

PATIENT-FRIENDLY VERSION OF

# Best Clinical Management of Tenosynovial Giant Cell Tumour (TGCT): A Consensus Paper from the Community of Experts

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**Disclaimer: patients' names within the paper have been changed for privacy. Language has been modified from the original paper to improve translatability to the patient community.**

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# INTRODUCTION

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Tenosynovial giant cell tumour (TGCT), previously called pigmented villonodular synovitis (PVNS), nodular synovitis, and giant cell tumour of the tendon sheath (GCT-TS), is a rare soft tissue tumour that arises from the the joint (synovium) and tissue surrounding tendons (tendon sheath). The tissue is often discolored due to hemosiderin. Hemosiderin is an iron storage compound which leads to rusty, yellow, red, orange pigmentation. This pigmentation gave PVNS its original naming. TGCT is characterized by a genetic abnormality in the tissue resulting in abnormal production in a protein called, colony-stimulating factor 1 (CSF1). The increase in the CSF1 protein is a result in a genetic abnormality that impacts only 2-16% of tumor tissue. The 2020 WHO Classification of Soft Tissue and Bone Tumours defines TGCT as a locally aggressive tumour disease. TGCT that becomes cancerous and spreads is exceedingly rare. Most patients affected by TGCT are young and, although usually TGCT is not life-threatening, the disease and its treatment may impact quality of life. Recent clinical trials for recurrent TGCT have raised awareness of the challenges that patients endure. Treatment varies by geographical- and resource-specific factors and many physicians do not understand the risks associated with repeat operations and unsuccessful treatment. Furthermore, effective medication options are not available in most countries. Therefore, this document was adapted as a patient version of the “Best Clinical Management of Tenosynovial Giant Cell Tumour (TGCT): A Consensus Paper from the Community of Experts” and produced by a program of the Life Raft Group, known as TGCT Support, and


Sarcoma Patient Advocacy Global Network (SPAGN) to provide information for patients with TGCT, no matter where they live in the world. This document was conceived to highlight and agree on key factors relating to the treatment of TGCT, for which there was little agreement previously. Fifty experts were broken down into working groups based on specialization and were tasked with writing a section. An international consensus meeting was held on June 21, 2022, in Frankfurt, Germany, involving international multidisciplinary sarcoma experts in collaboration with patient representatives from the SPAGN and TGCT Support, to define the best clinical practices in TGCT and generate recommendations presented herein. The version will be updated as treatments evolve.

## Methods, level of evidence and grade of recommendation

**A data literature search was conducted and in conjunction with expert opinion, the group reached consensus on key aspects of TGCT management. Due to the lack of research designed specifically for localized TGCT and only a few trials designed for advanced/diffuse disease, current practice is mainly based on data collected for a different purpose or in hindsight. Consequently, a degree of uncertainty needs to be accepted in the treatment of TGCT. We graded levels of evidence from I to V and used recommendation grades from A-D adapted from the Infectious Diseases Society of America-US Public Health Service Grading System 2 (Table 1).**

Table 1. Methods, level of evidence and grade of recommendation. Adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System.


## LEVEL OF EVIDENCE:



Higher Reliability

I	Evidence from at least one large-scale well designed (with randomization) controlled trial that was well conducted with a <u>low</u> potential of results being attributed to other factors or large analysis of well conducted trials without much variation in TGCT population ( <b>Highly reliable evidence</b> )
II	A clinical trial or analysis of multiple data with potential for results to be attributed to other factors and <u>lower quality</u> of design with variation in the studies with difficulty comparing directly ( <b>Moderately reliable evidence</b> )
III	Observational prospective study designed to study TGCT over time, but treatment is not assigned ( <b>Some evidence, with some reliability</b> )
IV	Observational study done in hindsight and designed to look at data collected previously in TGCT or an observational study that compares patients with different outcomes of treatment ( <b>Some evidence, less reliability</b> )
V	Studies without control/placebo groups, case studies, and experts' opinions based on anecdotal experience ( <b>Opinion or experience based</b> )

## GRADE OF RECOMMENDATION:



Evidence of benefit

A	Strong evidence for effectiveness with substantial meaningful benefit to how patients feel and function, <b>strongly recommended</b>
B	Strong or moderate evidence for effectiveness but with a limited benefit to how patients feel and function, <b>generally recommended</b>
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or disadvantages (including undesirable or harmful events and cost), <b>optional to consider by providers</b>
D	Moderate evidence against efficacy or for undesirable or harmful effects, <b>generally not recommended</b>
E	Strong evidence against efficacy or for undesirable or harmful effects, <b>never recommended</b>

When considering treatment recommendations as shown above/below, the threshold for strong or moderate recommendation is **B and A**.

## Nodular/Localized-type TGCT (N-TGCT) versus diffuse-type TGCT (D-TGCT): definitions

TGCT is comprised of two distinct subgroups, N-TGCT and D-TGCT. N-TGCT corresponds to localized disease, however, the naming of nodular TGCT accurately represent the tumour behavior. Thus, we chose “nodular” instead of “localized” to better reflect the appearance in imaging and the tumour behavior being well-defined and often rounded. N-TGCT typically occurs as a single tumour, often evolving slowly over many years often near a tendon, particularly occupying the fingers and toes. Occasionally, N-TGCT can erode bone or damage other areas of the limb, like the skin layer. Large joints are less frequently affected by N-TGCT. In contrast, diffuse TGCT (D-TGCT) shows extensive and infiltrative involvement of the joint and/or tendon sheath and may extend outside of the joint. D-TGCT can cause joint bleeds, destruction of the bone and cartilage with severe disability, as well as frequent recurrence.

TGCT can be life-limiting and cause substantial suffering, however, it is rarely life-threatening. An exception is malignant TGCT (M-TGCT), also known as a cancerous form of TGCT, which can arise from the start or following multiple recurrences. This is exceptionally rare and controversial.

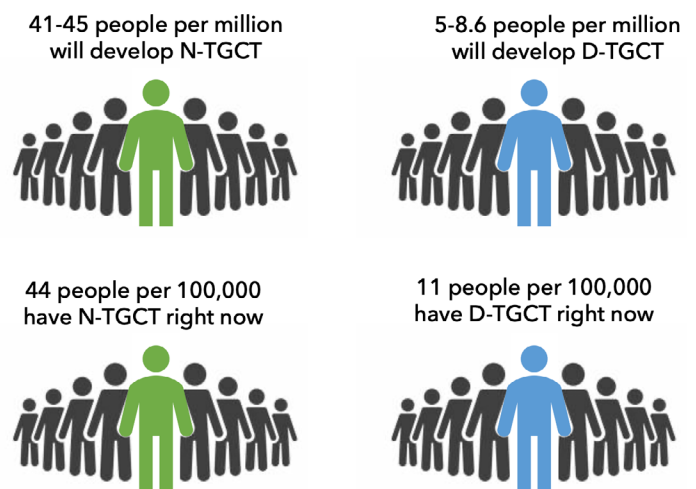
### Why is it important to know what type of TGCT you have?

The two subtypes of TGCT (nodular and diffuse) behave very differently. Each patient and their disease is unique, but the subtype can guide patient expectations, monitoring, and treatment options. For example, Tom was diagnosed with TGCT of the knee and intermediately had surgery. After his stitches were removed, he had no follow-up. Tom was not told what type of TGCT he had. A couple months after surgery, the pain and stiffness in his knee came back. Tom’s general practitioner requested an MRI of the knee. Tom’s TGCT was all over the knee joint and not amenable to another surgery. Tom was referred to oncology. However, if Tom was able to go to a multidisciplinary team before his surgery, he would have had a discussion of the subtype and all his options prior to his devastating recurrence.

## Who Gets TGCT and What Are the Outcomes

To understand how to best monitor, diagnosis and treat this disease, it is important to know how many people currently have it and who will develop it. Due to the rarity and differences in how TGCT affects different patients, data on who TGCT affects and trends within the disease are scarce and therefore, difficult to compare and draw conclusions from. In nationwide studies in Denmark and the Netherlands, it is expected that 30 to 34 people per million will develop N-TGCT affecting the digits and 11 people per million will develop N-TGCT in the extremities such as knee, hip, and ankle. It is expected that 5 to 8.4 people per million will develop D-TGCT. Hospital-based studies at expert institutions reported a higher proportion of D-TGCT (70-90%) compared to N-TGCT, likely due to expert centers attracting complex cases unsuccessfully treated in local settings. Additionally, a Danish study reported 44 per 100,000 people are living with N-TGCT and 11 per 100,000 people are living with D-TGCT.

Depending on the study, it may be reported that N- and D-TGCT are more common in females than males. Mean age at diagnosis is 35-50 years, with slight gender and subtype differences reported per paper.



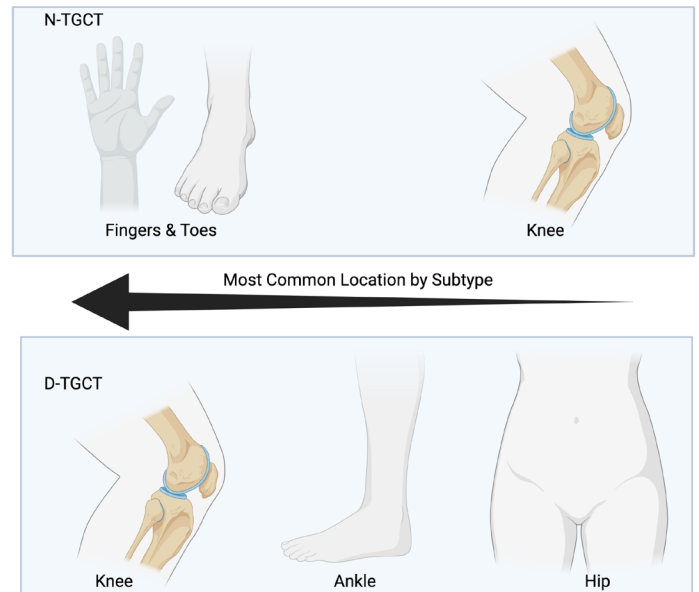
**Figure 1. Those who will develop N-TGCT and D-TGCT compared to those that currently have N-TGCT and D-TGCT. TGCT is a rare disease that impacts few people worldwide.**

TGCT can involve any joint. However, most N-TGCT affect the hands and wrist followed by the knee, while most D-TGCT arise from the knee followed by the ankle and hip (Figure 2). N-TGCT of the elbow is exceedingly rare. Recurrences are lower in N-TGCT (9-14%) than in D-TGCT (23-72%). The recurrence rate for patients initially treated at an expert center was 44% versus the recurrence rate of 92% for patients treated initially at community centers.

The 5-year recurrence rate for N-TGCT is 10-30% and 20-70% for D-TGCT. This data largely supports that patients should be treated within an expert center with a multidisciplinary care team of oncologists, orthopedic oncologists, radiologists, physical therapists, and others that specialize in similar diseases at the time of diagnosis.

Information on the frequency of TGCT occurring in children is scarce. In a study conducted in the Netherlands, it is estimated that 2.86 children per million will develop N-TGCT (excluding digits) and 1.30 children per million will develop D-TGCT. The knee was predominantly affected (46% N-TGCT, 66% D-TGCT), with slightly higher rates in females (54% N-TGCT, 62% D-TGCT).

After 2.5-years, recurrence after surgical treatment in children versus adults was identical. Children had similar recurrence rates to adults, with 15% children with N-TGCT recurring and 11% adults with N-TGCT



**Figure 2. TGCT subtype by location prevalence. The most common joint afflicted with N-TGCT is the fingers and toes while the second most common location is the knee. For D-TGCT, the knee is the most common, followed by ankle and hip.**

recurring within 2.5-years and 47% of children and 44% of adults with D-TGCT recurring within 2.5-years.

In rare circumstances, TGCT can become cancerous. This is called malignant TGCT (M-TGCT). M-TGCT has an incidence of less than one per million, so rare that it is disputed.

## IMAGING

### Why is Imaging important and what can go wrong when imaging is insufficient?

Imaging lets the doctor and patient know what disease and how much disease a patient has. This informs what options a patient may have for treatment. If imaging is inadequate, the disease may not be seen at all, it may appear smaller than it actually is, or it may appear larger than it actually is. All of these factors can inform the care a patient receives. For example, Marvin was diagnosed with TGCT of the knee after a traditional MRI to evaluate

a potentially torn ligament in his knee after he experienced long-term pain, stiffness, and swelling after a sports injury. However, the wrong technique was performed to detect TGCT. Based on the MRI, the doctor and Marvin chose to do surgery to fix the ligament without seeing the TGCT. However, while in surgery, Marvin was diagnosed with TGCT and a torn ligament. The doctor could not remove all of Marvin's disease and Marvin was referred to oncology after his recovery. Marvin's experience is an example when the right technique would have detected his diffuse disease and that could have informed surgery.

## LEVEL OF EVIDENCE:

Higher Reliability ↑	I	Highly reliable evidence
	II	Moderately reliable evidence
	III	Some evidence, with some reliability
	IV	Some evidence, less reliability
	V	Opinion or experience based

## GRADE OF RECOMMENDATION:

Evidence of benefit ↑	A	Strongly recommended
	B	Generally recommended
	C	Optional to consider by providers
	D	Generally not recommended
	E	Never recommended

When considering treatment recommendations, the threshold for **strong or moderate** recommendation is **B and A**.

### RECOMMENDATION (IV, A):

**Magnetic Resonance Imaging (MRI) is the preferred imaging method for this disease and can be used to determine diffuse vs. nodular TGCT.**

## Why does x-ray not detect this disease?

X-ray is a type of imaging that uses radiation to show parts of the body. Bone absorbs the x-ray and shows up in the image while the x-ray passes through soft tissue. Thus, the use of x-rays does not establish diagnosis in TGCT. However it may be obtained to rule out other potential different diagnoses and check the overall bone health.

### RECOMMENDATION (IV, A):

**The recommended minimal MRI protocol includes the techniques that determine the properties of the tissue such as T1-weighted (signal for fatty tissue is light/white and signal is dark for fluid), T2-weighted (signal for fluid is light/white and dark/grey signal for dense tissue), and fluid-sensitive sequences. This often includes contrast dye.**

### RECOMMENDATION (IV, A):

**Contrast dye, such as Gadolinium contrast, is recommended to allow with and without contrast dye subtraction.**

Contrast dye enhances the evaluation of blood flow to soft tissue, especially useful if the patient is not planning on immediate surgery. Baseline and follow-up examination should be performed in the same manner, consistency is important. There is insufficient evidence to recommend routine PET-CT or PET scans.

## N-TGCT

### N-TGCT inside the joint

Conventional x-ray/CT is normally used to show damage to bone. Erosion due to pressure from the tumour may be seen in small tight joints such as fingers and toes. Ultrasound may show a well-defined round mass. N-TGCT often appears more condensed than D-TGCT. Joint swelling may be absent in N-TGCT.

### N-TGCT outside the joint

Imaging findings are similar to N-TGCT within the joint. MRI demonstrates the tumour typically of the tendon sheath and less frequently seen in the joint or fat shock absorber, known as the bursa).

## D-TGCT

### D-TGCT inside the joint

D-TGCT presents with extensive joint involvement, joint swelling, potential bone erosion and bone cysts (a fluid-filled sac inside the bone), and it may be difficult to determine where healthy tissue and tumour tissue diverge. Erosion and cysts are predominantly seen in joints with less space, such as the hip, and may lead to joint destruction in long-standing disease.



## LEVEL OF EVIDENCE:

Higher Reliability ↑	I	Highly reliable evidence
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## D-TGCT outside the joint

D-TGCT may infiltrate into healthy tissue. Most damaged tissue occurs in soft tissue surrounding the joint, including muscle and fatty tissue.

## M-TGCT

**RECOMMENDATION (IV, A):**  
Since imaging features of M-TGCT are similar to benign disease, biopsy confirmation is required for diagnosis of M-TGCT.

MRI is the technique of choice to evaluate the disease.

## Radiologic assessment after recurrence or if medication is considered

**RECOMMENDATION (IV, A):**  
MRI is the imaging technique of choice to detect recurrence.

Follow-up after surgery is intended to evaluate recurrence and potentially progressive joint destruction following multiple recurrences of D-TGCT. Some providers use a baseline MRI at 3 months post-operation to determine what was left behind (residual) versus future recurrence.

**RECOMMENDATION (IV, A):**  
Beneficial response to the medication should be evaluated using tumor size, patient's function, patient's symptoms, and side effects.

MRI is also recommended to understand tumour shrinkage by evaluating dimensional changes in the tumours. Clinical trials currently use criteria to determine significant shrinkage. However, because of the typical irregular and diffused nature of TGCT, changes in the longest diameter of a tumor may underrepresent the degree of benefit a patient has and feels from the treatment. Measuring the volume of the tumour instead of the diameter may provide a better understanding of the degree of change related to a medication treatment.

For example, Elaine is on a medicine that is shrinking her tumor. After 6 months, her tumor has only shrank a small amount. However, Elaine is back to picking up her kids from school. She can socialize again and she has started working full-time. While the medicine did not eliminate her tumor by the measuring criteria, Elaine has benefitted from the medicine and decides to stay on it because her side effects are manageable and she is back to her regular routine again.

## Common Misdiagnoses for TGCT

The main diagnoses that resemble N-TGCT in the hands and feet includes:

- fibroma of tendon sheath
- ganglion cyst
- hemangioma
- angiomyoma
- bizarre parosteal osteochondromatous proliferation (BPOP, Nora's lesion)
- tophaceous gout

Major considerations for determining if a patient has TGCT or not has to do with hemosiderin.

## LEVEL OF EVIDENCE:

Higher Reliability ↑	I	Highly reliable evidence
	II	Moderately reliable evidence
	III	Some evidence, with some reliability
	IV	Some evidence, less reliability
	V	Opinion or experience based

## GRADE OF RECOMMENDATION:

Evidence of benefit ↑	A	Strongly recommended
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For N-TGCT within the joint of extremities such as the knee, the main diagnoses that resemble N-TGCT includes:

- synovial chondroma (which can be excluded certain MRI techniques and comparison with x-ray to determine minerals in the mass)

D-TGCT within the joint may resemble on scans:

- synovial osteochondromatosis (SOC)
- rheumatic disease
- chronic non-specific synovitis
- hemophilic arthropathy (joint damage due to blood disorders)

## PATHOLOGY AND MOLECULAR BIOLOGY

Under a microscope, N-TGCT and D-TGCT appear nearly identical. Both N-TGCT and D-TGCT are known for the over-production of the CSF1 protein caused by a gene abnormality only seen in the tumour tissue. Genes are condensed and located on chromosomes. All cells have their own chromosomes. Within TGCT, a fragment of one chromosome is reattached to another chromosome in an event called a chromosome translocation (Figure 2). This chromosome translocation leads to the over-production in CSF1, a protein critical for the survival and growth of TGCT. The abnormality that produces too much of the protein, CSF1, is present in only 2-16% of tumour cells, the rest of the cells resemble healthy normal tissue.

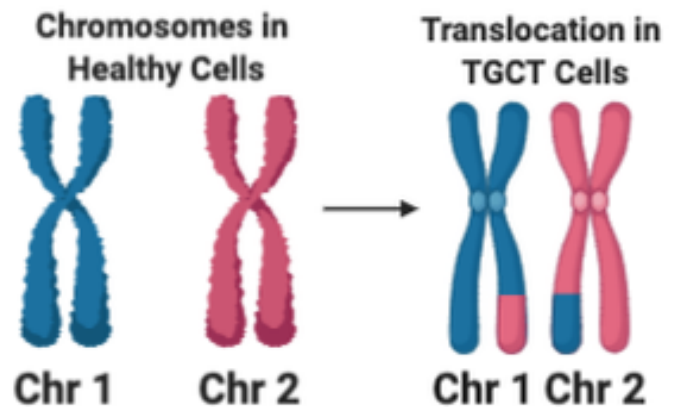
### NOT RECOMMENDED (IV, B):

It is not recommended to detect the CSF1 genetic abnormality by genetic analyses in patients for diagnosis, nor does it add value to patient care.

**RECOMMENDED (IV, B):** Pathology review by an expert specialist is recommended, particularly in the case of discrepancies between imaging and symptoms.

### Cell Appearance: Under the Microscope

N-TGCT are typically rounded tumours with variable yellow, tan, or whitish regions. D-TGCT can have increased blood flow that increases with the size of the joint. Disease that is outside the joint may



**Figure 3. Chromosome analyses in case of tenosynovial giant cell tumour (TGCT).** Following the examination of genetic information (genes held on chromosomes) in TGCT samples, it was found that chromosome 1 fragments and that separated fragment attaches to chromosome 2. This is known as a chromosome translocation and leads to the over-production of CSF1 in TGCT.

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have multiple small growths. TGCT is composed of multiple cell types. Within the tumour, there may be cells with single-rounded centers or giant cells with multi-rounded centers that are potentially capable of dissolving bone, foamy immune cells that engulf and digest foreign substances (e.g., bacteria, virus,

other microorganisms), and inflammatory cells. Both N-TGCT and D-TGCT are characterized by the presence of giant cells and hemosiderin, an iron storage compound that leaves a rusty, orange, tan, red pigment on the tissue. D-TGCT is more infiltrative into healthy tissue and has more foamy immune cells.

## PRINCIPLES OF TREATMENT

**RECOMMENDATIONS (III, A):** Patients affected with TGCT should be treated within expert centers or reference networks, by a dedicated, experienced sarcoma multidisciplinary treatment team, including a pathologist, radiologist, orthopedic surgeon, pain specialist, surgical, radiation, and medical oncologists.

Other specialists such as neurosurgeons and physical therapists should be involved as required.

### Diagnostic procedures

**RECOMMENDATION (IV, B):** For suspected D-TGCT, a biopsy is recommended either by image-guided biopsy or during arthroscopic synovectomy (keyhole surgery).

**RECOMMENDATION (III, B):** If a biopsy is pursued and there is a mass capable of being biopsied, a 14/16-gauge needle should be used.

**Recommendation (V, C):** Biopsy may be avoided if imaging is performed in an expert center, if the diagnosis is most obviously TGCT, and/or surgery is planned.

Pathology will then confirm diagnosis based on tissue removed during surgery and not with a biopsy prior.

### When active surveillance (AS) should be used versus surgery/medicine treatment

Active surveillance is the strategy of monitoring the disease before treating with surgery or medicine (also known as active treatment). Pain and symptoms can be multifaceted and are not always directly related to TGCT. Pain can be caused by surgery, activity, as well as the disease. For some patients, actively monitoring their disease may benefit them instead of immediately intervening.

For example, Seyi has diffuse TGCT of the hip and has had multiple surgeries over the course of 7 years. Seyi has stiffness when she gets up and pain if she sits too long. She reports that her symptoms are manageable

**LEVEL OF EVIDENCE:**

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**GRADE OF RECOMMENDATION:**

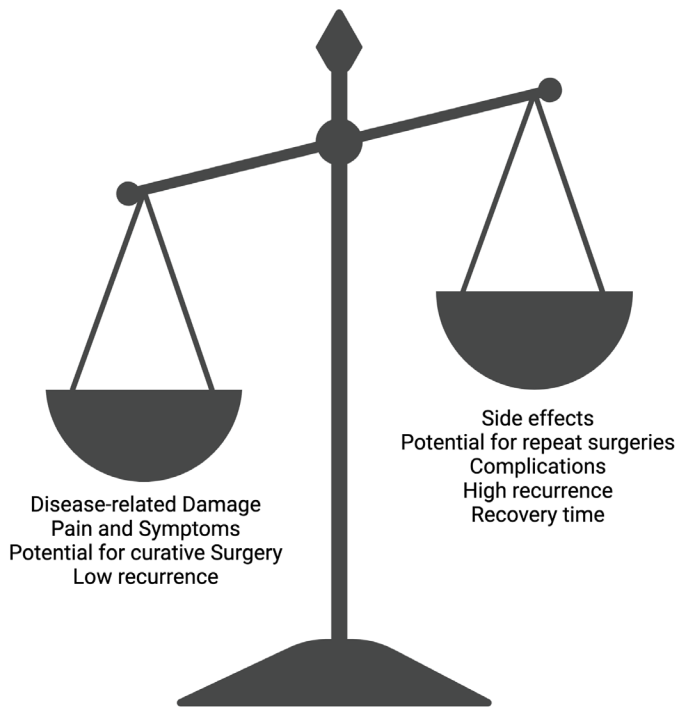
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but that they limit her ability to do high-impact activity. It is unknown if Seyi’s pain and stiffness is coming from the disease or scar tissue developed during her many surgeries. Because Seyi’s symptoms are manageable and she can still do activities she loves with modifications, Seyi and her provider chose to actively monitor her disease instead of actively treat. Seyi’s pain has reduced significantly by modifying activity, adding physical therapy and hydrotherapy. Seyi’s disease has also not progressed. If Seyi had

been treated with surgery or medication, she may have been over-treated. Seyi’s experience highlights the importance of active surveillance and the role of multidisciplinary team providing patient centric care.

Symptoms of TGCT can include pain, swelling, limitations to range of motion, joint instability, locking, numbing, although many patients may be asymptomatic or have manageable mild symptoms. In N- and D-TGCT, the decision to treat should be balanced by the potential for treatment to result in a cured patient versus the potential damage of disease left-behind or risk of repeat surgeries (Figure 4). In some patients, TGCT may cause little or no pain. Additionally, in some patients, TGCT causes little to no damage to the joint. Presentation of disease can be as diverse as the patients impacted.



**Figure 4. Balancing the potential treatment-related complications with the suffering caused by the disease.** Symptoms, pain, and potential joint damage should be balanced with recurrence risks, potential for a durable response to treatment with reasonable recovery times and quality of life of the patient.

**RECOMMENDATION (IV, B):** The decision to use active treatments such as surgery or medicine should balance the possibility of a cure, the impact the disease has on the patient, the risk of recurrence after surgery, and the potential for surgery-related complications and suffering.

The decision for active surveillance versus surgery/ medication should be shared with the patient after a thorough discussion of the risk and benefit within the multidisciplinary team approach.

**RECOMMENDATION (V, B):** When active surveillance is selected, the frequency of follow-up should be individualized based on tumour growth determined by MRI assessment, location of disease, and symptoms experienced by the patient.

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**RECOMMENDATION (V, B):** Active surveillance should be considered as the first option for asymptomatic patients. For symptomatic patients, active surveillance should also be considered if there is risk of major complications or suffering from surgery or medical treatment (e.g., history of severe toxicity from previous drug treatments, repeat operations and joint damage).

## SURGERY

### When should I treat with surgery?

Surgery is useful when the disease can be removed and a patient is symptomatic. The preferred approach is surgical removal either with less invasive surgery for N-TGCT or with extensive removal of the joint in D-TGCT with complete joint and/or tendon sheath involvement. Surgery can be performed as a keyhole with 2 or 3 small incisions, known as an arthroscopic synovectomy, or as an open synovectomy which includes a large incision site. *For purposes of this document, arthroscopy, arthroscopic synovectomy, and keyhole surgery are synonymous procedures.* Standard treatment for symptomatic TGCT is surgery when it can be accomplished without significant suffering or complications.

The type of surgery and expected outcomes from surgery should be discussed with a multidisciplinary team and the patient. The preoperative MRI should be reviewed for any hidden tumours or damage not visible with a standard surgical approach.

**RECOMMENDATION (III, A):** Surgical removal should be used when the disease is entirely capable of being removed and it can be accomplished without significant complications or long-term suffering, without recurrence, and if it improves quality of life.

The value of removing only part of the disease (debulking) and not the entire disease is controversial and should always be discussed in a multidisciplinary team balanced against other potential treatment options such as medications. Whether this type of partial removal should be done by an extensive open removal of the joint tissue (open synovectomy) or by an arthroscopic approach or a combination is debatable.

### What does a joint replacement do and why does it not treat the disease?

Traditional joint replacement effectively addresses joint pain and damage due to degeneration of the joint and erosion of the bone. The replacement does not address the disease itself. The disease within the joint may be removed during the replacement. However, there is a high degree of recurrence. Some patients are diagnosed after a joint replacement.

**RECOMMENDATION (III, B):** More radical removal and reconstruction of the joint and bone with a megaprosthesis (a form of reconstruction that replaces a large region of the bone) may be warranted but has higher failure rates.

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### RECOMMENDATION (V, C):

Amputation may be considered for functional reasons in rare, selected cases within expert centers after full discussion with the patient and having ruled out other options.

Use of medications before and/or after surgery aiming to reduce the amount present for surgical removal and/or risk of recurrence is investigational and unclear. There is no current data to understand whether this will be an effective strategy and more data is required before a recommendation can be made. Location and extent of the disease, surgical experience, and management by a multidisciplinary team are major factors in choosing whether to receive a medication instead of surgery. Surgery in recurrent cases has significantly higher risks for recurrence.

## N-TGCT

N-TGCT can be managed often by complete removal during surgery with low recurrence rates.

### N-TGCT within the joint: Knee

#### RECOMMENDATION (IV, B):

In N-TGCT located in the front of the knee, treatment involves removal of the tumour by a keyhole arthroscopic synovectomy.

The tumour is revealed and removed. Additional findings during the surgery should be removed or shaved away, therefore, recurrence remains low. Recurrence due to spreading TGCT around the joint during surgery rarely occurs but a large multicenter study of N-TGCT suggests that recurrence rate after open (13%) may be lower than after arthroscopic surgery (20%).

### N-TGCT within the joint: Hip

#### RECOMMENDATION (IV, B):

Depending on the location, either an approach from the front of the hip or from the back side can be used.

Recurrence rates are low. The only necessity for the open surgery is due to disease in a location attached to the ligament at the head of the femur with disease into regions unreachable by keyhole surgery.

### N-TGCT within the joint: Ankle and subtalar joint

#### RECOMMENDATION (V, B):

In disease that is in the back region of the ankle, either surgically approaching it from a backsides or center (postero-lateral or medial) approach with attention to the back blood vessels is recommended.

### N-TGCT within the joint: Shoulder

#### RECOMMENDATION (V, C):

Most N-TGCT may be resected from the front. Arthroscopic approach is an option.

### N-TGCT within the joint: Elbow

#### RECOMMENDATION (IV, C):

The surgical approach is defined by the specific involvement of the joint. In expert centers, arthroscopic approach may be used.

## LEVEL OF EVIDENCE:

Higher Reliability ↑	I	Highly reliable evidence
	II	Moderately reliable evidence
	III	Some evidence, with some reliability
	IV	Some evidence, less reliability
	V	Opinion or experience based

## GRADE OF RECOMMENDATION:

Evidence of benefit ↑	A	Strongly recommended
	B	Generally recommended
	C	Optional to consider by providers
	D	Generally not recommended
	E	Never recommended

When considering treatment recommendations, the threshold for **strong or moderate** recommendation is **B and A**.

### N-TGCT within the joint: Other uncommon sites

Locations such as the midfoot, mandible, or spine can only be treated surgically with partially removing the joint/tumours. Other/additional treatments may be considered.

### N-TGCT outside the joint

Most N-TGCT that exists outside the joint originates in the tendon sheath of the hand or foot, but also along tendons. Involvement in the bursa (fat pad that acts as a shock absorber) is possible.

#### RECOMMENDATION (III, B):

**In any case, removal of the entire tumour is necessary and recurrence risk is low.**

### D-TGCT

Surgery for D-TGCT is associated with high recurrence risk and post-operative complications. All cases should be discussed with a multidisciplinary team.

### D-TGCT within the joint: Knee

Surgery can be completed in a one-stage or two-stage procedure, unless one side of the knee is not significantly involved. Removal of the joint tissue (synovectomy) from the front (anterior) can be done through a keyhole/arthroscopic approach. The recurrence rate seems higher compared to that of open surgeries, however, this is controversial. A meta-analysis of 630 patients with D-TGCT of the knee found that lower recurrence rate was observed in patients that had open surgeries (24%) or a combination of an open back and arthroscopic front

surgery (14%) compared to an arthroscopic surgery alone (38%). Two other studies showed consistent results with lower recurrence with open surgery versus arthroscopic synovectomy. By contrast, a large meta-analysis of 1,019 patients showed lower recurrence rate after arthroscopic (16%) compared to an open surgery (23%). Thus, it is unclear which surgical approach yields the best result and should be based on patient centric discussion amongst a multidisciplinary team and the patient.

#### RECOMMENDATION (IV, B):

**Total removal of the joint requires aggressive removal of the synovium, commonly including the joint capsule.**

#### RECOMMENDATION (IV, B):

**Any disease extending into the proximal tibial fibular joint (a synovial joint at the top of where the tibia and fibula meet) should be removed and may require a separate entry incision into the joint.**

Disease at the back of the knee (posterior) often grows near the top part of the calf muscles which should be released or cut to expose the tumour. Healthy tissue removal must be done based on the amount and aggressiveness of disease shown on MRI. Bone destruction may require scrapping the tumour out. Continuous movement/motion without voluntary effort (e.g., a continuous movement machine or passive range of motion in physiotherapy) after surgery greatly enhances the recovery of the joint function compared to immediate active movement and weight bearing. Total joint

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replacement may be required for secondary osteoarthritis. One option is total joint replacement (arthroplasty) with a front (anterior) synovectomy to remove the joint and removal of the back portion of the knee joint if the backside is involved. D-TGCT undergoing joint replacement has an elevated risk of stiffness and may require subsequent procedures such as revision surgeries.

#### D-TGCT within the joint: hip

If there is joint destruction, total hip replacement (arthroplasty) gives excellent outcomes with low recurrence rates. In the absence of joint destruction, joint dislocation may be considered to gain access to the whole hip joint. **The approach(es) must allow the removal of the joint tissue (synovium) of all involved parts of the joint.**

#### D-TGCT within the joint: ankle and subtalar joint

Most patients need at least two incisions (and in extended cases three). In this case a two-stage procedure should be considered.

#### RECOMMENDATION (V, B):

**The recurrence rate is high (28% with an open surgery and 44% with an arthroscopic/keyhole surgical approach).**

#### D-TGCT within the joint: Shoulder and elbow

Arthroscopic approaches might be adequate based on the amount and aggressiveness of the disease. At the elbow, one incision might not be enough.

#### D-TGCT within the joint: Other

Locations in the spine and around the jaw rely on the experience of spinal and head/ neck surgeons.

#### D-TGCT outside the joint

#### RECOMMENDATION (IV, B):

**Removal of the entire tissue and some healthy tissue surrounding the tumour is the method of choice but requires larger incisions to remove the involved muscles or soft tissue.**

#### TGCT in children

We did not address the surgical approach to TGCT in children with growth plates that are still open for growth (skeletally-immature).

Treatment of adolescents (those without open growth plates and skeletally mature), should follow the same treatment principles as adults.



## LEVEL OF EVIDENCE:

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When considering treatment recommendations, the threshold for **strong or moderate** recommendation is **B and A**.

# RADIOTHERAPY (RADIATION) AND OTHER TREATMENTS

**RECOMMENDATION: The available literature provides insufficient evidence to propose a recommendation, thus we do not recommend the use of radiotherapy, either external beam and locally injected into the joint, as a standard treatment for TGCT.**

Most of the expert panelists do not use this treatment, particularly in patients with diffuse and recurrent disease. Published reports and studies are limited by small size, short follow-up, and are non-randomized, in hindsight, leading to challenges in interpreting data. Non-randomized treatments often lead to bias in disease severity, patient specific qualities, and institution expertise which may play a role in the results. **As TGCT patients are generally young with non-life-threatening disease, the long-term risk of cancerous formation and joint scarring, joint stiffness, or other complications associated with radiotherapy are of significant concern.** Whether radiotherapy should be considered in select cases with no alternative treatment options is a matter of debate.

Historically, radiation was used to treat TGCT. Patients recount their experience with radiation therapy. For instance, Jack had radiation after his third recurrence of diffuse TGCT in the ankle. He was

told that an ankle fusion would restrict the movement required for many of the activities he enjoyed such as wakeboarding and snowboarding. He elected for radiation prior to any medication options being available. Jack successfully completed his treatment but over the course of a few months later, his ankle began to deteriorate. The radiation had caused tissue and bone damage. Later, Jack elected into a below knee amputation and enjoys all his prior activities with a prosthetic. Jack's journey is not the typical after the advent of the medicines, however, his experience represents considerations that must be discussed with a multidisciplinary team about risks of treatments.

Lastly, radio-synoviorthesis, the injection of Yttrium-90 into the joint, has not shown to be effective in D-TGCT so far. It is not a method to compensate for inability to fully remove the disease during surgery. Higher quality prospective research is needed to better understand which is the potential role of this treatment modality for TGCT patients.

## Cryotherapy

Cryotherapy, the use of extreme cold to freeze or remove abnormal tissue, is investigational as available data is insufficient and limited to support the value of this procedure in TGCT.

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## MEDICATION/MEDICINE

Medicines that get into the circulating blood stream and are able to reach all over the body are called systemic therapies. Many of the medicines being investigated and used in TGCT are systemic therapies. These medicines are intended to shrink the tumor and improve patient's feeling and function.

It is worth noting that tumour shrinkage is measured by the sum of diameter of the target tumour and is an imperfect measurement due to the irregular and diffuse nature of TGCT. Often, this criterion underestimates the shrinkage of the tumour and therefore, volume of the tumour may be more accurate. However, the volume of the tumour as a measurement of treatment effectiveness is still being verified. Thus it is worth keeping in mind that shrinkage is not perfectly captured in the current measurements.

### TGCT that can be removed but with unacceptable amount of risk, complication, or suffering

There are patients that may be able to have their disease removed, but the risk of complications and future suffering outweighs the potential benefit. A patient with this experience is Marla, a patient with D-TGCT of the knee. Marla was diagnosed during a knee replacement after an x-ray had indicated severe arthritis. During the replacement, the tumors and joint tissue were removed. However, a portion of her tumor wrapped around an artery in the back of the knee. Instead of taking the risk of trying to separate the tumor from the artery, the tumor was left and

Marla was referred to an oncologist to discuss future treatment options. Marla's situation is an example of when there is an unacceptable amount of risk of complications. After surgery, Marla was asymptomatic and active surveillance was preferred for 2 years until her disease location required treatment.

The potential benefits of any medication/systemic treatment need to be carefully weighed against side effects and impact on quality of life. In contrast to life-threatening cancers where tumour shrinkage is often an indicator for improved long-term survival, this is not the case for TGCT where tumour shrinkage does not always represent benefit to the patients' symptoms. Assessment of benefit in TGCT must also include changes in symptoms and/or functional status. Without improvement in quality of life, tumour shrinkage is not a useful indicator of improvement because the patient is still suffering from a debilitating disease. TGCT can remain stable, unchanged, for prolonged periods. Consequently, in the later stages of disease several different scenarios can be encountered:

#### RECOMMENDATION (IV, B):

**In asymptomatic disease, active surveillance is the initial preferred approach, as the risk of over-treatment with surgery or medication, and complications from over-treatment, appears to outweigh the potential concerns with delaying medication.**

However, a medication may be justified in the rare asymptomatic cases in which disease location is potentially life-threatening (e.g., spine).

## LEVEL OF EVIDENCE:

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## GRADE OF RECOMMENDATION:

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### RECOMMENDATION (IV, B):

**In symptomatic disease, active surveillance can still be offered particularly if patients can manage the symptoms without difficulty, like with reasonable modification of activities or use of supportive care.**

However, disease location as well as location within the joint may affect the risk of permanent joint damage.

### RECOMMENDATION (IV, B):

**These aspects may justify starting a medicine, particularly if disease progression may affect quality of life**

Patients with difficulty managing symptoms, symptomatic disease, or patients with moderate/severe functional impairment may be candidates for a medicine if surgery would be associated with complications, suffering, or risks that outweigh the prospective benefit such as requirements for repeat surgeries.

### RECOMMENDATION (IV, B):

**Conventional chemotherapy that works by killing fast-growing cancer cells is commonly used for patients affected by sarcoma but is not useful in TGCT and should be limited to M-TGCT.**

CSF1 is overproduced in TGCT, this provides a basis for medicines to be created which specifically target and inhibit the TGCT cell's ability to use CSF1 for growth. CSF1 is mainly produced by immune cells. Blocking the interaction and dialogue between the immune cells and the tumour cells achieves substantial shrinkage of the tumour, improvement in symptoms and function of the joint. These medicines can be made from laboratory-engineered proteins that are locally injected into the joint (IA) or intravenously (IV) administered or small compounds taken orally.

### RECOMMENDATION (II, A):

**Medicines that target the abnormal production of CSF1, a major driver of the growth of TGCT, are considered standard and a detailed list of available tumor response per medicine option is presented in Table 2.**

When available, clinical trials should be offered.

### RECOMMENDATION (IV, A):

**In countries without approved medicines, the preferred option should be clinical trial participation or off-label drugs that target CSF1 (e.g., imatinib, nilotinib) when available.**

The optimal duration of treatment remains unclear (outside of clinical trials that have clearly defined study durations) and should be based on tolerance, preference of patient, patient lifestyle, and discussion with a multidisciplinary team.

**Table 2. Current medicines available in various settings**

MEDICINES	PERCENT OF PATIENTS THAT HAVE SIGNIFICANT SHRINKAGE (%)
Pexidartinib (Turalio)	39-62
Imatinib (Gleevec)	31
Nilotinib (Tasigna)	6
CLINICAL TRIAL MEDICINES	
Vimseltinib (DCC-3014)	49
Emactuzumab	71-85
Cabiralizumab	45

**\*AMB-05X has not published their trial results at this time and thus could not be included**

Pexidartinib (Turalio) represents the only approved treatment, but it is only available in the United States. Pexidartinib is an orally taken inhibitor of CSF1. In the pivotal clinical trial, 39% of patients demonstrated at least tumour shrinkage of at least 30% in the longest diameter of the tumour after 6 months of treatment. Four percent (5 out of 140) of patients treated with pexidartinib experienced severe liver toxicity and all recovered between 1 and 7 months after they discontinued the medication. Pexidartinib was approved by the United States Food and Drug Administration in 2019 for adult patients with symptomatic TGCT associated with severe symptoms and limitations in function that surgery is unlikely to provide benefit, or the risks associated with surgery outweighed potential benefit. Pexidartinib was approved with a Risk Evaluation and Mitigation Strategy (REMS) program that reduces the frequency and severity of liver-related side effects by frequent monitoring and provider-specific training that is required to prescribe the medication. This was not approved by the European Medicines Agency (EMA). The findings in ongoing studies have provided further support to improve the surveillance of liver related side effects and no additional deaths have been noted.

Imatinib (Gleevec) inhibits CSF1 indirectly. It was created to target a protein that is similar to CSF1 in chronic myeloid leukemia. It was approved two decades ago, and the side effects are well known. In a retrospective study of advanced TGCT, 30% of patients taking imatinib had significant shrinkage and symptom improvement. Patients were followed for 52 months, and imatinib suppressed the growth of disease for a median of 18 months. Imatinib is generally well tolerated, and the toxicity is low. **While it is not approved for TGCT, it is used off-label and available as a generic, reducing cost and making it widely accessible globally.**

Nilotinib (Tasigna) shows a potent reduction of CSF1. In a clinical trial for inoperable TGCT, nilotinib showed 6% of patients had shrinkage of 30% or more where 96% of patients had the same response at 12 weeks and 53% of patients had the same response after 5 years. Nilotinib is not approved for TGCT but used off-label.

### Trial Medicines

Vimseltinib (DCC-3014) is an oral, selective inhibitor of CSF1. Pexidartinib works directly at the region where CSF1 interacts with the cells, whereas Vimseltinib is a second generation and works at a separate region that has a longer effect. Because of this different site of action, Vimseltinib can be taken twice weekly instead of daily. Based on promising data from the first and second clinical trial which showed significant shrinkage in majority of TGCT patients, a pivotal clinical trial has closed recruitment to the last clinical trial prior to potential approval. The main severe side effects include elevation of blood creatine kinase, liver enzyme elevation, and high blood pressure.

Emactuzumab is an IV injectable medicine that is comprised of a laboratory engineered protein that directly targets and the signal of CSF1. In 85% of TGCT patients, tumours shrank 30% or more and symptoms and quality of life improved based on the clinical trial results published. Serious side effects include facial and eye swelling, an autoimmune disease where the body attacks itself (lupus erythematosus), skin that is redness, warmth, tenderness, and swollen, sore and inflamed mouth and gut (mucositis). There is no open clinical trial currently.

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## GRADE OF RECOMMENDATION:

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Cabiralizumab is another IV protein-based inhibitor of CSF1. In the first and second clinical trial, it was shown that 45% of patients had a response of 30% or more in tumour shrinkage. Serious side effects included creatine kinase elevation, swelling of the face and eyes, and high blood pressure.

Open questions still exist on the optimal way and demographic for using these medicines in the treatment of TGCT.

## QUALITY OF LIFE, SYMPTOM MANAGEMENT, AND PHYSIOTHERAPY

D-TGCT is commonly associated with joint instability, joint destruction, pain, swelling, decrease range of motion, stiffness, locking, slipping, and popping. Surgical resection can also lead to joint damage, scar tissue buildup, stiffness, and other consequences that impact quality of life. These symptoms persist in about 50% of patients even after they've been treated. Additionally, long-term medications may be accompanied by side effects. Consequently, D-TGCT often has significant impact on quality of life, patients' ability to perform daily tasks, exercise, work, and this may result in a change in occupation or pre-emptively retiring, and overall healthcare costs that burden the patient. Patients and their support systems lack help to cope with emotional, psychological, and financial obstacles related to their disease and care. They recount anxiety and often feel their experience is minimized by the perception of the disease being benign.

These experiences with the disease can be measured using qualitative scales, called Patient-reported outcome (PRO).

### RECOMMENDATION (III, A):

**These PROs are an essential part of the assessment and can influence treatment decision making.**

They also allow providers to understand how certain treatments may benefit the person with the disease instead of by just measuring the size of the tumour.

### RECOMMENDATION (V, B):

**Patients should be referred to pain specialists.**

For example, a TGCT patient should be referred to palliative care when they are experiencing physical and psychosocial distress, the initiation of tumour-specific therapies, patients' or family concerns, serious comorbidities, and multiple hospitalizations.

### RECOMMENDATION (II, B):

**There is no data that specifically addresses management of pain in TGCT, and so existing guidelines on chronic pain treatment should be followed.**

Pain management should be part of a multidisciplinary assessment to identify surgical, rehabilitation or systemic interventions which can be temporarily supported using low to moderate strength analgesics. Anti-inflammatory medications and opioids are among the most used medications. Eventual side effects or consequences of long-term pain therapies should also be considered. The chronic use of narcotics should be managed with a pain specialist to reduce potential for addiction and withdrawal. Future studies should elucidate the impact of TGCT location on symptoms, physical therapy optimal schemes and the impact of the different therapeutic options on quality of life.

## Follow-up Care

There are no data to indicate the optimal length and frequency for follow-up of completely removed TGCT. Currently, routine follow-up schedules differ

across institutions and may be driven by symptom onset and/or based on growth-patterns, tumour location, and patient preferences. In D-TGCT, most centers recommend an MRI every 6–12 months for patients with symptomatic disease. Some institutions perform a baseline MRI at 3-months post-operation to determine if disease was left behind (residual). A more frequent disease assessment (e.g., every 3–4 months) is usually applied in patients receiving a medication. While there is no data to support a recommended length and frequency of follow-up, based on the experience of advocacy organizations involved in this paper, routine follow-up for D-TGCT aids in a patient's confidence in their medical team and reduces anxiety associated with recurrence.

Discussions on future treatment options should occur at these follow-ups.

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## SUPPORT SERVICES

TGCT, like many rare diseases, can be isolating to the patient and their support system. Based on the specific needs of the patient, additional resources may be necessary for adequate care and support. Resources can be found in many places including:

- [TGCT Support](#)
- [SPAGN](#)
- Social workers at local hospital/cancer centre
- Mental health crisis lines
- Physiotherapists
- Occupational Therapists

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## FUTURE PERSPECTIVES

While several open questions regarding the optimal treatment strategy in TGCT are left to be addressed by future studies, a global effort is needed to make medicines available to TGCT patients worldwide and avoid discrimination. An overall decision tree for treatments is depicted (Figure 5).

There are several open questions among the experts and the advocacy community regarding the optimal treatment strategy in TGCT that need to be addressed by future studies and prospective patient registries. Among others:

### Should a patient have surgery after being on a medication?

It remains unclear the role of these medicines as an addition to surgery or following complete removal to prevent recurrence.

### How long should a patient use the medications?

Based on current evidence available, TGCT patients who are inoperable (where disease is unlikely to be successfully removed without severe suffering or risks) even after a response to medications will likely stay on treatment life-long, with options for

on/off periods based on the functional impact of the disease and on the symptoms. However, data on the long-term use and toxicity of medications in TGCT are still limited. Several prospective studies indicate that recurrence after treatment interruption is not consistent. Some patients who halt medication seem to have growth immediately while others have a sustained response from the medications. There are reports in literature describing  $\geq 50\%$  of patients are without growth at 2-years despite interruption of treatment after a year of therapy. Meaning, more than half of patients that have an interruption after a year of treatment maintain their response and don't have additional growth. Similarly, there are almost no data on the proportion of patients with resistance to these CSFR1 inhibitors. It is also unknown whether the reintroduction of CSFR1 inhibitors following disease growth after stopping therapy is an effective option, in which proportion of patients, and if it is better to consider a new CSFR1 inhibitor or reuse the original medication.

Further prospective collaborative studies are required to answer these questions and identify the optimum use of this class of agents, highlighting the importance that patients affected by TGCT and requiring a medication are referred and followed up at expert centers.

## **How should researchers assess quality of life and tumour response to maximize our understanding of the disease and patient experience in clinical trials?**

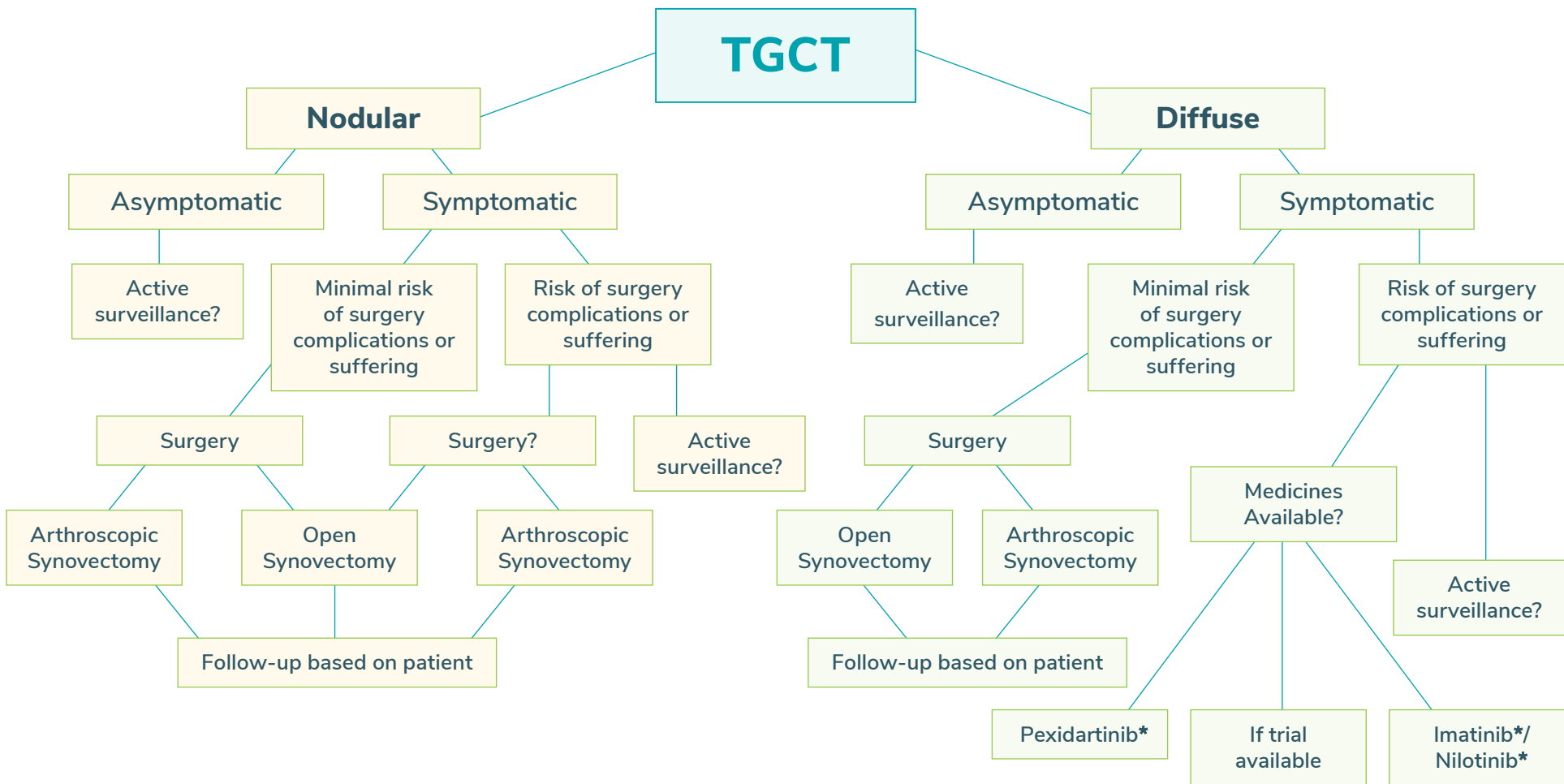
Measuring how a patient responds to treatments is challenging, as partially discussed when evaluating how researchers measure tumours on MRI. It is important to distinguish, however, the quantitative, objective response assessments required for reporting research studies from more qualitative, subjective changes that can be observed during routine clinical care. For example, MRI measurement of tumour is an objective response and quantitative whereas how a patient feels when they walk, carry

groceries, or sit for long periods is a subjective measurement that can be observed by a local provider. For a disease that is not life-threatening such as TGCT, reduction in tumour size alone is an insufficient outcome for the patient if symptoms are not improved. Assessment of functional outcomes such as how a patient feels and functions is a critical outcome for research studies, including measurements of pain, functional limitations, range of motion, and quality of life. In some circumstances, baseline values for these measures may be affected by prior surgeries or disease-related joint destruction and may not show significant improvement, although often patients can distinguish between "TGCT pain" and "arthritic pain". For routine clinical care, the quantitative measurement of changes in imaging is less important because whether a patient benefit is typically obvious by how they feel. But it is equally important to assess changes in pain, range of motion, and limitations in activities whether through qualitative, open-ended questions or through the use of more formal quality of life questionnaires.

The majority of TGCT patients treated with pexidartinib have so far shown a clinical and measurable response to treatment. However, whether a patient feels better, usually characterized by decreases in pain and swelling and increases in function and range of motion, can appear earlier, and do not always correlate with degree of tumour shrinkage. Meaning, some patients benefit from the treatment without significant or complete shrinkage occurring.

## **Is there a role for alternative therapies in TGCT?**

Alternative therapies often can be categorized as supplements, herbals, and dietary modifications. It remains to be determined the role these play in TGCT, whether they are a useful tool to aid in symptom management is unclear. There is insufficient data to support the use of alternative therapies as a treatment for the disease, however, alternatives may be used in complementary to traditional medical approaches. It is recommended to speak to a multidisciplinary care team about the best use of alternatives.



\*Accessibility and availability of medications are geographically dependent

Figure 5. Decision Tree on Potential Treatments.

Note: This decision tree is not in the original text and was interpreted by TGCT Support using the original consensus paper and discussions at the consensus meeting.