Received: 10 February 2022 | Accepted: 14 June 2022

DOI: 10.1002/jso.26991

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

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

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Abstract

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

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

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

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

KEYWORDS

diffuse type, pigmented villonodular synovitis, sarcoma, surgery, tenosynovial giant cell tumor

1 | INTRODUCTION

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

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

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

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study was a retrospective, observational, monocentric cohort study. Consecutive patients with D-TGCT related to the larger joints, who underwent primary surgery between 2000 and 2020 in one sarcoma center, were eligible for inclusion. Larger joints were defined as all joints proximal to metatarsophalangeal and metacarpophalangeal joints. TGCT was histologically confirmed in all patients by dedicated bone and soft tissue tumor pathologists.

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

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

2.2 | Data

Demographic characteristics, TGCT presentation, treatment characteristics, and follow-up data were collected from patient records. Total follow-up concerned time from surgery until the moment of data collection. For two-stage synovectomies, defined as two synovectomies performed on different sides of a joint within 6 months, the date of the last surgery was taken as the start of follow-up. The first postoperative MRIs were assessed on POT after surgery (interquartile range [IQR] 4–12 months). Radiological progression during follow-up was defined as considerable progression of tumor on MRI. The postoperative radiological status and progression rates were assessed for patients that underwent isolated open synovectomies. Also, clinical deterioration was measured for these patients, defined as a return to the outpatient clinic with

symptomatic worsening of the affected joint after postoperative recovery. Data were collected after approval of the institutional review committee and according to the Declaration of Helsinki.

2.3 | Statistical analysis

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

3 | RESULTS

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

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

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

TABLE 1 Patient demographics

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

Abbreviation: SD, standard deviation.

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

3.1 | Complications

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

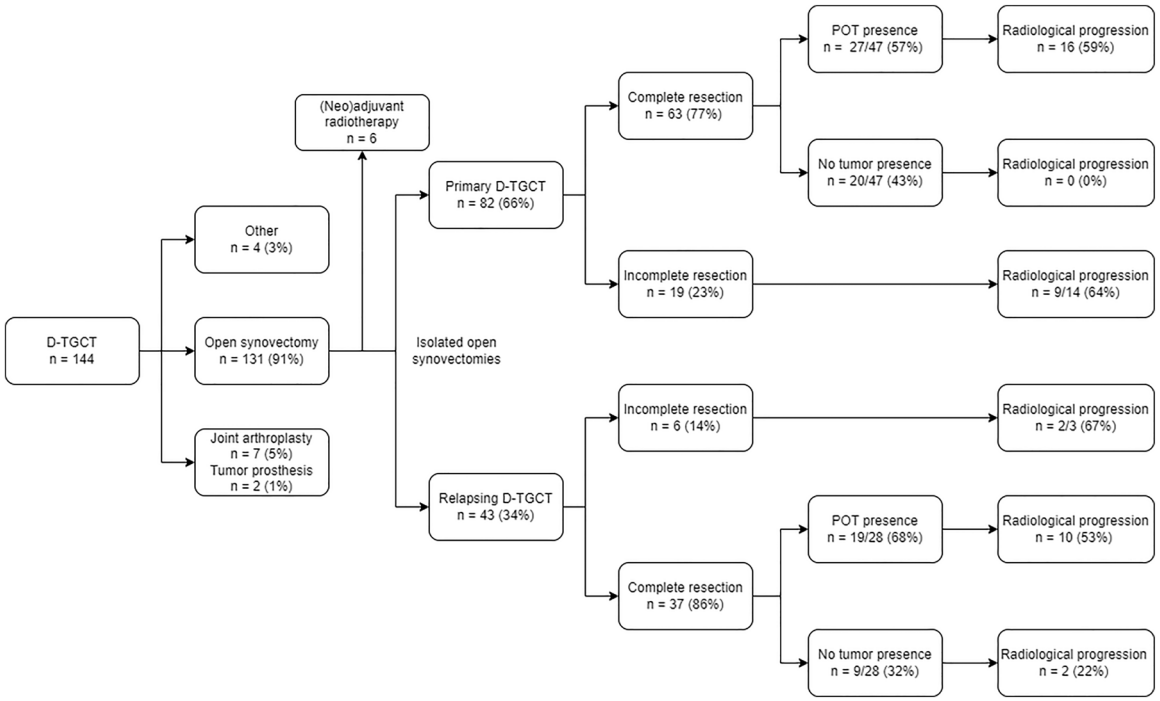


FIGURE 1 Flowchart of D-TGCT patients surgically treated between 2000 and 2020. D-TGCT, diffuse-type tenosynovial giant cell tumors; POT, postoperative tumor presence.

TABLE 2 Follow-up of diffuse-type TGCT treated solely by open synovectomy

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

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging; TGCT, tenosynovial giant cell tumor.

TABLE 3 Follow-up of diffuse-type TGCT treated solely by open synovectomy

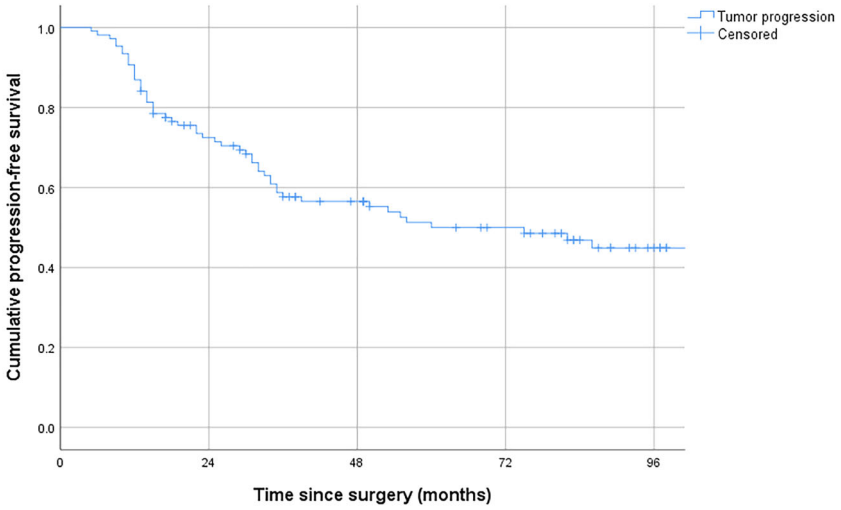
Features	Therapy-naïve *n* = 82 (%)	Relapsing *n* = 43 (%)	Total *n* = 125 (%)
Median follow-up (months) after surgery (IQR; Q1–Q3)	63.5 (36.5–95.3)	67.0 (33.0–96.0)	64.0 (35.5–95.5)
Radiological status during follow-up			
Median time till first postoperative MRI (months) (IQR; Q1–Q3)	6.0 (4.0–11.0)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

Abbreviations: IQR, interquartile range; MRI magnetic resonance imaging; TGCT, tenosynovial giant cell tumor.

4 | DISCUSSION

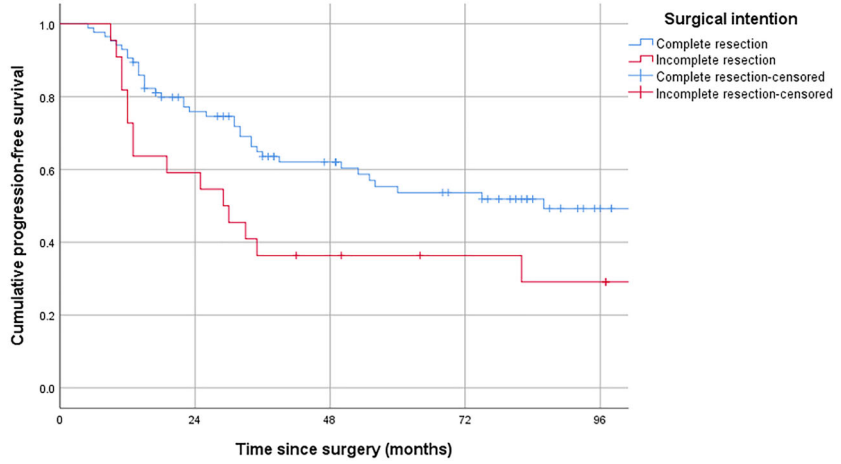
Surgery remains the mainstay of treatment for TGCT, predominantly performed open. However, achieving a cure even in experienced surgical hands remains challenging, especially for D-TGCT. It is widely acknowledged that complete resection can be difficult or undesirable in some cases due to the extensive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

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



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

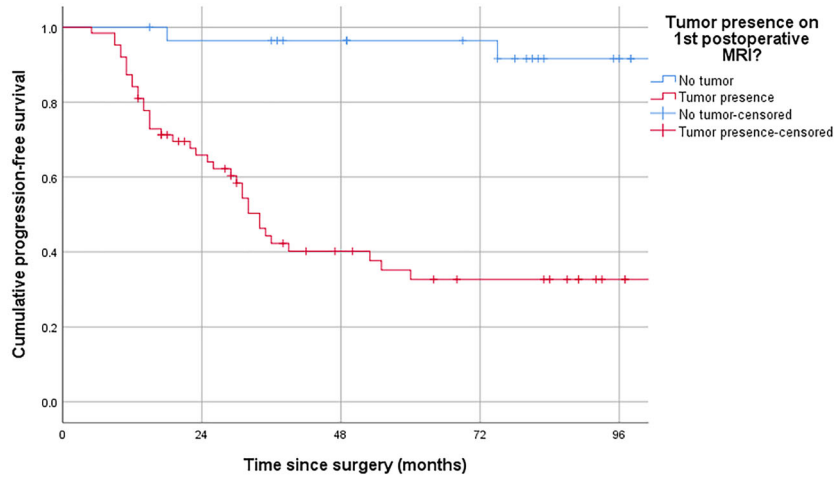
FIGURE 2 Progression-free survival curve and survival table of D-TGCT patients with ≥1 MRI (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumors; MRI, magnetic resonance imaging.



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

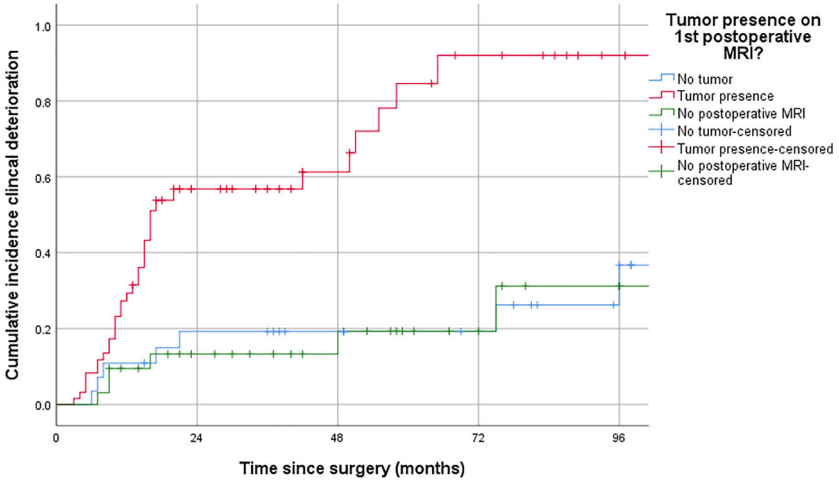
FIGURE 3 Progression-free survival curves and survival table of D-TGCT patients, stratified on preoperative surgical intention (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumors.

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



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

FIGURE 4 Progression-free survival curves and survival table of D-TGCT patients, stratified on tumor presence of first postoperative MRI (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumors; MRI, magnetic resonance imaging.



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

FIGURE 5 Cumulative incidence curves and survival table of D-TGCT patients that clinically worsened, stratified on first postoperative MRI status (Kaplan–Meier analysis). D-TGCT, diffuse-type tenosynovial giant cell tumors; MRI, magnetic resonance imaging.

treatment decisions are best made in multidisciplinary teams within sarcoma centers with experience in TGCT care.

Neoadjuvant therapies could be considered for preoperative downstaging of the tumor to facilitate a (more) complete excision in advanced TGCT. Neoadjuvant therapies could consist of CSF1R inhibitors or antibodies, but evidence regarding neoadjuvant therapies in TGCT is scarce. Gelderblom et al.[14] reported that a secondary resection following nilotinib treatment did not affect PFS. Other CSF1R inhibitors are not investigated as neoadjuvant therapy to date. CSF1R inhibitors may be indicated as a stand-alone treatment for patients not amenable to surgery. Recent studies showed promising results of CSF1R inhibitors, and new therapies are in the pipeline.[15,16,23,24] The role of adjuvant radiotherapy in TGCT treatment, consisting of external beam radiotherapy (EBRT) or radiosynoviortheses, remains controversial. Mollon et al.[25] claimed that perioperative EBRT might reduce recurrence rates in D-TGCT, but the level of evidence was low. During this 20 years cohort, our MDTB indicated radiotherapy in only a few cases, and thus the actual

TABLE 4 Surgery-related complications

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

treatment effect could not be determined. Radiotherapy may result in disproportionate complications such as early-onset osteoarthritis, avascular necrosis, skin problems, and even radiation-induced sarcomas, which is unacceptable in a nonmalignant disease in a young patient population.[25,26]

During total follow-up, D-TGCT radiologically progressed in 50% of the patients. However, this may be under- or overestimations since these rates were based on patients who underwent ≥1 MRI during follow-up. This also applies to observed POT presence. Besides the first postoperative MRI, additional MRIs are mainly performed when patients are symptomatic or when joint destruction is expected. Since patients without residual tumor or progression are expected to be symptomatic less often, MRIs are presumably performed less frequently potentially causing bias. Contrarily, patients could also have an asymptomatic tumor (growth), which would not be observed if no MRI was made. To date, it is unclear when radiological progression coincides with clinical deterioration and vice versa. This study showed that the clinical situation deteriorated in several TGCT patients, even without considerable radiological progression on MRI. In these cases, other causes than tumor progression may lead to a symptomatic worsening of TGCT, such as joint destruction, joint effusion, or synovitis flare-up. Additionally, radiological tumor progression on MRI did not lead to clinical deterioration in a substantial number of D-TGCT patients. It remains unclear whether or when treatment is required for these patients and we believe shared decision-making is essential in such cases. TGCT is often treated aggressively due to its conceivably destructive behavior, resulting in irreversible joint damage in the longer term. However, data about the natural course of TGCT is lacking. In the placebo group of the ENLIVEN trial, TGCT remained stable at 78%.[16] POT diagnosed by MRI in our study may therefore be regarded as residual more than the recurrent disease. The exact underlying molecular mechanism for disease progression is unknown.[9,22,27] Identifying patients with a higher risk of relapse or joint destruction would be a tremendous breakthrough in TGCT treatment. However, at this moment, we feel that an experienced MDTB in a high-volume center is the best approach to recognizing patients at risk.[28]

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

5 | LIMITATIONS

The retrospective study design resulted in not having an MRI performed on all patients and some missing data. MRIs were mainly performed around 6 months postoperatively and additional MRIs when patients become symptomatic due to this benign character of TGCT. Since no strict follow-up protocol was followed, MRIs were performed at different intervals and not at fixed moments, which can be considered a major limitation. Additionally, the assessment of scans was performed in clinical practice without predefined (response) criteria, such as RECIST or tumor volume score. Predefined MRI (response) criteria should be applied to obtain better tumor quantification in future studies. In future studies, scans can be performed sooner after surgery to determine whether POT is residual or recurrent. However, it might not be possible to discriminate between postoperative changes and residual lesions. Still, a single-center cohort introduces homogeneity in imaging data, treatment, and follow-up policies, and available data were collected more trustworthy than in a multicenter study. Conversely, the generalizability of a single-center study is limited.

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

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

6 | CONCLUSION

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

CONFLICT OF INTEREST

Geert Spierenburg and Michiel A. J. van de Sande report research grants from Daiichi Sankyo to the Department of Orthopedic Surgery of the Leiden University Medical Center.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Spierenburg G, Heijden LVD, Mastboom MJL, et al. Surgical management of 144 diffuse-type TGCT patients in a single institution: a 20-year cohort study. *J Surg Oncol*. 2022;126:1087-1095. doi:10.1002/jso.26991