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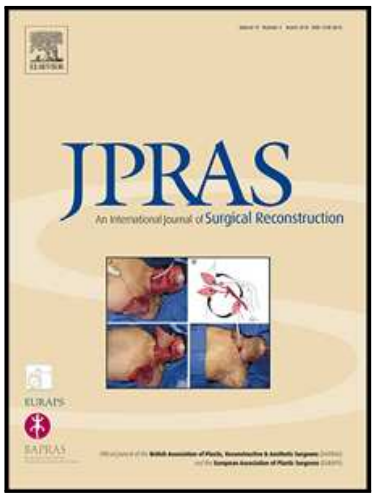

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Tenosynovial Giant Cell Tumours of the Hand: A Multicentre Case Control Study

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Abstract

Many factors have been proposed to contribute to the risk of recurrent TSGCT (Tenosynovial Giant Cell Tumours); 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 age and sex matched cases of recurrence 1:1 with controls over 10 years. Using Cox regression, we present hazard ratios (HR) for recurrence with 95% confidence intervals (CI). Out of 285 cases, 28 individuals developed recurrence after a median 2.4 years. Recurrent TSGCT had a higher mitotic count/mm2 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], p=0.001) meaning that for every additional mitosis, the risk of recurrence increased by 10% per annum. Mitotic rate of the primary tumour is associated with the risk of recurrence although we recommend a prospective cohort study to validate our findings.

Introduction

TSGCT (Tenosynovial Giant Cell Tumours) is the second most common tumour in the hand (3, 6, and 8). Chassaignac first described these soft-tissue masses in 1852, and although benign, described 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, 21, and 20).The WHO (World Health Organisation) 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 localized of 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 radiotherapy has been suggested in severe cases (24). Recurrence rates vary widely from 4–44 %(3, 5, 11, 10, 16, 17, 20 and 26) and there is little reliable published work 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 which may contribute to recurrence and histologically we investigated the mitotic rate to link this factor into the 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– 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, as well as identify cases of recurrence.

The primary outcome was disease recurrence and so 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. Cases were one-to- one age (+/- one year) and sex matched to controls (patients without recurrence).

Histological analysis was performed using haematoxylin and eosin (H&E) stained slides and 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 mitosis per mm2 within the tumour. The number of discrete nodules within the tumour was recorded 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, so are presented as medians with the interquartile range (IQR) and compared using the Wilcoxon signed rank test. Proportions are presented as frequencies with percentages (%) and compared using Fisher's exact test. Missing dates of excision were imputed with the study start date (1st January 1996, eight cases) and follow-up was the date of diagnosis of recurrence or censorship (31st 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 co-variates and giant cell proportionality as categorical covariate. 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 re-sampling 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 (9.8%) 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 the 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 in each group. There were no significant differences in any clinical or histopathological features of cases or controls in either centre. (Table 1 summarises the baseline clinicopathological characteristics). Individuals with recurrent TSGCT had a higher mitotic count per mm2 in the primary tumour (median increase of 3 [(IQR 1, 7]) compared to controls (Figure 1). Otherwise, there were no statistically significant differences between groups.

Univariate analyses suggest that a higher mitotic count within the primary tumour was associated with higher risk of recurrence but no other tumour characteristic was significantly associated. The association between mitotic count and the risk of recurrence was maintained after adjustment for the matching variables and bootstrapping and 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 with 7 or more mitoses 75% of patients recurred within a decade.

Discussion

We have shown that 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 is in keeping with the literature and shows that females are more commonly affected, in the 5th decade of life (2, 6, 8, 10, 17, and 20). TSGCT is a slow growing, often painless tumour that can present anywhere on the hand, but more commonly occurs on the volar aspect of the radial digits (2, 7, 8, 9, 17 and 20). Our study was not designed to examine this aspect, but we found no evidence that recurrent TSGCT occur more commonly in a particular anatomical site.

The recurrence rates of TSGCT vary from 4–44 % and factors relating to recurrence are still not fully understood (3, 5, 10, 11, 16, 17, 20, 25). Age, gender, size, 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 into Type 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 multi- lobulated lesion surrounded by a common pseudo- capsule (c). Type II tumours have no common pseudo-capsule and were either (a) one main nodule accompanied by 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 is not in agreement for tumour size and nodularity. Rao (19) showed an important correlation 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, showing a linear association between the number of mitoses and risk of recurrence (Figure 2) This is corroborated in an antecedent review by Fotiadis (6) 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 figures are associated histological figures 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, including satellite lesions, whilst preventing pseudo-capsule puncture and seeding (4, 6, 8, 15, 16, 17 and 22). Factors suggested increasing the risk of recurrence, such as DIPJ locality, bony erosion, adjacent arthritis and type II tumours (3, 20) are possibly surrogate markers of "incomplete or difficult surgical excision". Williams et al. (25) found that involvement of flexor or extensor tendons, or joint capsule was associated with a higher recurrence rate (Figure 3) and Glowacki (8) recognised that sufficient excision of involved extensor tendons may necessitate reconstruction. Mongahan (17) attributed their low rate of recurrence (4%) to their excision margins of >1mm; 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.

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, avoid 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 prior to 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; so the true recurrence rate and predictors cannot be verified. Matching introduces confounding, and to minimise this 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 is conducted in a longitudinal design.

In conclusion, although TSGCT is the second most common tumour in the hand, we are still 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: Nil Funding:Nil

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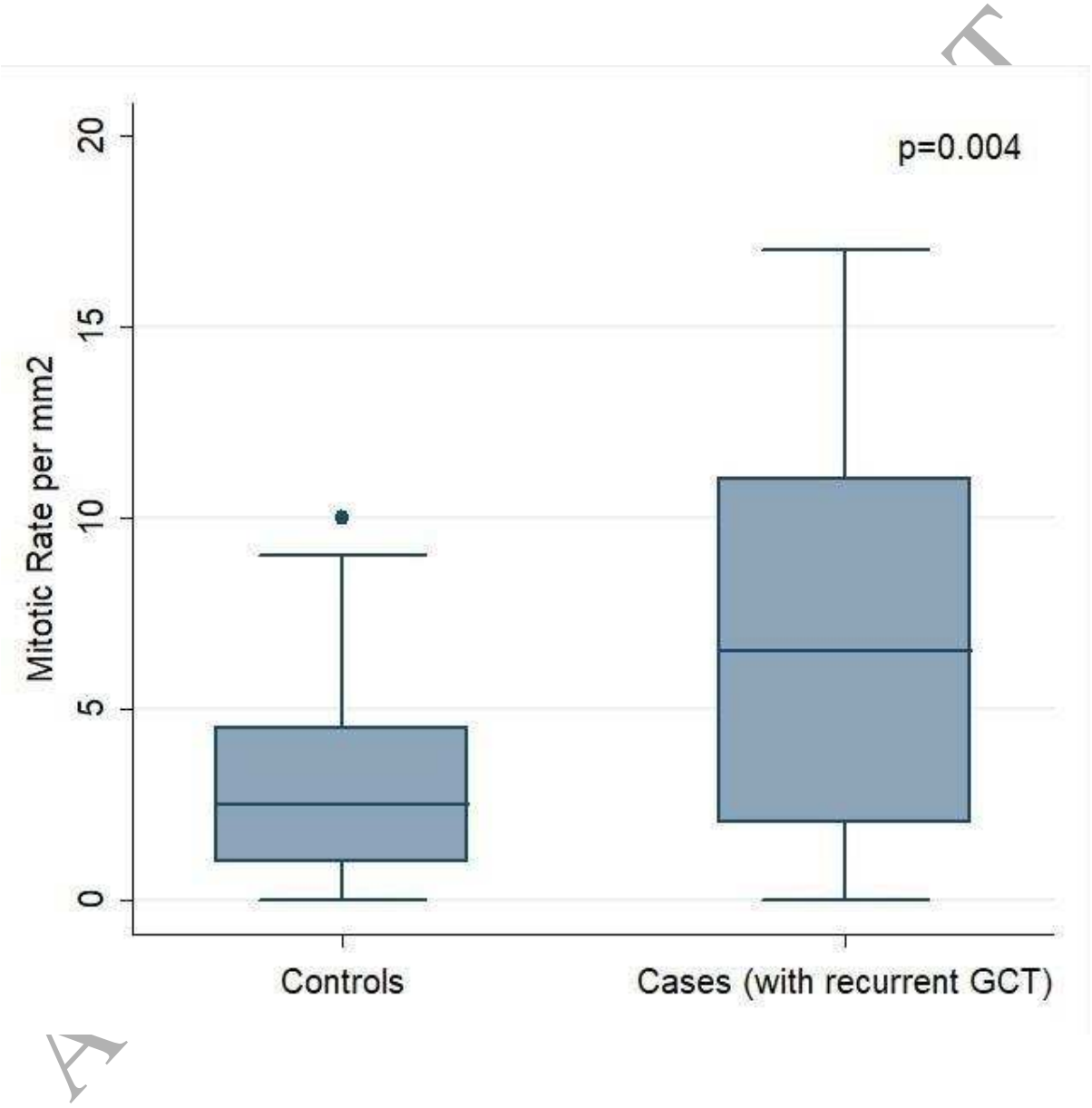
Figure 1 - A boxplot of mitotic rate between groups; p-value derived from a Wilcoxon signed rank test for matched data.



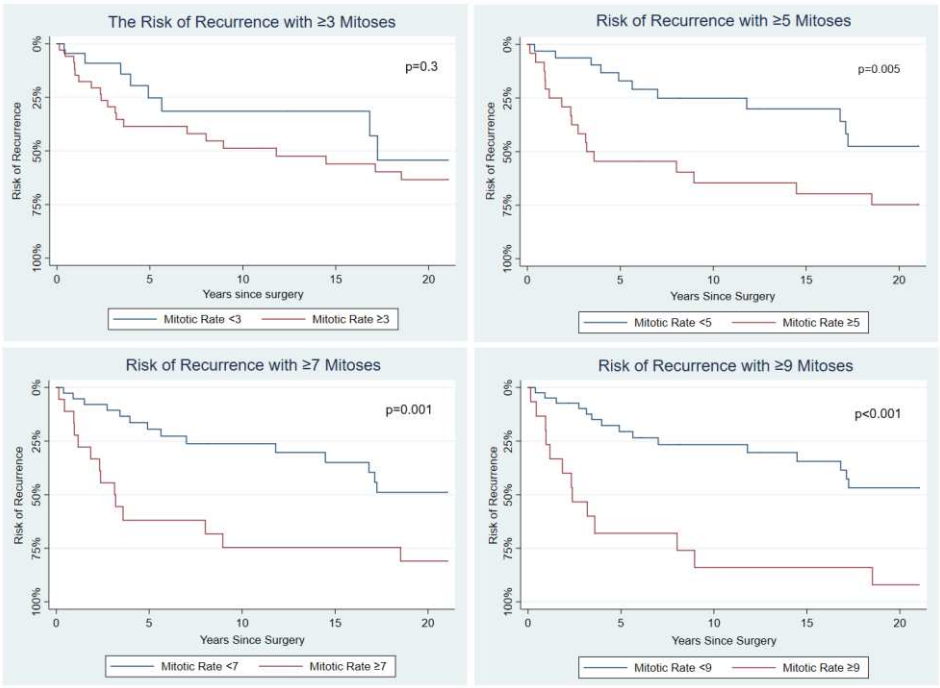


Figure 2 - Four Kaplan Meier plots showing an increasing risk of recurrence over time when more mitoses are observed. The p-values are derived from log rank tests."

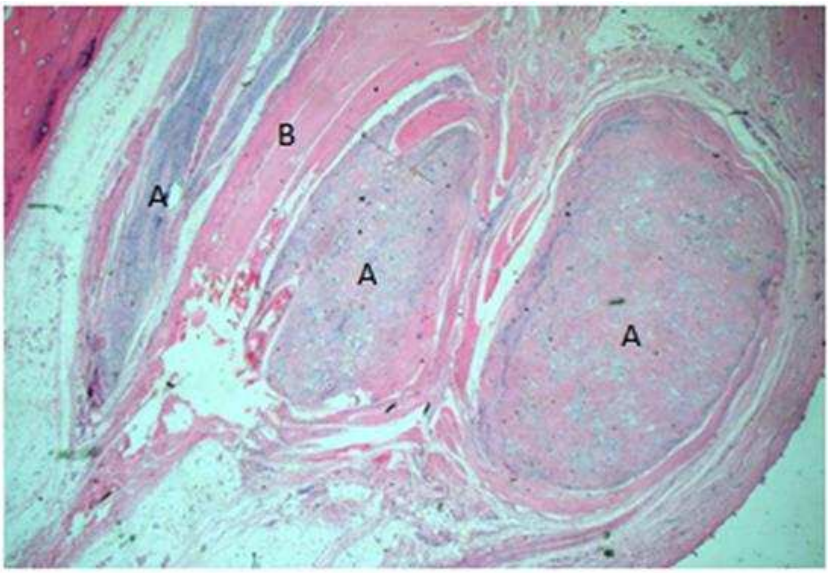


Figure 3. Pathology specimen of a cross sectional view of a digit showing TSGCT and the extensor apparatus. A = nodules B =extensor tendon

Tables

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	1.0
	33-66%	0	0	
	>66%	2	1	
Location Of The Primary Tumour (%)	Thumb	6	6	0.5
	Index	8	7	
	Middle	9	5	
	Ring	1	5	
	Little	2	3	
	Palm	1	2	
	Wrist	1	0	

Table 1 shows baseline clinicopathological characteristics.

Table 2		Univariate HR (95% CI) for recurrence	p-value	Adjusted* HR (95% CI) for recurrence	p-value	Resampled[¥] 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)		

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

*Multivariable Cox regression with age as a continuous variables and sex as a categorical variable, which are not shown as these are the matching factors.

[¥] Bootstrapped by lossless non-parametric resampling with replacement, with 1000 iterations.