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Localized and diffuse tenosynovial giant cell tumor: real-world results from a patient observational registry

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ABSTRACT

Background: Tenosynovial Giant Cell Tumor (TGCT) is a rare, locally aggressive neoplasm that adversely impact patients' physical function and quality of life (QoL). This cross-sectional analysis leverages real-world data from the TGCT Support Patient Registry to elucidate the patient experience with TGCT and the disease burden across healthcare systems.

Research design and methods: A total of 497 patients from 32 countries, 71.4% ($n = 355$) with diffuse-TGCT (D-TGCT), 18.9% ($n = 94$) with localized TGCT (L-TGCT), and 9.7% ($n = 28$) with unspecified TGCT were included in this cross-sectional analysis of the TGCT Support Registry.

Results: A majority of patients (61.2%, $n = 304$) were diagnosed by orthopedic/sports medicine surgeons, half ($n = 248$) were misdiagnosed prior to their TGCT diagnosis, and 32% ($n = 278$) of patients were diagnosed > 24 months following symptom onset. 79.1% ($n = 393$) of all patients had ≥ 1 resection and 63% of those patients reported ≥ 1 recurrence. Of those patients that had recurrence following resection, 59% had ≥ 2 recurrences. 23% of patients ($n = 115$) changed occupations or prematurely retired due to TGCT and the proportion of patients increased with > 2 surgeries.

Conclusion: Greater awareness of TGCT among HCPs is needed to facilitate diagnosis and referral to multidisciplinary teams is warranted to reduce recurrence rates, number of surgical interventions, and improve QoL.

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Sarcoma; quality of life; real-world evidence; solid tumors; diagnosis; patient registry

1. 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 mesenchymal neoplasm affecting the synovium, bursa, or tendon sheath. TGCT describes two radiographically distinct subtypes, localized and diffuse-type, which share a common pathogenesis and are typically characterized by a chromosomal aberration that disrupts the 3′ end of *colony stimulating factor 1(CSF1)* gene [1–3]. Despite their shared pathophysiology, the *localized* (also referred to as "nodular") subtype (L-TGCT) typically demonstrates an indolent disease course whereas the *diffuse* subtype (D-TGCT) describes an infiltrative and locally aggressive course [4,5]. "Localized" was chosen instead of "nodular" as the preferred term, as it reflects the term patients are most familiar with. L-TGCT comprises the majority of TGCT cases, is most often found in small joints, and is treated surgically with high success rates. In contrast, D-TGCT represents 10–20% of all TGCT cases, typically occurs in large joints, and is associated with a high local recurrence rate(LRR) [6–9].

Clinical disease presentation is complex and unpredictable, with symptoms ranging from asymptomatic to debilitating [4,5]. Most often, patients with TGCT experience pain, swelling, limited range of motion, and stiffness [10]. Due to the non-specific nature of symptoms and rarity of disease, patients may experience a delay in diagnosis [11,12]. For symptomatic patients, the frontline treatment is surgical resection with either marginal excision for L-TGCT or extensive synovectomy for D-TGCT [13,14]. Surgery is curative for most patients with L-TGCT. However, the difficulty of achieving microscopic complete resection with D-TGCT results in high risk of LRR [15,16]. The benefit of debulking surgery for symptom management is controversial [15,16].

Targeted therapies have provided a promising intervention and alternative to surgery for patients with symptomatic and recurrent D-TGCT. Due to the well-characterized aberration in CSF1 expression, CSF1 receptor (CSF1R) has become the key therapeutic target in TGCT [2,17]. Pexidartinib was approved for treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and are not amenable to improvements with surgery in the US in

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Article highlights

- The TGCT Support Registry provides longitudinal, multinational, observational data, created in September 2022, to provide real-world evidence depicting the patients-reported journey through diagnosis, treatment, and thereafter.
- Out of 497 patients with TGCT, a majority of patients (61.2%, $n = 304$) were diagnosed by orthopedic/sports medicine surgeons, half ($n = 248$) were misdiagnosed prior to TGCT diagnosis, and 32% ($n = 278$) of patients were diagnosed >24 months following symptom onset.
- Once patients receive a diagnosis of TGCT, there are many HCP specialties involved in care, notably orthopedic oncologists. Over half of patients reported that they had consulted an orthopedic oncologist at some point in their journey compared to a quarter at diagnosis.
- Out of 497 patients with TGCT, 79.1% ($n = 393$) of all patients had ≥ 1 resection and 63% of those patients reported ≥ 1 recurrence. Of those patients that had recurrence following resection, 59% had ≥ 2 recurrences.
- Twenty eight percent of patients reported consulting a medical oncologist during their journey. The relatively low utilization of systemic therapies may represent a lack of availability of systemic therapies globally, lack of referral from orthopedic surgeons to medical oncology, intolerable toxicity profiles, and a lack of provider awareness of clinical trials or prescription/off-label treatments.
- Pain was the most common reported symptom (92.0%, $n = 457$) and more than 80% of patients reported pain interfered with their day-to-day activities and enjoyment of life. Further functional limitations impacted patients ability to complete household chores, walk for at least 15 minutes, shop or run errands, and many other critical activities of daily life.
- 23% of patients ($n = 115$) changed occupations/prematurely retired due to TGCT and the proportion of patients increased with > 2 surgeries.
- Greater awareness of TGCT among HCPs is needed to facilitate diagnosis and referral to multidisciplinary teams is warranted to reduce recurrence rates, number of surgical interventions, and improve QoL.

2019, vimseltinib was approved for treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitations or severe morbidity in 2025, and many more CSF1R inhibitors are in clinical development [17–21]. Other systemic therapies such as nilotinib and imatinib are used off-label [22,23]. Despite these advancements, the lack of awareness of these therapies, lack of clarity surrounding clinical application, limited global access, and lack of standards for care has limited use.

To date, natural history studies that leverage real-world evidence in this population have been limited [12,24,25]. Most epidemiological studies are small retrospective studies that focus on outcomes and rarely describe the patient experience or disease burden . Questions remain about the impact of TGCT on quality of life (QoL), the typical diagnostic journey, providers involved in diagnosis and treatment in real-world settings, misdiagnosis rate, duration to diagnosis, duration from diagnosis to treatment, LRR, and challenges associated with care. While scarce in literature, the evidence of suboptimal treatment is exceedingly high in daily practice.

The TGCT Support Registry provides longitudinal, multinational, observational data, created in September 2022, to provide real-world evidence depicting the patient-reported journey through diagnosis, treatment, and thereafter. This study provides a cross-sectional analysis of patient experiences to describe the heterogeneity of healthcare providers (HCPs) involved in diagnosis and care, typical diagnostic journey, surgical outcomes, and burden of disease in a large population of varying geographical distribution, independent of treatment institution.

2. Methods

2.1. Study population

TGCT Support, a program of the Life Raft Group (LRG), is an international, nonprofit patient advocacy organization. The TGCT Support Registry started in 2022 and includes a patient questionnaire to capture baseline characteristics and changes in their experiences every 6 months. The registry aims to describe the patient experience associated with TGCT and treatment burden. At the time of data cutoffs, 625 patients with TGCT were recorded (Supplementary Figure S1). 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, eligible patients were ≥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 <18 years of age ($n = 110$), or if the participant did not provide written consent ($n = 18$).

Recurrence was defined as symptomatic relapse, residual disease, and/or radiographic disease progression following surgical resection.

2.2. Survey design

An electronic questionnaire was developed using RedCap, an electronic data capture tool. The registry questions were selected by a focus group of 8 patients with TGCT and revised based on feedback provided on a 5-point Likert-scale about agreement with the utility of each question and their comprehension. Cronbach's coefficient alpha (CA) was used to test internal consistency and questions were removed if their CA value was under 0.7. The final questionnaire consists of 168 fields with branching logic to record clinical information, and patient-centric QoL 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 duration of delays in diagnosis, treatments discussed at initial diagnosis, treatments received, LRR, and patient-reported outcomes (PROs) related to pain, physical function, and quality of life in structured and unstructured fields.

A bank of questions derived from PROs tools such as PROs Measurement Information System (PROMIS-PF), were included (PFA21, PFB1, PFA10, PFA12, and PF4) [10,26]. The included banked questions were selected as most relevant by patients (Supplementary Table S1). The PROs results are displayed as a descriptive summary including the percentage of respondents that chose each option on the ordinal 1–5 scale.

The target population was patients with TGCT globally, and these patients were derived from membership of patient

support groups on social media platforms and newsletter sent out by TGCT Support. To minimize the risk of sampling bias, there was no individual recruitment for participation in the registry. The current cross-sectional analysis includes the initial entry of a subject as determined by the timestamp of submission between 6 October 2022 to 6 December 2023.

2.3. Statistical analysis

All analyses were performed in R v4.2.0 and SAS v9.4 by two independent reviewers.

All descriptive statistics were stratified across TGCT subtypes: diffuse, localized, or unknown. Treatment-related responses were further stratified for patients in the US. All data included in the study were considered complete and percentages were calculated based on the population or subpopulation of available data. Categorical variables were summarized as number of observations and percentages (%) of the observations in each category. Continuous variables were summarized by mean, standard deviation, median, and range. Treatments were compared between patients with L-TGCT and D-TGCT and US patients and non-US patients by χ^2 test for categorical variables. A p-value less than 0.05 was the cutoff for statistical significance.

This analysis intends to describe the experience of patients with TGCT cross-sectionally and therefore, there was no formal hypothesis testing.

3. Results

3.1. Baseline characteristics

Description of 497 patient demographics from 32 countries and their disease characteristics are summarized in Table 1. A majority of patients in the study were female ($n = 370$, 74.4%), with a median age of 45 years (18–81) at enrollment and a median age at diagnosis of 38 years (7–74). Fifty-six percent of patients were in the US (56.3%, $n = 280$), 64.6% were employed full-time or part-time ($n = 321$), and 59.9% had a bachelor's degree or higher ($n = 298$). Of the 497 patients, 71.4% were diagnosed with D-TGCT ($n = 355$) and the knee joint was predominantly affected by both patients with D-TGCT ($n = 256/355$, 72.1%) and L-TGCT ($n = 57/94$, 60.6%). Other joints involved include hip (D-TGCT, $n = 35$, 9.9%; L-TGCT, $n = 15$, 16.0%), ankle (D-TGCT, $n = 35$, 9.9%; L-TGCT, $n = 7$, 7.5%), and other (D-TGCT, $n = 29$, 8.2%; L-TGCT, $n = 15$, 15.9%).

3.2. Diagnostic journey

Approximately 50.0% of patients reported that they were misdiagnosed prior to receiving their diagnosis of TGCT ($n = 248$). 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 (Table 2).

The main symptom, which led to patients seeking diagnosis, was pain ($n = 210$, 42.3%) or swelling ($n = 189$, 38.0%). Thirty-two percent of patients reported that the duration between symptom onset and diagnosis was >24 months ($n = 161$) (Table 2). HCPs responsible for diagnosis were largely orthopedic surgeons ($n = 304$, 61.2%) and orthopedic oncologists ($n = 118$, 23.7%).

To address symptoms of disease, patients reported taking over-the-counter analgesics (59.2%), non-steroidal anti-inflammatories (71.2%), gabapentinoids (13.1%), narcotics (15.9%), corticosteroids (25.6%), receiving joint aspiration (22.5%), or other (9.0%) (Supplementary Table 2).

3.3. Treatment journey

Surgical, systemic, and other treatments discussed by HCPs at initial diagnosis include tumor resection ($n = 451$, 90.7%), systemic therapies ($n = 79$, 15.9%), clinical trials ($n = 25$, 5.0%), either external beam radiation or intra-articular radiation ($n = 73$, 14.7%), amputation ($n = 17$, 3.4%), and active surveillance ($n = 140$, 28.2%) (Table 3). Excluding pexidartinib which is approved in the US, similar trends in the discussed treatments at initial diagnosis were seen in the subpopulation analysis of US patients compared to non-US patients ($p = 0.919$)(Supplementary Table 3).

From the time of initial diagnosis to the first treatment, 55.1% of patients ($n = 274$) 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 (>3 months: 55.2% vs. 45.7%, $p = 0.10$). Similar trends were observed in US and non-US patients (Supplementary Table 3).

Orthopedic surgeons were the most common HCP involved in treatment ($n = 371$), followed by orthopedic oncologists ($n = 306$) (Table 3). Twenty-eight percent of patients reported that they have consulted a medical oncologist ($n = 139$). Across all patients, the most common treatment for TGCT was surgery ($n = 393$, 79.1%). Other common treatments were systemic therapies ($n = 95$, 19.1%), active surveillance at some point in the patients' journey ($n = 201$, 40.4%), external beam radiation ($n = 23$, 4.6%), and intra-articular radiation ($n = 16$, 3.2%) (Table 3). The treatments received by US patients and non-US patients were not statistically different ($p = 0.14$) (Supplementary Table 3).

3.3.1. Surgical approach and outcomes

A majority of patients reported ≥ 1 surgical resection ($n = 393$, 79.1%) such as the following treatments: arthroscopic surgery ($n = 217$, 43.7%), open resection ($n = 218$, 43.9%), combined arthroscopic and open approach ($n = 79$, 15.9%), and joint replacement ($n = 45$, 9.0%)(Table 3). Patients with D-TGCT reported arthroscopic surgery (47.0% vs 34.0%, $p = 0.02$), combined arthroscopic and open approach surgery (19.2% vs 9.6%, $p = 0.03$), and joint replacement (10.4% vs 3.2%, $p = 0.03$) significantly more frequently than patients with L-TGCT. Surgical approaches differed by joint (Supplementary Table 4). Patients had an average of 2.7 ± 2.0 surgeries (0–13). Specifically, patients with D-TGCT had 2.8 ± 2.9 surgeries (0, 13) compared to 1.8 ± 1.6 surgeries for patients with L-TGCT (0–11) (Table 4).

Of those with D-TGCT and prior surgery ($n = 289$), 71.6% of patients ($n = 207$) reported ≥ 1 recurrence and of those with L-TGCT and prior surgery ($n = 68$), 33.8% of patients ($n = 23$)

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.
D-TGCT; diffuse tenosynovial giant cell tumor, L-TGCT; localized tenosynovial giant cell tumor.

reported ≥ 1 local recurrence. Of those with a prior recurrence ($n = 246$), 58.9% of patients ($n = 145$) reported ≥ 2 recurrence.

In a subgroup analysis of patients with joint replacements ($n = 45$), patients had a median age of 50 years (19–78), D-TGCT ($n = 37$), were diagnosed at median age of 36 years (16–72), and on average had 5.1 ± 3.8 surgeries (1–11). Most patients had TGCT of the knee ($n = 31$)(Supplementary Table 4). Sixty-seven percent of patients with joint replacement ($n = 30$) reported ≥ 1 recurrence and 55.6% ($n = 25$) reported ≥ 2 recurrences (Table 4).

3.3.2. Systemic therapies

Nineteen percent of patients reported using systemic therapies (i.e., tyrosine kinase inhibitors) intended to treat TGCT ($n = 95$) (Table 3). Of the 95 patients that reported treatment with systemic therapies, 86 patients have D-TGCT (90.5%), 3 patients have L-TGCT (3.2%), and 6 patients have TGCT of an unknown subtype (6.3%). Most patients on systemic therapies ($n = 95$) have received one therapy (71.6%, $n = 68$) and 24.2% of patients have received 2 systemic therapies ($n = 23$). Pexidartinib was the most common (59.0%) followed by imatinib (39.0%).

In the US subgroup analysis of patients on systemic therapies ($n = 66$), 81.8% of patients reported receiving pexidartinib ($n = 54$), 30.3% reported receiving imatinib ($n = 20$), and 13.6% reported receiving vimseltinib ($n = 9$) (Supplementary Table 5). In the non-US subgroup analysis of patients on systemic

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 (23.7%)
Medical 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; ROM, range of motion; TGCT, tenosynovial giant cell tumor.
[a]denotes statistical significance between D-TGCT and L-TGCT determined by χ^2 test, $p < 0.05$ (D-TGCT; diffuse tenosynovial giant cell tumor, L-TGCT; localized tenosynovial giant cell tumor).

therapies ($n = 29$), 6.9% of patientsreported receiving pexidartinib ($n = 2$), 58.6% reported receiving imatinib ($n = 17$), and 31.0% reported receiving vimseltinib ($n = 9$).

At the time of the survey, 64.2% of patients that reported administration of systemic therapy remained on systemic therapies ($n = 61$) and of those that discontinued ($n = 34$), 47.1% withdrew due to side effects ($n = 16$), 11.8% discontinued due to treatment failure ($n = 4$), 11.8% switched to another treatment such as surgery ($n = 4$), 17.5% were on a drug holiday ($n = 6$), and 11.8% discontinued due to other reasons such as drug cost, insurance coverage, or drug-drug interactions ($n = 4$) (Supplementary Table 6).

3.4. Burden of disease for patients with TGCT

Pain was the most common reported symptom (92.0%, $n = 457$) with no differences between patients with D-TGCT and L-TGCT (93.2% vs 90.4%)(Supplementary Table 7). All patients indicated ≥ 1 TGCT-related symptoms (e.g., pain, swelling, stiffness, limited range of motion). Patients reported that TGCT limited their range of motion (85.1%, $n = 423$) and patients with D-TGCT experienced limitations in range of motion more frequently than patients with L-TGCT (89.0% vs 73.4%, $p < 0.001$). Most patients (83.1%, $n = 413$; 80.9%, $n = 402$) reported that in the 7-days prior to their entry, pain interfered with their day-to-day activities and their enjoyment of life, respectively (Supplementary Table 7). Patients reported that pain impacted their household chores (77.9%, $n = 387$), family life (75.9%, $n = 377$), ability to concentrate (71.3%, $n = 355$), and social activities (77.9%, $n = 387$). In the 7-days prior, patients reported any level of difficulty with chores such as vacuuming or yard work (73.9%, $n = 368$), going for a walk of at least 15 minutes (63.3%, $n = 315$), running errands and shopping (62.0%, $n = 309$), and going up and down stairs at a normal pace (77.1%, $n = 384$).

Overall, 23.1% of patients ($n = 115$) 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 and pain leading to functional limitations as the main cause. Patients reported the inability to participate in their occupation due to pain itself (e.g., pain impacting concentration), receiving pain management (e.g., narcotic or gabapentin use), or pain leading to functional limitations (e.g., a teacher who is unable to stand for lectures or a mechanic who cannot bend down to work under vehicles). Further, financial, and emotional hardship due to TGCT impacted their self-identity and roles in their community. Patients with increasing number of surgeries changed their occupation or prematurely retired in higher proportions. Thirty-nine percent of patients with > 2 surgeries ($n = 113$) reported that they changed occupations or prematurely retired due to TGCT or sequelae compared to 12.5% of patients without any prior surgery and 20.6% of patients with one prior surgery (Table 4).

4. Discussion

The TGCT Support Registry represents the largest disease registry for TGCT, and this analysis represents a cross-section

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

	Diffuse ($n = 355$) (n, % column)	Localized ($n = 94$) (n, % column)	Unknown ($n = 48$) (n, % column)	Total ($n = 497$) (n, % column)
Providers Involved in Care (Check all that apply)				
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 (Check all that apply)				
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 (Check all that apply)				
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%)

GP, general practitioner; PCP, primary care provider.
[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, $p < 0.05$ (D-TGCT; diffuse tenosynovial giant cell tumor, L-TGCT; localized tenosynovial giant cell tumor).

of the typical journey experienced by patients with TGCT from symptom onset to diagnosis, treatment, and thereafter (Figure 1). Overall, these data highlight the typical patient journey in the US and globally in a comprehensive and meaningful manner.

The present study confirms that patients with TGCT are young, well-educated, and many work either full-time or part-time. While there are reports that demonstrate a female predominance, the degree of bias toward female and well-educated patients may be an artifact of those who seek out social support, are involved with TGCT Support, and knew about this project and agreed to participate [7].

A majority of patients had symptom onset ≥1 year prior to their initial diagnosis and strikingly, half of patients reported a misdiagnosis prior to receiving their TGCT diagnosis. Misdiagnosis is complex; in some cases, a patient may perceive differential diagnoses as misdiagnoses. However, due to the nonspecific nature of the symptoms, TGCT may mimic other more prevalent conditions and providers may be unfamiliar with the disease, contributing to the significant delay in diagnosis and misdiagnosis rate [11,27]. General orthopedic/sports medicine surgeons were the most common HCP responsible for diagnosis of TGCT. If TGCT is treated inadequately, the impact can be chronic represented by high LRR and multiple surgical resections, affecting an otherwise healthy patient's QoL, financial status, and ability to maintain work [28]. Overall, these results demonstrate a high misdiagnosis rate, general orthopedists and sports medicine surgeons as the typical diagnostic providers, and the lack of familiarity with TGCT. Educating providers to distinguish TGCT from other prevalent diseases serves as a potential educational focus to shorten the diagnostic timeline and facilitate timely referral to multidisciplinary teams. Improving the timeliness of diagnosis would reduce inappropriate treatments (e.g., cortisone injections) and the chances patients experience disease progression, potentially

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%)

Change in Occupation or Premature Retire due to TGCT, n (%)	0 surgery ($n = 104$)	1 surgery ($n = 170$)	2 surgeries ($N = 110$)	>2 surgeries ($N = 113$)	Total ($n = 497$)
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.

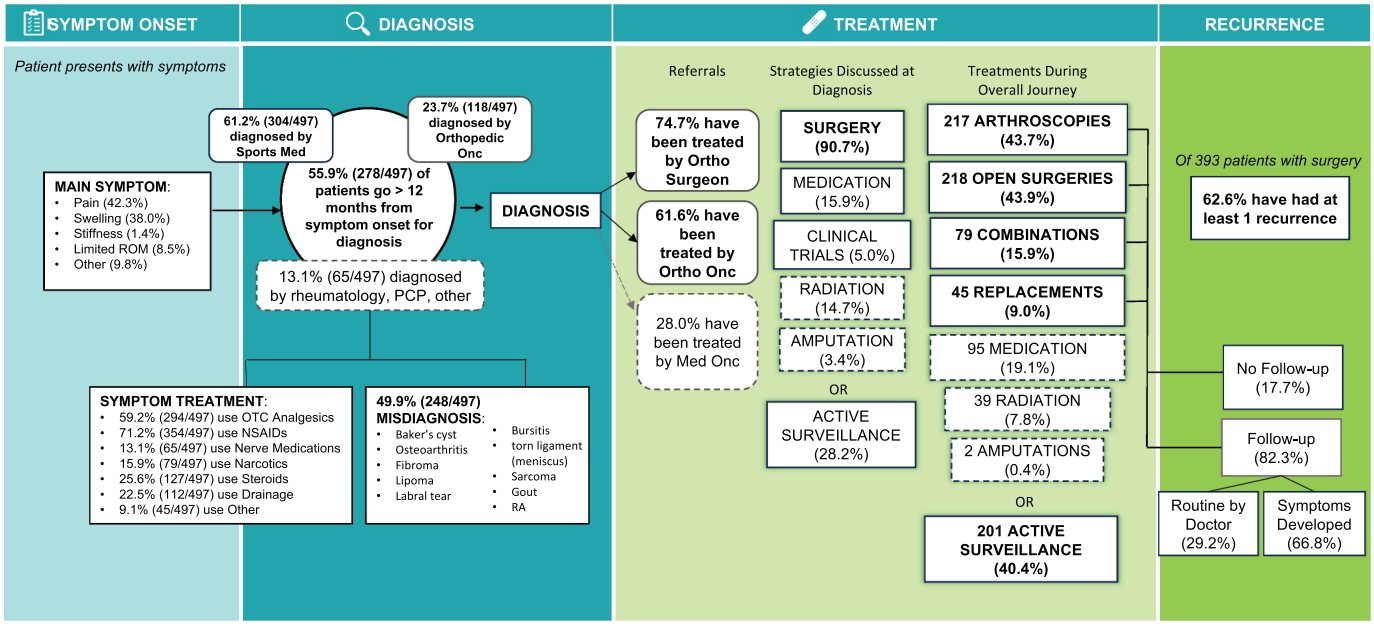

Figure 1. A summary schematic of the patient-reported journey of TGCT from symptom onset to treatment and thereafter.
TGCT; tenosynovial giant cell tumor.

complicating future surgical resection and worsening symptoms. Furthermore, earlier diagnosis may reduce the financial burdens associated with TGCT [29], as highlighted by this study where 23% of patients have changed their occupation or prematurely retired due to TGCT or sequelae.

All patients observed ≥ 1 of the associated symptoms such as pain, swelling, limitations in range of motion, and stiffness. While narcotic use was reported by a minority of patients (16%, $n = 79$), pain represents a major challenge experienced by almost all patients in this study. Currently, there is no TGCT-specific guideline for the treatment of pain and management of TGCT-related pain is managed as nonspecific chronic pain [15]. Further evaluation of the role of palliative care in the management of TGCT-associated symptoms is necessary to understand whether symptoms are being well-managed and whether a guideline could be created unique to TGCT.

Once patients receive a diagnosis of TGCT, there are many HCP specialties involved in care, notably orthopedic oncologists. Over half of patients reported consulting an orthopedic oncologist at some point in their journey compared to a quarter who

had done so at the time of diagnosis. Surgical resection represents the predominant treatment despite high LRR for patients with D-TGCT following repeat resections. Treatments discussed at initial diagnosis were largely surgical approaches either performed arthroscopically, open, or a combined approach. This is consistent with prior studies which demonstrate surgery as the mainstay treatment, regardless of the surgical technique [11,25,30,31]. Whether US or non-US patients, treatments discussed at initial diagnosis did not differ despite the differences in globally available therapies.

Systemic therapies were rarely discussed at the time of diagnosis, which may be attributed to general 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 those diagnosed by orthopedic surgeons, highlighting potential differences in familiarity of different treatments and relevance of the involvement of oncology specialists (data not shown). These results were regardless of geographical location.

Twenty-eight percent of patients reported consulting a medical oncologist during their journey. The relatively low utilization of systemic therapies may represent a lack of availability of systemic therapies globally, lack of referral from orthopedic surgeons to medical oncology, intolerable toxicity profiles, and a lack of provider awareness of clinical trials or prescription/off-label treatments. Currently, there are several agents under investigation (e.g., pimicotinib, emactuzumab) and two approved systemic therapy in the United States [18–20,32,33]. One of the approved systemic therapies, pexidartinib, has a boxed warning advising providers and patients about the risk of serious and potentially fatal liver injury and is available in the US through a Risk Evaluation and Mitigation Strategy program to reduce the frequency and severity of hepatotoxic events [17]. This program may reduce the utility of this systemic therapy specifically due to provider burden and toxicity concerns. In Europe and other countries represented by the patients in this study, there are no approved therapies and the availability or accessibility of imatinib (an off-label treatment) is limited by the patients' geographical location and healthcare system. Pexidartinib was not approved by the European Medical Association due to the risk of hepatotoxicity and concerns for the toxicity profile. Provided by our analysis, treatment discontinuation was often due to adverse events highlights the need to refine treatment strategies. As new therapies enter the market alongside educational efforts to raise awareness and the development of systemic therapies with improved toxicity profiles, we expect an increase in the referral to medical oncologists and use of these systemic therapies.

Radiation therapy was discussed in the same proportion as systemic therapies at initial diagnosis despite the lack of consensus on the efficacy of radiation for treating TGCT and other risks associated with radiotherapy [34]. This contrasts the recommendation from Stacchiotti et al and highlights heterogeneity in TGCT management across different centers, emphasizing the need for referral and specialized education for HCP networks [15]. The absence of long-term safety assessment and supportive efficacy data for the clinical application of radiation therapy along with the bolstered efficacy assessment of many CSF1R inhibitors and greater availability of these therapies should lead to a reduction in use of radiotherapy.

While designed as a longitudinal patient registry to capture changes in the landscape of care and patient demographics, this cross-sectional analysis of the baseline data may be influenced by selection bias. 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. Therefore, these results could disproportionately reflect a population of patients more severely impacted by TGCT.

Another source of bias may be due to the patients reporting their own medical history and thus, medical literacy and recall bias may influence patients' responses. For instance, patients self-designated their TGCT subtype which may be a source of inflated LRR in patients with L-TGCT. However, the inflated LRR may be a result of healthcare team misclassification impacting self-reporting. A healthcare team survey conducted by Tap et al demonstrated that only 47% of specialized HCPs indicate high/very high confidence when distinguishing the TGCT subtypes [35]. It is well understood that the subtype of TGCT plays a role in prognosis and patient outcomes; however, classifying TGCT subtypes may require multidisciplinary team assessment to improve the confidence.

Our study also illustrates that 71.6% of patients with D-TGCT with a prior resection and 33.8% of patients with L-TGCT with a prior resection had ≥ 1 recurrence. Due to the lack of standardized follow-up protocols and the involvement of various specialtiesin care, patients may not have any follow-up imaging until symptoms return, making it difficult to distinguish radiographic recurrence or symptomatic relapse from residual disease. Further research is warranted to define the term within literature and provide standardized guidelines for follow-up to better assess the true recurrence rate of TGCT.

Patients with TGCT often experience significant delay in diagnosis, possibly due to disease unfamiliarity or misdiagnosis, and patients may be over-treated with multiple surgeries. Additionally, regardless of geography, patients have a considerable delay in diagnosis but are often treated quickly upon diagnosis regardless of literature suggesting the value of conservative approaches such as active surveillance [36].

More than half of patients report that pain or limited range of motion impact their daily life, highlighting a significant unmet need. Similarly, nearly a quarter of the patients with TGCT reported changing occupations or prematurely retiring due to TGCT, and the proportion of patients is higher among those with multiple surgeries. Further research is warranted to understand how these work-related costs and all-healthcare costs may impact patients with TGCT and how the impact on employment may influence their overall financial futures.

Although there are no current country- or region-specific guidelines for TGCT, the consensus article by Stacchiotti and colleagues emphasizes the importance of managing TGCT within specialized, multidisciplinary sarcoma centers to ensure optimal patient outcomes [15]. Stacchiotti and colleagues advocate for a treatment paradigm that prioritizes shared decision-making between patients and multidisciplinary tumor boards, recognizing the nuanced balance between the benign nature of TGCT and its potential to severely impact QoL [15]. The authors suggest that active surveillance may be an appropriate strategy, particularly for asymptomatic patients or those with manageable

symptoms, as it helps weigh the risks of treatment against potential benefits. This is especially relevant, considering that TGCT often has an indolent disease course and the potential morbidity and adverse effects associated with surgical or systemic interventions. Surgery is the preferred approach for patients who are symptomatic with resectable TGCT and low risk of morbidity; patients with symptomatic TGCT may be candidates for systemic treatment if surgery would be associated with significant morbidity and/or high LRR [15]. Active surveillance is preferred for patients with asymptomatic TGCT. Despite these recommendations, our analysis reveals that most patients are not initially diagnosed at specialized centers, and active surveillance is seldom discussed as a viable option regardless of symptom severity. Instead, surgical resection remains the predominant treatment approach, even in cases where it might lead to significant morbidity. Systemic therapies, although proposed as alternatives when surgery poses excessive risks, remain underutilized for reasons forementioned. Consequently, symptomatic relapse and LRR are common, with many patients undergoing repeated surgeries while experiencing persistent symptoms. By promoting the dissemination of the treatment algorithm proposed by Stacchiotti et al., which highlights multidisciplinary collaboration and personalized care plans, HCPs can improve the diagnosis, management, and ongoing monitoring of TGCT [15]. This approach not only aligns treatment with patient-specific needs but also addresses the challenges posed by the recurrent nature of TGCT and its impact on QoL.

In conclusion, TGCT Support, a nonprofit patient advocacy program, created resources to disseminate information to the community of patients with TGCT and built a registry and network available to all patients with TGCT. While novel therapies are being investigated, it is of the utmost importance to disseminate evolving information to HCPs involved in diagnosing and managing TGCT. Leveraging relationships and collaborations with all stakeholders (e.g., patient advocacy organizations, industry, academia) may promote awareness related to treatments and the understanding of the burden of disease. Educational efforts should target providers most commonly visited by younger patients with recurrent or idiopathic joint pain and swelling, in order to reduce delays in diagnosis and improve referrals to multidisciplinary teams when feasible.

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Author contributions

Sydney Stern was responsible for the conception and design of the study. Sydney Stern and Patrick McKenzie performed the statistical analysis. Sydney Stern, Shannon O'Neill, and Patrick McKenzie drafted the manuscript, after which Nicholas Bernthal, R Lorr Randall, Emanuela Palmerini, William Tap, Thomas Scharschmidt, Sara Rothschild revised the manuscript with important intellectual content.

All authors substantially contributed to the work reported.

Disclosure statement

Sydney Stern, Patrick McKenzie, Shannon O'Neill, and Sara Rothschild have no conflict of interest to declare.

Nicholas Bernthal has served as a consultant for Deciphera Pharmaceuticals and Daiichi Sankyo.

William Tap has served as a consultant for Daiichi Sankyo, Deciphera Pharmaceuticals, Abbisko, Cogent, Bayer Pharmaceuticals, Amgen, AmMax Bio, Boehringer Ingelheim, BioAlta, PharmaEssentia, Avacta, Ipsen, Sonata, Aadl, IMGT, Ratio, and C4 Therapeutics.

R Lorr Randall has served as a consultant for Zimmer, SpringWorks, OncoLive, and Deciphera Pharmaceuticals.

Emanuela Palmerini has served on advisory boards for Daiichi Sankyo, Deciphera Pharmaceuticals, Eusa Pharma, and SynOx Therapeutics.

Thomas Scharschmidt has served on advisory boards for Daiichi Sankyo, Deciphera Pharmaceuticals.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical declaration

This analysis was approved by an institutional review board, Advarra (Columbia, Maryland) and the approved protocol reference number is Pro00077310. Written informed consent was obtained from each patient who participated in the registry.

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•• **Most patients with TGCT, as shown in our research, are treated very quickly following diagnosis. Spierenburg et al de monstrates that patients with manageable symptoms are able to have active surveillance instead of active treatment.**