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Clinical management of tenosynovial giant cell tumors

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Tenosynovial giant cell tumors (TGCT) were first introduced into the medical literature in 1941 by Jaffe et al.[1] with the description of pigmented villonodular synovitis. According to the World Health Organization (WHO) classification, tumors that commonly originate from the tendon sheath are usually defined as giant cell tumor of the tendon sheath (GCT-TS) and are divided into two groups based on their clinical and histological features: diffuse-type giant cell tumor (Dt-GCT) and localized-type giant cell tumor (Lt-GCT). The localized type is commonly seen in small joints and presents as a superficial, locally confined, well-circumscribed nodular mass. It does not show intra-articular extension. The diffuse type commonly affects large joints and is characterized by an

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ABSTRACT

Objectives: This study aims to evaluate the demographic characteristics, anatomical distribution, diagnostic and treatment patterns, postoperative complications, recurrence rates, and recurrence-associated factors in patients diagnosed with tenosynovial giant cell tumors (TGCTs).

Patients and methods: A total of 246 patients diagnosed with TGCT and treated between January 2010 and March 2021, were retrospectively analyzed. Pre- and postoperative data of the patients were recorded. Histopathological diagnosis was reviewed, and tumors were classified as localized TGCT and diffuse-type TGCT. Recurrence was defined as the reappearance of a lesion at the same location following an initially complete surgical excision. Survival time was defined as the time elapsed since surgery. Recurrence-free survival was calculated from the date of the surgical procedure to the date of recurrence or the last follow-up.

Results: Of a total of 246 patients included in the study, 87 were male and 159 were female with a mean age of 44.3 ± 16.3 (range, 18 to 75) years. The lesions were most commonly located in the hand (62.6%), predominantly at the phalangeal level (89.6%). Foot involvement was mainly at the ankle region (40.8%), while the knee was the third most frequently affected site (15%), with 64.8% of knee lesions being intra-articular. Multiple lesions were observed in 3.3% of patients. Small joints were involved in 63% of cases. Excisional biopsy was the most common diagnostic approach (63.8%), followed by Tru-Cut biopsy (23.2%) and incisional biopsy (8.5%), while macroscopically complete marginal resection was performed in 4.5% of cases. Postoperative complications occurred in 15.4% of patients, including infection, sensory deficits, hematoma, motion restriction, and vascular complications. The median follow-up was 43 months, and recurrence occurred in 15.4% of patients, of whom 76.3% required reoperation.

Conclusion: Our study results suggest that TGCT is associated with a notable recurrence rate and postoperative morbidity. Accurate diagnosis, complete surgical excision, and long-term follow-up are essential for optimal management. Recurrence may be associated with factors such as pain at presentation, presence of multiple lesions, delayed treatment, and postoperative infection. Adequate surgical excision with sufficient margins is of utmost importance in reducing the risk of recurrence.

Keywords: Pigmented villonodular synovitis, soft tissue tumor, tendon sheath, diffuse type, tenosynovial giant cell tumor.

infiltrative and extensive synovial involvement with intra-articular extension.[2]

Tenosynovial giant cell tumors are defined as originating from the synovium and tendon sheath, and histopathologically characterized by a mixture of synovial lining cells that include hemosiderin, extracellular hemosiderin deposits, siderophages, lipid-laden foamy macrophages, and multinucleated osteoclast-like giant cells.[2-4] These tumors can occur in individuals of any age group, but is more commonly seen in female patients between 30 and 50 years of age.[5] Clinical features vary by subtype: the localized type typically presents as a long-standing mass, while the diffuse type is more often associated with pain, swelling, tenderness, and restricted range of motion (ROM), and tends to occur at a younger age.[6,7] Most commonly, it presents as a soft tissue mass adjacent to small joints in the hand or foot, arising from the tendon sheath or synovium. If it is fixed to deep tissues, it may abut bone and cause pressure erosion, and depending on its location, it can lead to nerve compression or joint dysfunction. In some cases, patients may also present with clinical complaints such as sensory loss due to nerve compression, carpal tunnel syndrome, Guyon's canal syndrome, knee locking (originating from the patellar tendon or intra-articular localization), limited joint mobility, or effusion, depending on the location of the mass.[8-10]

Diagnosis is based on patient history, physical examination, and imaging studies, particularly ultrasound; biopsy is recommended in cases of suspected malignancy. Excisional biopsy or total excision may be performed in appropriate cases. During surgery, the mass should be completely removed with its pseudocapsule while preserving neurovascular structures. Partial resection of the tendon sheath may be required to reduce recurrence risk. Radiotherapy is an alternative option in inoperable cases. Early surgical intervention reduces the risk of complications and recurrence.[11-13]

Although TGCT typically presents as a slow-growing mass, it is predisposed to high recurrence rates ranging from 5% to 30% for the localized type and 40% to 60% for the diffuse type. Due to its potential to cause complications such as bone erosion, joint motion limitations, deformities, and neurovascular issues, accurate diagnosis, appropriate surgical management, and careful timing of the surgery are critically important.[6] In the present study, we aimed to evaluate the demographic characteristics, anatomical distribution, treatment approaches, postoperative complications, recurrence rates, and recurrence-associated factors in patients diagnosed with TGCT including both localized and diffuse types.

PATIENTS AND METHODS

Study design and study population

This single-center, retrospective study was conducted at Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Orthopedics and Traumatology between January 1st, 2010 and March 1st, 2021. Patients aged between 18 and 75 years who were diagnosed with TGCT and treated at our institution during the study period were screened for eligibility. Patients were included if they had a tumoral lesion identified through clinical and radiological evaluation, histopathologically confirmed as TGCT, underwent surgical treatment at our institution, and were followed in our clinic for at least six months. Only patients with complete clinical, radiological, pathological, and follow-up data available for analysis were included. Patients who could not be followed for at least six months, deceased patients, and those with incomplete or inaccessible medical records, patients with suspected malignancy on biopsy were excluded from the study. Finally, a total of 246 patients who met the inclusion criteria were recruited. A written informed consent was obtained from each patient. The study protocol was approved by the Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Research Ethics Committee (Date: 24.02.2021, No: 2021-02/1044). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection and assessment

All study data were obtained through the examination of archived files and hospital system records, as well as through face-to-face and telephone interviews. No additional blood tests, biopsies, or radiological imaging were requested from any patients for the purposes of this research. Demographic data including age and sex of the patients, tumor-related data including presenting symptoms, symptom duration, time interval between detection of the mass and hospital admission, incidental detection, and associated symptoms such as pain, sensory loss, and deformity, and tumor-related variables including localization (hand, foot, knee, etc.), joint involvement (small or large joints), laterality (right/left), presence of single or multiple lesions, tumor subtype (localized or diffuse), tumor

size/volume, bone invasion, and neurovascular compression were recorded. Tumor size was primarily determined based on macroscopic pathological measurements, with radiological and magnetic resonance imaging (MRI) findings used as complementary sources for validation.

Histopathological and diagnostic evaluation

Histopathological diagnosis was reviewed, and tumors were classified as localized TGCT and diffuse-type TGCT. The distinction between localized and diffuse types was made based on the histopathological evaluation of excisional biopsy specimens in conjunction with surgical and intraoperative finding as well as MRI findings. In selected cases with large lesions and involvement of major joints, Tru-Cut biopsy was performed to support preoperative surgical planning.

Due to the retrospective design of the study, a strictly standardized diagnostic algorithm

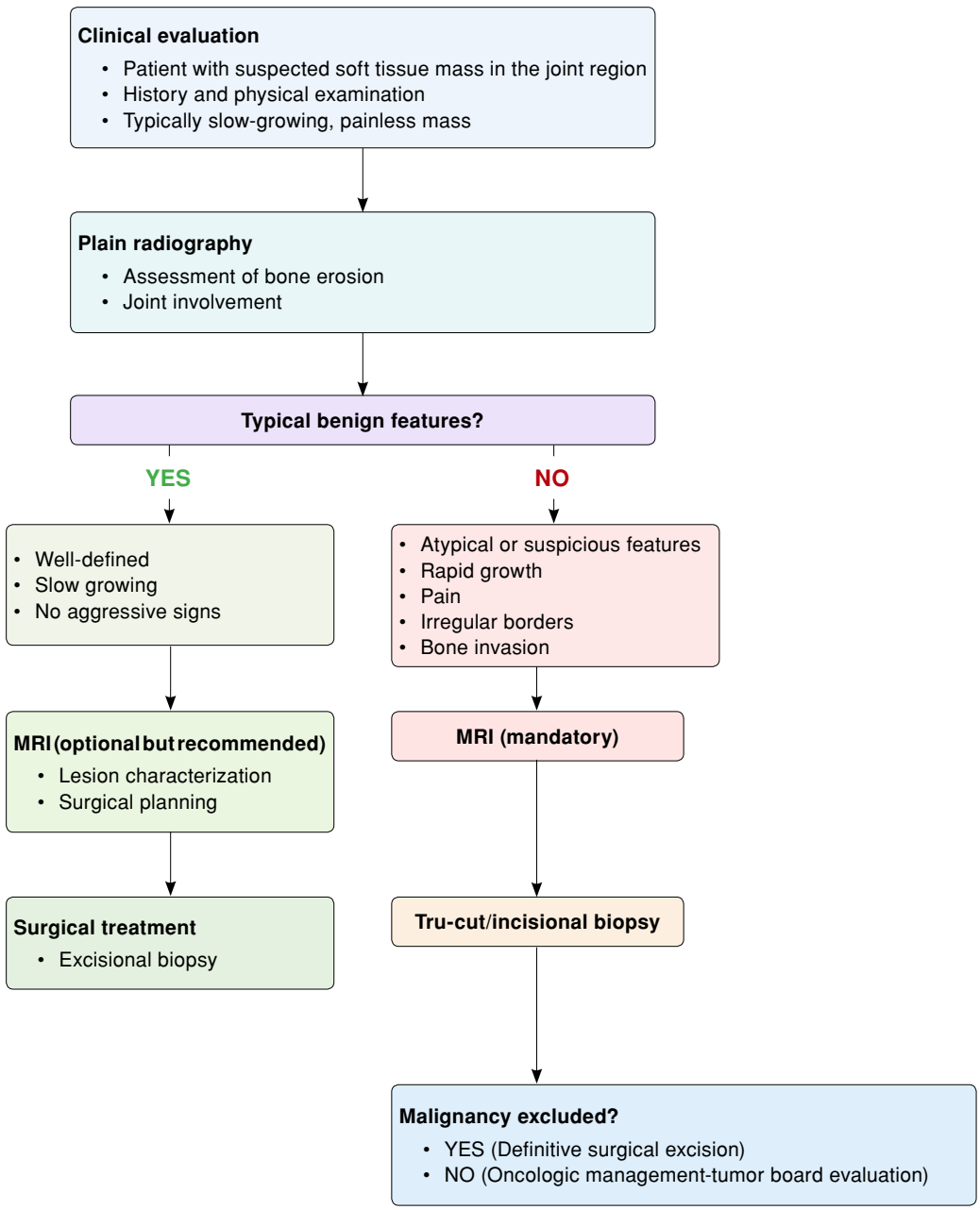


FIGURE 1. Proposed preoperative diagnostic algorithm for tendon sheath giant cell tumor.
MRI, magnetic resonance imaging.

was not applied in all cases. However, based on current literature and our institutional practice, a representative preoperative diagnostic approach is illustrated in Figure 1.

Diagnosis, surgical treatment, and postoperative outcomes

Excisional biopsy: A diagnostic procedure, usually unplanned or performed without predefined oncologic margins, in which the lesion is removed primarily for histopathological evaluation.

Tru-Cut biopsy: Tru-Cut biopsy was defined as a percutaneous core needle sampling technique performed under imaging guidance to obtain representative tissue for histopathological diagnosis.

Incisional biopsy: Incisional biopsy was defined as the surgical removal of a representative portion of the lesion for histopathological evaluation, typically performed when complete excision is not feasible or oncologically inappropriate.

Macroscopically complete marginal resection: A planned definitive surgical procedure performed with curative intent, in which the lesion is completely removed by marginal resection without intentionally obtaining wide or radical oncologic margins. In selected patients, this procedure may be performed as the initial surgical intervention without prior incisional or Tru-Cut biopsy, providing both definitive treatment and tissue for histopathological diagnosis. The objective is complete macroscopic removal of the lesion while preserving adjacent anatomical structures whenever appropriate.[14]

In patients who underwent incisional or Tru-Cut biopsy, definitive surgical treatment was subsequently performed after confirmation of the histopathological diagnosis. The surgical approach was determined according to the lesion characteristics, anatomical location, and extent of disease. The goal of surgery was complete macroscopic removal of the lesion while preserving adjacent anatomical structures whenever possible. Marginal resection was preferred in the majority of cases, whereas wide resections were reserved for selected lesions requiring more extensive surgery.

Surgical data included type of procedure performed and any reconstructive procedures. All surgical approaches were evaluated based on completeness of excision and preservation of surrounding structures.

Postoperative complications were defined and recorded after the first surgical procedure, focusing on early postoperative outcomes. Postoperative complications such as infection, hematoma or bleeding, sensory loss, limited ROM, and circulatory disorders or necrosis were recorded and analyzed.

Recurrence evaluation

Recurrence was defined as the reappearance of a lesion at the same location following an initially complete surgical excision. In our study, patients were considered to have recurrence, if a palpable mass was detected clinically at the same site and the lesion was confirmed radiologically, particularly by MRI.[14]

Follow-up duration, recurrence rate, time to recurrence, and need for reoperation were recorded and evaluated. Variables associated with recurrence included the presence of pain, multiple lesions, delayed presentation, diffuse tumor type, bone invasion, neurovascular compression, tumor size, postoperative infection, and overall complication status. These variables were analyzed in terms of their association with recurrence. Survival time was defined as the time elapsed since surgery. Recurrence-free survival was calculated from the date of the surgical procedure to the date of recurrence or the last follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test and histogram evaluation. Continuous data were presented in mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were presented in number and frequency. Group comparisons were performed using the Student t-test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables, as appropriate. Univariate and multivariate Cox regression analyses were performed to identify factors associated with recurrence. Variables with a p value of ≤ 0.150 in the univariate analysis were included in the multivariate model after assessment for multicollinearity (VIF ≤ 3). A backward likelihood ratio method was used for variable selection in the multivariate model. Kaplan-Meier survival analysis with the log-rank test was applied for categorical predictors. The receiver operating characteristic (ROC) curve analysis was performed for continuous predictors, and optimal cut-off values were determined using the Youden index. A p value of < 0.05 was considered statistically significant with 95% confidence interval (CI).

TABLE I
Clinical and demographic features of patients with giant cell tumor of the tendon sheath

Variables	n	%	Mean ± SD	Median	Min-Max	IQR
Age (year)			44.3 ± 16.3		18-75	
Sex						
Female	159	64.6				
Side of involvement						
Right	139	56.5				
Clinical presentation						
Pain	89	36.1				
Mass	211	85.8				
Sensory loss	22	8.9				
Range of motion limitation	33	13.4				
Deformity	14	5.7				
Incidental finding	11	4.5				
Mass localization						
Hand	154	62.6				
Phalanges	138	89.6				
Wrist	8	5.2				
Extremity	8	5.2				
Foot	49	19.9				
Phalanges	18	36.7				
Ankle	20	40.8				
Extremity	11	22.4				
Knee	37	15.0				
Intra-articular	24	64.8				
Elbow	1	0.4				
Hip	1	0.4				
Forearm	2	0.8				
Shoulder	1	0.4				
Scapula	1	0.4				
Multiple sides	8	3.3				
Type of joint involved						
Small joint	156	63.4				
Large joint	55	22.3				
Extremity	35	14.2				
Time from mass detection to clinical admission (months)				5	0-50	
Method of pathological diagnosis						
Incisional biopsy	21	8.5				
Excisional biopsy	157	63.8				
Tru-cut biopsy	57	23.2				
Marginal resection	11	4.5				
Tumor presentation						
Localized	201	81.7				
Diffuse	45	18.3				
Neurovascular compression	17	6.9				
Bone invasion	34	13.8				
Tumor volume (cm^3)					2.5	0.9-15
Postoperative complications	38	15.4				
Sensory loss	12	4.9				
Motor dysfunction	3	1.2				
Infection	13	5.3				
Bleeding/hematoma	8	3.3				
Circulatory disorder/necrosis	2	0.8				
Follow-up duration (months)				43	6-132	
Recurrence	38	15.4				
Reoperation for recurrence	29	76.3				

SD, standard deviation; IQR, interquartile range.

RESULTS

Of a total of 246 patients included in the study, 87 were male and 159 were female with a mean age of 44.3 ± 16.3 (range, 18 to 75) years. The median age of patients with TGCT in the hand (n = 154) and in the foot (n = 49) was 46 years and 38 years, respectively with a female predominance. The majority of patients presented with a palpable mass (85.8%), while 36.1% reported pain at the time of admission. In 4.5% of cases, the mass was detected incidentally. The median time from initial notice of the mass to clinical presentation was 5 (range, 0 to 50) months (Table I).

Most of the masses were located on the right side of the patient (56.5%). According to frequency, the most common localization of the mass was the hand, followed by the foot and the knee joint. The mass was usually localized in the hand (n = 154, 62.6%). In the hand, it was most commonly at the phalangeal level (n = 138, 89.6%). The second most frequent localization was the foot (n = 49, 19.9%), where ankle involvement was predominant (n = 20, 40.8%). The third most frequent localization was the knee joint and surrounding area (n = 37, 15%), with 64.8% of knee lesions being intra-articular. In eight patients (3.3%), multiple involvement was observed. In total, 63.4% of the affected joints (n=156) were small joints. This was followed by large joints at 22.3% and extremity regions at 14.2% (Table I).

Mass involvement was more common in the volar aspect of the wrist and hand (n = 11, 68.8%).

TABLE II
Characteristics of giant cell tumor of tendon sheath according to involvement in hand and foot joints

	Hand (n = 154)					Foot (n = 49)				
	n	%	Mean ± SD	Median	IQR	n	%	Mean ± SD	Median	IQR
Age (year)			46.7 ± 15.3					38.5 ± 15.7		
Sex										
Female	103	66.9				31	63.3			
Finger	138	89.6				18	36.7			
Wrist involvement	8	5.2				20	40.8			
Volar	4	2.5				N/A	N/A			
Dorsal wrist	4	2.5				N/A	N/A			
Plantar	N/A	N/A				5	10.2			
Dorsal foot	N/A	N/A				6	12.2			
1. Digit	33	23.9				7	38.8			
2. Digit	40	29.0				4	22.2			
3. Digit	33	23.9				3	16.6			
4. Digit	17	12.3				3	16.6			
5. Digit	15	10.9				2	11.1			
Proximal phalanx	65	43.6				13	72.2			
Middle phalanx	47	31.5				6	27.8			
Distal phalanx	37	24.8				0	0.0			
Simultaneous multiple masses in multiple phalanges	11	7.1				1	5.5			
Localized	150	97.4				41	83.7			
Diffuse	4	2.6				8	16.3			
Mass volume (cm^3)				1.3	0.5-3.2				9.0	3.0-36.7
Postoperative complication	18	11.7				14	28.6			
Sensory loss	8	5.2				4	8.2			
Motor dysfunction	1	0.6				2	4.1			
Infection	4	2.6				7	14.3			
Bleeding/hematoma	4	2.6				0	0.0			
Circulatory disorder/necrosis	1	0.6				1	2.0			
Recurrence	20	13.0				12	24.5			

SD, standard deviation; IQR, interquartile range; N/A, not available.

The involvement order was as follows: second finger (29%), first finger (23.9%), third finger (23.9%), fourth finger (12.3%), and least in the fifth finger (10.9%). The most frequent involvement was at the proximal phalanx level (n = 65, 43.6%), followed by the middle phalanx (31.5%) and distal phalanx (24.8%). Unlike the hand involvement, ankle involvement was more common in the foot (n = 20, 40.8%). In foot masses, the ratio of plantar to dorsum involvement was 6:1.2. The most common involvement was in the first toe (n = 7, 38.8%), followed by the second toe (n = 4, 22.2%), and the third and fourth toes (n = 3, 16.6% each). Eight foot masses (16.3%) were of the diffuse type.

TABLE III
Clinical characteristics of groups according to recurrence status

	Recurrence (+) (n = 38)					Recurrence (–) (n = 208)					
Variables	n	%	Mean ± SD	Median	IQR	n	%	Mean ± SD	Median	IQR	*p*
Age (year)			41.8 ± 19.7					44.8 ± 15.7			0.385
Sex											0.092
Female	20	52.6				139	66.8				
Side of involvement											0.851
Right	22	57.9				117	56.3				
Clinical presentation											
Pain	18	47.3				71	34.1				**0.020**
Mass	33	86.8				178	86.0				0.889
Sensory loss	7	18.4				15	7.2				**0.026**
Range of motion limitation	8	22.9				25	12.0				0.083
Deformity	5	13.2				9	4.3				**0.031**
Incidental finding	1	2.6				10	4.8				0.551
Mass localization											0.273
Hand	20	52.6				134	64.4				
Foot	12	31.6				37	17.8				
Knee	5	13.2				32	15.4				
Other*	1	2.6				5	2.4				
Hand finger	19	95.0				119	88.8				0.397
Foot toe	3	25.0				15	40.5				0.332
Multiple mass	35	92.1				203	97.6				0.079
Type of joint involved											0.421
Small joint	21	55.3				138	66.3				
Large joint§	15	39.5				62	29.8				
Extremity	2	5.3				8	3.8				
Time between first detection and examination (months)				8	4-17.2				4	2-9	**0.014**
Method of pathological diagnosis											0.224
Incisional biopsy	2	5.3				19	9.1				
Excisional biopsy	28	73.7				129	62.0				
Tru-Cut biopsy	5	13.2				52	25.0				
Marginal resection	3	7.9				8	3.8				
Pathological presentation											
Diffuse involvement	10	26.3				35	16.8				0.164
Vascular-nerve compression	7	18.4				10	4.8				**0.002**
Bone invasion	9	23.6				25	12				**0.004**
Tumor volume (cm^3)				10.2	1.6 -30.7				2.1	0.8-11.9	**0.006**
Postoperative complication	14	36.8				24	11.5				**< 0.001**
Sensory loss	1	7.1				11	45.8				**0.015**
Motor dysfunction	1	7.1				2	8.3				
Infection	9	64.3				4	16.7				
Bleeding/hematoma	3	21.4				5	20.8				
Circulatory disorder/necrosis	0	0.0				2	8.3				

SD, standard deviation; IQR, interquartile range; *, elbow, hip, forearm, shoulder, and scapular joints; §, shoulder and scapular joints were included in the large joint category due to the small sample size in this group.

The median tumor volume was 2.5 (range, 0.9 to 15) cm^3. The median mass volume in the hand was 1.3 (range, 0.5 to 3.2) cm^3. The masses in the foot were observed to be larger than those in the hand, with a median volume of 9.0 (range, 3.0 to 36.7) cm^3.

In the diagnosis of the mass, excisional biopsy was performed in 63.8% of cases. This was followed by Tru-Cut biopsy in 23.2%, and incisional biopsy in 8.5%. In 11 patients (4.5%), macroscopically complete marginal resection was performed. A total of 18.3% of the masses were of the diffuse type. Four lesions (2.6%) in the hand were of the diffuse type. Bone invasion was observed in 34 patients (13.8%), followed by neurovascular compression findings in 17 patients (6.9%) (Table I).

Postoperative complications were observed in 15.4% of patients. The most common complication was infection, seen in 13 patients (5.3%). This was followed by sensory loss in 12 patients, and bleeding or hematoma in eight patients. Movement disorder was observed in three patients, while circulatory disorder and/or necrosis was observed in two patients. Among patients who were followed for a median of 43 (range, 6 to 132) months, recurrence was observed in 15.4% (n = 38). Of these patients, 76.3% (n = 29) underwent reoperation (Table I).

Postoperative complications occurred in 18 patients (11.7%) with hand masses. These complications were as follows: n = 8 sensory loss, n = 4 infections, n = 4 bleeding or hematoma, one movement disorder and one circulatory disorder and/or necrosis (Table II).

Postoperative complications were observed in 28.6% of patients operated on for foot TGCT (n = 14). Of these complications, seven (14.3%) were infections, followed by sensory loss in 8.2% and movement disorders in 4.1%. Recurrence was observed in 24.5% of foot masses (n = 12) (Table II).

In patients who experienced recurrence, pain (47.3% *vs.* 34.1%), sensory loss (18.4% *vs.* 7.2%), and deformity (13.2% *vs.* 4.3%) were more common compared to those without recurrence. The patients with recurrence had a delayed presentation for examination, seeking medical attention four months later than those without recurrence (eight months *vs.* four months after first noticing the mass). Among the groups, diffuse involvement was more prominent in the recurrence group (22.3% *vs.* 13.8%). Vascular and nerve compression, as well as bone invasion, were more common in the recurrence group (18.4% *vs.* 4.8% and 34.2% *vs.* 14.9%, respectively). The size of the mass in the recurrence group was approximately five times larger compared to the non-recurrent group (10.2 cm^3 *vs.* 2.1 cm^3). The complication rate was three times higher in the recurrence group (36.8% *vs.* 11.5%). Infection complications were significantly higher in the recurrence group (64.3% *vs.* 16.7%). Other clinical characteristics showed similar distributions between the groups (Table III).

In the multivariate Cox regression analysis, patients presenting with painful clinical symptoms showed a significantly increased hazard of recurrence (hazard ratio [HR] = 2.256, $p = 0.027$). Patients presenting with multiple masses also demonstrated a higher hazard of recurrence (HR = 4.055, $p = 0.027$). Each additional month of delay after the first detection of the mass was associated with a 4% increase in the hazard of recurrence (HR = 1.043, $p = 0.004$). Patients who developed postoperative infectious complications were found to have a significantly higher rate of recurrence, indicating a strong clinical association (HR = 11.473, $p < 0.001$) (Table IV).

The Kaplan-Meier analysis also demonstrated significantly higher recurrence rates in patients with postoperative infectious complications compared to those without ($p < 0.001$) (Figure 2).

The ROC analysis revealed that a cut-off value of 5.5 months between the first detection of the mass and clinical evaluation predicted recurrence with 57.9% sensitivity and 58.8% specificity (area under the curve [AUC]: 0.625, 95% CI: 0.514-0.737, $p = 0.014$) (Figure 3).

DISCUSSION

In the present study, we evaluated the demographic characteristics, anatomical distribution, treatment approaches, postoperative complications, recurrence rates, and recurrence-associated factors in patients diagnosed with TGCT including both localized and diffuse types. The main finding of this study was the identification of painful presentation, multiple lesions, delayed presentation, and postoperative complications as independent predictors of recurrence. These findings suggest that clinical presentation and postoperative factors may play a more important role in recurrence than several tumor-related characteristics, emphasizing the importance of early diagnosis, meticulous surgical management, and careful postoperative follow-up.

TABLE IV
Predictors of recurrence in giant cell tumors of the tendon sheath

	Univariate			Multivariate		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Age (year)	0.991	0.971-1.010	0.338			
Sex						
Male	1.759	0.930-3.327	0.082	1.676	0.852-3.299	0.135
Side of the tumor	0.922	0.484-1.756	0.806			
Clinical presentation						
Pain	2.150	1.128-4.097	**0.020**	2.256	1.096-4.646	**0.027**
Mass	1.070	0.418-2.741	0.888			
Sensory loss	2.642	1.161-6.009	**0.021**	1.294	0.421-3.973	0.653
Limited mobility	2.090	0.949-4.602	0.067	0.367	0.127-1.056	0.063
Deformity	3.087	1.203-7.925	**0.019**	1.233	0.305-4.981	0.769
Incidental finding	0.603	0.083-4.396	0.618			
Tumor localization			0.233			
Hand	0.781	0.105-5.823				
Foot	1.627	0.211-12.526				
Knee	0.811	0.095-6.945				
Other*	Reference					
Hand finger	2.314	0.309-17.241	0.413			
Foot toe	0.532	0.144-1.968	0.345			
Multiple mass	2.614	0.804-8.504	0.110	4.055	1.176-13.986	**0.027**
Type of affected joint			0.549			
Small joint	0.706	0.300-1.661				
Large joint	1.015	0.386-2.668				
Extremity	Reference					
Time between first detection and examination (months)	1.042	1.019-1.066	**< 0.001**	1.043	1.013-1.073	**0.004**
Method of pathological diagnosis			0.357			
Incisional biopsy	0.341	0.057-2.039				
Excisional biopsy	0.637	0.194-2.095				
Tru-cut biopsy	0.332	0.079-1.393				
Marginal resection	Reference					
Pathological presentation						
Diffuse involvement	1.641	0.797-3.378	0.179	2.654	0.995-7.078	0.051
Vascular-nerve compression	3.833	1.685-8.720	**0.001**	1.522	0.620-3.737	0.360
Bone invasion	2.718	1.389-5.318	**0.003**			
Tumor volume	1.001	0.999-1.002	0.416			
Postoperative complication	3.944	2.032-7.655	**< 0.001**	0.772	0.245-2.429	0.658
Infection	8.284	3.894-17.623	**< 0.001**	11.473	4.344-30.298	**< 0.001**

CI, confidence interval; HR, Hazard ratio; *, elbow, hip, forearm, shoulder, and scapular joints; § shoulder and scapular joints were included in the large joint category due to the small sample size in this group.

The diagnosis, treatment, and recurrence of TGCT remain widely debated topics in the literature. Due to its considerable recurrence rates (5% to 30% for localized type and 40% to 60% for diffuse type), numerous studies have investigated the etiology and prognostic factors associated with recurrence.[2] In the present study, the 2020 WHO Tumor Classification was adopted, and both localized and diffuse disease patterns were evaluated. In addition, tumor localization, recurrence patterns, and clinical characteristics were assessed, with a particular focus on identifying potential predictors of recurrence and contributing to the existing literature.[2] Unlike previous studies focusing mainly on anatomical distribution or recurrence rates, our study assessed both localized and diffuse TGCT in

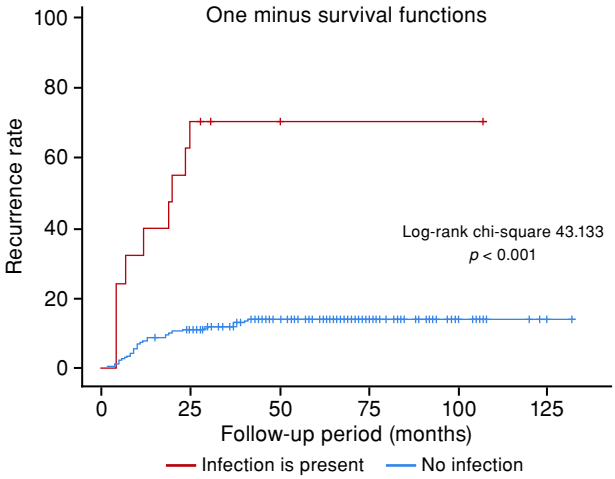


FIGURE 2. Kaplan-Meier analysis demonstrated a significantly increased recurrence risk in patients with postoperative infectious complications (log-rank $p < 0.001$).

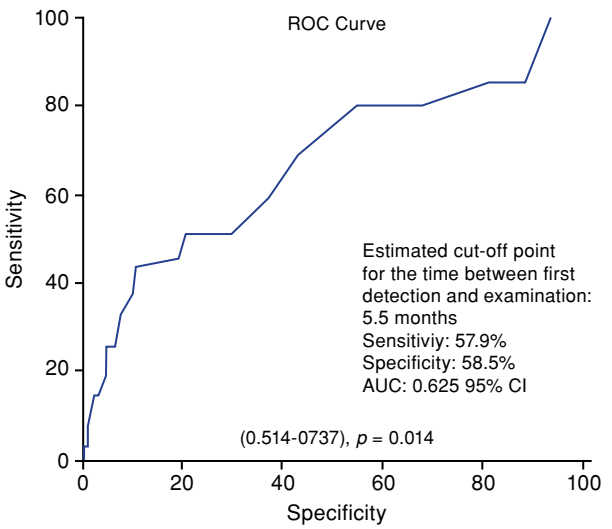


FIGURE 3. A cutoff value of 5.5 months between initial detection of the mass and first medical consultation demonstrated a sensitivity of 57.9% and a specificity of 58.8% for predicting recurrence (AUC: 0.625; 95% CI: 0.514-0.737; $p = 0.014$).

ROC, Receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

a relatively large cohort and identified independent predictors of recurrence using multivariate Cox regression analysis.

In general, TGCT has been reported to occur most commonly between the ages of 30 and 50 years and to show a female predominance.[15] Consistent with previous studies, a higher proportion of women was observed in our cohort.[5,15,16] The mean age of the patients was 44.3 ± 16.3 years, with most cases occurring between 35 and 55 years of age. No significant age difference was found between sexes. However, patients with foot-localized tumors were significantly younger than those with hand-localized tumors (38.5 ± 15 *vs.* 46.7 ± 15.3 years), suggesting that TGCT of the foot may present at an earlier age.

Previous studies have reported that hand TGCT most commonly involves the second and third digits.[17] Consistent with these findings, the second finger was the most frequently affected site in our cohort (29%). Previous studies have also reported that hand TGCTs most commonly occur in the proximal phalanx and distal interphalangeal joint regions.[15,18] Consistent with these findings, the proximal phalanx was the most frequently involved site in our cohort (43.6%), followed by the middle and distal phalanges. Diffuse-type involvement of the hand was uncommon, accounting for only 2.6% of cases. Furthermore, the literature indicates that hand TGCTs occur more frequently on the volar aspect and in the dominant hand.[19-22] Consistently, volar involvement predominated in our cohort, and tumors were more commonly located on the right side (56.5%).

Foot and ankle involvement is less common than hand involvement in TGCT and is typically reported in the forefoot.[23] In our cohort, 49 patients had foot involvement, with a median age of 38 years and a female predominance (63.3%). In contrast to previous reports, hindfoot (ankle) involvement was the most frequent location (40.8%), followed by the forefoot (36.7%). The first toe was the most commonly affected digit, and diffuse-type lesions accounted for 16.3% of foot tumors. In addition, our findings are consistent with previous reports demonstrating that localized-type TGCT is substantially more common than diffuse-type disease and that lesion distribution differs between these subtypes. While localized lesions predominantly occur in the hand, diffuse-type TGCT more frequently involves large joints, particularly the knee.[24-26] Consistent with these findings, localized-type TGCT represented the majority of cases in our cohort, whereas the knee was the most common site of involvement among patients with diffuse-type disease. This pattern may have clinical implications, as diffuse-type disease in large joints is often characterized by more extensive synovial involvement and periarticular extension, factors that may complicate surgical management and local disease control.[14]

Previous studies have suggested that diffuse-type TGCTs tend to be larger than localized lesions at the time of diagnosis.[20] Similarly, lesion size in our cohort showed considerable variability, with some of the largest tumors occurring in the knee. The larger size of knee lesions may be related to their deep location and non-specific clinical presentation, which can delay recognition and diagnosis. In addition, lesions located in the foot tended to be larger than those in the hand, possibly reflecting differences in anatomical location and the timing of clinical detection. Although lesion size may influence surgical complexity, it was not identified as an independent predictor of recurrence in our multivariate analysis.

Postoperative complications in TGCT appear to be multifactorial in nature, potentially arising from both surgical factors and disease-related characteristics such as lesion extent, anatomical location, and surgical complexity. The literature has reported osseous involvement in a minority of TGCT cases, most commonly in the form of cortical erosion.[5] In our cohort, bone involvement and neurovascular compression were observed in a subset of patients, indicating that TGCT may occasionally exhibit locally aggressive behavior, particularly in anatomically constrained regions. Such findings may increase the complexity of surgical management and require meticulous preoperative planning to achieve adequate excision while preserving function. Postoperative complications occurred at a rate comparable to that reported in previous series.[18] Postoperative infection may promote prolonged local inflammation and delayed wound healing, creating a microenvironment that supports the survival and proliferation of residual tumor cells, thereby potentially increasing the risk of recurrence. Furthermore, postoperative infection may also reflect technically demanding surgery or biologically aggressive lesions rather than being a direct cause of recurrence.[27,28] Infection was the most frequent complication and was also identified as an independent predictor of recurrence in our multivariate analysis, highlighting the importance of careful perioperative management and early treatment of wound-related complications. Although bone involvement may reflect greater local disease extent, it was not identified as an independent predictor of recurrence in the final multivariate model.

Review of the literature reveals recurrence rates ranging from 7% to 44% in TGCT, highlighting local recurrence as one of the principal challenges in disease management.[29,30] Previous studies have identified a variety of factors associated with recurrence, including lesion location, extent of disease, and involvement of adjacent tendon or capsular structures.[29,31] In a large multi-center study, reoperation rates were reported to be substantially higher in diffuse-type disease than in localized TGCT, emphasizing the more challenging clinical course of diffuse lesions.[23]

In the current study, recurrence occurred in 15.4% of patients during a median follow-up period of 43 months, and the majority of recurrent cases required reoperation. Although recurrence was more frequently observed in foot lesions and was associated in univariate analyses with pain, sensory loss, neurovascular compression, bone invasion, diffuse disease, larger tumor size, and postoperative complications, these findings should be interpreted with caution. In the multivariate analysis, pain at presentation, delayed consultation, the presence of multiple masses, and postoperative infection were identified as independent predictors of recurrence. Among these variables, postoperative infection showed the strongest association with recurrence; however, since it occurs in the postoperative period, this relationship should be interpreted cautiously and may reflect a complex interaction between disease burden, surgical difficulty, and postoperative course. Overall, these results suggest that factors related to delayed presentation and postoperative complications may be more important determinants of recurrence than several anatomical and tumor-related characteristics identified in univariate analyses. However, these findings should be interpreted as risk indicators rather than definitive determinants in clinical decision-making, and treatment should always be case-specific.

Nonetheless, this study has several limitations that should be acknowledged. First, due to its retrospective design, it relied on previously recorded medical data, which may have been incomplete or inconsistently documented. Second, the single-center nature of the study may limit the generalizability of the findings to other populations and clinical settings. Finally, functional outcomes and patient-reported outcome measures were not consistently available for all patients, limiting a more comprehensive assessment of postoperative recovery and long-term clinical outcomes. Further multi-center, large-scale, prospective studies are needed to confirm these findings.

In conclusion, this study provides a comprehensive evaluation of the clinical

characteristics, treatment outcomes, and predictors of recurrence in patients with TGCT. Although most patients achieved favorable outcomes following surgical treatment, recurrence remained relatively common, emphasizing the importance of careful postoperative surveillance. Painful presentation, multiple lesions, delayed presentation, and postoperative infectious complications were identified as independent predictors of recurrence, whereas tumor size was not an independent risk factor after adjustment for confounding variables. These findings may assist clinicians in identifying patients at increased risk for recurrence, optimizing surgical planning, and tailoring follow-up strategies. Further studies are warranted to validate these predictors and refine risk-stratified management approaches.

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

Author Contributions: E.K.B.: Contributed to conceptualization, investigation, project administration, and writing-original draft; C.U., S.M.A., I.B.A.: Contributed to methodology; E.T., M.B.K.: Contributed to investigation; M.S.C.: Contributed to formal analysis and writing. All authors reviewed and approved the final version of the manuscript.

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