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Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study

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Summary

Background Diffuse-type tenosynovial giant-cell tumour is a rare, locally aggressive, and difficult-to-treat soft tissue tumour. Clinical and surgical outcomes depend on multiple factors, including preoperative diagnostic assessment, the localisation and extent of disease, and possibly the choice of treatment modalities by orthopaedic surgeons. We did a retrospective cohort study to characterise global surgical treatment protocols, and assess surgical outcomes, complications, and functional results in patients with diffuse-type tenosynovial giant-cell tumours.

Methods In this international, multicentre, retrospective cohort study, we included consecutive patients treated in 31 sarcoma reference centres between Jan 1, 1990, and Dec 31, 2017. Eligible patients were of any age and had histologically proven diffuse-type tenosynovial giant-cell tumour of large joints. Patient data were retrieved from the local databases of participating centres. Patients with localised-type tenosynovial giant-cell tumour were excluded. In the analysis, we only included patients with complete core criteria data regarding admission status, date of treatment, type of treatment at participating centre, and first local recurrence after treatment. We used a non-parametric method to estimate recurrence-free survival at 3, 5, and 10 years after initial surgical resection in a tertiary centre. We used a multivariate Cox regression model to estimate the effect of risk factors. We also present subgroup analyses of disease status at presentation (primary *vs* recurrent disease) and recurrence-free survival by surgery type (open surgery *vs* arthroscopic synovectomy), and prespecified risk factors were tested in a univariate and multivariable analyses, with an endpoint of first local recurrence after treatment in a tertiary centre.

Findings Data collection for these analyses occurred between January, 2016, and May, 2018. We received the records of 1192 patients, of which 966 (81%) were surgically treated and had complete information on core criteria. 445 patients were admitted with therapy-naive disease of the knee and were primarily treated in a tertiary centre. Since patients with wait and see treatment do not have a starting date of treatment, these patients were excluded in the calculation of median follow-up time for all patients. For this calculation we used time of surgery as a starting date. 758 (64%) of 1192 patients had knee involvement and 628 (54%) of 1163 patients with complete data on type of surgery had one-staged open synovectomy. At a median follow-up of 54 months (IQR 27–97), recurrent disease developed in 425 (44%) of all 966 surgically treated cases, and recurrence-free survival was 62% (95% CI 59–65) at 3 years, 55% (51–58) at 5 years, and 40% (35–45) at 10 years. Surgical complications were reported in 105 (12%) of 906 patients who had complete data on surgical complications. Pain improved after surgical treatment in 255 (59%) of 434 patients and swelling improved in 328 (72%) of 453 patients who had complete data.

Interpretation This study of patients with diffuse-type tenosynovial giant-cell tumour provides a comprehensive and up-to-date disease overview, assessing the clinical profile and management of the disease in multiple specialised referral centres. Surgical treatment of diffuse-type tenosynovial giant cell tumours is not a definitive treatment for every patient because it involves a high risk for local recurrent disease and a relatively high risk for postoperative complications. After surgical treatment in treatment-naive patients, risk factors for recurrent disease in individual patients were not identified in what we believe is the largest cohort to date.

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*Listed in the appendix

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Introduction

In the most recent WHO classification,[1] giant-cell tumour of the tendon sheath and pigmented villonodular synovitis were unified by one overarching term: tenosynovial giant-cell tumours. This rare, monoarticular disease arises from the synovial lining of joints, bursae, or tendon sheaths, predominantly in young adults (<40 years).[1] Excluding digits, tenosynovial giant-cell tumours are most commonly diagnosed around the knee and can be found in other weight-bearing joints as well.[1–3]

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See Online for appendix

Research in context

Evidence before this study

Scientific literature on diffuse-type tenosynovial giant-cell tumours of large joints mainly consists of small, or larger but heterogeneous, case series. A retrospective cohort study is the highest achievable evidence to date, since randomised controlled trials on the role of surgery in patients with diffuse-type tenosynovial giant-cell tumours are unavailable. We searched PubMed, Embase, Cochrane, and Web of Science for papers from database inception to July 26, 2017 (appendix p 2) for evidence before the study start. We found no randomised controlled trials, 17 systematic reviews, and 1022 case series.

Added value of this study

Diffuse-type tenosynovial giant-cell tumours of large joints is a rare, locally aggressive, and difficult-to-treat soft tissue tumour with an incidence of 4·1 per million person-years. To our knowledge, this is the largest dataset of surgically treated patients with diffuse-type tenosynovial giant-cell tumours in the scientific literature, including recurrence-free survival estimates for the knee, hip, foot or ankle, and upper extremity localisation with long-term follow-up. These results will help patients and physicians alike in shared decision making for this orphan but debilitating disease.

Implications of all the available evidence

The standard of care for patients with diffuse-type tenosynovial giant-cell tumours is undecided and might include adjuvant or multimodality treatments, such as external beam radiotherapy, radiation synovectomy with Yttrium-90, or CSF1 inhibitors. To date, none of these CSF1 receptor inhibitors have been formally approved for use in this setting and the long-term activity of these therapeutic options is unknown. Our study showed that surgery is 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% (95% CI 51–58) at 5 years. Since complete resection of diffuse-type tenosynovial giant-cell tumours is often not possible and recurrence is frequent, 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 should no longer be regarded as the only treatment for patients with diffuse-type tenosynovial giant-cell tumours.

Two clinically and radiographically distinct subtypes of tenosynovial giant-cell tumours are defined with different natural courses of disease. The localised type is defined as a well circumscribed nodule. On the contrary, the diffuse-type tenosynovial giant-cell tumour is known as an ill circumscribed, locally aggressive, and invasive tumour.[1,4] Even though histopathology and genetics are similar between the localised and diffuse tumours, the biological behaviour of both subtypes is different and therefore patients need different assessments, analyses, and treatments. This retrospective study focuses on patients with diffuse-type tenosynovial giant-cell tumours of large joints, which show an infiltrative growth pattern that involves a large part, or even the complete, synovial lining of a joint with either a typical villous pattern (intra-articular) or a multinodular appearance (extra-articular). Definite diagnosis is based on microscopy by detection of an admixture of mononuclear cells (histiocyte-like and larger cells) and multinucleated osteoclastic-like giant cells, lipid-laden foamy macrophages (also known as xanthoma cells), siderophages (macrophages including haemosiderin depositions), stroma with lymphocytic infiltrate, and some degree of collagenisation.[1] Molecular analysis is generally not required to confirm the diagnosis. Malignant or metastatic transformation has been incidentally reported in case reports.

Pain, haemorrhagic and non-haemorrhagic joint effusion, stiffness, and limited range of motion are the main clinical symptoms of patients with diffuse-type tenosynovial giant-cell tumours.[5] These non-specific symptoms frequently cause a delay in diagnosis. There is not a consensus standard of care for patients with diffuse-type tenosynovial giant-cell tumours, but the predominant treatment option is surgical resection, either arthroscopically or with an open resection, or a combination of both to reduce debilitating symptoms and joint destruction caused by the disease process, to improve limb function, and to minimise the risk of local recurrence. Clinical and surgical outcomes after surgery largely depend on multiple factors, including preoperative diagnostic assessment, the localisation and extent of disease, and possibly the choice of treatment modalities by orthopaedic surgeons.[2,4,6–8] Diffuse-type tenosynovial giant-cell tumours frequently cause morbidity due to the invasiveness of the surgical resection and the high proportion of local recurrence after treatment (14–40%, depending on surgical procedure and follow-up time), with deteriorated health-related quality of life.[5–7,9–11] Therefore, treatment of diffuse-type tenosynovial giant-cell tumours might include adjuvant or multimodality treatments, such as external beam radiotherapy,[8,12] radiation synovectomy with Yttrium-90[13] or CSF1 receptor inhibitors.[14–16] Notably, so far none of these CSF1 receptor inhibitor options have been formally approved for use in the disease and long-term efficacy is unknown.

The incidence of diffuse-type tenosynovial giant-cell tumours of large joints is 4·1 per million person-years.[3] Therefore, the current literature mainly consists of small, or larger but heterogeneous, case series. Risk factors for recurrent disease in individual patients need to be identified by assessing outcomes of different treatment strategies. Since randomised controlled trials and large

cohorts of patients with tenosynovial giant-cell tumours treated with surgery are scarce, we aimed to collaborate with tertiary sarcoma centres across the globe to collect individual patient data and build a large cohort of patients with diffuse disease to provide comprehensive and up-to-date insights on the surgical treatment and outcomes of these patients.

Methods

Study design and participants

In this international, retrospective, cohort study, we included 1192 consecutive patients treated between Jan 1, 1990, and Dec 31, 2017, in 31 specialised sarcoma centres in Europe, North America, Canada, and Asia (appendix p 1). Identification of the patients and data collection was done in the centres of origin between January, 2016, and May, 2018, and data were analysed from initial treatment at these tertiary centres.

Eligible patients were of any age and had histologically proven diffuse-type tenosynovial giant-cell tumour of large joints. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints.

Patients with localised or unknown tenosynovial giant-cell tumour subtype were excluded. In the analysis, we only included patients with complete core data regarding admission status, date of treatment, type of treatment at participating centre, and first local recurrence after surgical treatment.

This study was done according to the Declaration of Helsinki (October, 2013) and was approved by the Institutional Review Board (Commissie Medische Ethiek [Dutch Research Ethics Board]) from the Leiden University Medical Center (May 4, 2016; G16.015). The study protocol is available in the appendix (pp 15–35).

Procedures

The principal investigator at each institution identified eligible patients and anonymised the data before transference to the international multicentre database at the Leiden University Medical Centre (Leiden, Netherlands), with patient data collection ending as of May 31, 2018. Data collected on patient, tumour, and treatment characteristics, including complications and functional results after surgical treatment, with corresponding definitions, are shown in the appendix (p 3). The following characteristics were defined as core criteria to define the analysis populations: admission status (therapy-naive, first recurrence, second recurrence, third 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 [ie, no treatment]); and first local recurrence after treatment (yes, no) in a tertiary centre (appendix pp 3–4). The term (tumour) prosthesis encompasses both joint prosthesis and endoprosthetic reconstruction. For reliable analyses, only patients with complete data on these core criteria were included in analyses.

For some patients, survival information was not available (appendix p 4). The recurrence indicator could be recovered and classified as having a recurrent disease if a patient had a second treatment (indicating recurrence) or if the patient had follow-up status of being alive with disease (indicating recurrence). The time of recurrence was approximated with a scheme: when the date of surgery to treat a recurrence was known, this date was used as the date of local recurrence instead; when this information was missing as well, the date of last recurrence was used as an upper bound. Otherwise the date of the last recorded follow-up was used as an upper bound for the time of recurrence. When data on recurrence status (recurrence yes *vs* no) or date of recurrence were missing and could not be recovered as described, patients were excluded for risk and survival analyses.

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 using multiple imputation.

Data on surgical complications were also collected, including no complication, superficial wound infection, deep wound infection, joint stiffness, haemorrhage, neurovascular damage, thrombosis, other, and unknown. Joint stiffness was only regarded as a surgical complication when it was not present before surgery and occurred within 3 months after surgery. Collection of functional results included pain, swelling, stiffness, and limited range of motion at final follow-up. Use of chronic analgesic was also considered (appendix p 3).

Statistical analysis

We did descriptive analyses for the main objective of this retrospective study to describe global treatment protocols, assess surgical outcome, complications, and functional results. Recurrence-free survival was defined as the time from initial treatment in tertiary centre until first recurrence. Recurrent disease was defined as the presence of new disease or progressive residual disease (as diagnosed by local investigators on repeated follow-up MRI) after resection was performed.

We calculated the proportion of patients with complications and functional outcome before surgical treatment and at last follow-up, and their occurrence in different treatment groups. We did not do statistical testing because the last follow-up time varied for patients and a fair comparison was therefore not possible.

To investigate the effect of risk factors associated with local recurrence, we did univariate and multivariable analyses on prespecified risk factors: admission status (therapy-naive *vs* recurrent disease), sex (men *vs* women), age (≤35 years *vs* >35 years), tumour localisation (knee *vs* hip *vs* foot or ankle *vs* upper extremity), bone involvement (present *vs* absent), surgical technique (open *vs* arthroscopic), and tumour size (<5 cm *vs* ≥5 cm). Using a

	Overall population (N=1192)
Admission status (N=1192)	
Therapy naive*	910 (76%)
≥1 surgery elsewhere†	282 (24%)
Sex (N=1192)	
Men	499 (42%)
Women	693 (58%)
Age at initial treatment, years (N=1122)	35 (26–48)
Tumour localisation (N=1192; appendix p 10)	
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%)
Duration of symptoms,§ months (N=744)	18 (6–36)
Type of surgery (N=1163)	
Arthroscopic synovectomy	159 (14%)
One-staged open synovectomy	628 (54%)
Two-staged open synovectomy¶	187 (16%)
(Tumour) prosthesis||**	63 (5%)
Amputation**	3 (<1%)
Wait and see**††	76 (7%)
Synovectomy not specified	47 (4%)
Tumour size initial treatment, cm (N=701)	5·4 (3·0–8·8)
<5	297 (42%)
≥5	404 (58%)
Adjuvant therapy at initial treatment (N=1033)	
External beam radiotherapy	58 (6%)
Yttrium-90	60 (6%)
Systemic or molecular targeted treatment	15 (1%)
Other	11 (1%)
None	889 (86%)

Data are n (%) or median (IQR). *Therapy-naive or primary admission status at a tertiary centre were considered similar. †One or more surgeries elsewhere or recurrent admissions were considered similar. ‡Digits are excluded. §Symptoms were defined as either pain, swelling, stiffness, or limited range of motion (appendix pp 7–8). ¶The designation two-staged synovectomy means the two synovectomies were performed separately and within 6 months of one another. ||An arthrodesis is classified as (tumour) prosthesis. **(Tumour) prosthesis, amputation, or wait and see as initial treatment are excluded from risk and survival analyses. ††Wait and see and conservative treatment were considered similar.

Table 1: **Patient characteristics**

Kaplan-Meier method for interval censored data, we calculated all time-to-event endpoints. We estimated the effect of risk factors with a multivariable Cox regression model on the subset of data with complete covariate information. We reported the results as hazard ratios (HR) and 95% CIs.

Although we initially prespecified we would analyse 2-year and 5-year recurrence-free survival, we calculated local recurrence-free survival at 3 years, 5 years, and 10 years because we collected more patient data, including some with longer follow-up, than expected. We calculated observed recurrence-free survival probabilities at 3, 5, and 10 years for all cases and subgroups based on admission status and localisation. We purposely did not provide an estimate of the median time to recurrence. Calculating such a median based on retrospective data 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.

For the statistical analyses, we excluded patients with a wait and see policy (ie, no treatment), with a (tumour) prosthesis as initial treatment, or an amputation. Additionally, we did not include data from patients with missing outcome information in the statistical analyses.[17] Furthermore, we did subgroup analyses on therapy-naive patients and therapy-naive patients who had a primary tumour in the knee.

Due to the aforementioned approximation of the time of recurrent disease by upper bounds in some cases, we substituted common survival analysis methods (Kaplan-Meier estimate, log-rank test) by methods that allow for interval censoring (see Procedures section). We calculated observed survival curves and probabilities using non-parametric maximum likelihood estimates for interval censored data with the R package interval.[18] We calculated p values for the univariate analyses using the score test of Sun, 1996.[19]

For the multivariable Cox regression analysis, we used the icenReg R package, which allows for interval censored data.[20] Proportional hazards assumptions were tested for all multivariable models. We applied the multiple imputation technique to impute missing follow-up time for patients without recurrent disease. We imputed five complete datasets using the R package Amelia II.[21] We did all statistical analyses on all datasets and we then pooled the results according to Rubin's rule.[22] Rubin's rule is a statistical method to combine results obtained from multiple imputed datasets to get a combined result. Statistical analyses were carried out using R version 3.4.1.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Three authors (MJLM, AJR-B, and MAJvdS) had full access to the raw data. The

corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Data collection for these analyses occurred between January, 2016, and May, 2018. We received the records of 1192 patients with diffuse-type tenosynovial giant-cell tumours, of which 966 (81%) received surgery as primary treatment, had complete survival data, and complete data on prespecified core criteria.

758 (64%) of 1192 had tumours in the knee (table 1). In 628 (54%) of 1163 patients who had complete data on type of surgery, primary treatment was one-staged open synovectomy. Of 966 patients with surgically treated diffuse-type tenosynovial giant-cell tumours, 425 (44%) had a tumour recurrence after treatment (appendix p 5). The different subgroups of patients analysed are shown in figure 1.

Patients characteristics are shown in table 1. At data cutoff (May 31, 2018), median follow-up for the 966 patients with surgically treated diffuse-type tenosynovial giant-cell tumours and complete core data was 54 months (IQR 27–97). Recurrence-free survival decreased with longer follow-up times (tables 2, 3).

In univariate analyses of 966 patients with surgically treated diffuse-type tenosynovial giant-cell tumours and complete core data, the risk factor admission status was significantly associated with recurrence: recurrence-free survival at 5 years was 64% (95% CI 60–68) for therapy-naive patients compared with 25% (19–31) for patients entering the tertiary hospital with recurrent disease ($p<0·0001$; figure 2A). This difference was also found in the multivariable Cox regression analysis based on 538 patients with complete information on all covariates included in the model (HR 5·0 [95% CI 3·7–6·8]; $p<0·0001$). All patients entering a tertiary hospital with recurrent disease had low recurrence-free survival at 10 years (figure 2A).

The results of the univariate analyses for therapy-naive patients are shown in table 4. Surgical technique showed a significant association with first local recurrence. This effect did not remain significant in a multivariable Cox regression analysis based on 438 patients with complete clinical information (HR 1·2 [95% CI 0·7–2·0]; $p=0·56$). Proportional hazards assumptions were not violated.

In a subgroup analysis of therapy-naive patients with diffuse-type tenosynovial giant-cell tumours affecting the knee (n=471), surgical technique was not associated with first local recurrence (univariate analysis $p=0·11$; multivariable analysis $p=0·63$; figure 2B).

When comparing recurrence based on tumour localisation in treatment-naive cases (of the knee, hip, foot or ankle, and upper extremity localisation), the highest proportion of patients with recurrent disease had tenosynovial giant-cell tumours affecting the knee (appendix p 9). A progressively declining recurrence-free survival was seen at 3, 5, and 10 years in a subgroup analysis of the knee, hip, foot or ankle, and upper extremity localisations in patients either admitted with

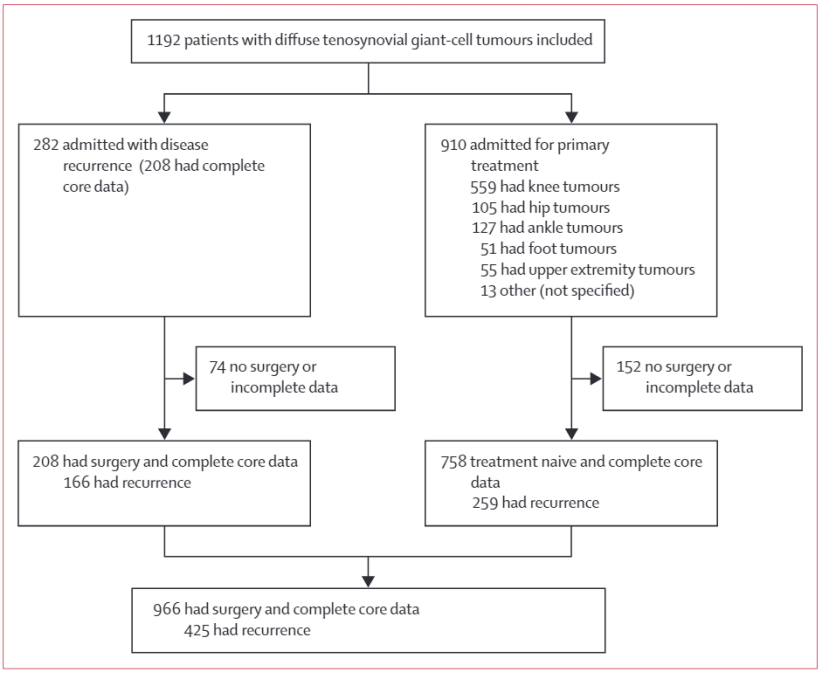

Figure 1: **Cohort and subgroups included in the analyses**
Treatments other than arthroscopic synovectomy and open synovectomy were not included in this figure (eg, tumour prosthesis, amputation, and wait and see treatment). Recurrences refer to a single event of recurrent disease.

	Patients with primary surgery
First local recurrence after initial treatment at tertiary centre (N=966)	
Present	425 (44%)
Absent	541 (56%)
Total number of recurrence events (N=425)	
1	267 (63%)
2	85 (20%)
≥3	73 (17%)
Total number of surgeries (N=707)	2·0 (1–5)
Total number of surgeries in patients with recurrent disease (N=425)	2·7 (1–6)
Follow-up, months (N=966)	54 (27–97)
Status at last follow-up (N=891)	
No evidence of disease	587 (66%)
Alive with disease—being followed up	190 (21%)
Alive with disease—awaiting treatment	31 (3%)
Death from other disease	10 (1%)
Lost to follow-up*	73 (8%)

Data are n (%) or median (IQR). *Lost to follow-up was defined as follow-up less than 6 months or stratified during follow-up because lost to follow-up.

Table 2: **Surgical outcomes after treatment for all patients who had primary surgery**

	Patients who received primary treatment (n=966)	Therapy-naive patients (n=758)
3 years	n=474; 62% (59–65)	n=372; 70% (67–74)
5 years	n=297; 55% (51–58)	n=227; 64% (60–68)
10 years	n=89; 40% (35–45)	n=70; 50% (44–56)

Where n is number of patients at risk. Data are recurrent-free survival (95% CI).

Table 3: **Recurrence-free survival outcomes**

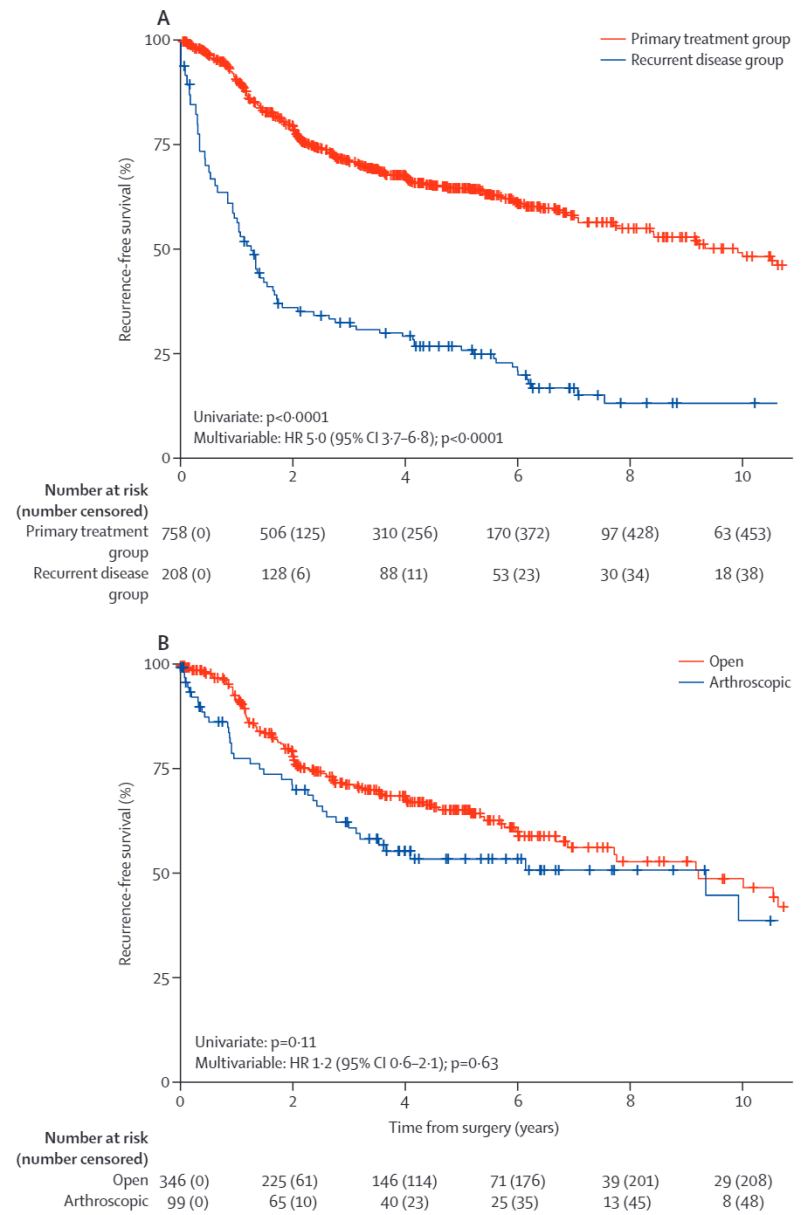

Figure 2: **Recurrence-free survival**
(A) By admission status in all patients who had surgery and complete core data (n=966). (B) By surgery type in therapy-naive patients with diffuse disease of the knee (n=445). Time zero was date of initial resection at tertiary centre. HR=hazard ratio.

therapy-naive tenosynovial giant-cell tumours or patients admitted with recurrent tenosynovial giant-cell tumours (appendix p 9).

A total of 105 (12%) complications in 906 patients (with complete data on surgical complications) occurred after surgical treatment of diffuse-type tenosynovial giant-cell tumours (appendix p 6). Of these, 86 (11%) were reported after 815 open synovectomies and 12 (8%) after 159 arthroscopic synovectomies. Before surgical treatment, most patients had symptoms of pain (738 [76%] of 969 patients with complete data on pain) and swelling (579 [75%] of 775 patients with complete data on swelling; appendix p 7). At final follow-up, these symptoms largely disappeared, although 233 (37%) of 630 patients with pain and 149 (24%) of 627 patients with swelling were still symptomatic. Joint stiffness was present in 161 (21%) of 759 patients and limited range of motion in 209 (28%) of 760 patients, and these symptoms were reported to be slightly less frequent after treatment (105 [17%] of 617) and at final follow-up (118 [19%] of 624).

A mean of 578 patients with diffuse-type tenosynovial giant-cell tumours had complete data on symptoms both before initial treatment and at final follow-up (appendix p 8). Most patients had pain and swelling before initial treatment, in whom 255 (59%) of 434 and 328 (72%) of 453 were resolved after surgical treatment(s). Patients with initial complaints of limited range of motion (128 [23%] of 572) also generally improved after surgery (48 [8%] of 572). Although the proportion of patients with reported stiffness decreased after surgery from 14% (82/567) to 8% (47/567), patients who did not report stiffness before surgery did complain thereafter (55 [10%] of 567). Therefore, the total proportion of patients reporting stiffness increased from 14% to 18% post-operatively.

A higher proportion of patients with pain, swelling, stiffness, and limited range of motion at final follow-up had recurrent disease (for pain [n=229], 126 [55%] had recurrence *vs* 103 [45%] with no recurrence; swelling [n=146], 96 [66%] *vs* 50 [34%]; stiffness [n=105], 53 [51%] *vs* 52 [49%]; limited range of motion [n=117], 65 [56%] *vs* 52 [44%]). More patients with recurrent disease (68 [22%] of 316) used chronic analgesic treatment at last follow-up then patients without recurrent disease (24 [6%] of 386).

Surgical technique did not influence functional outcome at last follow-up (pain, 47 [41%] of 114 patients had symptoms after arthroscopic synovectomy *vs* 158 [37% of 430 patients after open synovectomy; swelling, 33 [29%] of 112 *vs* 93 [22%] of 429; stiffness, 14 [13%] of 111 *vs* 77 [18%] of 421; limited range of motion, 18 [16%] of 111 *vs* 90 [21%] of 427; chronic analgesic treatment, 22 [18%] of 122 *vs* 56 [12%] of 475).

16 (24%) of 67 patients using chronic analgesic treatment had a complication compared with 50 (10%) of 482 patients without a complication who were not using analgesic treatment.

Discussion

This international, multicentre, retrospective study offers new insights into the outcomes of patients with the orphan and heterogeneous diffuse-type tenosynovial giant-cell tumours. To our knowledge, this is the largest collection of surgically treated patients with diffuse-type tenosynovial giant-cell tumours in the scientific literature, including recurrence-free survival estimates by tumour localisation.

The fundamental question of whether curative treatment should be attempted in patients with non-lethal diffuse-type tenosynovial giant-cell tumours often arises in the literature. Debilitating symptoms and progressive joint destruction commonly result from untreated diffuse-type tenosynovial giant-cell tumours but can also occur after treatment. At present, the choice of treatment is established by the preference of the patient and treating physician and might differ by treatment centre. Surgical treatment for the locally aggressive diffuse-type tenosynovial giant-cell tumours is challenging because pathological tissue can be spread widely throughout the joint and might be technically difficult to access and remove. In patients with extensive disease, less than radical or only partial resection could be preferred to improve symptoms with joint preservation in mind. However, higher recurrence have been described after macroscopically incomplete resections.[6,23]

Some reports consider arthroscopic management of tenosynovial giant-cell tumours superior to open surgery because of less morbidity and a shorter recovery period.[24,25] Standard arthroscopy of the knee with the use of only anteromedial and anterolateral approaches, however, does not allow surgical access to remove all areas in which diseased tissue is likely to be present. Therefore, Blanco and colleagues[26] and Mollon and colleagues[27] used multiple portals, including posteromedial and posterolateral in arthroscopic synovectomy.[28] Chin and colleagues[29] stated that knee arthroscopy alone is an inferior treatment for extra-articular tenosynovial giant-cell tumours. Open synovectomy, either one-staged or two-staged, seems to be the preferred surgical approach for diffuse-type tenosynovial giant-cell tumours in most centres because of improved tumour visibility and reported a lower short-term proportion of patients with recurrent disease than with arthroscopy.[9] The disadvantage of a one-staged or two-staged open resection could be deteriorated joint function accompanied with decreased patient health-related quality of life.[10] A systematic review[9] showed lower proportions of recurrence for open synovectomy (average 14%, maximum 67%) than arthroscopic synovectomy (average 40%, maximum 92%) in patients with diffuse-type tenosynovial giant-cell tumours. Patel and colleagues[7] reported a significantly higher risk of recurrence in 214 patients with diffuse-type tenosynovial giant-cell tumours after arthroscopic synovectomy than with open synovectomy (83·3% *vs* 44·8%; risk ratio 1·86 [95% CI 1·32–2·62]; p=0·0004). Palmerini and colleagues[6] did not find a difference in 206 patients with recurrent disease based on surgical technique for localised and diffuse-type tenosynovial giant-cell tumours combined. The present study calculated recurrence-free survival for patients with diffuse-type tenosynovial giant-cell tumours at 3 years, at 5 years, and at 10 years. These results clearly underline that with longer follow-up, recurrence continues to increase, but they also reflect the tertiary character of care and hypothesised increase severity of disease within our study population.

A combined anterior arthroscopic and posterior open synovectomy in the knee might be a viable option but is only incidentally reported. Mollon and colleagus[27] 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. Colman and colleagues[30] retrospectively assessed 11 patients with diffuse-type tenosynovial giant-cell tumours treated with the combined approach and also reported a low short-term recurrence (9%). A randomised controlled trial for arthroscopic synovectomy versus open synovectomy has not been done. The surgical treatment of diffuse-type tenosynovial giant-cell tumours should therefore be balanced to the extent of the disease, the surgical experience, the preference of the surgical and multidisciplinary team, and finally the expectations and preferences of the patient. Arthroscopic surgical resection is mostly done in dedicated centres

	N (%)	Recurrence-free survival at 5 years (%)	95% CI	p value
Age (n=755)				
≤35 years	391 (52)	64	59–70	0·94
>35 years	364 (48)	63	57–69	
Sex (n=758)				
Men	307 (41)	63	56–69	0·86
Women	451 (59)	64	59–70	
Tumour localisation (n=512)				
Knee	471 (62)	61	56–66	0·10
Hip	70 (9)	65	54–77	
Foot or ankle	158 (21)	72	64–81	
Upper extremity	59 (8)	59	44–74	
Tumour size (n=512)				
<5 cm	217 (42)	71	64–78	0·42
≥5 cm	295 (58)	64	58–71	
Bone involvement (n=583)				
Present	158 (27)	61	52–69	0·82
Absent	425 (73)	64	58–69	
Surgical technique (n=715)				
Open surgery	595 (83)	66	61–70	0·03
Arthroscopic synovectomy	120 (17)	54	44–64	

Table 4: Univariate analyses for recurrence-free survival in therapy naive patients (n=758)

that include both sports (arthroscopy) and oncological orthopaedic teams. Intra-articular resection can safely be performed through a less invasive arthroscopic approach, but if arthroscopic experience in the treatment of tenosynovial giant-cell tumours is not present, we would advise a complete open synovectomy.

In our analysis, for therapy-naive patients referred to a tertiary centre, the greatest risk factor for local recurrence seems to be arthroscopic synovectomy. The suspicion arises that more (macroscopic) tumour tissue remains after arthroscopic synovectomy; however, the volume of remaining tissue largely depends on the extent of the arthroscopy performed, whether multiple and posterior portals were used to access and remove disease throughout the knee joint, and whether this approach was combined with an open approach to remove residual intra-articular disease or extra-articular disease extension. However, none of the assumed risk factors yielded statistical significant differences when the analysis was performed in a subgroup of therapy-naive patients with diffuse-type tenosynovial giant-cell tumours affecting the knee, which could be attributed to the near impossibility of achieving a complete macroscopic resection in widely spread, ill defined diffuse-type tenosynovial giant-cell tumours neither with an arthroscopic nor open resection. This possibility is suggested by the fact that greatest risk factor for local recurrence is recurrent disease at presentation. Possibly this effect should be regarded a proxy for the biological heterogeneity of this disease activity, localisation, severity, or extent at presentation and first surgical treatment.

High short-term recurrent disease, confirmed by the present study, indicates the need for adjuvant therapies to improve treatment outcomes for patients with diffuse-type tenosynovial giant-cell tumours. This study was unable to analyse adjuvant therapies since the populations were too heterogeneous to analyse, including insufficient numbers of events. Gortzak and collegaues[13] reported no significant differences in residual disease, complication percentages, and overall physical and mental health scores between patients surgically treated for tenosynovial giant-cell tumours of the knee with (n=34) or without (n=22) adjuvant Yttrium-90 radiotherapy, after a mean follow-up of 7·3 years (IQR 2·5–25·4). Griffin and colleagues[8] reported on 49 patients with diffuse-type tenosynovial giant-cell tumours, most of whom had both intra-articular and extra-articular and recurrent disease, with three (6%) recurrences after synovectomy plus radiotherapy. A meta-analysis[12] suggested that open synovectomy (n=19 studies; n=448) or synovectomy combined with perioperative radiotherapy (n=11 studies; n=123) is associated with a reduced recurrence. Mollon and colleagues[27] reserved the use of external beam radiothreapy for patients at high risk for local recurrence, if they had the characteristics of multiple episodes of recurrent intra-articular disease, extra-articular extension, or gross residual disease remaining after surgery. Large cohorts are scarce to support the use of external beam radiotherapy for primary treatment; however, we feel it should only be performed in specific instances, such as extensive or recurrent diffuse-type tenosynovial giant-cell tumours.

In patients with locally advanced tenosynovial giant-cell tumours or multiple recurrence, systemic therapies targeting the CSF1–CSF1 receptor axis have been investigated, including nilotinib, imatinib, pexidartinib (PLX3397), emactuzumab (RG7155), and cabiralizumab (FPA008). Some systemic treatments (eg, nilotinib, imatinib) for patients with tenosynovial giant-cell tumours have been proven to be active,[14,15] and novel and potentially more potent drugs (eg, pexidartinib [PLX3397], emactuzumab [RG7155], and cabiralizumab [FPA008]) are under investigation.[16] 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 are warranted.

Patients with aggressive disease accompanied with a high risk of recurrence after surgery alone should be selected for new systemic and neoadjuvant or adjuvant treatment modalities. Some patients present with tumours that are surgically easy to access and might not require neoadjuvant or adjuvant therapies. Mastboom and colleagues[4] defined the most extensive, widespread diffuse-type tenosynovial giant-cell tumours subgroup on MRI as having diffuse-type tenosynovial giant-cell tumours, including intra-articular and extra-articular disease, and involvement of at least one of three tissues: muscle, tendon or ligament. These patients seem to be the most eligible for multimodality or adjuvant strategies.

The existing literature on tenosynovial giant-cell tumours frequently lacks descriptions of complications after surgical treatment. The current study reported that 12% of patients with diffuse-type tenosynovial giant-cell tumours had a complication after surgical management. 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 proportion of complications might be even higher, since it is suspected that not all complications are reported.

Tenosynovial giant-cell tumour-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 and colleagues[5] concluded that not all patients experience all symptoms to the same extent (eg, swelling but not pain, or pain and swelling but not stiffness or limited range of motion). Symptoms before initial treatment at a tertiary centre were compared for each patient with symptoms at last follow-up. Joint stiffness was only regarded a surgical complication when it was not present before surgery and occurred within 3 months thereafter. Initial symptoms of pain and swelling improved after treatment(s) in 43–56% of patients.[5] This improvement is similar to that of a crowdsourcing study[11] in 337 patients with tenosynovial

giant-cell tumours from 30 countries. In most 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 and not all patients were included with complete data. Nevertheless, pain and swelling are the main tenosynovial giant-cell tumour-related complaints initially, and frequently improve after surgical treatment(s).

In light of the retrospective study design with missing data, the main limitation of this study is selection bias, since data on patients with histologically proven tenosynovial giant-cell tumours treated at non-specialised centres were scarce and were not included in this study because we wanted to have a fair analysis of patients with tenosynovial giant-cell tumours treated at specialised centres. Selection bias of affected joints seems absent when comparing percentages of affected joints with an incidence calculation study, including nationwide coverage (64% of diffuse-type tenosynovial giant-cell tumours affect the knee).[3] Since data were collected by local investigators or physicians according to the retrospective 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. No central histopathological review was performed because it was assumed that each centre provided the correct diagnosis as set by their histopathology department, and all included cases were histologically proven to be tenosynovial giant-cell tumour. Within our study, we did not collect information about which patient had multiportal arthroscopy or standard anterior portal arthroscopy. Centre-specific collection procedures for follow-up data and missing follow-up data is another limiting factor for our study. Recurrence could either be overestimated or underestimated. Overestimation could occur because the follow-up status of alive with disease was classified as recurrence (if recurrence data were missing). On the contrary, underestimation 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 than 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 performed recently, patients also had shorter follow-up times and are still at risk of recurrence.

Even though considered a benign disease, diffuse-type tenosynovial giant-cell tumours 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.[10] In this study, most patients were surgically treated. Patients with a wait and see policy were excluded from analyses. Long-term outcomes for this approach are awaited before it can be used to treat diffuse-type tenosynovial giant-cell tumours.

To our knowledge, this is the largest study on patients with diffuse-type tenosynovial giant-cell tumours and provides a comprehensive and up-to-date disease overview on the clinical profile and management of these patients. Our study suggests that surgery is 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 moderate 5 years recurrence-free survival after surgery. In the era of multimodality therapy, standalone surgical resection can no longer be regarded as the only treatment for patients with diffuse-type tenosynovial giant-cell tumours, and alternative or combined approaches should be considered. This manuscript can further support a consensus paper on future directions of multimodality treatment for these patients.

Contributors

MJLM, EP, SS, ELS, HG, and MAJvdS conceived and designed the study. MJLM, EP, FGMV, SS, GRS, PCJ, WA, AL, DD, AT, QT, XN, JSW, TGCT study group, and MAJvdS acquired the data. MJLM, FGMV, AJR-B, SS, JSW, and MAJvdS managed quality control of data and algorithms. MJLM, EP, FGMV, AJR-B, SS, ELS, JSW, and MAJvdS analysed and interpreted the data. MJLM prepared the manuscript. MJLM, EP, FGMV, AJR-B, SS, ELS, PCJ, AL, JSW, and MAJvdS edited the manuscript. MJLM, EP, FGMV, AJR-B, SS, ELS, GRS, PCJ, WA, HG, AL, DD, AT, QT, XN, JSW, and MAJvdS reviewed the manuscript. All authors gave final approval to submit the manuscript.

Declaration of interests

EP, ELS, HG, and MAJvdS are on the advisory board for Daiichi Sankyo and receive funding for clinical research studies to their institutions. SS receives funding from Daiichi Sankyo and Novartis for clinical research studies to her institution. All other authors declare no competing interests.

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