach of a multiportal anterior and posterior arthroscopy and a posterior open synovectomy largely for resection of extra-articular popliteal disease, and reported two recurrences in 15 patients[38]. Colman et al. retrospectively evaluated 11 diffuse-TGCT patients treated by the combined approach and also reported relatively low short-term recurrence rates (9%)[43]. A randomized controlled trial for arthroscopic synovectomy versus open synovectomy has not been performed.

The present study calculated recurrence free survival rates for diffuse-TGTC at 3, 5 and 10 years of 62%, 55% and 40%, respectively. This clearly underlines that with longer follow-up, recurrence rates continue to increase (*table 2-3, figure 3*). The greatest risk factor for local recurrence is recurrent disease at presentation in a tertiary centre (HR 3.5 95% CI 2.8-4.4 in multivariate analyses). In therapy naïve patients with primary treatment in a tertiary centre, the largest risk factor for local recurrence was arthroscopic synovectomy. The suspicion arises that more (macroscopic) tumour tissue remains after arthroscopic synovectomy; however this largely depends on the extend of the arthroscopy performed, whether multiple and posterior portals were used to access and remove disease throughout the knee joint, and whether this approach is combined with an open approach to remove residual intra-articular disease and/or extra-articular disease extension. However, none of the assumed risk factors yielded significant differences when the analysis was performed in a subgroup of therapy naïve patients with diffuse-TGCT affecting the knee. This could be attributed to the near impossibility of achieving a complete macroscopic resection in widely spread, ill-defined diffuse-TGCT patients and the impossibility of an R0 resection: macroscopically and microscopically complete resection, neither with an arthroscopic- nor open resection.

Multimodality treatment

Within the current era of systemic targeted and multimodality therapies (some only available in trial settings) in TGCT, standalone surgical resection can no longer be regarded as the only treatment for more severe diffuse forms of the disease. Surgery has been considered the treatment of choice for decades, and the current study which included patients from 1990 onwards, consists mainly of patients treated with a surgical procedure.

High recurrence rates, as confirmed by the present study, indicate the need for adjuvant therapies to improve treatment outcomes for patients with diffuse-TGCT. Nonetheless, Gortzak et al. reported no significant differences in residual disease, complication rates and overall physical and mental health scores between patients surgically treated for TGCT of the knee with (N=34) or without (N=22) adjuvant ^{90}Yttrium, after a mean follow-up of 7.3 years[17]. Verspoor et al. evaluated 12 patients treated with surgical synovectomy and additional cryosurgery. They did not find better results compared to surgical resection alone[44]. Griffin et al. reported on 49 patients with diffuse-TGCT, most of whom had both intra- and extra-articular and recurrent disease. They reported 3 (6%) recurrences following synovectomy and radiation[10]. A meta-analysis suggested that open synovectomy (N=19 studies, N=448) or synovectomy combined with perioperative radiotherapy (11 studies, N=123) is associated with a reduced rate of recurrence[16]. Mollon et al. reserved the use of external beam radiation for patients at high risk for local recurrence, if they had the following characteristics: multiple episodes of recurrent intra-articular disease, extra-articular extension, or gross residual disease remaining following surgery[38]. Currently, sufficient data including adequate patient numbers is lacking to support the use of external beam radiation in primary cases, however the authors feel it should only be performed in specific instances such as extensive or recurrent diffuse-TGCT cases.

In patients with locally advanced TGCT or (multiple) recurrence(s), systemic therapies targeting the CSF1/CSF1R axis have been recently investigated including nilotinib, imatinib, pexidartinib (PLX3397), emactuzumab (RG7155) and cabiralizumab (FPA008). Some systemic treatments for TGCT have been proven to be effective[18, 19], and novel and potentially more potent agents are under investigation[20-22]. The disadvantages of adjuvant or targeted therapies are acute and long-term side-effects of different degrees. Therefore, additional long-term follow-up studies in this field remain indicated.

Patients with aggressive disease accompanied with a high risk of recurrence following surgery alone should be selected for (new) systemic and (neo)adjuvant treatment modalities. Diffuse-TGCT presents as a heterogeneous disease with different disease severities. Some patients present with tumours that are surgically relatively easy to access and these patients might not require (neo)adjuvant therapies. Mastboom et al. defined the most severe diffuse-TGCT subgroup on MR imaging as having diffuse-type TGCT including intra- and extra-articular disease and involvement of at least one of the following three tissues: muscle, tendon or ligament)[5]. These patients seem most eligible for multimodality or (neo)adjuvant strategies.

Complications

The literature on TGCT frequently lacks descriptions of complications after surgical treatment. This study reported a complication rate of 12% following surgical management of patients with diffuse-TGCT, predominantly after open resection (82%). The most common complication was joint stiffness after open synovectomy, which might be difficult to prevent after the surgical treatment of extensive disease. The true complication rate might be even higher, since it is suspected that not all complications are scored.

Symptoms

TGCT related symptoms are mainly pain, swelling, stiffness and limited range of motion, but these are reported with a great variability in degree and severity. Gelhorn et al. concluded that not all patients experience all symptoms to the same extent (e.g. swelling but no pain, or pain and swelling but no stiffness or limited range of motion)[6]. Symptoms prior to initial treatment at a tertiary centre were compared for each patient with symptoms at last follow-up. Initial symptoms of pain and swelling improved following treatment(s) in 43-56% of patients. This is comparable with a crowdsourcing study in 337 TGCT patients originating from 31 countries[14]. In the majority of patients, stiffness and limited range of motion did not seem to be principal symptoms either initially, or at last follow-up. These symptoms are subjective for each patient and not all patients were included with complete data. Nevertheless, pain and swelling are the main TGCT-related complaints initially and frequently improve after surgical treatment(s).

As expected, diffuse-TGCT patients with recurrent disease demonstrated higher rates of symptoms at final follow-up, including a 3.5-fold higher rate of chronic analgesic use, compared to patients without local recurrence at last follow-up. Also, patients using chronic analgesics had a higher rate of complications.

Interestingly, after arthroscopic synovectomy in diffuse-TGCT, patients exhibited more pain, swelling and a higher use of chronic analgesics, compared with open synovectomy. On the contrary, open synovectomy was associated with higher rates of stiffness and limited range of motion, which can be attributed to the larger surgical procedure resulting in additional scar tissue.

Joint specific analyses

Within this individual participant data meta-analysis, a homogeneous subgroup analysis for diffuse-TGCT affecting the knee of therapy naïve patients was performed (*figure 3b*). Despite the large number of patients in this study with diffuse-TGCT cases, the numbers in other joint locations were too small to allow analysis of those specific groups.

Limitations

The main limitation of this study is selection (referral) bias, since data on patients treated at non-specialized centres was lacking. Selection bias of affected joints seems absent when comparing percentages of affected joints (*table 1, figure 2*) with a recent incidence calculation study including nationwide coverage (in both studies 64% of diffuse-TGCT affects the knee)[4].

Even though TGCT is a benign disease, particularly diffuse-TGCT can become a chronic illness with substantial morbidity to the joint leading to functional and patient health-related quality of life impairment, caused by the course of the disease itself and multiple treatments[13]. As data were collected by local investigators or physicians according to the multicentre study design, data quality depended on data registry on site. Only data available in the source data file of the patients could be retrieved. In addition, interpretation of individual parameters could differ. No central histopathological review was performed, as it was assumed that each centre provided the correct diagnosis as set by their histopathology department. Within our study we did not collect which patient had multiportal arthroscopy or standard anterior portal arthroscopy.

Recurrence rates could either be over-estimated or under-estimated. Over-estimation could occur because the follow-up status 'alive with disease' was classified as recurrence (if recurrence data were missing). On the contrary, under-estimation could be present if patients with recurrent disease, did not return at all or did not return to their original centre. It should be noted that patients with recurrent disease had a longer follow-up compared to patients without recurrent disease. The explanation could be that patients without symptoms and (assumed) without recurrent disease were dismissed from follow-up and therefore had shorter follow-up times. In addition, if treatments were recently performed, patients also had shorter follow-up times and are still at risk of recurrence.

Conclusion

This is the largest global individual data study on patients with diffuse-type TGCT and provides a comprehensive and up to date disease overview, evaluating the clinical profile and management of TGCT. Our study demonstrated that surgery is by far the most frequently performed treatment in tertiary referral hospitals. However, even in specialised centres, local control of this heterogeneous orphan disease, remains a major issue, with overall recurrence free survival of 55% at 5 years.
Since complete resection of diffuse-TGCT is often impossible and recurrence rates are high after both arthroscopy and open synovectomy of the knee, the optimal surgical approach should be left to the discretion of an experienced surgical and multidisciplinary team. However, in the era of multimodality therapy, standalone surgical resection can no longer be regarded as the only effective treatment for patients with diffuse-TGCT and alternative or combined approaches should be considered.

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