Giant cell tumour of tendon sheath of the digits. A systematic review

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Abstract

Background We reviewed the literature to evaluate the demographic, clinical and histological profile of giant cell tumour of tendon sheath of the digits (GCTTSD). The overall recurrence rate and the factors affecting tumour recurrence were also assessed.

Methods We searched for published articles regarding the GCTTSD in the English literature the last 30 years using the PubMed search engine. All retrieved papers were analysed and their reference lists were also screened if relevant. Clinical studies with less than five patients and follow-up less than 2 years were excluded from further evaluation. For each report, information was gathered related to trial characteristics and study population. Location and multicentricity of lesions, kind and severity of symptoms, type of applied treatment modality and

histopathological features of the excised tumours were additionally recorded. A meta-analysis for estimating the pooled recurrence rate after surgical excision was also conducted. Statistical significance was assumed for $p \leq 0.05$.

Results We found 21 studies with histological confirmation of GCTTS. However, only 10 studies including 605 patients were reviewed according to selection criteria (average follow-up 36.7 to 79 months). The male-to-female ratio was 1:1.47 ($p < 0.005$) and the mean age ranged from 32 to 51 years. Pain or sensory disturbances reported only in 15.7% and 4.57% of cases, respectively. A definite history of trauma recorded in 5% of lesions. The most frequent tumour location was the index finger (29.7%). In total, 14.8% of patients had tumour recurrence. Type I tumours (single lesions) were more frequently detected (78.7%) than type II tumours (two or more distinct tumours that were not joined together) (21.3%) but the latter were associated with a higher recurrence rate ($p < 0.001$). Study design also affected the possibility of recurrence as it was lower in prospective studies compared to retrospective studies ($p = 0.003$). Even though bone erosion was detected in 28.39%, recurrence was not more common in this group. In addition, recurrence was not significantly associated with a specific finger or phalanx.

Conclusions Intrinsic biology of the tumour seems to play a more fundamental role in recurrence than tumour location or local invasiveness. More prospective well-designed studies including a large number of cases are necessary to identify tumours prone to recurrence and determine the proper treatment protocol for each individual patient.

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Introduction

Giant cell tumour of tendon sheath (GCTTS) is the second most common tumour of the hand after ganglion [4, 20]. It is a slowly growing, usually painless benign lesion localised at the extremities [14]. The tumour affects individuals between the age of 30 and 50 years old and is found more often in women than men [14]. Despite its benign character, local recurrence after excision has been reported in up to 45% of cases [9].

The origin and pathogenesis of the lesion are still unclear. Metabolic, neoplastic and inflammatory diseases have been proposed as etiologic factors, but with no definite proof [18]. The most widely accepted pathogenic hypothesis is reactive or regenerative hyperplasia associated with an inflammatory process [18]. Local excision, with or without radiotherapy, has provided good results [1, 4, 6, 8, 9, 15, 18, 20, 23]. However, the role of tumour characteristics and adjuvant radiotherapy in recurrence rate has not been clearly addressed to date.

We reviewed the English literature the last 30 years to evaluate the demographic, clinical and histological profile of giant cell tumour of tendon sheath of the digits (GCTTSD) and determine what factors may contribute to tumour incidence and recurrence.

Materials and Methods

We searched for published articles at all levels of evidence regarding the GCTTSD in the English literature the last 30 years (January 1980 to December 2009) using the PubMed search engine. The keywords used were as follows: giant cell tumour, tendon sheath, digit(s), hand tumour(s) and soft tissue tumour(s). All retrieved papers were analysed and their reference lists were also screened if

relevant. Case report studies or trials having less than five patients, follow-up less than 2 years and no histologic diagnosis were excluded from further evaluation.

For each report, information was gathered on characteristics of the trial and study population. Furthermore, location and multicentricity of lesion as well as kind and severity of symptoms were also recorded. Finally, we extracted data related to the applied treatment modality, histopathological examination of the excised tumour and recurrence rate.

We found 21 studies with histological confirmation of a GCTTS [1–6, 8–10, 12–23]. However, only 10 studies including 605 patients were reviewed according to the selection criteria [1, 4–6, 8, 9, 15, 18, 20, 23]. Specifically, five studies were excluded due to missing or incomplete data [2, 3, 13, 14], [22], three studies had not reported the overall follow-up of the patients [17, 19, 21] and three studies were not in English literature [10, 12, 16].

Four papers [1, 6, 8, 20] included exclusively patients with GCTTS of the phalanges. The other six papers described also tumours from non-digit areas [4, 5, 9, 15, 18, 23], but only data from patients with GCTTSD were used for further analysis. The average follow-up of the studies ranged from 36.7 to 79 months postoperatively (Table 1).

Macroscopically, the tumours were classified into two main types, depending on whether the entire tumour was or was not surrounded by pseudocapsule. In type I, there was a single tumour, which might be round or multilobulated. In type II, there were two or more distinct tumours that were not joined together [1, 6].

Statistics

Studies that were included for analysis contained basically either tabulated individual patient data (IPD) or summary

Table 1 Studies about giant cell tumour of tendon sheath

Study	Patients (no.)	Male, female (no.)	Treatment	Follow-up (month)	Recurrences, no. (%)
Uriburu and Levy (1998)	15	7, 8	Local excision under magnification	36.7	2 (13)
Grover et al. (1998)	41	16, 25	Local excision	79	7 (17)
Reilly et al. (1999)	66	ND	Local excision	40	19 (29)
Kotwal et al. (2000)	46	17, 29	Local excision+local irradiation	52	2 (4.34)
Al-Qattan (2001)	43	19, 24	Local excision under magnification	48	5 (11.6)
Ozalp et al. (2004)	134	55, 79	Marginal excision (magnifying glasses in 48% of cases)	42	22 (16.41)
Kitagawa et al. (2004)	30	9, 21	Local excision	49	4 (13.3)
Ikeda et al. (2007)	18	7, 11	Local excision (surgical microscope for diffuse tumours)	64	1 (5.5)
Darwish and Haddad (2008)	46	13, 33	Local excision	48	12 (26)
Williams et al. (2010)	166	74, 92	Local excision	51	20 (12)

ND not defined

data with means, ranges and proportions of demographic details and outcomes. All available data was inserted in two data sheets. The first sheet included data as summaries of outcomes. The second sheet contained all available data in a way that every patient from each study was given his own individual number and variables. Categorical data were analysed using the chi square test or Fisher's exact test. Continuous numeric data were compared using Student's *t* test. Statistical significance was assumed for $p < 0.05$.

Recurrence data when available was placed on another data sheet for meta-analysis. According to recurrence data assessment, a significantly statistical heterogeneity that demonstrates the variability of recurrence rate between studies was found. Therefore, a random effects analysis model was used and the odds ratio and weight differences were calculated. The odds ratio indicates the likelihood of tumour recurrence after excision. The weight of each study is related to its sample size and shows its contribution to the overall average recurrence rate.

Results

From a total of 605 patients, there were 245 males and 360 females with a male-to-female ratio 1:1.47 ($p < 0.005$, *t* test). Average age in studies ranged from 32 to 51 years. The most frequent location of the tumour was the index finger (76/256 patients, 29.7%). Other tumour sites were the thumb (33/256 patients, 12.9%), the long (63/256 patients, 24.6%), the ring (43/256 patients, 16.8%) and little (41/256 patients, 16%) fingers [1, 6, 9, 15, 20].

The vast majority of patients presented with a painless swelling and only 15.7% (55/350 patients) had pain [1, 4, 9, 15, 18, 20]. Sensory disturbances of the digits were recorded in 4.57% of cases (16/350 patients) [1, 4, 9, 15, 18, 20]. The average duration of symptoms ranged from 6 to 30 months (range, 1 month to 10 years) [1, 4, 6, 8, 9, 15, 18, 20, 23]. Only 5% (28/564 patients) of the patients had a definite history of soft tissue trauma at the time of initial presentation [1, 4, 6, 8, 9, 15, 18, 20, 23].

Total odds ratio for recurrence of GCTTSD was 0.03. There was a statistically significant heterogeneity between studies concerning tumour recurrence ($p \leq 0.001$). The difference in sampling size and recurrence odds ratio between studies was the reason of this significant heterogeneity (Table 2).

Macroscopically, the average size of tumours ranged from 1.3 to 2.1 cm (min=0.5 cm, max=5 cm) [1, 4, 6, 8, 9, 15, 18, 20, 23]. Type I tumours were more frequently detected than type II tumours [78.7% (48/61 patients) vs. 21.3% (13/61 patients)] [1, 6]. Microscopically, all tumours contained multinucleated giant cells, histiocytes and haemosiderin deposits.

Only one paper described the number of mitoses per high-power fields. Specifically, Al-Qattan [1] found that the average number of mitoses was under two per 10 high-power fields. In the same study [1], mitoses (tumours with mitoses versus those with no mitoses) were investigated as a potential risk factor predicting recurrence. However, this histological factor was not proven to be significant.

Although bone erosion was detected in 28.39% (23/81 patients) [18, 20], none was associated with a bone fracture or higher recurrence rate [18, 20].

Regarding the selected operative approach, local excision was applied in 97.7% (591/605 patients) and local excision along with local irradiation in 2.3% (14/605 patients) [1, 4, 6, 8, 9, 15, 18, 20, 23]. In total, 14.8% of patients had tumour recurrence (83/559 patients) [1, 5, 6, 8, 9, 15, 18, 20, 23]. Fourteen patients where local irradiation was applied did not experience a tumour recurrence but due to the small number of cases this was not statistically significant [9].

Magnifying glasses or microscope were used in 15.1% (65/430 patients) [1, 4, 6, 8, 9, 18, 20, 23]; the recurrence rate was lower than without loupes but this did not display also a statistical significance [1, 6, 8, 9, 18, 20, 23] [10.8% with magnification (7/65 patients) vs. 14.4% without magnification (46/319 patients)].

According to the available data, type II lesions were significantly associated with higher recurrence rate ($p \leq 0.001$, chi square test) [1, 6]. Moreover, study design could also affect the possibility of recurrence. Specifically, prospective studies [1, 9, 23] showed a less frequent recurrence rate compared to retrospective studies [4–6, 8, 15, 18, 20] [10.6% (27/255 patients) vs. 19.9% (51/256 patients)] ($p = 0.003$, chi square test).

Recurrence was not significantly associated with a specific finger or phalanx [6, 18, 20]. However, there was a borderline significance between tumour recurrence and joint location as the relevant incidence was higher in cases with digital distal interphalangeal joint (DIP) involvement ($p = 0.044$, chi square test) [6, 18, 20].

Discussion

GCTTS remains a lesion of unknown nature with a relative high local recurrence rate up to 45% in some series [9]. Many risk factors have been reported in literature for localised GCTTS recurrence (Table 3). Rao and Vigorita [17] found that the increased cellularity and mitotic activity of the tumour was greater in recurrent lesions. However, the authors did not find any clear relationship between the number of mitoses and recurrence rate. On the other hand, Kitagawa et al. [8] and Al-Qattan [1] reported that neither cellularity nor mitoses could be considered significant

Table 2 Meta-analysis of studies including giant cell tumour of tendon sheath of the digits (GCTTSD)

Study (9 studies included) ^a	Weight of study (%)	Odds ratio (random effects method) (CI=confidence interval 95%)
Uriburu and Levy (1998)	7.4	0.02 (CI=0–0.19)
Grover et al. (1998)	12.4	0.04 (CI=0–0.13)
Reilly et al. (1999)	14.8	0.16 (CI=0.08–0.35)
Kotwal et al. (2000)	7.8	0 (CI=0–0.02)
Al-Qattan (2001)	11.4	0.02 (CI=0–0.06)
Ozalp et al. (2004)	15.5	0.04 (CI=0.02–0.08)
Kitagawa et al. (2004)	10.4	0.02 (CI=0.01–0.1)
Ikeda et al. (2007)	5	0 (CI=0–0.06)
Williams et al. (2010)	15.3	0.02 (CI=0.01–0.04)
Total	100	0.03 (CI=0.01–0.06)

Weight of studies, odds ratio and test of heterogeneity ($p<0.001$) are presented. Test of heterogeneity: $\tau^2=0.86$; $\chi^2=31.64$, $df=8$ ($p=0.0001$); $I^2=75\%$. Test for overall effect: $Z=9.45$ ($p<0.00001$)

^a Darwish and Haddad (2008) study was excluded because recurrences that occurred in cases with GCTTSD could not be sorted from the study's data

prognostic histological factors for recurrence. Monaghan et al. [14] found a higher number of mitoses than previously described (mean count five mitoses/10 HPF), but this feature did not seem to predict the clinical behaviour of the tumour. Recent advances in molecular oncology have defined a gene (nm 23) that expressed in normal cells and can inhibit infiltration. Giant cell tumours nm 23 negative are more aggressive and are associated with a greater recurrence rate [5]. However, Lorea et al. [11] failed to identify such a relation between nm 23 and recurrence rate.

Jones et al. [7] found in 53 out of 91 patients with GCTTSD that the joint from which the tumour arose or was very close to the mass had a clinical and/or roentgenographic evidence of traumatic or idiopathic degenerative joint disease. The authors proposed that the damaged joint might predispose to accumulation of histiocytes either in joint synovium or in adjacent tendon sheaths. Under certain conditions, those collections could proliferate, undergo metaplasia and produce a tumefaction with a histological pattern of giant cell tumour of tendon sheath. Giant cells, facultative fibroblasts or epithelioid cells usually predominate and constitute a large proportion of the tumour bulk. In addition, synovium of the joint as well as of the tendon sheath may harbour the tumours, which may be locally aggressive but more often they are indolent with limited growth potential [7]. In spite of this, the presence of adjacent degenerative joint disease increased the difficulty encountered in obtaining a complete surgical excision of the tumour [8].

Reilly et al. [18] and Grover et al. [5] noticed that bone erosion, as confirmed in plain X-rays, might be a reason for recurrence. However, Kitagawa et al. [8] did not support this theory. The authors advocated that bone involvement in patients with localised GCTTS was due to simple erosion,

caused by the pressure effect of the tumour, and was not a true invasion. Similarly, Al-Qattan [1] found that bony indentation did not have any significant effect on the recurrence rate. We also failed to identify a correlation between bone erosion and recurrence.

Location of GCTTSD has been also associated with tumour recurrence. Reilly et al. [18] observed that recurrence of giant cell tumour was much higher at the thumb interphalangeal joint (IP) and digital DIP joints. Similarly, Grover et al. [5] found a borderline association between the site of tumour and recurrence rate in thumb region. This finding might be attributed to the inherent difficulty of adequately excising the tumour distally at the IP and DIP joint levels, where the neurovascular structures are quite close to tumour margins and the surrounding soft tissue envelope is not ideal [8]. Williams et al. [23] reported that the high risk group was defined as tumour involvement of the extensor tendon, flexor tendon or joint capsule. On the other hand, Al-Qattan [1] and Uriburu et al. [20] showed that tumour location in terms of the affected finger or phalanx did not have any considerable effect on recurrence rate. Our results showed an increase of the relevant

Table 3 Proposed risk factors for localised GCTTS recurrence

1. Location at the distal interphalangeal joint of the finger or the thumb
2. Poor surgical technique (incomplete excision)
3. Osseous pressure erosion
4. Cellularity and mitotic activity on histological examination
5. Proximity to the arthritic joint
6. Tumours which are nm 23 negative
7. Type II tumours

incidence in index finger and DIP joint, but due to the limited number of patients no definite conclusions can be drawn [9, 18, 20].

Type II tumours have been associated with a higher recurrence rate compared to type I giant cell tumours [1]. Grover et al. [5] noticed that lesions with two or more nodules had a statistically greater possibility for recurrence. Ikeda et al. [6] reported that diffuse lesions (type II) were relatively difficult to be fully recognised and their reappearance after surgical excision was not uncommon. On the contrary, Kitagawa et al. [8] mentioned that the proliferative activity of localised GCTTS should not be considered a clear sign of local aggressiveness as it was not related to higher recurrence rate. It seems that the increased reappearance rate of type II multicentric tumours could be attributed to an undetected satellite lesion and subsequent incomplete excision. Therefore, it cannot be always considered as a true recurrence. The lower recurrence rate that was presented in the prospective studies might reflect the surgeon's concern of identifying tumour margins and subsequently achieving a good result. In addition, there may simply not be enough follow-up in these prospective studies to show the true recurrence value.

The importance of adequate tumour excision in decreasing the overall recurrence rate has been pointed out by some authors [14]. Ozalp et al. [15] mentioned that the use of magnifying glasses should be a common practise in GST resection. Likewise, Ikeda et al. [6] had only one recurrence in 18 patients with GCTTS after microscopic excision of the lesion. According to current review, a lower rate of recurrence should be expected when magnifying glasses or microscope is used at the time of mass resection.

Despite the role of intrinsic biology or excision level of GSTTS in tumour recurrence, postoperative radiation may be beneficial. Kotwal et al. [9] recommended postoperative radiotherapy of 20 Gy in divided daily doses of 2 Gy in case of possible incomplete excision, presence of mitotic figures and bone involvement. In their study, the recurrence rate by following this protocol was 0% (0 out of 14 patients). However, Jones et al. [7] reported that three of four patients treated with adjuvant postoperative irradiation after local excision of the lesion had tumour recurrence. In the latter scenario, repeat excision has shown good results but a wider and more meticulous resection is recommended [18]. Ushijima et al. [21] reported a 12.5% re-recurrent rate after the first local excision of the lesion. The available data regarding treatment of recurrent GCTTS have shown good results with minor surgical difficulty [16, 18].

In conclusion, type I tumours and complete excision of the mass by using magnifying glasses seem to be associated with the lowest recurrence rate. The role of intrinsic biology of the lesion and postoperative irradiation in decreasing

tumour appearance is still unknown and controversial. Therefore, more prospective well-designed studies with a large number of cases are necessary to identify tumours prone to recurrence and determine the proper treatment protocol for each individual patient.

References

1. Al-Qattan MM. Giant cell tumours of tendon sheath: classification and recurrence rate. *J Hand Surg Br.* 2001;26:72–5.
2. Batra VV, Jain S, Singh DK, et al. Cytomorphologic spectrum of giant cell tumor of tendon sheath. *Acta Cytol.* 2008;52:152–8.
3. Cavaliere A, Sidoni A, Bucciarelli E. Giant cell tumor of tendon sheath: immunohistochemical study of 20 cases. *Tumori.* 1997;83:841–6.
4. Darwish FM, Haddad WH. Giant cell tumour of tendon sheath: experience with 52 cases. *Singapore Med J.* 2008;49:879–82.
5. Grover R, Grobbelaar AO, Richman PI, et al. Measurement of invasive potential provides an accurate prognostic marker for giant cell tumour of tendon sheath. *J Hand Surg Br.* 1998;23:728–31.
6. Ikeda K, Osamura N, Tomita K. Giant cell tumour in the tendon sheath of the hand: importance of the type of lesion. *Scand J Plast Reconstr Surg Hand Surg.* 2007;41:138–42.
7. Jones FE, Soule EH, Coventry MB. Fibrous xanthoma of synovium (giant-cell tumor of tendon sheath, pigmented nodular synovitis). A study of one hundred and eighteen cases. *J Bone Joint Surg Am.* 1969;51:76–86.
8. Kitagawa Y, Ito H, Yokoyama M, et al. The effect of cellular proliferative activity on recurrence and local tumour extent of localized giant cell tumour of tendon sheath. *J Hand Surg Br.* 2004;29:604–7.
9. Kotwal PP, Gupta V, Malhotra R. Giant-cell tumour of the tendon sheath. Is radiotherapy indicated to prevent recurrence after surgery? *J Bone Joint Surg Br.* 2000;82:571–3.
10. Lorea P, Medina J, Navarro R, et al. Recurrence of finger tendon giant cell tumors after excision through a "shark teeth" approach. Report of 25 cases. *Ann Chir Plast Esthét.* 2001;46:607–10.
11. Lorea P, Van De Walle H, Kinnen L, et al. Giant cell tumours of the tendon sheath: lack of correlation between nm23-H1 expression and recurrence. *J Hand Surg Br.* 2004;29:67–70.
12. Messoudi A, Fnini S, Labsaili N, et al. Giant cell tumors of the tendon sheath of the hand: 32 cases. *Chir Main.* 2007;26:165–9.
13. Mizuno K, Ishikura H, Aizawa M. Giant cell tumor of tendon sheath. An immunohistochemical study of 28 cases. *Acta Pathol Jpn.* 1986;36:1487–94.
14. Monaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localised nodular tenosynovitis): clinicopathological features of 71 cases. *J Clin Pathol.* 2001;54:404–7.
15. Ozalp T, Yercan H, Kurt C, et al. Giant-cell tumors of the tendon sheath involving the hand or the wrist: an analysis of 141 patients. *Acta Orthop Traumatol Turc.* 2004;38:120–4.
16. Pan YW, Huang XY, You JF, et al. Malignant giant cell tumor of the tendon sheaths in the hand. *Zhonghua Wai Ke Za Zhi.* 2008;46:1645–8.
17. Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane). A review of eighty-one cases. *J Bone Joint Surg Am.* 1984;66:76–94.
18. Reilly KE, Stern PJ, Dale JA. Recurrent giant cell tumors of the tendon sheath. *J Hand Surg Am.* 1999;24:1298–302.

19. Rodrigues C, Desai S, Chinoy R. Giant cell tumor of the tendon sheath: a retrospective study of 28 cases. *J Surg Oncol*. 1998;68:100–3.
20. Uriburu JJ, Levy VD. Intraosseous growth of giant cell tumors of the tendon sheath (localized nodular tenosynovitis) of the digits: report of 15 cases. *J Hand Surg Am*. 1998;23:732–6.
21. Ushijima M, Hashimoto H, Tsuneyoshi M, et al. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. *Cancer*. 1986;57:875–84.
22. Walsh EF, Mechrefe A, Akelman E, et al. Giant cell tumor of tendon sheath. *Am J Orthop (Belle Mead NJ)*. 2005;34:116–21.
23. Williams J, Hodari A, Janevski P, et al. Recurrence of giant cell tumors in the hand: a prospective study. *J Hand Surg Am*. 2010;35:451–6.