

PATIENT-FRIENDLY VERSION OF

Pediatric Patients with Tenosynovial Giant Cell Tumor: Real-World Evidence from an Observational Registry

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TGCT SUPPORT IS A PROGRAM OF  The Life Raft
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SUMMARY OF PAPER

Background:

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive tumor originating in the joint lining, bursa (shock absorbers), and tendon sheath (tissue that protects tendons). TGCT typically affects individuals between 20 and 50 years of age and pediatric cases are considered ultra-rare. Research and clinical trials thus far have been focused on the adult TGCT population. However, data is needed to understand the differences between adult and pediatric TGCT and understand the impact of TGCT on pediatric patients' quality of life.

Patients and Methods:

A total of 122 pediatric patients were included from a 1,278-patient registry from TGCT Support. Nearly 10% of all patients were pediatric.

- 73.0% with diffuse TGCT (89 patients)
- 16.4% with localized TGCT (20 patients)
- and 10.6% with unspecified TGCT (13 patients).

Of all pediatric patients with TGCT, 14.5 years of age at diagnosis was the middle value for age (median).

Conclusions:

Pediatric patients had a significant disease burden, as compared to adults, which severely affected their quality of life. The reliance on surgical treatment and underuse of multidisciplinary care emphasizes the unmet need for provider education and treatment advancements tailored to this population.

Results:

- More than half of pediatric patients were initially misdiagnosed (62.3%) and pediatric patients were more likely to be misdiagnosed than adults (49.9%).
- 64.8% of pediatric patients were diagnosed by orthopedic surgeons.
- and 52.5% were diagnosed more than one year after symptom onset.
- Pediatric patients with diffuse TGCT (abbreviated as D-TGCT) underwent an average of 3.4 surgeries, compared to 1.8 surgeries for those with localized/nodular TGCT (abbreviated as L-TGCT).
- 66.3% of pediatric patients with D-TGCT had one or more recurrence(s) compared to 15.0% of L-TGCT pediatric patients. Recurrence rates among pediatric patients were similar to published data on recurrences in adults.
- Pediatric and adult patients went to medical oncologists for care at similar rates and medications for TGCT were prescribed similarly but infrequently overall (21 patients, 17.2% of all pediatric patients).

ABBREVIATIONS

CSF1, colony stimulating factor 1, a protein responsible for recruiting cells to become part of the TGCT;

D-TGCT, diffuse tenosynovial giant cell tumor;

L-TGCT, localized tenosynovial giant cell tumor;

PVNS, pigmented villonodular synovitis;

TGCT, tenosynovial giant cell tumor;

INTRODUCTION

Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive tumor affecting the synovium (joint tissue), bursa (fat pads/shock absorbers around the joint), or tendon sheath (tissue that lines tendons) of a single joint[1]. Historically, TGCT has been called pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath. However, these names are outdated now. In 2013, the World Health Organization consolidated the various existing naming to TGCT with two subtypes: diffuse and localized[2]. This change occurred largely because the other names were outdated, incorrectly described what we now know is a tumor process and led providers to treat a “synovitis” which means inflammation instead of a tumor.

- Diffuse TGCT describes an aggressive and, often, interwoven in the joint tissue and may extend beyond the inside of the joint into other structures (e.g., knee joint extending to calf)
- while localized TGCT describes a well-defined, marble-like mass that has no expansion into healthy tissues.

TGCT may occur in any single joint, but localized TGCT commonly affects the fingers and toes while diffuse TGCT instead tends to affect larger joints such as the knee, hip, and ankle[2, 3].

The various different naming that describes the same condition led to confusion among patients and providers and fragments research. Importantly, TGCT should be the only name used and should be recommended to all care teams going forward.

TGCT mostly affects adult patients between 20 and 50 years of age, with people commonly in their 40s[4]. Although TGCT predominantly affects adults, TGCT has also been reported in patients as young as 8-months-old[5]. TGCT in pediatrics is exceptionally rare with only:

- 2.86 cases per million for localized TGCT
- 1.30 cases per million for diffuse TGCT[6].

Adult patients with TGCT experience a wide range of symptoms, from none at all to extremely debilitating, often facing a significant disease burden. Quality of life is impacted not only by the disease itself but also by repeat surgeries and treatment-related complications[4, 7]. Few studies thus far have described pediatric TGCT which is believed to mimic the adult form and none have captured the patient experience[6, 8–12].

TGCT in adults and pediatrics likely has the same genetic abnormality which causes increased production of a protein, colony stimulating factor 1 (CSF1), responsible for the growth of this disease[13–15].

Surgery is the most common treatment for symptomatic patients with TGCT and medicines that target the abnormality in the TGCT have also been approved in the United States and European Union for symptomatic adults with TGCT[16, 17]. However, medicines, thus far, have been focused on the adult patient population, leaving a critical unmet need for treatment for pediatric TGCT populations who suffer similarly.

Real-world data are needed to understand the impact of TGCT on pediatric patients' quality of life and any differences between pediatric and adult patients with TGCT. We compared the impact of TGCT between these two groups using the world's largest global patient registry from TGCT Support. Created in September 2022, the TGCT Support Registry is a long-term, multinational observational study that captures information about patient or caregiver-reported experience from diagnosis through treatment and beyond[4]. This current registry represents the largest and most comprehensive dataset of pediatric TGCT to date, and the first to capture disease characteristics, treatment approaches, and outcomes from the patients' perspective.

METHODS

Survey Population and Survey Design

TGCT Support, a program of the Life Raft Group, is an international, non-profit patient advocacy organization. The TGCT Support Registry includes a questionnaire to capture baseline characteristics and changes made in TGCT patients' experiences every 6 months. The survey allows patients (when appropriate), caregiver, or legally authorized representatives to fill out the survey. The registry aims to describe the patient experience associated with the disease and treatment burden. At the time of this analysis, 122 pediatric patients with TGCT under 18 years of age were included. 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 (when appropriate), caregiver or legally authorized representative(s) who participated in the registry. For the analyses here, eligible patients were under 18 years of age at the time of last response with a diagnosis of TGCT.

The current analysis includes the initial entry between October 06, 2022, to November 26, 2024. TGCT subtype was self-reported as diffuse, localized, or unknown.

Pediatric patients were compared to a cohort of adult patients derived from previously published data from TGCT Support[4].

To join the registry and share your experience, go to TGCTSupport.org/registry

RESULTS

Baseline characteristics

Demographics are summarized for 122 pediatric patients with TGCT (Table 1). Pediatric patients were mostly female (67.2%), where 14.5 years old was the middle age value at the time of analysis. However, pediatric patients were diagnosed anywhere between the ages of 3 to 17 in our registry.

At enrollment of the study, patients were often 2 years into their journey and 16 years old was the middle value with a range of 4 to under 18 years old.

- 90% of pediatric patients were considered adolescents at diagnosis, defined as older than 11 years of age[18].
- Nearly half of pediatric patients resided outside the United States (U.S.) and the most common country outside the U.S. includes Canada, United Kingdom, Italy, Germany, and Australia.

Of the 122 pediatric patients, the majority were diagnosed with diffuse TGCT (73.0%) and the knee was the most common location regardless of TGCT subtype (83.6%). Other locations of TGCT include the hip (10.7%), the ankle (4.1%), and wrist or shoulder(1.6%).

The TGCT Support Registry excels at capturing the journey of patients with diffuse TGCT due to the creation of targeted resources; however, localized TGCT is more common in the real-world.

Diagnostic journey

Of the 122 pediatric patients, 62.3% had been misdiagnosed prior to receiving their TGCT diagnosis (Table 2).

Table 1. Pediatric patient characteristics

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Female, n (%)	59 (66.3)	14 (70.0)	9 (69.2)	82 (67.2)
Median age at Diagnosis, years (range)	14 (3 - 17)	15 (4 - 17)	14.5 (7 - 15)	14.5 (3 - 17)
Median age at enrollment, years (range)	16 (4-18)	17 (6-18)	15 (10-18)	16 (4-18)
Located in the US, n (%)	47 (52.8)	11 (55.0)	4 (30.8)	62 (50.8)
Age Group, n (%)				
Children (2-11 years)	8 (9.0)	3 (15.0)	1 (7.7)	12 (9.8)
Adolescents (12-18)	81 (91.0)	17 (85.0)	12 (92.3)	110 (90.2)
Race, n (%)				
White	79 (88.8)	19 (95.0)	9 (69.2)	101 (87.7)
African American	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)
Asian	6 (6.7)	0 (0.0)	1 (7.7)	7 (5.7)
Prefer not to say	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)
Other	2 (2.3)	1 (5.0)	3 (23.1)	6 (4.9)
Hispanic, n (%)	10 (11.2)	3 (15.0)	2 (15.4)	15 (12.3)
Location of disease, n (%)				
Knee	76 (85.4)	16 (80.0)	10 (76.9)	102 (83.6)
Hip	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)
Ankle	5 (5.6)	0 (0.0)	0 (0.0)	5 (4.1)
Other	0 (0.0)	0 (0.0)	2 (15.4)	2 (1.6)

Table 2. Diagnostic Journey

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Misdiagnosis	56 (62.9)	10 (50.0)	10 (76.9)	76 (62.3)
Main Symptom that Led to Diagnosis, n (%)				
Pain	37 (42.1)	12 (60.0)	6 (46.2)	55 (45.5)
Swelling	44 (49.4)	5 (25.0)	5 (38.5)	54 (44.3)
Stiffness	2 (2.3)	1 (5.0)	0 (0.0)	3 (2.5)
Limitations in Range of Motion	4 (4.6)	0 (0.0)	2 (15.4)	6 (5.0)
Other	2 (2.3)	2 (10.0)	0 (0.0)	4 (3.3)
Pediatric TGCT-Diagnosing HCP, n (%)				
Orthopedic/sports medicine	62 (69.7)	12 (60.0)	5 (38.5)	79 (64.8)
Orthopedic oncologist	19 (21.4)	7 (35.0)	0 (0.0)	26 (21.3)
Medical oncologist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatologist	4 (4.5)	1 (5.0)	4 (30.8)	9 (7.4)
General Practitioner/Pediatrician	4 (4.5)	0 (0.0)	4 (30.8)	8 (6.6)
Time from Symptom Onset to Diagnosis, n (%)				
<12 months	42 (47.1)	8 (40.0)	4 (30.8)	54 (44.3)
12–24 months	24 (27.0)	5 (25.0)	3 (23.1)	32 (26.2)
25–60 months	14 (15.7)	4 (20.0)	3 (23.1)	21 (17.2)
>60 months	6 (6.7)	3 (15.0)	2 (15.4)	11 (9.0)
Diagnosed during Surgery	3 (3.4)	0 (0.0)	1 (7.7)	4 (3.3)

HCP, healthcare provider;

Other diagnoses before pediatric patients received their accurate diagnosis included generalized anxiety disorder, growing related pains, baker's cysts, labrum or meniscus tears, juvenile rheumatoid arthritis, idiopathic rheumatoid arthritis, septic arthritis, sports injuries, ganglion cysts, ehlers danlos syndrome, algoneurodystrophy, tendonitis, and congenital anatomical defects.

Baker's cysts (19.7%), ligament and tendon tears, sprains and other sports injuries (32.9%), and juvenile rheumatoid arthritis (14.5%) were the most common misdiagnoses likely due to their higher likelihood in the adolescent population.

Pain (45.5%) and swelling (44.3%) were the most common symptoms that led patients to seek diagnosis (Table 2).

- Swelling was more common among pediatric patients with diffuse TGCT compared with localized TGCT.
- More than half (53%) of pediatric patients had symptoms for 12 months or longer before being diagnosed.

The healthcare providers (HCPs) responsible for diagnosing TGCT was predominantly general orthopedists or orthopedics in sports medicine (64.8%), except for those with unknown subtype who were diagnosed predominantly by rheumatologists or pediatricians (Table 2), possibly contributing to why their TGCT subtype was reported as 'unsure'.

The majority of pediatric patients have had an intermittent increase in TGCT-related symptoms, commonly referred to as a 'flare', within the last 6 months (67.2%). Pediatric patients with diffuse TGCT reported a flare more often than pediatric patients with localized TGCT (66.3% vs 40.0%).

Non-steroidal anti-inflammatory drugs (62.3%) and over-the-counter acetaminophen such as Tylenol or Paracetamol (76.2%) were often used to treat TGCT related pain and swelling.

Treatment

Surgical removal of TGCT is the most common treatment strategy proposed at initial diagnosis (n=115, 94.3%). Medications for TGCT were discussed with 15.6% of patients and radiotherapy (20.5%) was occasionally discussed. Actively monitoring TGCT is mentioned as an option for only 1 in 5 pediatric patients at their initial diagnosis. Overall, pediatric patients are treated quickly where 61.5% are treated within 3 months from time of diagnosis. Orthopedic surgeons were the most common healthcare provider (HCP for short) involved in 80.3% of treatments, followed by physiotherapists (40.2%), and orthopedic oncologists (36.9%) (Table 3). Medical oncologists were involved in one third of pediatric patients' care (33.6%), and more commonly involved with the care of pediatric patients with diffuse and recurrent TGCT.

Table 3. From Diagnosis to Treating Providers

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Time from Diagnosis to Treatment, n (%)				
< 1 Month	32 (36.0)	8 (40.0)	5 (38.5)	45 (36.9)
1-3 Months	22 (24.7)	7 (35.0)	1 (7.7)	30 (24.6)
4-6 Months	13 (14.6)	1 (5.0)	1 (7.7)	15 (12.3)
7-11 Months	8 (9.0)	2 (10.0)	0 (0.0)	10 (8.2)
≥ 12 Months	4 (4.5)	0 (0.0)	2 (15.4)	6 (4.9)
Active Surveillance	10 (11.2)	2 (10.0)	4 (30.8)	16 (13.1)
Pediatric TGCT-Treating HCPs, n (%)				
Orthopedic/sports medicine	74 (83.2)	16 (80.0)	8 (61.5)	98 (80.3)
Orthopedic oncologist	33 (37.1)	8 (40.0)	4 (30.8)	45 (36.9)
Medical oncologist	37 (41.6)	1 (5.0)	3 (23.1)	41 (33.6)
Rheumatologist	12 (13.5)	2 (10.0)	2 (15.4)	16 (13.1)
Physiotherapist	41 (46.1)	7 (35.0)	1 (7.7)	49 (40.2)
General Practitioner/Pediatrician	29 (32.6)	7 (35.0)	7 (53.9)	43 (35.3)

HCP, healthcare provider;

Surgery

Surgery was the mainstay treatment among all pediatric patients (82.0%) (Table 4). On average, pediatric patients with diffuse TGCT experienced 3.4 surgeries and pediatric patients with localized TGCT had 1.8 surgeries.

The main surgery types were arthroscopy, also known as ‘key hole’, where a surgeon makes several small incisions and inserts a scope to view the joint. The other common surgery is called the open approach surgery, where a surgeon makes a larger incision and can see the inside of the joint by eye.

Most pediatric patients have had ≥ 1 surgery to remove their TGCT (82.0%), including surgeries with the following surgical approaches:

- arthroscopy/key hole (57.4%),
- open surgery (44.3%),
- and combined front arthroscopic and open back approach for TGCT of the knee (23.8%).

Arthroscopies were more common in pediatric patients with diffuse TGCT compared to localized TGCT (62.9% vs 40.0%) potentially due to surgeons wanting to reduce the risks associated with large surgeries (e.g., stiffness, repeat future surgeries, long recovery) when the TGCT is likely to return.

Table 4. Treatment Modalities

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Tumor Resection, n (%)	76 (85.4)	16 (80.0)	8 (61.5)	100 (82.0)
Arthroscopic Surgery	56 (62.9)	8 (40.0)	6 (46.2)	70 (57.4)
Open Synovectomy	44 (49.4)	8 (40.0)	2 (15.4)	54 (44.3)
Combined Anterior/Posterior Synovectomy	26 (29.2)	3 (15.0)	0 (0.0)	29 (23.8)
Systemic Therapy, Check all that apply	20 (22.5)	0 (0.0)	1 (7.7)	21 (17.2)
Pexidartinib	7 (7.9)	0 (0.0)	1 (7.7)	8 (7.4)
Imatinib	12 (13.5)	0 (0.0)	0 (0.0)	12 (9.8)
Nilotinib	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)
Radiation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
External Beam	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intra-articular Yttrium-90	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Active Surveillance	43 (48.3)	9 (45.0)	8 (61.5)	60 (49.2)
Average surgeries, (SD)	3.4 (2.8)	1.8 (1.5)	1.1 (1.2)	2.8 (2.5)
Median	2	1	1	2
Local Recurrences, n (%)				
Yes	59 (66.3)	3 (15.0)	4 (3.8)	66 (54.1)
1 Recurrence	19 (21.3)	2 (10.0)	1 (7.7)	22 (18.0)
≥ 2 Recurrences	40 (44.9)	1 (5.0)	3 (23.1)	44 (36.1)
No	30 (33.7)	17 (85.0)	9 (69.2)	56 (45.9)
I have not had surgery	12 (13.5)	2 (10.0)	5 (38.5)	19 (15.6)
I am unsure	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)

Of those that have had prior surgery, the recurrence rate was 66.0% and recurrence was higher among pediatric patients with diffuse TGCT compared to pediatric patients with localized TGCT (66.3% of diffuse patients had recurrence vs 15.0% of localized). Future recurrence rates following additional surgeries were high among pediatric patients with diffuse TGCT, where 67.8% had a second recurrence following the second surgery.

Medications for TGCT

Medications were occasionally given to pediatric patients for their TGCT (17.2%)(Table 4). No medication has been approved for pediatric populations. However, TGCT medications that were prescribed were exclusively used in those with diffuse TGCT and in one patient with an unknown subtype of TGCT. Eighty-one percent of pediatric patients received a single medication for TGCT, while 19% of patients (4 patients to be specific) received two different medications. Imatinib was the most commonly used medication, followed by pexidartinib.

The medication dosages prescribed are aligned with what is given to adults (i.e., 500 mg total for pexidartinib, 400 mg daily for imatinib). Preliminary evidence from an analysis suggests that similar drug concentrations were achieved in blood by adult and pediatric patients following taking pexidartinib at 800 mg [19]. This means that adults and pediatric patients may be able to take the same doses. However, insufficient evidence is available to determine whether the same dose is as effective in pediatric population or whether lower doses could be effective to shrink TGCT.

None of the 3 pivotal trials with pexidartinib (n=61), vimseltinib (n=83), and pimicotinib (n=63) in TGCT enrolled pediatric patients and results await for whether emactuzumab enrolled patients > 12 years (<https://clinicaltrials.gov/NCT#05417789>). Thus, we may not know what the best and safest dose of the TGCT medications for pediatric patients with TGCT is.

This data establishes that pediatric patients and their caregivers may be willing to use medications approved for adults with TGCT when available. However, pediatric patients or their caregivers were

asked about their concerns regarding medications. The most reported concerns included concerns for fertility, lifestyle changes associated with aging (such as transitioning from high school to college), and the lack of data to support the use in young pediatric populations.

Burden of disease

Pain was the most common symptom reported in 94.0% of patients, regardless of TGCT subtype. TGCT limited range of motion for 89.3% of patients, and patients experienced similar limitations in range of motion regardless of TGCT subtype. It was unexpected that patients would experience similar limitations in range of motion regardless of subtype. This result potentially represents that localized TGCT may structurally impede movement (e.g., localized TGCT between the kneecap and the femur). However, the self-reported nature of the observational registry limits whether this can be confirmed or assessed by a doctor.

Pediatric patients with diffuse TGCT experienced swelling more frequently than those with localized TGCT (88.7% for diffuse vs 60.0% for localized). In the last week, 80.3% of pediatric patients' reported some degree of pain interference in their enjoyment of life. Similarly, pain interfered with pediatric patients' enjoyment of fun activities (82.8%).

Patients reported that TGCT impacted their ability to participate in sports, future career planning, and school choices. One patient recalls that they intended to join the military like their parents, however, they stated that TGCT will be the reason they can't pass the physical exams. Several pediatric patients mentioned TGCT impacting their ability to focus on school or relate to their friends.

Pediatric TGCT compared to adult TGCT

Overall, TGCT impacts adult and pediatric patients to a similar extent; however, several journey characteristics differed (Table 5). Similarly, adult and pediatric patients reported pain and swelling as the most common symptom that led to a sought-after diagnosis and pain was the most common symptom throughout their journey.

Table 5. Comparison between pediatric and adult TGCT patient journey

Variables	Pediatric TGCT (n=122)			Adult TGCT (n=497)		
	Localized (n=20)	Diffuse (n=89)	Unknown (n=13)	Localized (n=94)	Diffuse (n=355)	Unknown (n=48)
Female, n (%)	14 (70.0)	59 (66.3)	9 (69.2)	76 (80.9)	254 (71.5)	40 (83.3)
US, n (%)	11 (55.0)	47 (52.8)	4 (30.8)	53 (56.4)	203 (57.2)	24 (50.0)
TGCT of the knee, n (%)	16 (80.0)	76 (85.4)	10 (76.9)	57 (72.2)	256 (72.2)	26 (54.2)
Misdiagnosis, n (%)	10 (50.0)	56 (62.9)	10 (76.9)	41 (51.3)	182 (51.3)	25 (52.1)
Main Symptom that led to diagnosis, n (%)						
Pain, n (%)	12 (60.0)	37 (42.1)	6 (46.2)	48 (51.0)	141 (39.7)	21 (43.7)
Swelling, n (%)	5 (25.0)	44 (49.4)	5 (38.5)	23 (24.5)	152 (42.8)	14 (29.2)
Diagnosing HCPs, n (%)						
Orthopedic/Sports Medicine	12 (60.0)	62 (69.7)	5 (38.5)	51 (54.3)	222 (62.5)	31 (64.5)
Orthopedic Oncologist	7 (35.0)	19 (21.4)	0 (0.0)	30 (31.9)	83 (23.4)	5 (10.4)
GP/PCP/Pediatrician	0 (0.0)	4 (4.5)	4 (30.8)	3 (3.2)	12 (3.4)	3 (6.3)
Duration from Symptom Onset to Diagnosis, n (%)						
< 12 months	8 (40.0)	42 (47.1)	4 (30.8)	39 (41.5)	132 (37.2)	14 (29.2)
≥ 12 months	12 (60.0)	44 (49.4)	8 (61.5)	50 (53.2)	201 (56.6)	27 (56.3)
Duration from Diagnosis to Treatment, n (%)						
< 12 months	18 (90.0)	75 (84.2)	7 (53.8)	69 (73.4)	240 (67.6)	21 (43.8)
≥ 12 months	0 (0.0)	4 (4.5)	2 (15.4)	4 (4.3)	35 (9.8)	4 (8.3)
Treating HCP, n (%)						
Orthopedics/Sports Medicine	16 (80.0)	74 (83.2)	8 (61.5)	75 (79.8)	264 (74.4)	32 (66.7)
Orthopedic Oncologist	8 (40.0)	33 (37.1)	4 (30.8)	53 (56.4)	238 (67.0)	15 (31.3)
Medical Oncologist	1 (5.0)	37 (41.6)	3 (23.1)	6 (6.4)	122 (34.4)	11 (22.9)
Treatments						
Arthroscopy	8 (40.0)	56 (62.9)	6 (46.2)	32 (34.0)	167 (47.0)	18 (37.5)
Open surgery	8 (40.0)	44 (49.4)	2 (15.4)	42 (44.7)	168 (47.3)	8 (16.7)
Systemic Therapy	0 (0.0)	20 (22.5)	1 (7.7)	3 (3.2)	86 (24.2)	6 (12.5)
Active Surveillance	9 (45.0)	43 (48.3)	8 (61.5)	30 (31.9)	153 (43.1)	18 (37.5)
average surgeries± SD	1.8 ± 1.6	2.8 ± 2.7	1.7 ± 1.1	1.8 ± 1.5	3.4 ± 2.8	2.9 ± 2.5
LRR after surgery	n=17	n=76	n=8	n=68	n=289	n=36
1 or more Recurrence(s), n (%)	3 (17.6)	59 (77.6)	4 (50.0)	23 (33.8)	207 (71.6)	16 (44.4)

HCP, healthcare provider; GP, general practitioner; LRR, local recurrence rate; PCP, primary care provider.

However, pediatric patients with TGCT received a misdiagnosis significantly more often than adult patients (62.3% vs 49.9%). For pediatric patients that were misdiagnosed prior to receiving their TGCT diagnosis, psychological diagnoses such as generalized anxiety disorder were noted. These psychological diagnoses were not reported as differential diagnoses or misdiagnoses for adults with TGCT.

Despite the high misdiagnosis rate amongst pediatric patients, the duration from symptom onset to diagnosis among adult and pediatric patients was consistent, regardless of subtype. This may be because parents are avid advocates for their children when they are in pain. Additionally, most symptoms were managed similarly among adults and pediatrics. Although, pediatric patients received joint aspirations significantly more frequently than adult patients (47.5% vs 22.5%), likely representing the lack of oncology input in the management of TGCT and the large portion of pediatric patients that remain in the care of their primary team or general orthopedics.

Treatment approaches discussed were similar among pediatric and adult patients and most patients were treated within 3 months of their TGCT diagnosis, highlighting that patients are treated quickly once diagnosed and not given many alternative options. Although both pediatric and adult patients were diagnosed frequently by general orthopedic surgeons or sports medicine surgeons, adult patients shifted to care with orthopedic oncologists significantly more frequently than pediatric patients with TGCT (61.6% vs 36.9%). The management of TGCT more frequently involved primary care (i.e. pediatricians) in pediatric patients. We know from studies with adult TGCT patients that treatment by orthopedic oncologists leads to better patient outcomes.

Surgery is the mainstay treatment for both pediatric and adult patients with TGCT, as expected. Arthroscopic approaches to surgery were more commonly performed on pediatric patients with diffuse TGCT than adult patients (62.9% vs 47.0%) (Table 5). Both the average number of surgical resections were similar among adult and pediatric patients (2.7 vs 2.8) and local recurrence rates

following surgery were similar (Table 5). However, that also means by the time a pediatric patient becomes an adult, they have similar numbers of surgeries as the adult population, which has a median age of 44 years old.

Previous research has demonstrated no difference in the recurrence rate after surgical treatment in pediatrics compared to adults, 2 years after surgery (15% peds vs. 11% adults in localized TGCT; 47% peds vs. 44% adults in diffuse TGCT)[6], which is consistent with our study despite that we identified higher recurrence rates overall (66%). Our registry demonstrates higher recurrence rates compared with those reported in the Dutch study for both adults and pediatrics, as well [6]. This may reflect that patients self-select to respond to our survey and more severely affected patients rather participate or that patients in real-world settings are often treated outside specialty centers and have higher recurrences which is captured in our analysis because it is independent of institution and geography[4]. Notably, recurrence rates remained high (67.8%) following additional surgeries for diffuse TGCT, underscoring the need for treatment advancements.

Despite there being no approved medications available for patients under the 18 years of age, medical oncologists were involved in pediatric patients' care in a similar proportion as adult patients (33.6% vs 28.0%). Similarly, medications were prescribed in similar proportions in pediatric and adult TGCT, despite approved indications being limited to adults. Imatinib was the most common medication given its many years of safety data. The use of medications for TGCT was identical among pediatric and adult patients (17.2% vs 19.1%). Pediatric patients received imatinib more frequently than adult patients with TGCT (57.1% vs 30.3%), whereas pexidartinib was the most common medication among adults (81.8% vs 38.1%)(Table 5). This is likely due to the years of safety information of imatinib in pediatric populations.

Radiation was discussed as a treatment for pediatric TGCT, however, no pediatric patient received radiation therapy to treat TGCT. This contrasts with adults with TGCT where nearly 8% received

radiation[4]. It is possible that pediatric patients were not treated with radiation due to the growing concerns for the risk of cancerous development due to radiation and the lack of data supporting it helps

control disease. Importantly, a global position paper on this topic highlights that the available literature provides insufficient data for the use of radiotherapy as a treatment for TGCT[2].

DISCUSSION

Our findings demonstrate that, like adults, pediatric patients with TGCT face a long diagnostic journey, unmet treatment needs, and significant disease burden (Fig 1), but with higher misdiagnosis rates (62% vs 53%), more frequently have ongoing orthopedic care (36% vs 61% for adults), and often do not receive accurate or incomplete subtype classification when diagnosed by rheumatologists or pediatricians, suggesting limited familiarity with TGCT. Pediatric patients with TGCT have significant symptoms, specifically nonspecific symptoms such as pain and joint swelling in a single joint, and disease burden similar to adult patients. The nonspecific symptoms, rarity of disease, and lack of awareness may lead to significant delays in diagnosis and high misdiagnosis rate. Currently, treatment strategies for pediatric TGCT do not differ substantially from those used in adults; however, certain pediatric-specific considerations must be taken into account.

We propose a treatment paradigm which takes into consideration the current practices (Figure 2). This analysis and paradigm highlight that pediatric patients would benefit from multidisciplinary management of TGCT including pediatric oncologists, pediatric orthopedic surgeons, and other dedicated specialists. The expert community, together with patient advocates, should raise awareness of TGCT among pediatricians and other general specialists to enhance appropriate referral of patients for TGCT management in specialized centers from the onset of the disease, thus facilitating the development of tailored approaches for pediatric patients beyond repeat surgeries. Further research is warranted to understand the best treatment strategy in pediatrics.

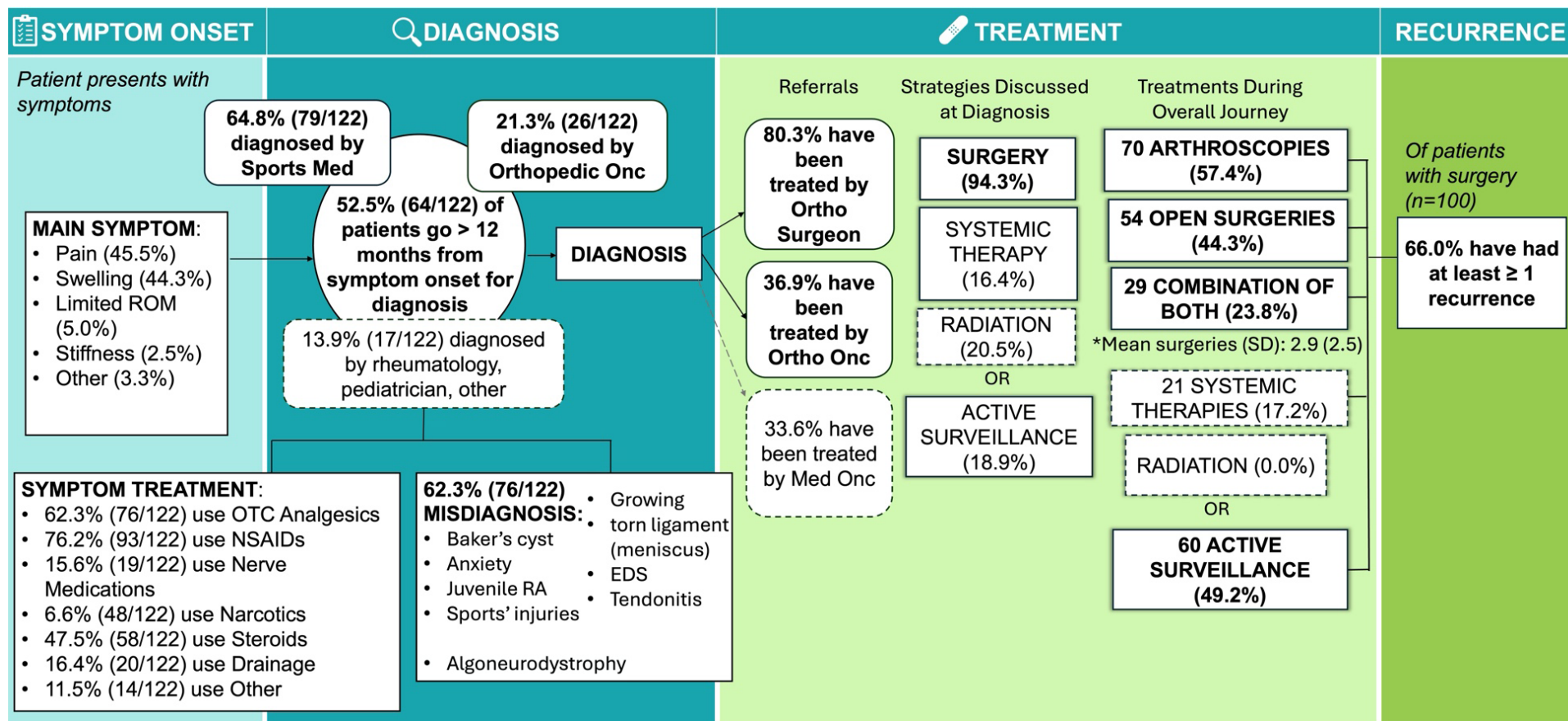
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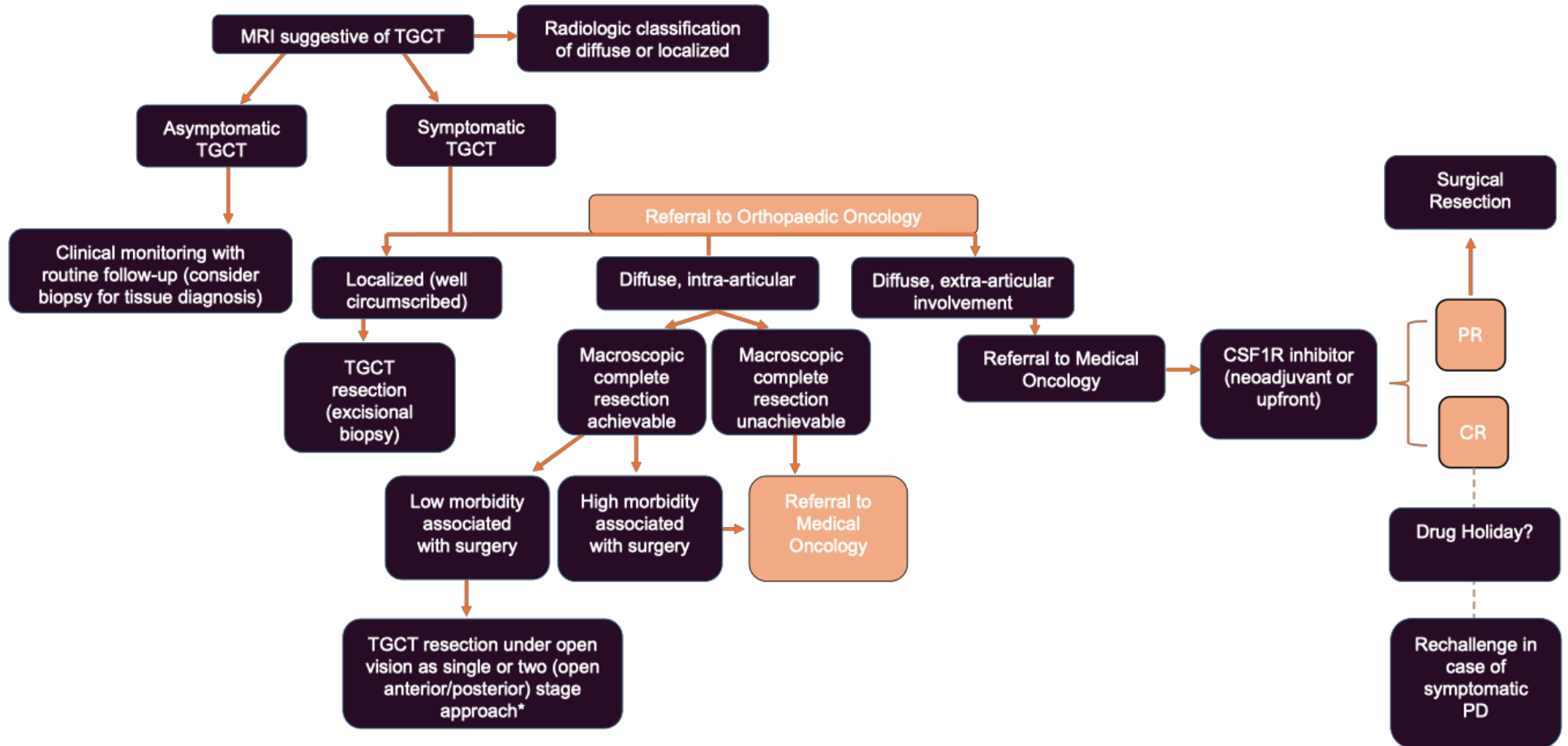
The analysis and paper were not funded.

Figure 1. Pediatric patient journey from diagnosis to treatment.



EDS, elder's danlos syndrome; NSAID, nonsteroidal anti-inflammatory drugs; OTC, over the counter; RA, rheumatoid arthritis

Figure 2. Treatment paradigm for pediatric TGCT



CR, complete response; PD, progressive disease; PR, partial response;

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