PATIENT-FRIENDLY VERSION OF

“Localized and Diffuse Tenosynovial Giant Cell Tumor: Real-World Results from a Patient Observational Registry”

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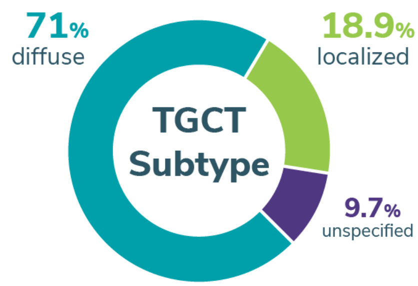
SUMMARY OF PAPER

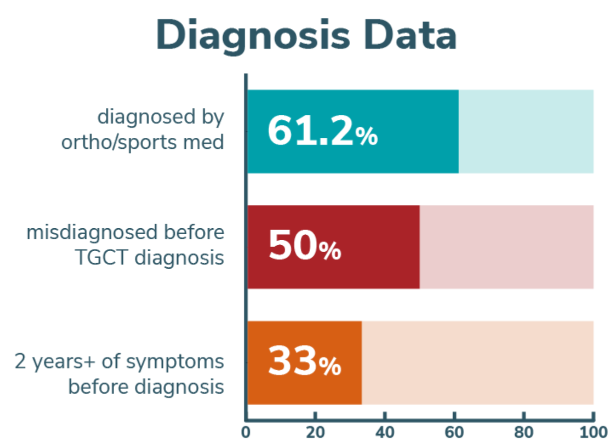
Tenosynovial Giant Cell Tumor (TGCT) is a rare tumor disease where patients experience many symptoms which make it difficult for affected patients to complete daily activities and reduces their quality of life (QoL). There are two subtypes of TGCT, known as localized or diffuse-type TGCT, which describe the extent a single joint is affected. Localized TGCT, sometimes called "nodular", includes an encapsulated tumor(s) which have a clear boundary on where they start and stop (like a marble). Diffuse TGCT means that the disease affects part or all of the joint and it is difficult to determine where the disease starts and stops (like gum smudged into carpet).

This analysis uses patient-reported data from the TGCT Support Patient Registry to show the patient experience with TGCT and how different healthcare systems approach this disease.

A total of 497 patients (with a median age of 45 years) from 32 countries were included. Seventy-one percent of patients had diffuse-TGCT (D-TGCT), 18.9% of patients with localized TGCT (L-TGCT), and 9.7% of patients were unspecified. Patients designated themselves as "unspecified TGCT" if they were unsure about the subtype.



Over half of patients (61.2%) were diagnosed by orthopedic/sports medicine surgeons and half were misdiagnosed prior to their proper TGCT diagnosis. A third of patients were diagnosed more than 2 years following when their symptoms started. Nearly 80% of all patients had 1 or more surgeries to remove their TGCT and 63% of those patients reported 1 or more recurrence(s). Of the patients that report a recurrence following surgery (defined as either symptoms returning and disease present after surgery), 59% had it return again after additional surgeries, meaning **multiple surgeries are unlikely to remove disease**. Lastly, 23% of patients changed occupations/prematurely retired due to TGCT and the proportion of patients that retired prematurely or changed occupations increased in patients with more than 2 surgeries. **This reflects that the disease and repeat treatments, such as multiple surgeries, has a negative effect on patients.**



Greater awareness of TGCT among healthcare providers is needed to improve how quickly patients get diagnosed and to identify more effective treatments to reduce recurrence rates, the number of surgeries, and improve patients' quality of life.

Abbreviations

Abbreviation	Full terminology
CSF1	colony stimulating factor 1
D-TGCT	diffuse TGCT
HCPs	healthcare providers
L-TGCT	localized TGCT
LRR	local recurrence rate
PVNS	pigmented villonodular synovitis
TGCT	Tenosynovial Giant Cell Tumor
US	United States
QoL	quality of life

INTRODUCTION

Tenosynovial giant cell tumor (TGCT), formerly known as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), is a rare, locally aggressive tumor affecting the synovium (joint), bursa (fat pads/shock absorbers around the joint), or tendon sheath (tissue that lines tendons). TGCT describes two distinct subtypes, localized and diffuse type, and MRI scans are used to determine the subtype of TGCT. The cells in these subtypes look similar under a microscope and have a genetic abnormality which causes increased production of a protein, colony stimulating factor 1(CSF1)[1–3]. This gene abnormality is not passed down nor inherited and only impacts a small proportion of the tumor cells (12-16%).

Despite their cell similarities, the localized, also referred to as "*nodular*", subtype (L-TGCT) is usually a slow-growing, and marble-like tumor whereas the diffuse subtype (D-TGCT) is often locally aggressive and may impact healthy tissues[4,5]. L-TGCT comprises the majority of TGCT cases, is most often found in small joints, like those in hands or feet, and is treated with high success by surgery alone. In contrast, D-TGCT represents a small proportion of cases, estimated 10-20% of all TGCT cases, typically occurs in large joints, like knees and hips, and is more likely to return after a surgery[6–9]. Neither type of TGCT will impact other joints or spread except around the same joint where it is originally found.

The way the disease affects each person is complex and unpredictable, with symptoms ranging from no symptoms to debilitating. Most often, symptomatic patients with TGCT experience pain, swelling, limited range of motion, and stiffness[10]. These symptoms are common in many other common diseases, which further complicates the journey to diagnosis. In combination with the rarity of disease, delays in diagnosis are common[11,12]. For symptomatic patients, the main treatment is surgical removal when complete removal is possible [13,14]. Surgery cures the disease for the majority of patients with L-TGCT. However, it is difficult to remove all the disease in patients with D-TGCT and patients often experience a return of the disease, known as a recurrence[15,16]. The benefit of removing only part of the disease is controversial.

Medicines that target the abnormal production of CSF1 have been developed and have become an important tool in the treatment of TGCT [2,17]. There are two approved medications in the United States (US), pexidartinib (known as Turalio; approved in 2019) and vimseltinib (known as Romvimza; approved in 2025). Other medicines such as nilotinib and imatinib (Glivec/Gleevec) are utilized off-label, meaning they were not originally created for TGCT but they have some effectiveness in shrinking tumors and improving symptoms[18,19]. Currently, there are no approved medications outside the US. Despite these advancements, the lack of awareness of these options, lack of clarity on how and when to use them, limited global access, and lack of standardized practice has limited their use.

To date, little evidence exists from real-world settings[12,20,21]. Majority of studies are small studies, focus on outcomes, and rarely describe the patient experience. Questions remain about the impact of TGCT on quality of life (QoL), diagnostic journey, providers involved in diagnosis and treatment, misdiagnosis rate, duration to diagnosis, duration from diagnosis to treatment, recurrence, and challenges associated with care. While the existing literature doesn't assess it, we know from experience that the wrong treatments are very common in daily practice (e.g., draining joint, steroid injections, too many surgeries, etc).

The TGCT Support Registry provides long term, multi-national, observational data, created in September 2022, to provide real-world evidence depicting the patients-reported journey through diagnosis, treatment, and thereafter. The TGCT Support Registry represents the **largest** disease registry for TGCT, and this analysis represents the typical journey experienced by patients with TGCT from initial symptoms to diagnosis, treatment, and their experience throughout the US and globally in a comprehensive and meaningful manner. This study provides an initial analysis of patient experiences to describe the different healthcare providers (HCPs) involved, surgical outcomes, and burden of disease in a large population of varying geographical distribution, independent of treatment institution. This is the first study to do so.

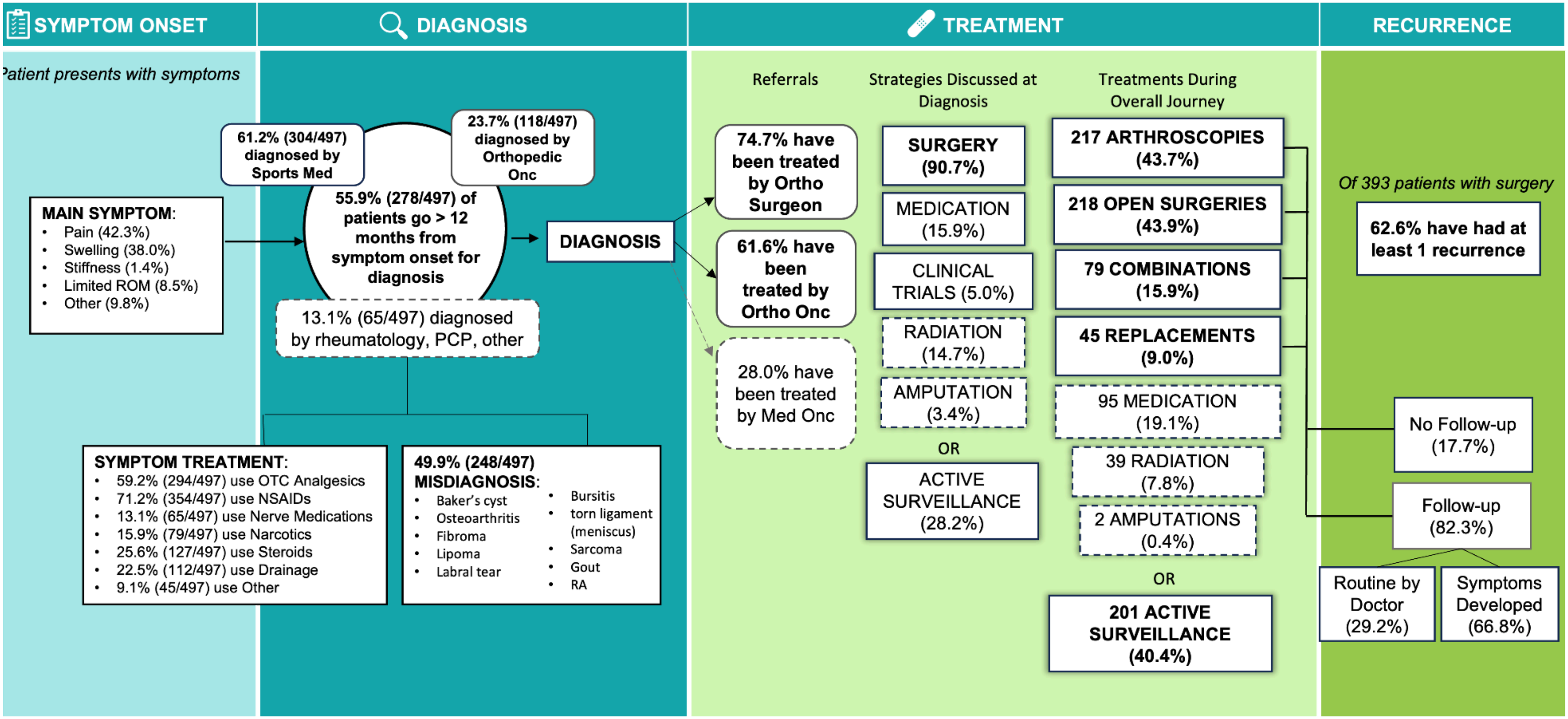
Description of Survey and Analysis

Study population

TGCT Support, a program of the Life Raft Group (LRG), is an international, non-profit patient advocacy organization. The TGCT Support Registry started in 2022 and includes a patient questionnaire to capture the initial experience and how it changes every 6 months. The registry aims to describe the patient experience associated with the disease and their treatment journey. When this data was analyzed, 497 patients, globally, with TGCT were included (Figure 1 in Supplementary 1). The institutional review board, Advarra (Columbia, Maryland), provided approval for the analysis of the TGCT Support Registry, and written informed consent was obtained from each patient who participated in the registry. For the analyses here, we included patients who were older than 18 years of age with a diagnosis of TGCT. Disease subtype was self-reported as diffuse, localized, or unknown. Patients were not eligible for this study if they were younger than 18 years of age (there were 110 of them), or if the participant did not provide written consent (there were 18 of them).

Recurrence was defined as asymptomatic relapse (no symptoms, but the disease has returned), residual disease (some disease was left over after the surgery), and/or radiographic progression of the disease following surgery (MRI showing the tumors have grown after the surgery).

Figure 1. A summary schematic of the patient-reported journey of TGCT from symptom onset to treatment and thereafter



Survey Design

An electronic questionnaire was developed using RedCap, an electronic data capture tool. The questionnaire consists of 168 questions to record clinical information, demographics, and quality of life survey responses. In particular, the questionnaire captured information on demographics, type of healthcare provider (HCP) involved in diagnosis and treatment, symptoms and onset, supportive care, misdiagnoses and delay in diagnosis, treatments discussed at initial diagnosis, treatments received, recurrence rate, and patient-reported outcomes related to pain, physical function, and quality of life, both as multiple choice questions and as testimonials. The current analysis includes the initial responses submitted between October 06, 2022 to December 06, 2023.

Statistical analysis

All descriptive statistics were analyzed separately across TGCT subtypes: diffuse, localized, or unknown. Treatment-related responses were separated for patients in the US and patients outside the US to identify impacts on care. This is because pexidartinib (Turalio) is available in the US and may influence care, whereas pexidartinib is not available in the rest of the world. Treatments were compared between patients with L-and D-TGCT and US patients and non-US patients.

RESULTS

Baseline Characteristics

Description of 497 patient demographics from 32 countries and their disease characteristics are summarized here. Majority of patients in the Registry were female (74.4%). It is worth noting that the female majority may be because individuals that identify as female are more likely to seek out social support, get involved with TGCT Support, and know about this project and agreed to participate[7], rather than a biological reason.

The median age is 45 years (range between 18-81 years) at the time of their entry and a median age at diagnosis of 38 years (range of 7-74 years old at diagnosis). Median refers to the middle value in a set of numbers, this is used instead of the average because it is not influenced by outliers. This age range matches prior literature which shows patients tend to be young and between 30-50 years old when diagnosed.

Fifty-six percent of patients resided in the US and the other 44% spanned countries such as the United Kingdom, Australia, Canada, and across Europe. Sixty-five percent of patients were employed full-time or part-time, and 59.9% had a bachelor's degree or higher. This is more than the U.S. average, meaning the population of patients that responded to the survey were considered more educated than the average person. This also may indicate that those participating are more educated and more likely to participate in research.

Of the 497 patients, 71.4% were diagnosed with D-TGCT. Although L-TGCT is more common than D-TGCT, most patients in our registry have D-TGCT due to our efforts to provide resources to patients' actively suffering. The knee joint was the most frequent location of the disease for both patients with D-TGCT and L-TGCT. Other joints involved include hip, ankle, and other (e.g., shoulder, elbow, spine).

Table 1. Patient demographics

Demographic Analysis	Diffuse (n=355, 71.4%)	Localized (n=94, 18.9%)	Unknown (n=48, 9.7%)	Total (n=497) (n, % column)
Sex, n (%)				
Male	99 (27.9%)	18 (19.1%)	8 (16.7%)	125 (25.2%)
Female	254 (71.5%)	76 (80.9%)	40 (83.3%)	370 (74.4%)
Prefer not to say	2 (0.6%)	0 (0.0%)	0 (0.0)	2 (0.4%)
Mean Age [years] ± *SD*	45.3 ± 14.3	44.4 ± 13.9	42.5 ± 14.8	45.1 ± 13.7
Min, Max	(18, 81)	(18, 77)	(22, 70)	(18, 81)
Median	46	43	44	45
Mean age at Diagnosis [years]± *SD*	39.3 ± 14.3	39.1 ± 12.6	38.0 ± 13.1	39.2 ± 14.0
Min, Max	(7, 74)	(10, 72)	(9, 69)	(7, 74)
Median	39	37	37	38
Regions, n (%)				
US	203 (57.2%)	53 (56.4%)	24 (50.0%)	280 (56.3%)
Non-US	152 (42.8%)	41 (43.6%)	24 (50.0%)	217 (43.7%)
Race, n (%)				
White	311 (87.6%)	83 (88.3%)	41 (85.4%)	435 (87.6%)
Black or African American	8 (2.3%)	3 (3.2%)	0 (0.0%)	11 (2.2%)
Asian	15 (4.2%)	2 (2.1%)	1 (2.1%)	18 (3.6%)
Native Hawaiian/ Pacific Islander	2 (0.6%)	2 (2.1%)	0 (0.0%)	4 (0.8%)
American Indian/Alaskan Native	4 (1.1%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Other	13 (3.6%)	4 (4.3%)	6 (12.5%)	23 (4.6%)
Prefer not to say	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Ethnicity, n (%)				
Hispanic or Latino	30 (8.5%)	4 (4.3%)	8 (16.7%)	42 (8.5%)
Not Hispanic or Latino	320 (90.1%)	89 (94.6%)	40 (83.3%)	449 (90.3%)
Prefer not to say	5 (1.4%)	1 (1.1%)	0 (0.0)	6 (1.2%)
Employment Status, n (%)				
Employed, Full-Time/Part-Time	**220 (62.0%)**[a]	**70 (74.5%)**	31 (64.6%)	321 (64.6%)
Homemaker	19 (5.4%)	3 (3.2%)	3 (6.3%)	25 (5.0%)
Student	26 (7.3%)	4 (4.2%)	3 (6.3%)	33 (6.6%)
Unemployed	13 (3.7%)	3 (3.2%)	2 (4.2%)	18 (3.6%)
Retired	41 (11.5%)	10 (10.6%)	4 (8.3%)	55 (11.1%)
Disabled	27 (7.6%)	2 (2.1%)	3 (6.3%)	32 (6.4%)
Other	9 (2.5%)	2 (2.1%)	2 (4.2%)	13 (2.6%)
Education Status, n (%)				
Elementary/Primary School	3 (0.8%)	1 (1.1%)	1 (2.1%)	5 (1.0%)
Secondary/ High school	35 (9.8%)	9 (9.6%)	7 (14.6%)	51 (10.3%)
Some College	79 (22.3%)	17 (18.1%)	12 (25.0%)	108 (21.8%)
University Degree	132 (37.2%)	27 (28.6%)	20 (41.6%)	179 (36.0%)
Postgraduate Degree	85 (23.9%)	29 (30.9%)	5 (10.4%)	119 (23.9%)
Technical or Vocational Degree	21 (5.9%)	11 (11.7%)	3 (6.3%)	35 (7.0%)
Location of Disease				
Knee	256 (72.2%)	57 (60.6%)	26 (54.2%)	339 (68.2%)
Hip	35 (9.8%)	15 (16.0%)	5 (10.4%)	55 (11.1%)
Ankle	35 (9.8%)	7 (7.5%)	5 (10.4%)	47 (9.5%)
Foot	6 (1.7%)	3 (3.2%)	0 (0.0%)	9 (1.8%)
Shoulder	6 (1.7%)	3 (3.2%)	1 (2.1%)	10 (2.0%)
Elbow	6 (1.7%)	4 (4.3%)	1 (2.1%)	11 (2.2%)

Wrist	2 (0.6%)	1 (1.1%)	3 (6.3%)	6 (1.2%)
Fingers/Toes	3 (0.8%)	2 (2.1%)	3 (6.3%)	8 (1.6%)
Other	6 (1.7%)	2 (2.1%)	4 (8.3%)	12 (2.4)

[a] denotes statistical significance between D-TGCT and L-TGCT determined by χ^2 test, $p < 0.05$

[b] "Other" included temporomandibular joint, cervical spine, thoracic spine, medial thigh, or multiple locations.

Diagnostic Journey

Approximately half of all patients reported that they were misdiagnosed prior to receiving their diagnosis of TGCT (248 of them). Misdiagnoses included Baker's cysts or unspecified cysts, osteoarthritis, rheumatoid arthritis, tophaceous gout, fibroma, labral tear, bursitis, meniscus or other ligament tear, sarcoma, scar tissue, or sprain. It is worth noting that misdiagnosis is complex, and in some cases, a patient may perceive providers ruling out other common diagnoses as misdiagnoses. For example, if a provider suspects a sprain and runs diagnostics to see if it is a sprain, a patient may see that as a misdiagnosis.

The main symptom which led to patients seeking diagnosis was pain or swelling. Nearly 60% of patients reported that the duration between when their symptoms started and diagnosis was more than a year and 32% had symptoms more than 2 years prior to diagnosis. Due to the fact that symptoms are not specific and experienced in more common diseases, and providers may be unfamiliar with the disease, which results in the significant delay in diagnosis and misdiagnosis seen in this population[11,23].

Orthopedic surgeons are surgeons that typically treat sports injuries and other anatomical abnormalities (e.g., clubbed feet). Orthopedic oncologists are surgeons that specialize in the surgical removal of tumors. Medical oncologists are specialists who do not perform surgeries, but prescribe medications. Healthcare providers (HCPs) responsible for diagnosis were largely orthopedic surgeons (61.3%) and orthopedic oncologists (23.7%). Over half of patients reported that they had consulted an orthopedic oncologist at some point in their journey compared to a quarter at diagnosis. Additionally, 28.0% of patients reported consulting a medical oncologist. The low proportion of patients that reported seeing a medical oncologist may reflect that orthopedic surgeons are unfamiliar with medication options and identifies a source of needed education.

Patients often manage their symptoms of TGCT by taking over-the-counter analgesics such as Tylenol/paracetamol (59.2%), non-steroidal anti-inflammatories such as naproxen/ibuprofen (71.2%), gabapentinoids such as gabapentin and pregabalin/lyrica (13.1%), narcotics (15.9%), corticosteroids (25.6%), joint aspiration/drainage (22.5%), or other (9.0%).

Table 2. Providers involved in diagnosis of TGCT, duration from symptom onset to diagnosis, main symptom that led to diagnosis, and misdiagnosis rate by TGCT subtype.

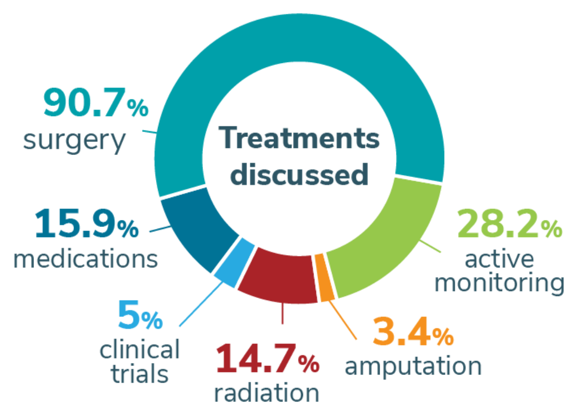
	Diffuse (n=355, 71.4%) (n, % column)	Localized (n=94, 18.9%) (n, % column)	Unknown (n=48, 9.7%) (n, % column)	Total (n=497) (n, % column)
Provider that Diagnosed Patient				

Orthopedic/Sports Medicine	222 (62.5%)	51 (54.3%)	31 (64.5%)	304 (61.2%)
Orthopedic Oncologist	83 (23.4%)	30 (31.9%)	5 (10.4%)	118 (23.8%)
Oncologist	8 (2.3%)	0 (0.0%)	2 (4.2%)	10 (2.0%)
Rheumatologist	10 (2.8%)	3 (3.2%)	4 (8.3%)	17 (3.4%)
PCP/GP	12 (3.4%)	3 (3.2%)	3 (6.3%)	18 (3.6%)
Other	20 (5.6%)	7 (7.4%)	3 (6.3%)	30 (6.0%)
Duration between Symptom Onset to Diagnosis				
< 1 Month	12 (3.4%)	10 (10.6%)	3 (6.3%)	25 (5.0%)
1-3 Months	25 (7.0%)	11 (11.7%)	3 (6.3%)	39 (7.9%)
4-6 Months	48 (13.5%)	9 (9.6%)	5 (10.4%)	62 (12.5%)
7-11 Months	47 (13.3%)	9 (9.6%)	3 (6.3%)	59 (11.9%)
12-24 Months	86 (24.2%)	18 (19.1%)	13 (27.0%)	117 (23.5%)
25-60 Months	59 (16.6%)	13 (13.8%)	10 (20.8%)	82 (16.5%)
More than 5 Years	56 (15.8%)	19 (20.2%)	4 (8.3%)	79 (15.9%)
I was diagnosed during surgery	17 (4.8%)	1 (1.1%)	6 (12.5%)	24 (4.8%)
Other	5 (1.4%)	4 (4.3%)	1 (2.1%)	10 (2.0%)
Main Symptom that Led to Diagnosis				
Pain	141 (39.7%)	48 (51.0%)	21 (43.7%)	210 (42.3%)
Swelling	**152 (42.8%)**[a]	**23 (24.5%)**	14 (29.2%)	189 (38.0%)
Stiffness	5 (1.4%)	1 (1.1%)	1 (2.1%)	7 (1.4%)
Limited ROM	29 (8.2%)	6 (6.4%)	7 (14.6%)	42 (8.5%)
Other	28 (7.9%)	16 (17.0%)	5 (10.4%)	49 (9.8%)
Misdiagnosis				
Yes	182 (51.3%)	41 (43.6%)	25 (52.1%)	248 (49.9%)
No	173 (48.7%)	53 (56.4%)	23 (47.9%)	249 (50.1%)

GP: general practitioner; PCP: primary care provider

[a] denotes statistical significance between D-TGCT and L-TGCT determined by χ^2 test, $p < 0.05$

Treatment Journey



Systemic treatments refer to medications that a patient takes either by mouth or as an injection and the medication enters blood circulation to get to its target location, such as TGCT in our case.

Surgical, systemic, and other treatments discussed by HCPs at initial diagnosis include tumor removal via surgery (90.7%), medications (15.9%), clinical trials (5.0%), radiation (14.7%), amputation (3.4%), and actively monitoring disease with scans (28.2%). The common discussion of surgeries is consistent with prior studies which demonstrate surgery as the main treatment, regardless of the surgical technique[11,21,25,26]. Medications were rarely discussed at the time of diagnosis, which may be attributed to orthopedic/sports medicine surgeons being primarily responsible for diagnosis. Patients who were diagnosed by orthopedic oncologists had discussions about available systemic therapies more frequently than patients that were diagnosed by orthopedic surgeons, highlighting potential differences in familiarity of different treatments (data not shown). Unexpectedly, radiation therapy was discussed in a similar proportion as medications despite the lack of efficacy supporting radiation for treating TGCT. There is a lack of effectiveness data for radiation, especially compared to medications. The use of radiation has been recommended against in the global consensus guideline, Stacchiotti et al, and highlights differences in TGCT management across different centers, need for referral, and specific education for providers[15].

Excluding pexidartinib (Turalio) which is approved only in the US, similar trends in the discussed treatments at initial diagnosis were seen regardless of geographical location, which means there is no difference between the way patients in the US and non-US are treated.

From the time of initial diagnosis to the first treatment, 55.1% of patients receive treatment within 3 months of diagnosis. Excluding those diagnosed during surgery, time to treatment from diagnosis was similar among patients with D- compared to L-TGCT. Similar trends were observed in US and non-US patients. This means that patients are treated extremely quickly once diagnosed and may not have the time to learn options for treatments or seeking other opinions. Additionally, actively monitoring the disease is an under-utilized option when a patient is managing symptoms.

Orthopedic surgeons were the most common HCP involved in treatment, followed by orthopedic oncologists. Twenty-eight percent of patients reported that they have consulted a medical oncologist. Despite the availability of medications in some geographical locations, medical oncologists were underutilized. With the approval and availability of more of these medications, the authors expect there will be an increase in the referral to medical oncologists and higher use of these medications. Patients should seek out multidisciplinary care to have all options available to them.

Across all patients, the most common treatment for TGCT was surgery (79.1%), matching that it was also the most commonly discussed treatment. Other common treatments were medications (19.1%), active surveillance (MRI at regular intervals to monitor progression of the disease, but no treatment) at some point in the patients' journey (40.4%), external beam radiation (4.6%) (using a machine outside of the body to deliver high-energy radiation beams at a tumor), and intra-articular radiation (3.2%) (injecting radioactive substance into the joint). There were no differences between treatments received by patients in the US compared to non-US patients.

Table 3. Treatments discussed at initial diagnosis and treatments received.

(Check all that apply)	Diffuse (n=355) (n, % column)	Localized (n=94) (n, % column)	Unknown (n=48) (n, % column)	Total (n=497) (n, % column)
Providers Involved in Care				
Orthopedic Surgeon/Sports Medicine	264 (74.4%)	75 (79.8%)	32 (66.7%)	371 (74.7%)
Orthopedic Oncologist	238 (67.0%)	53 (56.4%)	15 (31.3%)	306 (61.6%)
Medical Oncologist	122 (34.4%)	6 (6.4%)	11 (22.9%)	139 (28.0%)
Rheumatologist	38 (10.7%)	8 (8.5%)	6 (12.5%)	52 (10.5%)
Physical Therapist	139 (39.2%)	33 (35.1%)	10 (20.8%)	182 (36.6%)
PCP/GP	95 (26.8%)	30 (31.9%)	16 (33.3%)	141 (28.4%)

Radiology Oncologist	40 (11.3%)	7 (7.5%)	1 (2.1%)	48 (9.7%)
Other	17 (4.8%)	2 (2.1%)	4 (8.3%)	23 (4.6%)
Treatments Discussed at Initial Diagnosis				
Surgery	323 (91.0%)	92 (96.8%)	36 (75.0%)	451 (90.7%)
Pexidartinib/Turalio	**37 (10.4%)***	**4 (4.3%)**	2 (4.2%)	43 (8.7%)
Imatinib or Nilotinib	**29 (8.2%)***	**2 (2.1%)**	5 (10.4%)	36 (7.2%)
Clinical Trials	**23 (6.5%)***	**1 (1.0%)**	1 (2.1%)	25 (5.0%)
Radiation	52 (14.6%)	14 (14.9%)	7 (14.6%)	73 (14.7%)
Amputation	15 (4.2%)	2 (2.1%)	0 (0.0%)	17 (3.4%)
Active Surveillance[1]	99 (27.9%)	24 (25.5%)	17 (35.4%)	140 (28.2%)
Other	24 (6.8%)	0 (0.0%)	10 (20.8%)	34 (6.8%)
All Treatments Received				
Active Surveillance[1]	153 (43.1%)	30 (31.9%)	18 (37.5%)	201 (40.4%)
Arthroscopic Synovectomy	**167 (47.0%)**[a]	**32 (34.0%)**	18 (37.5%)	217 (43.7%)
Open Synovectomy	168 (47.3%)	42 (44.7%)	8 (16.7%)	218 (43.9%)
Combined Arthroscopic/Open Synovectomy	**68 (19.2%)**[a]	**9 (9.6%)**	4 (8.3%)	79 (15.9%)
Joint Replacement/Prosthesis	**37 (10.4%)**[a]	**3 (3.2%)**	5 (10.4%)	45 (9.1%)
External Beam Radiation	20 (5.6%)	2 (2.1%)	1 (2.1%)	23 (4.6%)
Intra-articular Radiation	14 (3.9%)	2 (2.1%)	0 (0.0%)	16 (3.2%)
Systemic Therapy	**86 (24.2%)**[a]	**3 (3.2%)**	6 (12.5%)	95 (19.1%)
Pexidartinib	51 (59.3%)	1 (33.3%)	4 (66.7%)	56 (59.0%)
Imatinib	32 (37.2%)	2 (66.7%)	3 (50.0%)	37 (39.0%)
Nilotinib	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Vimseltinib	18 (20.9%)	0 (0.0%)	0 (0.0%)	18 (19.0%)
AMB-05X	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Emactuzumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cabiralizumab	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pimicotinib	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other Investigational Products	3 (3.5%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
Ankle Fusion	2 (0.6%)	1 (1.1%)	0 (0.0%)	3 (0.6%)
Amputation	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Other	16 (4.5%)	14 (14.9%)	8 (16.7%)	38 (7.6%)

[1] Active surveillance was defined as a wait-and-see approach at any time in the patient journey

[a] denotes statistical significance between D-TGCT and L-TGCT determined by χ^2 test, $p < 0.05$

Surgical Approach and Outcomes

Majority of patients reported 1 or more surgeries to remove TGCT (79.1%) and 1 or more of the following treatments: arthroscopic surgery (43.7%), open surgery (43.9%), combined arthroscopic and open approach (15.9%), and joint replacement (9.0%) (Table 3). Patients with D-TGCT reported arthroscopic surgery, combined arthroscopic and open approach surgery, and joint replacement significantly more frequently than patients with L-TGCT. Differences in surgical approach by joint were observed. Patients had an average of 2.7 surgeries. Specifically, patients with D-TGCT had almost double the number of surgeries compared to patients with L-TGCT.

Recurrence cannot occur unless disease is attempted to be removed via surgery. However, patients are often unable to determine if they have had disease removed successfully, as the surgeon may or may not have shared that information with them. Due to the lack of standardized protocols for follow-up and various specialties involved in care, patients may not have any follow-up imaging until symptoms return, thus making it difficult to tell the difference between MRI with proven regrowth of tumors compared to the return of symptoms from tumors left over from the surgery (residual disease). Within this survey, recurrence was self-reported by patients and may not reflect patients who have had their disease entirely removed. 71.6% of patients with D-TGCT and prior surgery reported at least 1 recurrence and 33.8% of those with L-TGCT and prior surgery reported at least 1 local recurrence. Of those with a prior recurrence, 58.9% of patients reported a second recurrence. This means repeat surgeries are unlikely to be successful and disease may not be removed with repeated surgeries.

It is worth noting that while this data shows a 33.8% recurrence for L-TGCT, existing literature has this number closer to 10%. The potential reasons for the results in this paper may be due to patients seeking support having more severe disease, or that patients are miscategorized as L-TGCT when they have D-TGCT. This is supported by a healthcare team survey conducted by Tap et al that demonstrated that only 47% of specialized providers indicate high/very high confidence when distinguishing the TGCT subtypes, representing another potential source of misclassification and patients may not have been told the right subtype[27].

In a subgroup analysis of patients with joint replacements (45 patients), patients had a median age of 50 years (range of 19-78), they all had diffuse TGCT, were diagnosed at median age of 36 (16-72) years, and on average had 5.1 surgeries. Most patients with joint replacements had TGCT of the knee (31 patients). Sixty-seven percent of patients with joint replacement reported 1 or more recurrence and 55.6% reported subsequent recurrences. This means the recurrence rate for those with replacements is the same as the recurrence rate of those with other forms of surgery. Joint replacements treat bone damage and do not address TGCT; therefore, it is a misconception that joint replacements are curative.

Table 4. Patients' history of surgery and burden of disease by surgeries.

	Diffuse (n=355, 71.4%)	**Localized (n=94, 18.9%)**	**Unknown (n=48, 9.7%)**	**Total (n=497)**

Change in Occupation or Premature Retire due to TGCT, n (%)					
Yes		84 (23.7%)	16 (17.0%)	15 (31.3%)	115 (23.1%)
No		223 (62.8%)	70 (74.5%)	28 (58.3%)	321 (64.6%)
N/A		48 (13.5%)	8 (8.5%)	5 (10.4%)	61 (12.3%)
Mean # of surgeries ± SD		2.8 ± 2.7	1.8 ± 1.6	1.7 ± 1.1	2.7 ± 2.0
median		3	2	1.5	2
(min, max)		(0, 13)	(0, 11)	(0, 3)	(0, 13)
LRR after surgery, n (%)		**n=289**	**n=68**	**n=36**	**n= 393**
Yes		207 (71.6%)	23 (33.8%)	16 (44.4%)	246 (62.6%)
1 recurrence		84 (29.1%)	13 (19.1%)	4 (11.1%)	101 (25.7%)
≥ 2 recurrences		123 (42.6%)	10 (14.7%)	12 (33.3%)	145 (36.9%)
No		45 (15.6%)	33 (48.6%)	12 (33.3%)	90 (22.9%)
Unsure		37 (12.8%)	12 (17.6%)	8 (22.3%)	57 (14.5%)
LRR after joint replacement, n (%)		**n=37**	**n=3**	**n=5**	**n=45**
Yes		27 (73.0%)	0 (0.0%)	3 (60.0%)	30 (66.7%)
1 recurrence		5 (13.5%)	0 (0.0%)	0 (0.0%)	5 (11.1%)
≥ 2 recurrences		22 (59.5%)	0 (0.0%)	3 (60.0%)	25 (55.6%)
No		7 (18.9%)	2 (66.7%)	2 (40.0%)	11 (24.4%)
Unsure		3 (8.1%)	1 (33.3%)	0 (0.0%)	4 (8.9%)
	0 surgery (n=104)	**1 surgery (n=170)**	**2 surgeries (N=110)**	**> 2 surgeries (N=113)**	**Total (n=497)**
Change in Occupation or Premature Retire due to TGCT, n (%)					
Yes	13 (12.5%)	35 (20.6%)	23 (20.9%)	44 (38.9%)	115 (23.1%)
No	73 (70.2%)	119 (70.0%)	69 (62.7%)	61 (54.0%)	322 (64.8%)
N/A	18 (17.3%)	16 (9.4%)	18 (16.4%)	8 (7.1%)	60 (12.1%)

LRR: Local recurrence rate

Medication Therapies

Nineteen percent of patients reported using medications intended to treat TGCT such as imatinib (Glivec/Gleevec), pexidartinib (Turalio), vimseltinib (Romvimza), etc. Of the patients that reported medication use, 90.5% of patients have D-TGCT, 3.2% patients have L-TGCT, and 6.3% patients were unknown. Majority of patients on medications have been on one medication (71.6%) and 24.2% of patients have been on 2 medications to treat TGCT. Pexidartinib (Turalio) was the most common (59.0%) followed by imatinib (Glivec/Gleevec) (39.0%).

In the US subgroup analysis, 81.8% of patients on medications reported receiving pexidartinib (Turalio), 30.3% reported imatinib (Glivec/Gleevec), and 13.6% reported vimseltinib (Romvimza). In the non-US subgroup, 6.9% of patients on medications reported receiving pexidartinib (2 patients), 58.6% reported imatinib (Glivec) (17 patients), and 31.0% reported vimseltinib (9 patients). This reflects that pexidartinib (Turalio) is not available outside the US and the 2 patients who reported using it were doing so as a part of the clinical trials.

At the time of the survey, 64.2% of patients that reported using medications remained on them and of those that stopped using them, half withdrew due to side effects, 11.8% discontinued due to failure to control disease, 11.8% switched to another treatment such as surgery, 17.5% were taking a short-term break and intend to take the medications again, and 11.8% discontinued due to other reasons such as drug cost, insurance coverage, or drug interactions with other medications they were receiving.

While novel therapies are being investigated, it is of the utmost importance to disseminate evolving information to HCPs involved in diagnosing and treating TGCT. Leveraging relationships and collaborations with all stakeholders (e.g., patient advocacy organizations, industry) may improve awareness related to treatments and the understanding of the burden of disease.

Burden of Disease for Patients with TGCT

Pain was the most common reported symptom (92.0%) with no differences between patients with D- and L-TGCT. All patients indicated at least 1 TGCT-related symptoms (e.g., pain, swelling, stiffness, limited range of motion). 89.0% of patients with D-TGCT experienced limitations in range of motion significantly more than patients with L-TGCT (73.4%). Majority of patients (80.0%) reported that pain interfered with their day-to-day activities and their enjoyment of life, respectively. Patients reported that pain impacted their household chores (77.9%), family life (75.9%), ability to concentrate (71.3%), and social activities (77.9%). In the 7 days prior, patients reported some level of difficulty with chores such as vacuuming or yard work (73.9%), going for a walk of at least 15 minutes (63.3%), running errands and shopping (62.0%), and going up and down stairs at a normal pace (77.1%).

Overall, 23.1% of patients reported that they changed their occupation or retired prematurely due to TGCT. Patients who reported that they retired or changed occupations due to TGCT described pain as the main cause. Further, financial and emotional hardship due to TGCT impacted their self-identity and roles in their community. The more surgeries patients had, the more likely they were to change their occupation or prematurely retire, meaning that repeated surgery may contribute to a higher rate of disability. Thirty-nine percent of patients with more than 2 surgeries reported that they changed occupations or prematurely retired due to TGCT or its treatments compared to 12.5% of patients without prior surgery and 20.6% of patients with one prior surgery.

If TGCT is treated inadequately, the impact can be chronic, represented by high recurrence and multiple surgeries, affecting an otherwise healthy patient's quality of life, financial status, and ability to maintain work[24].

LIMITATIONS IN INTERPRETATION OF RESULTS

While designed as a long term patient registry to capture changes in the landscape of care and patient demographics, this single time point analysis of the baseline data may be influenced by patients' ability to recall information correctly and biased towards negative experiences (e.g., people with noteworthy negative experiences are more likely to report them, if you think of Yelp!). The survey was circulated among patient support groups which largely include patients currently impacted by disease and may represent patients with severe and recurrent cases. In addition, patients report their own medical history and thus, medical understanding and recall of it may influence patients' responses.

REFERENCES

1 Cupp JS, Miller MA, Montgomery KD *et al.* Translocation and Expression of CSF1 in Pigmented Villonodular Synovitis, Tenosynovial Giant Cell Tumor, Rheumatoid Arthritis and Other Reactive Synovitides. *American Journal of Surgical Pathology* 31(6), 970–976 (2007).

2 Brahmi M, Alberti L, Tirode F *et al.* Complete response to CSF1R inhibitor in a translocation variant of teno-synovial giant cell tumor without genomic alteration of the CSF1 gene. *Annals of Oncology* 29(6), 1488–1489 (2018).

3 Ho J, Peters T, Dickson BC *et al.* Detection of *CSF1* rearrangements deleting the 3' UTR in tenosynovial giant cell tumors. *Genes Chromosomes & Cancer* 59(2), 96–105 (2020).

4 Mastboom MJL, Verspoor FGM, Hanff DF *et al.* Severity classification of Tenosynovial Giant Cell Tumours on MR imaging. *Surgical Oncology* 27(3), 544–550 (2018).

5 Mastboom MJL, Hoek DM, Bovée JVMG, Van De Sande MAJ, Szuhai K. Does *CSF 1* overexpression or rearrangement influence biological behaviour in tenosynovial giant cell tumours of the knee? *Histopathology* 74(2), 332–340 (2019).

6 Ehrenstein V, Andersen SL, Qazi I *et al.* Tenosynovial Giant Cell Tumor: Incidence, Prevalence, Patient Characteristics, and Recurrence. A Registry-based Cohort Study in Denmark. *J Rheumatol* 44(10), 1476–1483 (2017).

7 Mastboom MJL, Verspoor FGM, Verschoor AJ *et al.* Higher incidence rates than previously known in tenosynovial giant cell tumors: A nationwide study in The Netherlands. *Acta Orthopaedica* 88(6), 688–694 (2017).

8 Colman MW, Ye J, Weiss KR, Goodman MA, McGough RL. Does Combined Open and Arthroscopic Synovectomy for Diffuse PVNS of the Knee Improve Recurrence Rates? *Clinical Orthopaedics & Related Research* 471(3), 883–890 (2013).

9 Patel KH, Gikas PD, Pollock RC *et al.* Pigmented villonodular synovitis of the knee: A retrospective analysis of 214 cases at a UK tertiary referral centre. *The Knee* 24(4), 808–815 (2017).

10 Gelhorn HL, Tong S, McQuarrie K *et al.* Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. *Clinical Therapeutics* 38(4), 778–793 (2016).

11 Van Der Heijden L, Gibbons CLMH, Hassan AB *et al.* A multidisciplinary approach to giant cell tumors of tendon sheath and synovium—A critical appraisal of literature and treatment proposal. *Journal of Surgical Oncology* 107(4), 433–445 (2013).

12 TOPP Study Group, Bernthal NM, Spierenburg G *et al.* The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective multicenter study. *Orphanet J Rare Dis* 16(1), 191 (2021).

13 Gronchi A, Miah AB, Dei Tos AP *et al.* Soft tissue and visceral sarcomas: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. *Annals of Oncology* 32(11), 1348–1365 (2021).

14 Ravi V, Wang W-L, Lewis VO. Treatment of tenosynovial giant cell tumor and pigmented villonodular synovitis. *Current Opinion in Oncology* 23(4), 361–366 (2011).

15 Stacchiotti S, Dürr HR, Schaefer I-M *et al.* Best clinical management of tenosynovial giant cell tumour (TGCT): A consensus paper from the community of experts. *Cancer Treatment Reviews* 112, 102491 (2023).

16 Sharma V, Cheng EY. Outcomes after Excision of Pigmented Villonodular Synovitis of the Knee. *Clinical Orthopaedics & Related Research* 467(11), 2852–2858 (2009).

17 Lamb YN. Pexidartinib: First Approval. *Drugs* 79(16), 1805–1812 (2019).

18 Verspoor FGM, Mastboom MJL, Hannink G *et al.* Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumor. *Sci Rep* 9(1), 14551 (2019).

19 Spierenburg G, Grimison P, Chevreau C *et al.* Long-term follow-up of nilotinib in patients with advanced tenosynovial giant cell tumours. *European Journal of Cancer* 173, 219–228 (2022).

20 Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented Villonodular Synovitis: A Retrospective Single-Center Study of 122 Cases and Review of the Literature. *Seminars in Arthritis and Rheumatism* 40(6), 539–546 (2011).

21 Palmerini E, Healey JH, Bernthal NM *et al.* Tenosynovial Giant Cell Tumor Observational Platform Project (TOPP) Registry: A 2-Year Analysis of Patient-Reported Outcomes and Treatment Strategies. *The Oncologist* 28(6), e425–e435 (2023).

22 Instrument: PROMIS Pain Interference - Short Form 6b V1.0.

23 Xie G, Jiang N, Liang C *et al.* Pigmented Villonodular Synovitis: A Retrospective Multicenter Study of 237 Cases. *PLoS ONE* 10(3), e0121451 (2015).

24 Burton TM, Ye X, Parker ED, Bancroft T, Healey J. Burden of Illness Associated with Tenosynovial Giant Cell Tumors. *Clinical Therapeutics* 40(4), 593-602.e1 (2018).

25 Palmerini E, Staals EL, Maki RG *et al.* Tenosynovial giant cell tumour/pigmented villonodular synovitis: Outcome of 294 patients before the era of kinase inhibitors. *European Journal of Cancer* 51(2), 210–217 (2015).

26 Mastboom MJL, Palmerini E, Verspoor FGM *et al.* Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. *The Lancet Oncology* 20(6), 877–886 (2019).

27 Tap WD, Pollack S, Carter JD, Heggen C, McKinnon KE. Quality care for patients with tenosynovial giant cell tumor: A multidisciplinary quality improvement initiative. *JCO* 40(28_suppl), 56–56 (2022).

28 Spierenburg G, Staals EL, Palmerini E *et al.* Active surveillance of diffuse-type tenosynovial giant cell tumors: A retrospective, multicenter cohort study. *European Journal of Surgical Oncology* 50(2), 107953 (2024).