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ONCOLOGY

Tenosynovial giant cell tumours: experience at an Australian tertiary referral centre for musculoskeletal tumours with minimum two-year follow-up

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Aims

Tenosynovial giant cell tumour (TGCT) is a rare benign tumour of the musculoskeletal system. Surgical management is fraught with challenges due to high recurrence rates. The aim of this study was to describe surgical treatment and evaluate surgical outcomes of TGCT at an Australian tertiary referral centre for musculoskeletal tumours and to identify factors affecting recurrence rates.

Methods

A prospective database of all patients with TGCT surgically managed by two orthopaedic oncology surgeons was reviewed. All cases irrespective of previous treatment were included and patients without follow-up were excluded. Pertinent tumour characteristics and surgical outcomes were collected for analysis.

Results

There were 111 total cases included in the study; 71 (64%) were female, the mean age was 36 years (SD 13.6), and the knee (n = 64; 57.7%) was the most commonly affected joint. In all, 60 patients (54.1%) had diffuse-type (D-TGCT) disease, and 94 patients (84.7%) presented therapy-naïve as "primary cases" (PC). The overall recurrence rate was 46.8% for TGCT. There was a statistically significant difference in recurrence rates between D-TGCT and localized disease (75.0% vs 13.7%, relative risk (RR) 3.40, 95% confidence interval (CI) 2.17 to 5.34; p < 0.001), and for those who were referred in the ”revision cases” (RC) group compared to the PC group (82.4% vs 48.9%, RR 1.68, 95% CI 1.24 to 2.28; p = 0.011). Age, sex, tumour volume, and mean duration of symptoms were not associated with recurrence (p > 0.05).

Conclusion

Recurrence rates remain high even at a tertiary referral hospital. Highest rates are seen in D-TGCT and “revision cases”. Due to the risks of recurrence, the complexity of surgery, and the need for adjuvant therapy, this paper further supports the management of TGCT in a tertiary referral multi-disciplinary orthopaedic oncology service.

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Introduction

Tenosynovial giant cell tumour (TGCT), previously known intra-articularly as pigmented villonodular synovitis (PVNS), is a rare benign tumour of the synovium, tendon sheath, or bursa.[1] It is now believed to be a true neoplasm due to discovery of autocrine and paracrine stimulatory properties, despite initial theories purporting an inflammatory origin.[2,3] The tumour has a female predilection and can present at any age, but most frequently presents in the knees of adults

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between the ages of 30 to 50 years.[4,5] It has an extremely vague clinical presentation, often leading to significant delays in diagnosis and initiation of treatment.[6]

In 2013, the World Health Organization (WHO) reclassified TGCT into localized-type (L-TGCT) and diffuse-type (D-TGCT) based on clinical and radiological features.[1] While these subtypes share common histopathological characteristics, their clinical behaviour is divergent.[7] D-TGCT is proliferative and locally destructive and, if untreated, can lead to an increase in intra-articular pressure, eroding cartilage and subchondral bone, leading to debilitating arthritis necessitating joint arthroplasty and reduced quality of life.[8-10] Comparatively, L-TGCT often presents as a well-defined nodule that can remain clinically dormant for many years and is occasionally found incidentally during the investigation or treatment of other joint pathology.[11]

Treatment options include surgical excision, either via an arthroscopic or open approach, or a combination of both. Given its neoplastic properties, radiotherapy has been used with varying degrees of success an adjuvant treatment or for inoperable cases.[12] Most recently, medical therapy using tyrosine kinase inhibitors that selectively blocks colony-stimulating factor 1 (CSF-1) have been shown to successfully decrease tumour volume in refractory cases of TGCT.[13-16]

Despite the promising emergence of medical therapy, surgical excision remains the principal treatment for both types. Open approaches are favoured, with arthroscopic procedures shown to have higher rates of recurrence particularly for D-TGCT.[17,18] This has led some to suggest that TGCT should be treated in conjunction at tertiary musculoskeletal tumour centres.

The aim of the current study was to present the surgical experience of an Australian tertiary referral orthopaedic oncology centre (Royal Prince Alfred Hospital, Camperdown), and to identify potential risk factors for recurrence. Our hypotheses were that recurrence rates would be higher for D-TGCT, for cases who had index surgery undertaken at non-tertiary referral centres, cases affecting the knee, and for larger volume disease.

Methods

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,[19] and was approved by the Sydney Local Health District Ethics Review Committee (RPAH Zone) for our institution (X18-0297 & LNR/18/RPAH/407).

Data extraction. A retrospective review of a prospective database (Bone and Soft-tissue tumour Database) from an Australian tertiary referral centre for musculoskeletal tumours was performed. The institution is a major public, university-affiliated teaching hospital of Australia (Royal Prince Alfred Hospital) and a state-wide referral centre for musculoskeletal tumours. Two independent reviewers (RK, SK) used a pre-formed data collection template. All included cases had received surgical treatment at the institution (by PS or RB). Duration of symptoms was calculated as the longest length of time from when any of the symptoms were experienced. All follow-up occurred routinely either at the institution or in the surgeons' private rooms at two weeks and six months post-surgery, or unless clinically indicated.

Patient selection. All consecutive cases of TGCT surgically treated between 2007 and 2018 by two orthopaedic oncology surgeons were included. Patients with no follow-up data or incidental diagnoses were excluded from analysis. All cases had preoperative MRI with diagnosis of tumour type confirmed by histopathology after consensus at weekly multidisciplinary team (MDT) meetings consisting of orthopaedic surgeons, specialized musculoskeletal tumour radiologists and pathologists. For mode of presentation, we defined "primary cases" (PC) as those who were therapy-naïve and had their index surgery at our institution while the "revision cases" (RC) group were cases referred to our institution for recurrence following index surgery elsewhere. Tumour volume was calculated in centimetres for each resected specimen based on the longest measurement from width, depth, and height. Subgroup analysis of the knee joint was performed given the globally higher incidence of disease occurring in this joint with respective surgical therapy.[20]

Treatment modality. For the knee joint, an open approach was usually performed. Where required, a posterior approach was undertaken, in similar to the procedure described by Chin et al,[21] with the patient prone via an "s-shaped" incision, careful dissection, protection of neurovascular structures, and an arthrotomy performed after retraction of the gastrocnemius heads. For D-TGCT, meticulous en bloc compartmental synovectomy was performed. Patients with evidence of multi-compartment disease underwent a planned two-stage total synovectomy completed within two to four months. The anterior approach to the knee was via the universal medial parapatellar approach. All patients were provided with surgical antibiotic prophylaxis with doses of first-generation cephalosporin. Intraoperatively, a tourniquet was inflated to 300 mmHg, while postoperatively all inpatients received deep venous thrombosis (DVT) prophylaxis with enoxaparin as per institution protocol. Following surgery, all patients had early active and passive range of motion exercises initiated with physiotherapists. Selection of patients (n = 15) for adjuvant therapy with the only available medical treatment at that time was confined to medically fit adult patients who presented with refractory disease, and was in the form of nilotinib as part of a phase II clinical trial at a pre-specified dosing regimen of 400 mg twice daily, or local radiation therapy.[22] Recurrence was diagnosed by MRI, and all patients with D-TGCT had

Table I. Patient demographics.

Variable	D-TGCT	L-TGCT	Primary	Recurrent	Patients (n = 111)
Patients, n (%)	60 (54.1)	51 (45.9)	94 (84.7)	17 (15.3)	111 (100)
Mean age, yrs (SD)	35.9 (13.8)	36.1 (13.4)	36.8 (13.6)	31.6 (16)	36.0 (13.6)
Sex, n (%)					
Female	36 (60)	35 (68.6)	60 (63.8)	11 (64.7)	71 (64.0)
Male	24 (40)	16 (31.4)	34 (36.2)	6 (35.3)	40 (36.0)
Side, n (%)					
Right	34 (56.7)	27 (52.9)	48 (51.1)	13 (76.5)	61 (55.0)
Left	26 (43.3)	24 (47.1)	46 (48.9)	4 (23.5)	50 (45.0)
Tumour type, n (%)					
D-TGCT			46 (48.9)	14 (82.4)	60 (54.1)
L-TGCT			48 (51.1)	3 (17.7)	51 (45.9)
Joint involved, n (%)					
Knee	43 (71.7)	21 (41.2)	51 (54.3)	13 (76.5)	64 (57.7)
Foot	4 (6.7)	14 (27.5)	17 (18.1)	1 (5.9)	18 (16.2)
Ankle	6 (10)	5 (9.8)	9 (9.6)	2 (11.8)	11 (9.9)
Hip	6 (10)	1 (2)	6 (6.4)	1 (5.8)	7 (6.3)
Hand	0 (0)	7 (13.7)	7 (7.4)	0 (0)	7 (6.3)
Wrist	0 (0)	2 (3.9)	2 (2.1)	0 (0)	2 (1.8)
Shoulder	1 (1.7)	1 (2)	2 (2.1)	0 (0)	2 (1.8)

D-TGCT, diffuse-type tenosynovial giant cell tumour; L-TGCT, localized-type tenosynovial giant cell tumour; SD, standard deviation.

routine surveillance MRI at six-monthly intervals out to two years from their surgery or when clinical symptoms raised concerns for recurrence.

Statistical analysis. Statistical analysis was undertaken using SPSS v. 24.0 (SPSS, USA). Continuous data was evaluated using the mean difference for normally distributed data, or median (range) for skewed data. Categorical data was evaluated as frequencies (percentage), with groups condensed as appropriate. Differences in distributions of variables was assessed using independent-samples *t*-test or Mann-Whitney U test for continuous variables, and chi-squared test or Fisher's exact test for categorical variables, where appropriate. Significance was set at p = 0.05.

Results

Patient and tumour characteristics. Overall, 111 patients were included in the study; of those, 60 (54.1%) presented with D-TGCT and 51 (45.9%) with L-TGCT. A total of 94 patients (84.7%) presented in PC, while 17 (15.3%) presented as RC. There was a statistically significant higher rate of RC presenting with D-TGCT compared to PC (82.4% vs 48.9%, relative risk (RR) 1.68, 95% confidence interval (CI) 1.24 to 2.28; p = 0.011). The knee was the most common site of disease with 64 cases (57.7%). Overall, 71 (64.0%) of cases were female, with an mean age of presentation of 36 years (standard deviation 13.6) and a mildly increased rate of right-sided disease presenting compared to left (Table I).

Symptoms at presentation included swelling in 90.0% (n = 100) of patients, pain in 81.9% (n = 91), and stiffness in 19.8% (n = 22). There was no difference in proportion of presenting symptoms between D-TGCT and L-TGCT or between PC versus RC groups (p > 0.05).

For mode of index surgery, 98.9% of PC group had an open synovectomy at our institution compared to 29.4% in the RC group. There was a statistically significant difference in patients who had arthroscopic surgery in the PC group compared to the RC group (1.1% vs 70.1%, RR 0.02, 95% CI 0.00 to 0.11; p < 0.001).

Within the 64 patients of the knee sub-group, 43 (67.2%) had D-TGCT compared to 21 (32.8%) with L-TGCT, and the majority of patients presented in the PC group (n = 51; 79.7%) (Tables I and II). There was a statistically significant difference in the rate of arthroscopic approaches as the index surgery in the PC group when compared to the RC group (2.0% vs 92.3%, RR 0.02, 95% CI 0.00 to 0.15; p = 0.001).

Outcomes. Overall, 52 patients (46.8%) had recurrence of their disease, with median time to recurrence of approximately 12.9 months (6.1 to 27.4) (Table III). There was a statistically significant difference in the rate of recurrence between D-TGCT and L-TGCT (86.5% vs 13.5%, RR 3.40, 95% CI 2.17 to 5.34; p < 0.001) (Table III). The recurrence rate in those presenting in the RC group compared to PC group was also found to be statistically significant (71.7% vs 28.5%, RR 8.51, 95% CI 2.04 to 35.5; p < 0.001). Recurrence rate in the knee joint was high (n = 34; 53.1%), yet this was not statistically significant when compared to other joints (RR 1.286, 95% CI 0.93 to 1.77; p = 0.122). Age, sex, tumour volume, and duration of symptoms did not show any difference in recurrence rates (p > 0.05) (Table III).

Table II. Tenosynovial giant cell tumour of the knee.

	Tumour type		Mode of presentation		
Variable	**D-TGCT**	**L-TGCT**	**Primary**	**Recurrent**	**Total**
Patients, n (%)	43 (67.2)	21 (32.8)	51 (79.7)	13 (20.3)	64 (100)
Mean age, yrs (SD)	34.2 (13.5)	33.6 (12.6)	35.1 (12.9)	29.8 (13.6)	34.0 (13.1)
Sex, n %					
Female	23 (53.5)	15 (71.4)	31 (60.8)	7 (53.8)	71 (64.0)
Male	20 (46.5)	6 (28.6)	20 (39.2)	6 (46.2)	40 (36.0)
Laterality, n (%)					
Right	24 (55.8)	13 (61.9)	26 (51.0)	11 (84.6)	61 (55.0)
Left	19 (44.2)	8 (38.1)	25 (49.0)	2 (15.4)	50 (45.0)
Tumour type, n (%)					
D-TGCT			32 (62.7)	11 (84.6)	60 (54.1)
L-TGCT			19 (37.3)	2 (15.4)	51 (45.9)
Surgical modality, n (%)					
Open localized synovectomy	15 (34.9)	20 (95.2)	33 (64.7)	2 (15.4)	35 (54.7)
Arthroscopic localized synovectomy	2 (4.7)	0 (0)	0 (0)	2 (15.4)	2 (3.1)
Two-stage total synovectomy	21 (48.8)	0 (0)	16 (31.4)	5 (38.5)	21 (32.8)
Open total synovectomy	2 (4.7)	0 (0)	1 (2.0)	1 (7.7)	2 (3.1)
Arthroplasty	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Open anterior synovectomy	1 (2.3)		0 (0)	1 (7.7)	1 (1.6)
Arthroscopic local excision	2 (4.7)	1 (4.8)	1 (2.0)	2 (15.4)	3 (4.7)

D-TGCT, diffuse-type tenosynovial giant cell tumour; L-TGCT, localized tenosynovial giant cell tumour; SD, standard deviation.

Table III. Recurrent cases.

Variable	No recurrence	Recurrence	p-value*
Overall, n (%)	59 (53.2)	52 (46.8)	
Mean age, yrs (SD)	35.6 (13.3)	36.5 (14.0)	0.716
Sex, n (%)			
Female	38 (64.4)	33 (63.5)	
Male	21 (35.6)	19 (36.5)	0.918
Mean tumour volume, cm (SD)	3.9 (2.7)	4.3 (3.5)	0.522
Tumour type, n (%)			
D-TGCT	15 (25.4)	45 (86.5)	
L-TGCT	44 (74.6)	7 (13.5)	< 0.001
Mean duration of symptoms, mnths (SD)	20.5 (26.0)	29.2 (34.4)	0.150
Mode of presentation, n (%)			
Primary	57 (96.6)	37 (71.7)	
Recurrent	2 (3.4)	15 (28.5)	< 0.001
Joint involved, n (%)			
Knee	30 (50.8)	34 (65.4)	
Other joints	29 (49.2)	18 (34.6)	0.122
Symptoms initially, n (%)			
Swelling	51 (86.4)	49 (94.2)	0.295
Pain	46 (78.0)	45 (86.5)	0.283
Stiffness	11 (18.6)	11 (21.2)	0.878
Median time to recurrence, mnths (IQR)	Nil	12.9 (6.1 to 27.4)	< 0.001
Requiring further surgery, n (%)	6 (10.2)	25 (48.1)	< 0.001
Mean number of surgeries (SD)	1.1 (0.4)	2.0 (0.9	< 0.001
Mean follow-up, mnths (SD)	67.5 (46.7)	62.2 (40.1)	0.530

*Independent-samples *t*-test or Mann-Whitney U test for continuous variables, and chi-squared test or Fisher's exact test for categorical variables.
D-TGCT, diffuse-type tenosynovial giant cell tumour; IQR, interquartile range; L-TGCT, localised-type tenosynovial giant cell tumour; SD, standard deviation.

Within the investigated sample, 25 patients (20.7%) required further surgery after treatment at our hospital

due to recurrence. Of these, 18 patients (78.2%) were in the primary group and 16 (69.6%) were in the knee. Eventually, five patients (4.5%) required total joint arthroplasties, three of which were in the knee and two in the hip. One patient required a ray amputation for TGCT in the foot.

There was a statistically significant risk of requiring more than two further procedures for those in the RC group (RR 4.73, 95% CI 2.10 to 10.62; $p < 0.001$).

Complications included two patients (3.1%) experiencing superficial wound infections that resolved with oral antibiotics, and two patients (3.1%) had a DVT requiring anticoagulation. One patient developed neuropraxia of the sural nerve. Furthermore, two patients (50.0%) who had nilotinib therapy terminated due to mild side effects of nausea and hepatotoxicity.

Discussion

This the first Australian study examining surgical outcomes of patients with TGCT, and our results add to current global literature. As predicted, TGCT occurred most commonly between the ages of 30 to 40 years, and was found to have a clear predilection for the knee joint (57.7%) and in females (64.0%). There was a higher percentage of D-TGCT (59.6%) in this study given the institution represents an orthopaedic oncology referral centre, thereby likely receiving more complex and diagnostically ambiguous cases as mirrored by other orthopaedic oncology referral centres around the globe.[11,23]

This study confirmed our hypothesis that D-TGCT and RC group had higher risk for recurrence. The recurrence rate in the knee was 53.1% vs 38.3% in other joints, but this did not reach significance ($p > 0.122$). Volume of disease did not correlate with recurrence.

The surgical challenge of D-TGCT is in its remarkably high rate of recurrence for a benign entity, as demonstrated by the 55% recurrence-free survival at five years in a multinational study of musculoskeletal tumour referral centres.[18] This compares with our recurrence rate of 86.5% in D-TGCT cases, which was significantly higher than the rate experienced in L-TGCT cases (13.5%). These very high recurrence rates further support the need to identify and utilize adjuvant medical therapies in this population.[13]

A systematic review comparing surgical methods for recurrence in the knee found a clear benefit of open approaches compared to arthroscopic approaches (14.5% vs 39.6%) for D-TGCT by potentially minimizing the risk contamination.[20,24] This finding has been further strengthened in the knee joint through the systematic review by Chandra et al,[17] who reported an increased risk of recurrence for arthroscopic synovectomy over open approaches. Our institution employed an aggressive treatment philosophy for those with D-TGCT of the knee, as reflected in the 48.8% of patients (n = 21) who underwent a two-stage dual-approach total synovectomy, yet a high percentage of patients (80.9%) still experienced a recurrence. There are ongoing concerns about patient morbidity from those who advocate for arthroscopic surgery, yet a large multinational study by Mastboom et al[18] did not demonstrate any functional differences between patients who had open approaches to arthroscopic surgery.

In our study, 17 patients were in the RC group, having been referred to our centre due to recurrent disease. We found the risk of recurrence was 88.2% in the RC group and this was statistically significant when compared to the PC group (RR 8.51; $p < 0.001$). This result confirms further confirms secondary (or revision) surgery as a significant risk factor for recurrence as demonstrated in numerous large cohort studies.[18,25,26] In a UK study, Patel et al[20] attributed this higher rate of recurrence in their "revision cases" group (73.9%) to the complexity of the cases that were referred. Theoretically, inadequate index surgical excision can lead to the oncological concept of "seeding", which occurs primarily in aggressive malignant musculoskeletal tumours, such as osteosarcoma, thus contributing to the high recurrence rates.[27,28] The results of a large international study by Mastboom et al[29] promoted credibility to this theory, with the authors concluding that the single biggest risk factor for recurrence was being in the RC group.

In our population, the majority of knee cases (92.3%) in the RC group underwent arthroscopic synovectomy as their primary surgery, irrespective of tumour type. This is similar to a study published by Van der Heijden et al.[30] Unfortunately, peripheral hospitals may choose arthroscopic surgery for subjective reasons without MDT input and operative reports can often lack descriptive surgical details. A Dutch cohort study of 107 patients at a tertiary referral centre highlighted that 50.0% of patients in the recurrent group had an "unknown" degree of synovectomy during their index surgery.[25]

The choice of surgical approach is greatly influenced by expert interpretation of MRI findings, topographical anatomy and tumour characteristics, all of which are carefully considered in tertiary referral centres for musculoskeletal tumours. Interestingly, the notion of centralisation for rare tumours, such as TGCT, are addressed by some authors, underscoring the benefits of case volume and multidisciplinary experience. In their study, Bruns et al[31] reported centres treating <20 cases per year of TGCT had higher risks of recurrence. It is well known that management of rare musculoskeletal tumours require multidisciplinary care, musculoskeletal being concentrated at major tertiary referral hospitals. In Australia, the Australia and New Zealand Sarcoma Association (ANZSA) has cemented early recognition, awareness, and referral in its strategic plan, acknowledging improved patient

outcomes being dependent on expert review, scientific research, and clinical trials, all of which are secondary to centralization. For D-TGCT, the importance of more aggressive surgical approaches, and the use of adjuvant therapies, supports the management of D-TGCT at multidisciplinary tertiary referral centres for musculoskeletal tumours.

Fortunately, complications appear to be infrequent and joint arthroplasty remains an uncommon yet viable option in these patients. Overall, 4.5% of patients in our study eventually required a joint arthroplasty, similar to the 8% published by Colman et al.[32] In the largest series of patients undergoing total knee arthroplasty for TGCT, Casp et al[33] demonstrated no difference in infection rate, stiffness, or revision rates for these patients when compared to a control group. The authors did not explicitly explore recurrence rates in their study, yet it appears to be a safe and reasonable salvage option for those who develop end-stage osteoarthritis secondary to TGCT, while acknowledging that there is a need for longer-term outcomes in that cohort.

There are several limitations to this study. First, this study was designed to be a retrospective cohort study for investigating the characteristics of TGCT presenting to an Australian tertiary referral centre; as such, selection bias in this cohort is inherent within the study population. The rarity of the tumour however, precludes other robust study designs, as evidenced by multicentre consensus statements.[16] Second, successful treatment of TGCT in peripheral hospitals may be occurring, albeit uncommonly, and thus an over-estimation of recurrence rates may have been reported. In order to address this, a national registry for TGCT paralleling our Dutch and Danish colleagues' initiatives are warranted to accurately capture incidence and analyze future surgical outcomes.[4,5] Third, due to the retrospective nature of the study, cases that were deemed to be partially unresectable were not identified. Therefore, it is possible that our high recurrence rate is attributed to the aggressive nature of the condition with a partially resected tumour. Finally, this study was conducted pragmatically to provide a snapshot of the surgical experience of a large tertiary referral centre in Australia given that contemporaneous medical therapies despite their promising early clinical results, remain difficult to access.[16]

In conclusion, TGCT is a rare proliferative tumour of the musculoskeletal system. The mean age of presentation is 36 years, is more common in females, and more commonly affects the knee joint in Australians. Recurrences rates are generally high, with the highest rates observed for D-TGCT and RC. Due to the risks of recurrence, the complexity of surgery, and the need for adjuvant therapy, management of TGCT should be referred early to a tertiary referral centre for musculoskeletal tumours who have access to appropriate multidisciplinary teams.

Take home message

- Tenosynovial giant cell tumour is a rare benign musculoskeletal tumour that can have aggressive features leading to significant patient morbidity.
- This study aims to demonstrate the clinical burden of disease in the Australian population undergoing surgical resection.

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