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Tenosynovial giant cell tumours of the hand: A multicentre case-control study☆

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Summary Many factors have been proposed to contribute to the risk of recurrent tenosynovial giant cell tumours (TSGCT); however, we remain unable to predict those at risk, which formed the rationale for this multicentre retrospective case-control study of 28 patients with recurrence. We included cases of recurrence in a 1:1 ratio matched for age and sex with controls over 10 years. Using Cox regression, we present hazard ratios (HRs) for recurrence with 95% confidence intervals (CIs). Out of 285 cases, 28 individuals developed recurrence after a median of 2.4 years. Recurrent TSGCT had a higher mitotic count/mm^2 in the primary tumour (median increase of 3 [IQR 1, 7]). Mitotic count in the primary tumour was associated with the risk of recurrence (adjusted HR 1.1 [95% CI 1.1, 1.2]) meaning that for every additional mitosis, the risk of recurrence increased by 10% per annum. We recommend a prospective cohort study to validate our findings.

Introduction

*Tenosynovial giant cell tumours (**TSGCT**)* are the second most common tumours in the hand.[3,6,8] Chassaignac first described these soft tissue masses in 1852 and, although benign referred their biologic potential as 'cancers of the tendon sheath'. Many theories have been proposed for the aetiology of TSGCT, which include trauma, disturbed lipid metabolism, osteoclastic proliferation, infection, vascular disturbances, immune mechanisms, inflammation, neoplasia and metabolic disturbances, but there remains no consensus.[1,6,12,13,21,20] The WHO (World Health Organization) classification of soft tissue tumours and bone was published in 2013. This now clarifies the nomenclature for these types of tumours and identifies them as fibrohistiocytic tumours.

TSGCT can be either localised or diffuse, presenting as a slowly enlarging and commonly painless soft tissue mass over the digits.[6,8] It is a benign condition, and the accepted treatment is complete surgical excision using surgical loupes or an operating microscope.[3,4,8,17,5,11] External beam radio-

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Table 1 Shows baseline clinicopathological characteristics.

	Table 1	Controls	Cases (recurrent GCTTS)	*p*-value
Median tumour size in mm^2 (IQR)		15 (13-20)	13 (10-19)	0.07
Median mitotic count per mm^2 (IQR)		3 (1-5)	7 (2-11)	0.004
Median nodule count (IQR)		7 (4-80)	10 (4-13)	0.2
Proportion of giant cells within the primary tumour (%)	<33%	26	27	
	33-66%	0	0	1.0
	>66%	2	1	
Location of the primary tumour (%)	Thumb	6	6	
	Index	8	7	
	Middle	9	5	
	Ring	1	5	0.5
	Little	2	3	
	Palm	1	2	
	Wrist	1	0	

therapy has been suggested in severe cases.[14,24] Recurrence rates vary widely from 4% to 44%,[3,5,11,10,16,17,20,26] and there are few published articles concerning risk factors for recurrence. In this multicentre study, we aimed to investigate factors associated with recurrent TSGCT to help us understand the clinicopathological features that may contribute to recurrence, and histologically, we investigated the mitotic rate and studied the association of this factor with recurrence rates.

Methods

This is a retrospective case-control study written in accordance with the STROBE guidance.[23] Using a digital database, we identified all cases of TSGCTs in two plastic surgery centres between 1996 and 2016. Inclusion criteria were any histologically confirmed TSGCT found on the hand or wrist in adults. As this was a retrospective analysis, ethical approval was deemed unnecessary. We excluded TSGCTs on other anatomical sites. Case notes, operation records and histology reports were reviewed to provide demographic and anatomical data and to identify cases of recurrence.

The primary outcome was disease recurrence, and hence, cases were defined as those with histopathologically confirmed recurrent TSGCT. We defined controls as those with no clinical features of recurrent TSGCT at final follow-up. Patients were matched one-to-one for age (±one year) and sex with controls (patients without recurrence).

Histological analysis was performed using haematoxylin and eosin (H&E), and the stained slides were assessed in tandem by two authors (plastic surgery registrar and consultant dermatopathologist). The maximum diameter (mm) of the formalin-fixed specimen at the time of macroscopic examination was documented. The giant cell population within the tumour was categorised as <33%, 33-66% and >66%. The mitotic rate was defined as the number of mitoses per mm^2 within the tumour. The number of discrete nodules within the tumour was recorded as $n=X$. A 'discrete nodule' was defined as an area of tumour rimmed by fibrous tissue in more than 75% of the circumference of the nodule. The time to recurrence was defined from the date of primary surgery to the date of histopathological confirmation of recurrence.

Data were analysed using Stata. Continuous data were skewed or discrete and hence presented as median and interquartile range (IQR), and they were compared using the Wilcoxon signed-rank test. Proportions are presented as frequencies and percentages (%) and compared using Fisher's exact test. Missing dates of excision were imputed with the study start date (1 January 1996, eight cases), and follow-up was the date of diagnosis of recurrence or censorship (31 December 2015).

Multivariable Cox regression was used to estimate the hazard ratio (HR) of recurrence according to tumour diameter, mitotic rate and nodule counts as continuous covariates and giant cell proportionality as categorical covariates. We also adjusted the multivariable model for the matching criteria of age and sex because matching may introduce confounding. No adjustment for clustering was made because there were no expected or observed differences. Internal validity was tested with bootstrapping by lossless non-parametric resampling with replacement, with 1000 iterations as per TRIPOD guidance. We corrected the family-wise error rate according to Šidák to $p<0.004$. Confidence intervals are generated to the 95% level.

Results

A total of 285 cases of TSGCT of the hand were identified. There were 28 individuals (10%) who developed recurrent TSGCT during the study period, of whom three had two recurrences, and one developed three episodes of recurrence. The median time to first recurrence was 2.4 years (IQR 1, 3.2 years; range 4 months to 7 years). The median age of the cohort was 56 years (IQR 47, 64).

There were 18 females and 10 males who developed recurrence. There were no significant differences in any clinical or histopathological features of cases or controls (Table 1 summarises the baseline clinicopathological characteristics). Individuals with recurrent TSGCT had a higher mitotic count per mm^2 in the primary tumour (median increase of 3 [(IQR 1, 7]) than controls (Figure 1). Otherwise, there were no statistically significant differences between groups.

Univariate time-to-event analyses suggest that a higher mitotic count within the primary tumour was associated

Table 2 Shows the risk of recurrence based on histopathological features.

Table 2		Univariate HR (95% CI) for recurrence	*p*-value	Adjusted[a] HR (95% CI) for recurrence	*p*-value	Resampled[b] *p*-value
Tumour size in mm^2		1.0 (0.9, 1.0)	0.1	0.9 (0.9, 1.0)	0.1	0.2
Mitotic count per mm^2		1.1 (1.1, 1.2)	0.001	1.1 (1.1, 1.2)	0.001	0.03
Number of nodules		1.0 (1, 1.1)	0.3	1.0 (1, 1.1)	0.1	0.2
Proportion of GCTs Within the primary tumour (%)	<33%	1 (referent)	0.06	1 (referent)	0.9	0.9
	>66%	0.9 (0.1, 7.0)		0.9 (0.1, 6.0)		

[a] Multivariable Cox regression with age as a continuous variable and sex as a categorical variable, which are not shown, as these are the matching factors.
[b] Bootstrapped by lossless non-parametric resampling with replacement, with 1000 iterations.

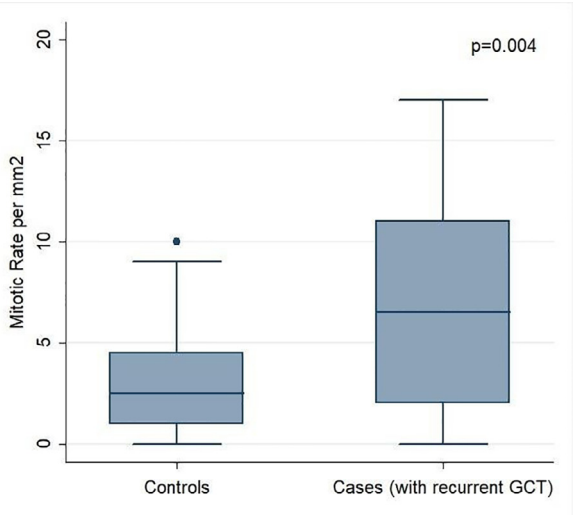

Figure 1 A boxplot of mitotic rate between groups; *p*-value derived from a Wilcoxon signed-rank test for matched data.

with higher risk of recurrence, but no other tumour characteristic was significantly associated with this risk. The association between mitotic count and the risk of recurrence was maintained after adjustment for the matching variables and bootstrapping, which suggests that for every observed mitosis, the risk of recurrence increases by approximately 10% per year (Table 2). Figure 2 shows four Kaplan–Meier plots stratified by mitotic rate, which demonstrates that as the number of mitoses increases beyond 5 per mm^2, there is a clinically and statistically significant increase in the risk of recurrence, whereby 50% of tumours with 3 or more mitoses recurred within a decade and 75% of tumours with 7 or more mitoses recurred within a decade.

Discussion

We have shown that the mitotic rate of the primary tumour appears to be independently associated with the risk of recurrence. This is an important finding because it may allow clinicians to better stratify patients into high- and low-risk groups for recurrence, therefore better rationalising clinical and radiological surveillance.

Our data are in line with the data in the literature and show that females are more commonly affected than male, in the fifth decade of life.[2,6,8,10,17,20] TSGCT is a slow growing, often painless tumour that can present anywhere on the hand, but more commonly, it occurs on the volar aspect of the radial digits.[2,7-9,17,20] Our study was not designed to examine this aspect, but we found no evidence that recurrent TSGCT occurs more commonly in a particular anatomical site.

The recurrence rates of TSGCT vary from 4% to 44%, and factors relating to recurrence are still not fully understood.[3,5,10,11,16,17,20,25] Age, gender, size, and location within the digit (dorsal or volar) is not thought to influence recurrence rates.[20]

However, in particular, there are histopathological and treatment factors that have been implicated in the increased risk of recurrence of TSGCTs.

Histopathological factors

In 2001, Al Qattan[3] classified giant cell tumours as types I and II. Type I tumours have a surrounding pseudo-capsule, and this group was further classified according to singular nodularity with a thick (a) or thin (b) capsule or a multilobulated lesion surrounded by a common pseudo-capsule (c). Type II tumours have no common pseudo-capsule and were either (a) one main nodule along with separate satellite lesions; (b) diffuse with multiple granular-like lesions or (c) multicentric with separate discrete lesions in the same digit. They found a statistically significant difference in recurrence rate between the two groups (Type I 0% vs Type II 38% recurrence ($p = 0.001$)). Their suppositions were that satellite or multicentric aspects of the lesions had been missed, which attributed to the recurrences. Increased number of nodules has been associated with higher recurrence rates by others too presumably for similar reasons.[10] We did not use this categorisation but rather counted the nodules, as scaling a variable provides greater statistical power for modelling.

Tumour size, nodularity, mitotic rate and cellularity have been implicated in the risk of recurrence[10,26]; however, our data are not in agreement for tumour size and nodularity. Rao[19] showed an important association between mitotic rate and recurrence. They classified tumours with 3 or more mitoses per high-powered field as more likely to recur, and whilst this was disputed,[3,17] our research corroborates the finding and advances the field, again showing an association between the number of mitoses and the risk of recurrence

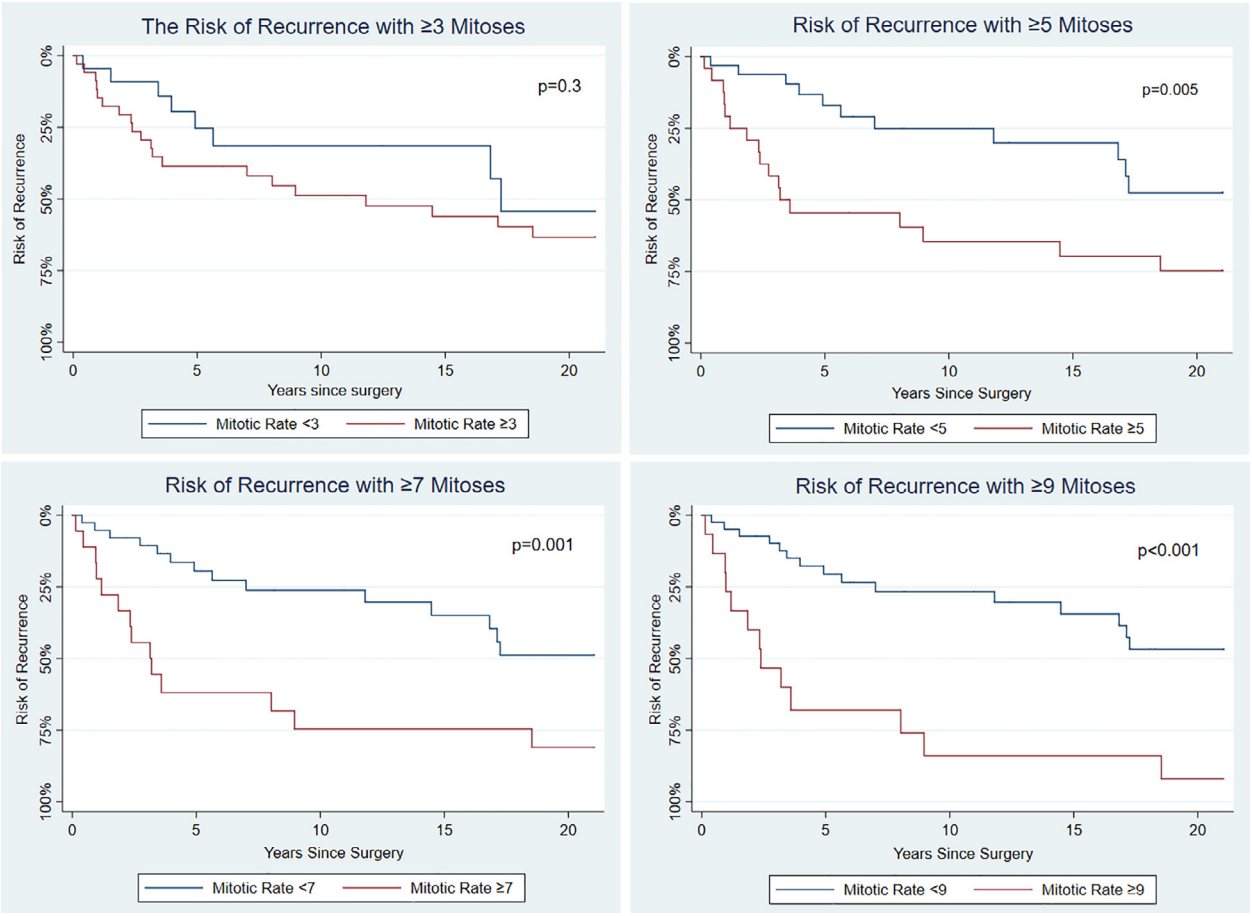

Figure 2 Four Kaplan–Meier plots showing an increasing risk of recurrence over time when more mitoses are observed. The *p*-values are derived from the logrank test.

(Figure 2). This is corroborated in an antecedent review by Fotiadis,[6] who concluded that internal biology contributed most to the risk of recurrence. The potential importance of the mitotic rate was previously suggested by Monaghan[17] who concluded that mitotic and apoptotic analyses results are associated with histological analysis results but do not predict clinical behaviour.

Treatment

It is accepted that complete surgical excision reduces recurrence.[6,11,16,18,20,] Surgeons should aim for complete excision of lesions including satellite lesions, whilst preventing pseudo-capsule puncture and seeding.[4,6,8,15-17,22] Factors which suggest an increased risk of recurrence include tumours located around the distal interphalangeal joint, bone erosion, adjacent arthritis and type II tumours[3,20]; these factors are colloquially termed surrogate markers of 'incomplete or difficult surgical excision'. Williams et al.[25] found that the involvement of flexor or extensor tendons or the joint capsule was associated with a high recurrence rate (Figure 3), and Glowacki[8] recognised that sufficient excision of involved extensor tendons may necessitate reconstruction. Mongahan et al.[17] attributed the low rate of recurrence (4%) to the excision margins of >1 mm; this is not always possible without deleterious effects on function. To best plan for complete excision, Darwish[5] suggest preoperative ultrasound and/or magnetic resonance imaging.

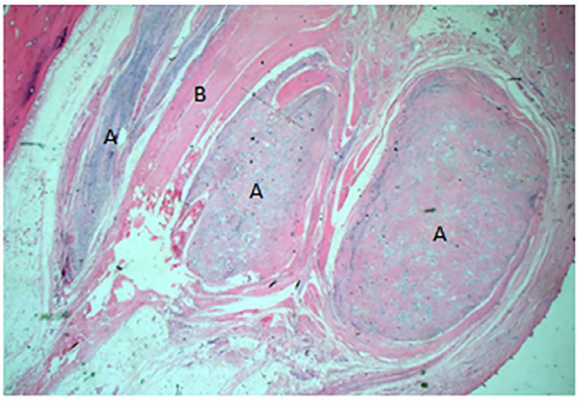

Figure 3 Pathology specimen of a cross-sectional view of a digit showing TSGCT and the extensor apparatus. A = nodules, B = extensor tendon.

We have shown that mitotic rate may be an important predictor of recurrence. Given that this is still an uncommon condition, we suggest that the next step is to undertake an adequately powered multicentre cohort study, examining all

patients with giant cell tumours of the hand and wrist, using time-to-event models adjusted for clustering. Adequate follow-up of patients would be essential.

This would better allow the effect of individual clinicopathological features to be studied, avoiding concerns over confounding introduced by matching, but various biases would have to be considered. Whilst prospective observational research is favourable given the reductions in biases of measurement, given than TSGCT is uncommon and recurrence even more rare, we suggest that a nationwide retrospective study would be the next most logical step.

Limitations

Time to follow-up was from surgery to the last clinical review of the patient before discharge. Patients were not contacted after discharge, and we recognise that this is a limitation of this paper, as it is possible that they developed a recurrence that was not yet clinically detectable, or they presented for treatment elsewhere; therefore, the true recurrence rate and predictors cannot be verified. Matching introduces confounding, and to minimise this confounding, controls should be matched >1:1 and ideally 4:1 with cases; however, this was not achieved in our study and may explain why no significant differences were observed in some outcomes, or equally, this could be the cause of the observed differences. We recommend that future research should be conducted in a longitudinal design.

In conclusion, although TSGCT is the second most common tumour of the hand, we remain unable to predict those at risk of recurrence. Primary tumours with a higher mitotic rate may be at the greatest risk of recurrence, but better follow-up and preoperative diagnosis are mandatory to provide reliable data to analyse risk factors of local recurrence.

Conflict of interest

None.

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