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Diffuse Tenosynovial Giant Cell Tumor: A Systematic Literature Review on Management and Treatment Strategies

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Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar- Universidade do Porto.

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RESUMO

Introdução:

O tumor de células gigantes tenossinovial do tipo difuso (D-TGCT) é uma lesão rara e benigna, mas com comportamento localmente agressivo. Origina-se maioritariamente no revestimento sinovial das articulações, bainhas dos tendões e bursas e pode causar dor e limitação funcional. Apesar de ser considerado benigno, está associado a altas taxas de recidiva. Existem várias opções de tratamento disponíveis atualmente, no entanto, ainda não existe consenso relativamente à abordagem mais eficaz, principalmente nos casos de doença recidivante ou inoperável.

Objetivo:

O objetivo desta revisão sistemática foi reunir e analisar de forma detalhada as evidências mais recentes sobre as estratégias de tratamento do D-TGCT, focando principalmente nas abordagens terapêuticas, na recidiva e no papel das terapêuticas emergentes. Ao reunir todos os avanços recentes da terapêutica, esta revisão permite oferecer aos clínicos uma orientação mais clara, levando a decisões informadas e partilhadas.

Materiais e métodos:

Foi realizada uma pesquisa sistemática nas bases de dados PubMed, Scopus e Web of Science, incluindo estudos publicados entre 2000 e janeiro de 2025. Foram selecionados artigos originais que descrevessem resultados do tratamento em doentes com D-TGCT. A seleção dos estudos e a extração de dados foram efetuadas de forma independente por dois revisores. A avaliação da qualidade metodológica foi realizada com recurso à checklist do Joanna Briggs Institute (JBI) para estudos de coorte. Os dados foram analisados de forma descritiva, devido à heterogeneidade dos estudos incluídos.

Resultados:

Foram incluídos 52 estudos, que no seu conjunto analisaram um total de 4279 doentes. A cirurgia foi a abordagem inicial mais utilizada, embora associada a elevadas taxas de recidiva, especialmente após sinovectomia por via artroscópica. A radioterapia adjuvante demonstrou ser eficaz na redução do risco de recidiva em casos selecionados. As terapêuticas sistémicas emergentes, nomeadamente os inibidores do CSF1R, mostraram benefícios a curto prazo em doentes com doença inoperável ou recorrente. No entanto, persistem dúvidas relativamente à sua duração, efeitos secundários, eficácia a longo prazo, segurança e relação custo-benefício. Nos casos assintomáticos, a vigilância ativa surge como uma alternativa viável.

Conclusão:

O tratamento do D-TGCT requer uma abordagem personalizada e deve envolver uma equipa multidisciplinar num centro de referência. Apesar dos avanços recentes, ainda não existe um protocolo terapêutico padronizado, sendo necessária mais investigação para definir a sequência e combinação de tratamentos mais eficaz. Abordagens multimodais, incluindo cirurgia, radioterapia e tratamentos sistémicos, parecem oferecer melhores resultados em casos de maior complexidade.

ABSTRACT

Introduction:

Diffuse-type tenosynovial giant cell tumor (D-TGCT) is a rare and benign tumor that originates in the synovial lining of joints, tendon sheaths, or bursae. Despite being benign, it is associated with locally aggressive behavior and high risk of recurrence, leading to pain, swelling and significant functional impairment. Several treatment options are currently available, but there is still no clear consensus on the most effective approach, particularly for recurrent or inoperable cases.

Objective:

This systematic review explores current evidence on the management of D-TGCT, focusing on treatment strategies, recurrence rates, and outcomes, while also discussing new therapeutic alternatives. By bringing together all recent advances, this review aims to help clinicians make informed and patient-tailored decisions when managing this tumor.

Materials and methods:

A systematic search was conducted in PubMed, Scopus, and Web of Science, including studies published between 2000 and January 2025. Original articles reporting treatment outcomes in patients with D-TGCT were selected. To ensure accuracy and reduce bias, two reviewers independently selected studies and extracted relevant data. The methodological quality of the included studies was assessed using the JBI Critical Appraisal Checklist for Cohort Studies. Due to the heterogeneity across study methodologies and outcomes, a narrative synthesis was considered the most appropriate method to summarize the results.

Results:

Fifty-two studies, including 4279 patients, were reviewed. Surgery, especially open synovectomy, remains the standard of treatment but is associated with considerably high recurrence rates. Adjuvant radiotherapy can help reduce recurrence in selected patients. In inoperable or recurrent tumors, systemic therapies, such as CSF1R inhibitors, have shown some short-term benefits. However, their toxicity and long-term effects are still unclear. For asymptomatic patients, active surveillance can be a viable option.

Conclusion:

The management of D-TGCT requires a tailored and multidisciplinary approach, coordinated in a referral center. While treatment options have expanded over the years, there is still no standardized treatment algorithm. Therefore, further research is needed to establish clearer guidelines and treatment protocols. Multimodal strategies combining surgery, radiotherapy, and systemic therapies can offer the best outcomes particularly when individualized to the patient's condition and tumor behavior.

LIST OF ABBREVIATIONS

BPI – Brief Pain Inventory

CSF1 – Colony-Stimulating Factor 1

CSF1R – Colony-Stimulating Factor 1 Receptor

D-TGCT – Diffuse-type Tenosynovial Giant Cell Tumor

EBRT – External Beam Radiotherapy

EQ-5D-5L VAS - EuroQol 5-Dimensions 5-Levels Visual Analogue Scale

FDA – Food and Drug Administration

FU – Follow-up

GCTB – Giant Cell Tumor of Bone

JBIR – Joanna Briggs Institute

L-TGCT – Localized-type Tenosynovial Giant Cell Tumor

MCID – Minimal Clinically Important Difference

MeSH – Medical Subject Headings

MRI – Magnetic Resonance Imaging

NCCN – National Comprehensive Cancer Network

NRS - Numeric Rating Scale

ORR – Objective Response Rate

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROMIS – Patient-Reported Outcomes Measurement Information System

PVNS – Pigmented Villonodular Synovitis

QoL – Quality of Life

RANK – Receptor Activator of Nuclear Factor Kappa-B

RANKL – Receptor Activator of Nuclear Factor Kappa-B Ligand

RCT – Randomized Controlled Trial

RECIST – Response Evaluation Criteria in Solid Tumors

REMS – Risk Evaluation and Mitigation Strategy

RFA – Radiofrequency Ablation

RSO - Radiosynoviorthesis

TGCT – Tenosynovial Giant Cell Tumor

TVS – Tumor Volume Score

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INTRODUCTION

Giant Cell Tumors (GCT's) are rare and locally aggressive tumors, typically benign but associated with significant impact on patients' functional impairment and quality of life. They are classified into two main types: Giant Cell Tumor of Bone (GCTB) and Tenosynovial Giant Cell Tumor (TGCT). These tumors differ in several aspects, including their anatomical location, clinical features and biological behavior. GCTB is most commonly found in the epiphyseal regions of long bones especially around the knee. Their pathogenesis involves dysregulation of the RANK/RANKL/OPG signaling pathway leading to excessive bone resorption. Conversely, TGCT typically originates in the synovial lining of joints, tendon sheaths and bursae. Despite sharing some histological features, their differences in location, behavior and underlying mechanism call for distinct diagnostic and therapeutic approaches.¹²

Tenosynovial Giant Cell Tumor (TGCT), previously known as Pigmented Villonodular Synovitis in its diffuse form, is a rare and proliferative disease, typically with mono-articular involvement, originating in the synovium and affecting both intra- and juxta-articular regions. This tumor can be divided into two main subtypes: localized-type (L-TGCT) and diffuse-type (D-TGCT). This systematic literature review will focus on the latter.

Over time, these tumors have been described using various names, including Giant Cell Tumor of the Tendon sheath, Synovial Giant Cell Tumor, or Pigmented Villonodular Synovitis (PVNS). Evidently, this lack of consensus in the nomenclature has led to confusion in literature. Therefore, recent efforts have been made to standardize terminology under the term TGCT, based on their similar histological and molecular features. This will allow for improved clarity in diagnosis and treatment strategies.³ In the 2013 edition of the World Health Organization classification of soft tissue and bone tumors, the terms “giant cell tumor of the tendon sheath” and “pigmented villonodular synovitis” were replaced by “localized-type TGCT” and “diffuse-type TGCT”, respectively.⁴

TGCT is considered a rare disease, sometimes referred to as “orphan” due to the lack of effective treatment options and unaddressed clinical needs. The localized-type TGCT (L-TGCT) has an estimated incidence of around 45 million cases per million person-years, while the diffuse-type is significantly less common, with only 5 cases per million person-years. There is a slightly higher incidence in females, and it usually affects adults aged between 30 and 50 years old, but it can occur at any age. The affected locations are different for both subtypes: while the L-TGCT often appears in the fingers and toes, D-TGCT tends to be more aggressive, affecting larger joints, mainly the knee (70%) and the hip (15%).^{5, 67}

Clinical presentation is very nonspecific and can vary considerably between patients. The most reported symptom is joint pain, but swelling, stiffness, hemarthrosis or limited articular movements can also be present. Patients can be asymptomatic for long periods, leading to a delayed diagnosis, representing one of the main challenges associated with this disease. Although a history of trauma is sometimes reported, a causal relationship between these two occurrences has not been established yet.^{8, 9}

D-TGCT is histologically benign but tends to behave in a locally aggressive manner and is characterized by a high rate of local recurrence. MRI is the imaging modality of choice for

diagnosis, as it provides detailed assessment of TGCT's typical features such as synovial proliferation, joint effusion, joint bulging, and characteristic hemosiderin deposits. Sequences like gradient-echo and contrast enhanced imaging are particularly useful.^{10 11} D-TGCT can be detected by multilobulated lesions with synovial thickening, villous projections and hemosiderin deposits that often can extend into the extra-articular tissues. It is frequently associated with cartilage loss, bone erosions and osteophyte formation. However, histological confirmation through biopsy remains essential for definitive diagnosis. It is frequently obtained through image-guided core needle biopsy.¹²

Achieving effective local control of D-TGCT can be very challenging. Surgical resection is the main treatment option, with radical synovectomy performed for extensive disease using either an open or an arthroscopic approach. Surgical management is often complex, primarily due to the diffuse type's deep anatomical location and indistinct margins. Therefore, recurrence rates remain high, ranging from 23% to 55%, with long-term studies showing that only around 40% of patients remain recurrence-free after 10 years. This recurrence is particularly high in the knee. This leads to the necessity of multiple and repeated surgeries, increasing the risks of complications, morbidity, mortality, functional impairment and decreased quality of life (QoL).^{13 14 3}

To reduce these recurrence rates, the identification of effective adjuvant systemic treatments becomes particularly important, including radiotherapy and systemic pharmacotherapy. In this context, external beam radiation and radiosynoviothrosis (RSO, involving the use of intra-articular radioisotopes), have been explored as an adjunct to surgery. Although some studies support its utility^{15 16} and suggest it may be beneficial, especially when combined with surgery, concerns about long-term side effects, such as the risk of radiation-induced malignancy, have limited its widespread use.¹⁷

TGCT is a neoplastic-like disorder, presenting villonodular hyperplasia, dense fibrosis, and hemosiderin deposition. Recent insights into the TGCT's molecular drivers and pathogenesis, particularly the overexpression of colony-stimulating factor 1 (CSF1) due to chromosomal translocations, have led to the development of targeted systemic therapies. CSF1 receptor (CSF1R) inhibitors, such as Pexidartinib, have shown promise for patients with inoperable or recurrent disease.^{18 19 20} However, these treatments require careful patient selection due to the risk of systemic toxicity and side effects.

Malignant transformation of TGCT is very rare, but a few cases have been documented in the literature. While no clear risk factors have been established, some authors suggest that the risk of malignant progression can be slightly higher in patients with long-standing disease, multiple recurrences or severe joint damage. Although the evidence is limited, these observations highlight the importance of long-term follow-up.¹⁵

Despite its benign nature, TGCT can cause a considerable burden for both patients and healthcare systems. A large retrospective study identified a considerably high increase in healthcare costs during the year after the diagnosis. The largest shares of expenses consisted of ambulatory care and physical therapy.^{21 22} Therefore, this disease can significantly affect patients' daily functioning and quality of life. There is a need to improve treatment strategies, not only to achieve local tumor control, but also to decrease the emotional, physical and economic impact caused by TGCT.

This systematic literature review aims to summarize the current evidence on the management of diffuse-type TGCT and explore emerging treatment modalities, focusing on local recurrence, their treatment and complications. The goal is to help define a more standardized approach of care for this challenging disease and improve treatment strategies.

MATERIALS AND METHODS

The research for this systematic literature review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²³ The goal was to identify and evaluate the current evidence on the management strategies for Diffuse Tenosynovial Giant Cell Tumor (D-TGCT).

Two reviewers independently extracted and selected papers using the predetermined criteria.

Eligibility Criteria

We included original studies that evaluated treatment strategies or outcomes in patients diagnosed with Diffuse Tenosynovial Giant Cell Tumor. Eligible study designs included randomized controlled trials, prospective studies, cohort studies, case-control studies, and case series with more than 7 patients to gather the maximum available data. Only articles with full text available were included.

To achieve a complete analysis, the selected studies had to meet the following criteria: published in English or Portuguese, between 2000 and January 2025 and involving adult human subjects (aged 18 years or older). The studies had to address management approaches (e.g., surgical, medical, or radiotherapeutic interventions) for D-TGCT specifically, and discuss recurrence and its management. Additionally, the tumor location had to be in the appendicular or axial skeleton (excluding tumors located in the head, face, thoracic girdle, or retroperitoneal region).

Exclusion criteria were case reports, narrative reviews, editorials, conference abstracts, descriptive only trial designs, animal studies, under 18 years old, *in vitro* studies, studies focusing exclusively on localized-type TGCT, and studies not reporting treatment outcomes or recurrence treatment. This review excluded publications prior to 2000 to prioritize more current evidence and ensure the relevance of the included literature.

Information sources and search strategy

A systematic search was conducted in the following databases: PubMed, Scopus, and Web of Science. The last search was made on January 10, 2025.

Ethical approval and informed patient consent was not necessary for this review as all the data included was taken exclusively from previously published, peer-reviewed studies.

The initial search was made using a combination of MeSH terms and keywords including: ("Tenosynovial giant cell tumor, diffuse type" OR "pigmented villonodular synovitis" OR "diffuse TGCT" OR "PVNS") AND ("treatment" OR "management" OR "therapy" OR "drug therapy" OR "surgical treatment" OR "Radiotherapy" OR "tyrosine kinase inhibitors" OR "immunotherapy").

The initial search across the three selected databases resulted in 2337 articles. These results were narrowed down using a series of filters, based on the previously defined inclusion criteria: publication date between 2000 and 2025, language restricted to English and Portuguese, studies involving human subjects aged 18 years or older, and availability of abstract and full text. The

number of records was reduced to 1331. A total of 1050 articles remained for screening, after removing case reports and other non-eligible study types.

To ensure reliable results, two reviewers (CEM and VO) independently screened the titles and abstracts for eligibility, resulting in the selection of 285 articles for further assessment. After removing duplicates using Mendeley reference manager, 174 articles remained. These were retrieved for full-text evaluation. Thereafter, a detailed review and application of the inclusion and exclusion criteria led to the selection of 52 studies that were included in the final qualitative synthesis.

The study selection process is detailed in a PRISMA flow diagram presented in Figure 1 – PRISMA Flow diagram.

This systematic review was not prospectively registered in PROSPERO or other public databases.

Quality Assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies,²⁴ which is appropriate for both prospective and retrospective observational designs. The checklist consists of 11 items assessing risk of bias across the domains of participant selection, exposure and outcome measurement, confounding factors, follow-up, and statistical analysis. The checklist application followed the 2020 JBI Manual for Evidence Synthesis.²⁵

Two reviewers independently assessed each study. Each item was rated as “Yes”, “No”, or “Unclear”. Rather than generating a numerical score, an overall judgment was made for each study. Based on the number and nature of limitations identified, studies were categorized as having low, moderate, or high risk of bias. Discrepancies between reviewers were resolved through discussion and consensus.

A summary of the risk of bias ratings is presented in Table I : Summary of the Risk of Bias Rating Using the JBI Critical Appraisal Checklist for Cohort Studies. This quality assessment informed the interpretation of the findings but was not used as a criterion for study exclusion.

Data extraction and synthesis

A standardized data extraction form was used to collect information from the included studies. This process included various details, such as author, year of publication, study design, patient sample size, anatomical location of the tumor, treatment provided, local recurrence rate, recurrence’s treatment, re-recurrence rate, treatment- related complications and mean follow-up time.

RESULTS

A total of 52 studies published between 2000 and 2025 were included in this systematic review. These studies reported on 4279 patients diagnosed with D-TGCT, confirmed with MRI imaging and histology. Both prospective (37%) and retrospective (63%) studies were included. The most frequently affected joint was the knee, reported in nearly 87% of studies, followed by the ankle (52%) and hip (47%). Less common locations like the wrist, hand, shoulder, and spine were occasionally mentioned. The duration of follow-up among the included studies ranged from 0 to 528 months, with the shortest being observed in studies with immediate post-treatment evaluations^{26,27} and the longest in retrospective cohorts such as Cao et al. (2023)²⁸, which followed patients for up to 44 years.

Table II : Summary of the Main Characteristics and Findings of the Studies Included in the Systematic review summarizes the 52 studies included in this systematic review. It outlines relevant information such as the authors, year of publication, sample size, treatment strategies, recurrences and their management, complications and follow-up.

1. Treatment approach

Surgery was the most frequent first treatment strategy reported in 36 out of the 52 included studies (69.2%). There were two main approaches for the synovectomy: open synovectomy was performed in 53% of cases while arthroscopic in 39%. A combined approach was also reported in 8% of cases, depending on the location and extent of the disease.

Adjuvant radiotherapy, either external beam or radiosynoviorthesis, was used in 33 studies (63%), often combined with surgery (92%). It was particularly helpful to improve local control in more diffuse or recurrent cases. Examples include Griffin et al. (2012)¹⁵, Heyd et al. (2010)²⁹, and Lee et al. (2005)³⁰, all reporting favorable outcomes with low-dose radiation following surgery. In Kodiyan et al. (2017)³¹, there is evidence that radiotherapy alone can be used in cases of incompletely resected D-TGCT.

Systemic therapies, particularly CSF1/CSF1R inhibitors, belong to a group of emerging therapies with great therapeutic potential. They were reported in 15 of the studies (29%). These included Pexidartinib, the only FDA-approved agent at the time, and others non-FDA approved such as Imatinib, Sunitinib, Sorafenib, Emactuzumab, Nilotinib, and Vimseltinib. Among these, Pexidartinib was the most frequently studied, featured in 11 studies including the pivotal ENLIVEN study.^{32 33 27} This type of treatment is mostly reserved for patients with inoperable tumors, major surgery risks, recurrent or extensive disease or when unacceptable morbidity is expected after surgery.

These studies provided evidence that systemic therapies, especially Pexidartinib, were able to provide local control with significant tumor shrinkage, changes in resectability status and improve physical function and stiffness. With these therapies, there was an objective tumor response, with partial or complete responses observed in 60 to 80% of patients, as documented by Desai et al. (2025)³⁴, Brahmi et al. (2020)³⁵, Tap et al. (2015)³⁶, and Tap et al. (2019)²⁷. Also, improvements in patient-reported outcomes, such as stiffness and physical function (measured by PROMIS-PF and EQ-5D-5L scores) were pointed out in about 40% of these studies, as the ones by Desai et al. (2025)³⁴, Brahmi et al. (2020)³⁵, and Tap et al. (2019)²⁷. Although progression-free survival

exceeded 90% at 12 weeks in several studies, it declined to 57% at 48 months in the study by Gelderblom et al. (2018)³⁷. Spierenburg et al. (2022)³⁸ and Gelderblom et al. (2018)³⁷ revealed systemic therapy could convert inoperable lesions into operable, enabling surgery after medical treatment.

Furthermore, the study by Healey et al. (2023)³³ showed a moderate pain reduction, sustained for at least 50 weeks. Pexidartinib led to greater pain reduction compared to placebo, with 31% of patients achieving a decrease in worst-weekly pain versus 15% with placebo. A clinically meaningful improvement (MCID ≥ 2 points) was observed in 31% of patients treated with Pexidartinib versus 14% in the placebo group ($p = 0.02$). The mean reduction in pain from baseline to week 25 was -2.5 points with Pexidartinib compared to -0.3 with placebo ($p < 0.001$), with further improvement maintained up to week 50. However, despite being promising, their results are not sufficient to justify the regular use of Pexidartinib for pain management, especially considering that complete pain data were missing for a greater number of patients, due to several different reasons. Lin et al. (2024)²⁶ also showed a significant improvement in pain and stiffness during Pexidartinib treatment. Although pain remains the most significant symptom associated with TGCT, many patients also suffer from concomitant degenerative conditions, such as osteoarthritis, which can complicate the assessment of treatment outcomes.

Finally, active surveillance was reported in 3 studies (6%). This strategy is reserved for asymptomatic patients with small lesions, or when other treatments are not available.

Out of the 15 studies that employed systemic therapies, 12 (80%) used it alone, whereas the other 3 combined it with either surgery or radiotherapy, reflecting the need for a multimodal approach.

2. Recurrences

Local recurrence significantly differed across studies, ranging from 0% to 93%, depending on the treatments adopted and patient compliance. 44 of the 52 studies reviewed (85%) reported recurrences.

The lowest recurrence rates were reported when complete surgical resection and adjuvant radiotherapy were combined, using either external beam or isotopic RT. This is demonstrated in the work by Berger et al. (2007)¹⁶, Elattar et al. (2020)³⁹, Tie et al. (2013)⁴⁰, Lee et al. (2005)³⁰, and Shabat et al. (2002)⁴¹, which achieved 0% recurrence using this treatment modality.

Among the 25 studies using radiotherapy, most recurrence rates reported were under 20%. Radiotherapy was usually used as an adjuvant modality, following surgical resection or, less frequently, as a standalone treatment in inoperable cases, as mentioned previously. Nineteen of those 25 utilized external beam radiotherapy (EBRT) and 7 isotopic radiotherapy with yttrium-90 (for example Shabat et al. (2002)⁴¹ and Koca et al. (2013)⁴²), or with intra-articular chromic phosphate injection⁴³. Examples of studies that used EBRT are, among others, Griffin et al. (2012)¹⁵, Berger et al. (2007)¹⁶. When comparing both radiotherapy approaches, the recurrence rate among studies that used EBRT was lower (median of 9.7%) than in those using isotopic radiotherapy (median of 22.7%).

The highest recurrence rates were typically associated with surgery alone, particularly with arthroscopic synovectomies, ranging from 13.3% to 63.7% and up to 93% in some subgroups.⁴⁴ For

example, in the study by van der Heijden et al. (2014)⁴⁴, arthroscopically treated patients showed a 93% recurrence rate, while only 29% of those treated with open surgery showed recurrence. Another example is the study by van der Heijden et al. (2016)⁴⁵ which demonstrated that 58% of the arthroscopic group showed recurrence, compared to only 36% in the open surgery group.

Regarding systemic therapies, such as Pexidartinib, local recurrence and disease progression are influenced by treatment adherence and disease severity. Desai et al. (2025)³⁴ observed that after interrupting Pexidartinib, 55% of patients had disease progression, while those who maintained continuous therapy didn't show either progression or recurrences. However, Brahmi et al. (2020)³⁵ reported that 87% of patients treated with CSF1R inhibitors (Imatinib, Nilotinib, Pexidartinib, Emactuzumab) had tumor progression. The progression-free survival rates decreased from 56% after first-line therapy to 25% and 20% after second and third-line treatments, respectively. Despite the use of systemic CSF1R inhibitors, 60% of patients experienced progression, often in the first year. Gelderblom et al. (2021)⁴⁶, observed a complete or partial response in 60% of patients, with stable disease in 20% and progression in 1%. Tumor Volume Score (TVS) based response was 65%, with most of these responses (77%) occurring within the first 6 months. By comparison, RECIST response rates reached 62% within the same period. Overall, 11% of patients progressed during treatment and 2% after discontinuation. Studies by Tap et al. (2015)³⁶, Tap et al. (2019)²⁷, and Van de Sande et al. (2021)³² observed improvements in functional outcomes, correlating tumor shrinkage with reductions in stiffness and improvements in physical function scores.

3. Recurrence Treatment

Local recurrence was commonly treated with repeated synovectomies (48.6% of studies), often complemented with adjuvant radiotherapy, either external beam radiation or isotopic synoviorthesis. For example, Griffin et al. (2012)¹⁵ and Zhang et al. (2024)⁴⁷ both described successful control of recurrence with repeat resections followed by adjuvant radiotherapy. Patients who underwent arthroscopic surgery as their primary treatment often required multiple interventions, with some undergoing up to nine procedures, as reported by van der Heijden et al. (2014)⁴⁴.

A minority of studies (11.4%) opted to manage recurrence with radiotherapy or radiosynoviorthesis alone, without additional surgeries. Heyd et al. (2010)²⁹, Zook et al. (2011)⁴³, Kat et al. (2000)⁴⁸, and Gortzak et al. (2018)⁴⁹ employed either external beam or isotopic radiotherapy with positive results.

Patients initially treated with systemic therapies (either alone or combined with surgery) showed fewer recurrences and reduced disease progression. Pexidartinib was used for recurrences, often with effective local control. For example, Desai et al. (2025)³⁴ specifically evaluated the discontinuation and rechallenge of Pexidartinib in a cohort of 32 patients. They observed that of the eleven patients who stopped treatment, six (54.5%) experienced disease progression during a median of 22.8 months off therapy. Three of them then restarted treatment, and all regained disease stabilization. After that, two reported improved physical function and quality of life scores (PROMIS-PF and EQ-5D-5L). There were no new concerns regarding safety during the rechallenge.

With disease progression, total joint arthroplasty may be necessary, especially after repeat surgery.⁵⁰ In the study by Li et al. (2023)⁵¹, all patients who had recurrence after failed arthroscopy underwent total hip arthroplasty. This type of surgery is usually needed after repeated unsuccessful surgeries or when there is significant joint destruction.

Overall, several treatment options are available for managing recurrence. Treatment choice should be made according to patient factors, disease extent, and prior interventions.

4. Re-recurrence

Re-recurrence can be defined as a second local recurrence following treatment of the first recurrence. 9 of the 52 studies (17.3%) reported re-recurrences, more frequently in patients who had previously undergone surgery alone, and less commonly in those who had received systemic therapy or adjuvant radiotherapy. The highest rates were observed in the study by Cao et al. (2023)²⁸, where 50% of patients treated with reoperation alone showed re-recurrence, and Ottaviani et al. (2011)⁹ in which 33% of the re-treated knees recurred. Furthermore, van der Heijden et al. (2014)⁴⁴ reported that the re-recurrence rate was significantly higher in patients treated with repeat arthroscopic synovectomy (63% recurrence) compared to those treated with open surgery (7%).

In Gortzak et al. (2018)⁴⁹, 36% of patients (9 out of 25) treated with radiosynoviorthesis required a third surgical intervention. In comparison, in Desai et al. (2025)³⁴ patients who restarted Pexidartinib after recurrence or disease progression maintained local control and showed no further progression. Similarly, studies using salvage radiotherapy, such as Heyd et al. (2010)²⁹ and Kat et al. (2000)⁴⁸, reported no further progression after re-treatment.

5. Complications

Complications related to treatment were reported in a considerable portion of studies (63%), although the nature and severity of these adverse events varied depending on the treatment modality. Systemic treatments, particularly Pexidartinib, accounted for the most reported side effects, though the majority were mild to moderate. In the study by Desai et al. (2025)³⁴, 67% of patients in the continuous treatment group and 100% of those re-treated experienced adverse effects, including liver enzyme elevation, hypertension and COVID-19 infection. Similarly, the studies by Tap et al. (2019)²⁷ and Gelderblom et al. (2021)⁴⁶ observed hepatotoxicity in up to 13% with liver enzyme elevation in 92%, hair color changes in up to 75%, fatigue in 61% and nausea in 47%. These treatment-related adverse effects led to the need for dose reduction in 34% of patients in Dharmani et al. (2024)⁵² and monitoring under the Risk Evaluation and Mitigation Strategy (REMS) program, due to the risk of hepatotoxicity.

In contrast, surgical interventions were associated with fewer but more functional and mechanical complications, such as joint stiffness, infection, arthrosis or osteonecrosis, especially in open or repeated resections. For example, Mollon et al. (2016)⁵³ reported avascular necrosis, lymphedema and wound dehiscence; Chin et al. (2002)⁵⁴ observed stiffness in 7.5% of patients, wound

complications in 10%, reflex sympathetic dystrophy in 3%, and total knee replacement was required in 3% of cases; In Cao et al. (2023)²⁸, surgical complications were reported in 56% of patients, with higher rates in those undergoing complete total resection (60%) compared to subtotal resection (33%).

Radiotherapy, both external beam and radiosynoviorthesis, was usually well tolerated and presented mostly mild complications, including dermatitis (25%), joint effusion (23%), and reduced range of motion (4%) in Lin et al. (2020)⁵⁵. No radiation-related malignancy was reported. Regarding yttrium-90 synoviorthesis, no systemic leakage or radiation-related complications were observed in Shabat et al. (2002)⁴¹ nor in Ottaviani et al (2011)⁹.

DISCUSSION

This systematic review evaluated the different management strategies for diffuse-type tenosynovial giant cell tumor (D-TGCT), focusing on local recurrence, re-recurrence, treatment-related complications, and patient outcomes. D-TGCT's diagnosis is often delayed due to its vague or absent symptoms⁸ which can significantly impact patients' quality of life (QoL) and impose a considerable economic burden, particularly associated with successive recurrences and required interventions.

The knee is the most frequently affected joint, followed by the ankle and hip. Multifocal disease is very rare but has been reported. Recurrence rates varied significantly across studies (from 0% to 93%), depending on the treatment modality, extent of disease, and follow-up duration.

Surgical resection continues to be the initial treatment approach for D-TGCT. Complete synovectomy via open surgery is associated with lower recurrence rates, when compared to arthroscopic techniques. Patel et al. (2017)¹⁴ documented substantially lower recurrence rates with open synovectomy (44.8%) compared to arthroscopic synovectomy (83.3%). Van der Heijden et al. (2014)⁴⁴ similarly demonstrated worse outcomes when using arthroscopy, therefore recommending primary open surgery to prevent recurrence. However, a study by Gu et al. (2014)⁵⁶ found no significant differences between open and arthroscopic approaches. Colman et al. (2013)¹³ showed that combining open posterior and arthroscopic anterior synovectomy can lead to lower recurrence rates (9%) when compared to either only arthroscopic (62%) or open approaches (64%). However, it is important to consider that patient allocation to each surgical technique may have been influenced by disease severity, tumor size and extension, or anatomical factors, which can introduce potential selection bias. Therefore, these results must be interpreted with caution. Complete resection remains the goal for cure, regardless of the surgical approach.

Even though open procedures are often associated with higher morbidity, especially if double approach is required (anterior and posterior), there is no definitive evidence from randomized controlled trials (RCTs) confirming this difference when compared to arthroscopy. For example, arthroscopic synovectomy, particularly when incomplete, can lead to fibrous tissue formation, meniscal retraction, and cellular paucity.⁵⁷ To date, complication profiles appear similar between approaches.¹³ The assessment of medium and long-term outcomes for the surgical approaches can be complicated, as the outcomes can be influenced by the necessity of additional interventions to treat recurrences.

The analysis of the 52 studies in this review revealed that a 0% recurrence rate was consistently achieved when combining surgical resection with adjuvant radiotherapy. This highlights the benefits of a multimodal approach to achieving local control, particularly for managing diffuse and high-risk cases. Re-recurrences were more frequent after repeated arthroscopic procedures or open surgeries without adjuvant therapy. In contrast, systemic treatments and radiotherapy offered more durable control, especially for recurrent or inoperable cases.

Adjuvant radiotherapy can help reduce the recurrence risk. External beam radiation therapy (EBRT) showed superior local control compared to intra-articular yttrium-90 radiosynoviorthesis. The latter was linked to more complications such as skin necrosis, draining sinus formation, and chronic pain.^{17 49}

For patients with inoperable tumors, recurrent or treatment-resistant D-TGCT, systemic therapies, such as the CSF1/CSF1R inhibitors (e.g. Pexidartinib and Imatinib), provide effective alternatives. There are 5 ongoing prospective studies on CSF1R inhibitors for TGCT, and one retrospective study on Imatinib. The ENLIVEN trial demonstrated Pexidartinib's significant efficacy compared to placebo, leading to its FDA approval for symptomatic D-TGCT unsuitable for surgery.²⁷ However, due to hepatotoxicity risks, Pexidartinib is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.¹⁹ Imatinib remains a category 2A recommendation for TGCT in the NCCN guidelines.^{27 58 59}

Treatment duration and safety during temporary discontinuation of systemic therapies remain unclear. Desai et al., 2025³⁴ studied the discontinuation of Pexidartinib in patients who had previously responded to therapy. They observed that, even though the disease may progress during treatment-free periods, restarting it can restore local tumor control. No new safety concerns were reported during the restart, supporting the potential use of intermittent treatment strategies in selected patients.

Emactuzumab, another CSF1R inhibitor, achieved promising results in a phase 1 trial, in which patients with diffuse TGCT experienced high objective response rates. Cassier et al. (2015)⁵⁸ reported early tumor shrinkage and partial responses in 79% of patients. However, additional treatment cycles did not result in stronger responses. They also identified a significant decrease in peripheral blood monocytes, expressing high levels of CSF1R, indicating a pharmacodynamic effect of the therapy.

These findings have led to the ongoing phase 3 clinical trial, known as the TANGENT study. It is a randomized, double-blind, placebo-controlled multicenter study evaluating Emactuzumab's efficacy and safety in patients for whom surgery is not viable. Even though no peer-reviewed publications from this trial have been released, there is strong interest in its progress due to the need for more well-tolerated and safe systemic treatment options. The trial's initiation and FDA Fast Track designation underscore the relevance of this therapeutic approach and its potential to help define the best use of CSF1R inhibitors in D-TGCT.

Emerging therapies like Vimseltinib, a selective CSF1R inhibitor, and Zaltoprofen, a non-steroidal anti-inflammatory drug with PPAR γ (Peroxisome Proliferator-Activated Receptor Gamma) activation properties, are also showing promise. Vimseltinib demonstrated a 40% objective response rate and improved patient-reported outcomes with a favorable safety profile in the MOTION phase III trial, leading to its FDA approval in February 2025.⁶⁰ Zaltoprofen has been studied in placebo-controlled trials involving patients with unresectable D-TGCT, with positive results and good safety profile.⁶¹ However, further studies are needed to confirm these benefits and compare them with current treatments. Additionally, for patients with asymptomatic or stable disease, active surveillance can be a safe and effective approach, provided it includes close and consistent monitoring.¹¹

Several innovative early-stage approaches are being investigated, such as intra-articular TNF-alpha inhibitors and colloidal systems designed to target the tumor's inflammatory environment. While these methods are still in the experimental stage, they may offer positive responses with fewer systemic effects. Spierenburg et al. (2022)⁶² discussed some of these strategies, including anti-TNF agents and monoclonal antibody administration within the joint.

Radiofrequency ablation (RFA) can be suggested to patients with D-TGCT when their lesions involve surgically challenging regions, for example the posterior knee. RFA can help relieve symptoms and reduce tumor size in the short term. However, this available data comes mostly from small case series and case reports. Its ability to provide durable local control is limited and long-term outcomes are still unclear.⁶³ RFA can cause some adverse effects including damage to healthy tissues, neurovascular injury, and chondral lesions.

Healey et al. (2020)¹ observed that while some patients treated with systemic therapy achieved partial responses, many eventually showed signs of progression. This shows the importance of long-term follow-up and suggests that even though systemic therapy may help with disease control, it is unlikely to provide a definitive cure.

The timing of recurrence is another important aspect that needs to be discussed. Some studies, such as Palmerini et al. (2015)³, found that most recurrences occurred within the first 2 years after treatment. Therefore, close monitoring during early follow-up is essential, especially in high-risk patients or in those treated initially with arthroscopy alone.

One of the most important aspects to treatment success is achieving good functional outcomes. Both surgery and systemic therapies can improve patient-reported symptoms, including stiffness, pain and mobility. Moreover, arthroplasty has demonstrated benefits in improving function and reducing flexion contractures in TGCT patients, particularly total knee arthroplasty (TKA).⁶⁴ However, a history of D-TGCT increases the risk of requiring additional procedures after arthroplasty. For this reason, TKA is generally reserved for older patients, where joint-preserving options are no longer effective or feasible.

In addition to tumor control, the impact of D-TGCT on quality of life (QoL) must be a key factor in treatment selection. Symptoms such as pain, stiffness and joint instability can severely affect the daily activities and professional life of patients, particularly in those younger and active. Although surgical excision often provides symptom's relief, recurrences and the need for repeated procedures can lead to joint damage and loss of function. As people live longer and remain physically active for more years, preserving joint function becomes just as important as preventing recurrence. For this reason, treatment decisions should not focus only on tumor control but also aim to maintain quality of life and everyday functioning.

Systemic therapies such as Pexidartinib have demonstrated improvements in patient-reported outcomes, including PROMIS physical function and EQ-5D scores.²⁷ However, their use can be limited by potential side-effects, particularly hepatotoxicity. On the other hand, active surveillance may help preserve quality of life in asymptomatic patients by avoiding unnecessary treatments. Regular monitoring must be ensured due to the risk of tumor progression. Therefore, it is important that future studies focus on quantifying functional outcomes across the various treatment modalities to support more patient-tailored decisions.

Nonetheless, even with optimal symptom control, long-term consequences such as structural joint damage can still occur. Due to repeated recurrences and the local aggressiveness of both the tumor and its treatment, secondary osteoarthritis is often observed, and may eventually require total joint replacement surgery.^{64 8 50 51 65}

Even though malignant transformation of TGCT is extremely rare, it has been documented. Therefore, long-term surveillance is necessary to detect this malignancy early.^{3 16 28} According to Kemp et al. (2025)⁶⁶, the incidence of sarcomatous transformation reported is approximately 0.1%, with less than 30 cases described in the literature. In cases of malignant transformation, systemic treatment with CSF-1 inhibitors loses its effectiveness, as observed by Verspoor et al. (2019)⁵⁹ in a series of four patients. Nevertheless, recurrent TGCT is rarely fatal but often leads to debilitating and chronic condition. Significant joint morbidity and progressive decline in quality of life often result not only from the disease itself but also from the cumulative impact of the multiple interventions required for treatment.^{44 9}

Younger age, obesity, diffuse intra-articular disease, and extensive joint involvement are risk factors that can be associated with poorer outcomes.^{44 53 28 27} TGCT and rheumatoid arthritis share some similarities, including the involvement of proinflammatory cytokines like CSF-1. As TGCT shows both inflammatory and neoplastic features, both pathways can be targeted for future molecular research.⁵⁸¹⁹⁶⁷ The understanding of these biological mechanisms has led to the search for alternative therapies for more recurrent or refractory cases. For instance, patients with bone invasion may benefit from alternative agents like Denosumab, a RANK-L inhibitor. However, evidence remains extremely limited due to the rarity of these presentations.^{14 67}

Based on the findings of this systematic literature review and our clinical experience, we support the conclusion of Palmerini et al. (2015)³ that repeat surgery alone is often insufficient to achieve disease control following the first local recurrence. Therefore, the incorporation of adjuvant treatments, including systemic therapies, is crucial for disease control, particularly in high-risk patients.

A multidisciplinary approach is needed, involving orthopedic surgeons, oncologists, pathologists, radiologists, and radiation oncologists. The study by van der Heijden et al. (2012)⁶⁸ argues the outcomes are better when there is dedicated imaging, thorough histological evaluation and coordinated planning. The latter is particularly important when considering surgery combined with adjuvant radiotherapy or systemic therapy. Therefore, this collaboration between specialties is essential for optimizing both health and quality of life in these patients.

D-TGCT is associated with a considerable economic burden. This results not only from the need for repeated surgeries and imaging, but also because of the high costs of systemic treatments and long-term pain management. In addition, these functional limitations can compromise patients' ability to work and affect their overall quality of life. For example, Pexidartinib is associated with a complex risk management program, as mentioned previously, that requires regular monitoring of liver function, leading to increased costs. Tap et al. (2019)²⁷ and Smith et al. (2020)⁶⁷ both mentioned the need for future studies that evaluate cost-effectiveness and for the development of policies that improve access to care, particularly in settings with limited resources.

Overall, this systematic review demonstrates the importance of a personalized and multimodal approach to managing D-TGCT, particularly in cases where surgery is not an option or when complex anatomical locations are involved. Surgical excision is the most effective strategy for achieving local control, ideally open or combined with adjuvant radiotherapy. When the surgery risks are too high or the tumor is inoperable, systemic therapies are a viable alternative. Novel agents such as Vimseltinib and Emactuzumab, along with other alternative modalities like RFA and

active surveillance, are rapidly expanding treatment options and should play a role in future patient care.

The data presented here suggest that close follow-up is critical due to the high risk of early recurrence, particularly in the first two years after treatment. For asymptomatic patients, active surveillance can be considered, only when the tumor is small in size and when robust imaging and clinical follow-up are ensured. There is a need for an update of the current treatment strategies and clinical guidelines given the growing evidence supporting non-surgical approaches.

Based on the findings of this review, we propose two clinical decision algorithms to support the management of D-TGCT. These diagrams reflect the most consistent patterns identified across the included studies and suggest practical strategies for both primary lesions (Figure 2 : Proposed Management Approach to Primary Lesions of D-TGCT Based on Systematic Review Findings) and recurrent disease (Figure 3: Proposed Management Approach to Recurrences of D-TGCT Based on Systematic Review Findings).

This review has several limitations that warrant acknowledgment. The included studies exhibited considerable variation in design and treatment approach, with many relying on retrospective analyses. Additionally, the available evidence is limited by inconsistent terminology in the literature, challenges in diagnosing D-TGCT, and the use of diverse definitions of recurrence. The variability in outcome measures and follow-up durations across studies further complicates comparisons and limits the ability to draw robust, long-term conclusions.

Notably, the lack of high-quality, multicenter randomized controlled trials, particularly those directly comparing treatment approaches such as systemic therapy versus surgery combined with radiotherapy, poses a significant gap in the evidence base. This absence of strong comparative data challenges the ability to determine the most effective strategies. Moving forward, research should prioritize the development of standardized treatment protocols, safer systemic therapies, and the identification of predictive biomarkers and molecular targets to enable a more personalized treatment approach.

This study's relevance is evident given the current lack of consensus concerning the optimal management of D-TGCT, including both primary and recurrent cases. By reviewing all the available evidence, it sheds light on existing gaps in knowledge and areas of uncertainty, offering valuable insights to guide future research and clinical practice. Given the variability in treatment approaches and the deficiency of robust data, this review serves as a concise resource for promoting more standardized, consistent and evidence-based approaches.

Reflecting this need for clarity, the upcoming BOOM Meeting 2026, a global expert consensus conference, will focus specifically on TGCT. This gathering aims to address unresolved issues, establish guidelines, and identify unmet clinical needs. Furthermore, it is expected to encourage collaboration in developing robust, prospective multicenter studies to resolve these critical questions.

Based on this systematic review, several important questions remain unanswered, highlighting clear priorities for future research. These include reconsidering whether the current classification of TGCT as a benign tumor is still appropriate, given its clinical behavior, or if it should be reclassified as an intermediate tumor. A primary focus should be on improving the accuracy of

diagnosing D-TGCT, as well as identifying key prognostic factors to guide decision-making and define the most effective management strategies, including their ideal sequencing and combination. It is particularly important to clarify the efficacy of systemic and targeted therapies, particularly CSF1R inhibitors, and their optimal treatment duration. The role of radiotherapy and intra-articular adjuvant treatments in reducing recurrence requires further investigation, as well as establishing clear criteria for when active surveillance is appropriate.

Future research should determine whether local tumor control suffices or if curative treatment should be pursued more aggressively. Defining patient selection criteria for various treatment modalities is crucial, including both clinical and molecular risk factors while balancing surgical risks with systemic therapy side effects. To strengthen the current evidence base, there is an urgent need for prospective multicenter studies using standardized criteria for diagnosis, response assessment, and recurrence definitions. Developing reliable prognostic tools, for example those based on CSF1R rearrangements or monocyte-based tests, could enhance risk assessment and guide personalized treatments.

In parallel, regarding systemic treatments, long-term studies are required to evaluate their response durability, define optimal treatment durations, and assess their impact on quality of life and long-term safety. Ongoing trials should clarify the best treatment combinations and sequences while minimizing toxicity.

Finally, the economic implications of TGCT management require attention. As the use of systemic and targeted therapies becomes more common, evaluating their cost-effectiveness and accessibility will be essential to support sustainable and equitable care.

In summary, multidisciplinary care in specialized centers, led by experienced teams and reinforcing shared decision-making with patients, remains central in managing Diffuse Tenosynovial Giant Cell Tumor.

CONCLUSION

This systematic review brings together the latest strategies for managing diffuse-type tenosynovial giant cell tumors (D-TGCT), a rare but locally aggressive condition. Effective treatment requires a multidisciplinary approach in a specialized center, combining surgery, radiotherapy, systemic therapy, and, in some cases, active surveillance or localized interventions. Even though evidence is growing, there is still no consensus on the most effective strategy for managing both primary and recurrent disease.

While open surgery paired with radiotherapy has proven effective, optimal treatment is shifting towards a more personalized approach, factoring in anatomical location, disease extent, and individual patient needs. Even with recent progress, recurrence rates after surgery remain high, particularly with arthroscopic approaches or incomplete resections. For patients with inoperable tumors, major surgery risks or recurrent disease, systemic therapies like the CSF1R show promise, though questions about their long-term efficacy, safety, and cost-effectiveness persist. Active surveillance, radiofrequency ablation, and emerging targeted agents continue to expand therapeutic options.

Despite these recent advances, the lack of standardized treatment protocols and comparative clinical trials challenges the determination of the most effective approach. Therefore, personalized and multidisciplinary management is crucial. The clinical decisions should consider not only the extent and location of the disease, but also the functional outcome and quality of life for each patient.

Further research is needed to establish treatment sequences, identify biomarkers, and assess long-term outcomes. Larger prospective studies and clear protocols are essential to achieve effective and individualized care. By bringing together all recent advances and remaining uncertainties, this review aims to guide clinicians in making informed and collaborative decisions for managing D-TGCT.

APPENDIX

1. Figures

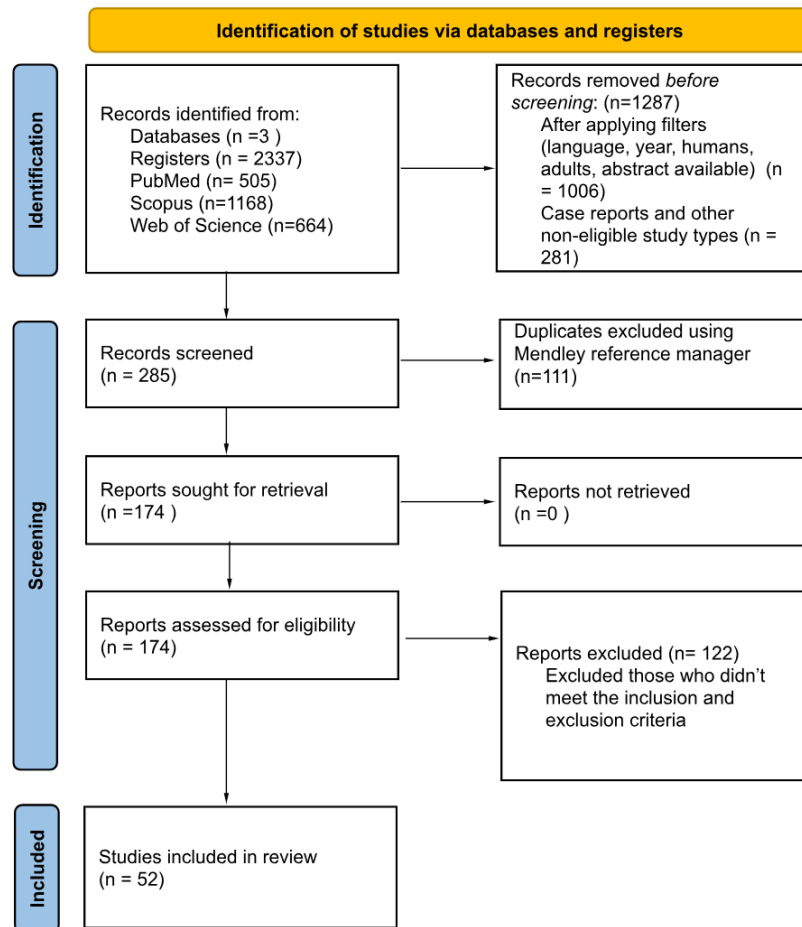


Figure 1 – PRISMA Flow diagram

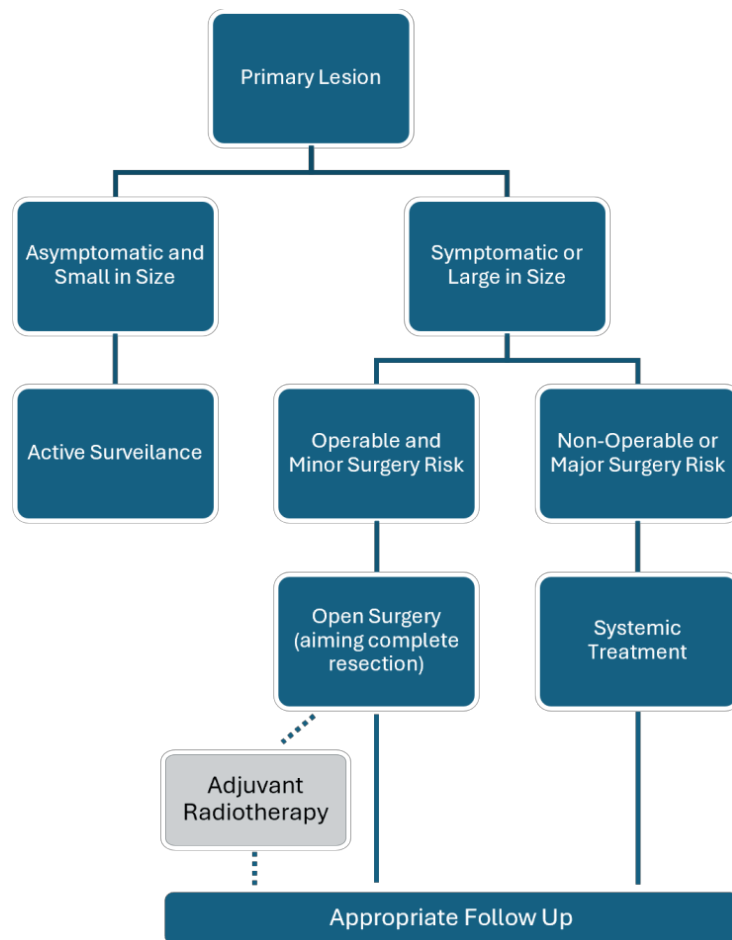


Figure 2 : Proposed Management Approach to Primary Lesions of D-TGCT Based on Systematic Review Findings

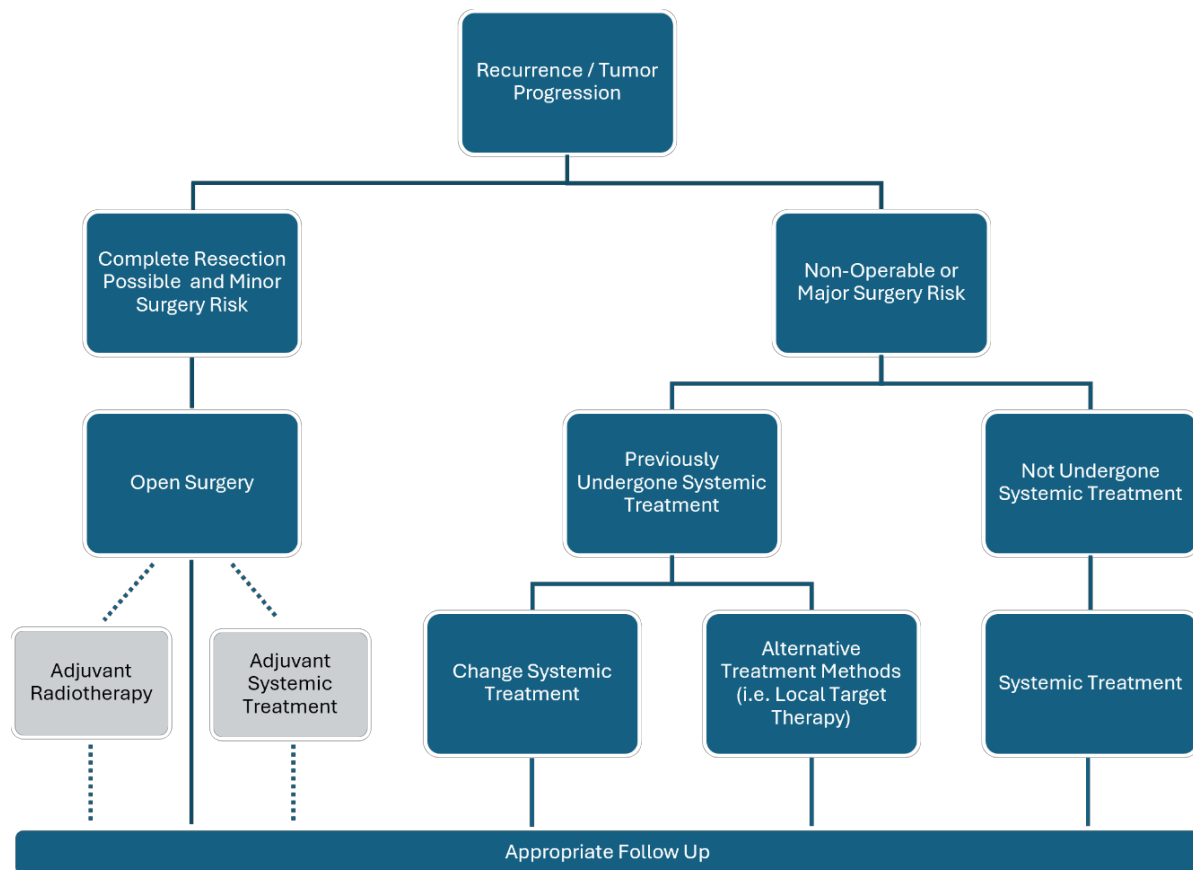


Figure 3: Proposed Management Approach to Recurrences of D-TGCT Based on Systematic Review Findings

2. Tables

Table I : Summary of the Risk of Bias Rating Using the JBI Critical Appraisal Checklist for Cohort Studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall Risk of Bias
Baniel et al. (2023) ⁶⁹	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	N/A	No	Moderate
Berger et al. (2007) ¹⁶	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Bernthal et al. (2021) ²	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Bernthal et al. (2022) ⁷⁰	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Brahmi et al. (2020) ³⁵	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Brien et al. (2004) ⁷¹	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	No	Moderate
Cao et al. (2023) ²⁸	N/A	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Capellen et al. (2018) ⁷²	Yes	Yes	Yes	Yes	U/C	U/C	Yes	Yes	Yes	Yes	No	Moderate
Cassier et al. (2015) ⁵⁸	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Chien et al. (2021) ⁵⁰	Yes	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	No	Moderate
Chin et al. (2002) ⁵⁴	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	N/A	Yes	Moderate
de Carvalho Jr. et al. (2012) ⁷³	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	N/A	No	Moderate
Desai et al. (2025) ³⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Dharmani et al. (2024) ⁵²	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Dürr et al. (2019) ⁷⁴	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	N/A	Yes	Moderate
Elattar et al. (2020) ³⁹	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Gelderblom et al. (2018) ³⁷	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Gelderblom et al. (2021) ⁴⁶	Yes	Yes	Yes	Yes	U/C	No	Yes	Yes	Yes	Yes	No	Moderate
Gelderblom et al. (2024) ⁶⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Gortzak et al. (2018) ⁴⁹	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Moderate
Griffin et al. (2012) ¹⁵	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Healey et al. (2023) ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Heyd et al. (2010) ²⁹	N/A	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Horoschak et al. (2009) ⁷⁵	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Kat et al. (2000) ⁴⁸	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Moderate
Koca et al. (2013) ⁴²	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Kodiyan et al. (2017) ³¹	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	No	Moderate
Kotwal et al. (2000) ⁷⁶	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	N/A	No	Moderate
Lee et al. (2005) ³⁰	N/A	Yes	Yes	No	No	Yes	Yes	Yes	Yes	N/A	No	Moderate
Li et al. (2015) ⁷⁷	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Li et al. (2023) ⁵¹	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	N/A	Yes	Moderate
Lin et al. (2020) ⁵⁵	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Lin et al. (2024) ²⁶	Yes	Yes	U/C	Yes	U/C	Yes	Yes	U/C	Yes	Yes	Yes	Moderate
Mastboom et al. (2019) ⁷⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Mollon et al. (2016) ⁵³	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Nassar et al. (2008) ⁷⁹	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	No	Moderate
Ottaviani et al. (2011) ⁹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	U/C	Yes	No	Moderate
Palmerini et al. (2023) ⁸⁰	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Park et al. (2012) ⁸¹	Yes	Yes	Yes	Yes	U/C	No	Yes	Yes	Yes	Yes	No	Moderate
Rodriguez Blanco et al. (2001) ⁵⁷	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Shabat et al. (2002) ⁴¹	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	No	Moderate
Spierenburg et al. (2022) ⁸²	Yes	Yes	Yes	Yes	U/C	No	Yes	Yes	Yes	Yes	No	Moderate
Tap et al. (2015) ³⁶	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

Tap et al. (2019) ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Tie et al. (2023) ⁴⁰	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
van de Sande et al. (2021) ³²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
van der Heijden et al. (2014) ⁴⁴	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Moderate
van der Heijden et al. (2016) ⁴⁵	Yes	U/C	U/C	Yes	Yes	Yes	Yes	Yes	U/C	Yes	Yes	Moderate
Verspoor et al. (2019) ⁵⁹	N/A	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Yao et al. (2024) ⁸³	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Moderate
Zhang et al. (2024) ⁴⁷	Yes	Yes	Yes	Yes	U/C	U/C	Yes	Yes	Yes	Yes	No	Moderate
Zook et al. (2011) ⁴³	N/A	Yes	Yes	U/C	No	No	Yes	U/C	U/C	N/A	No	Moderate

Table II : Summary of the Main Characteristics and Findings of the Studies Included in the Systematic review

Author(s)	Year	Study Type	N	Anatomical Location	Treatment	Local recurrence (%)	Treatment of Recurrence	Re-recurrence	Complications	Follow-up Duration (months)	Others
Daniel et al. ⁶⁹	2023	Retrospective	30	Knee (73%), ankle (16%), hand (10%)	Surgery followed by postoperative external beam radiotherapy (median dose 36 Gy)	0% after RT (24/30 no relapse; 6 with relapse pre-RT, all controlled)	Salvage therapy post-RT (details not specified)	0% after salvage; 100% local control at last follow-up	No radiation-induced malignancies; 86% good/excellent joint function	82 (3–211)	
Berger et al. ¹⁶	2007	Retrospective	7	Knee (71%), hip (14.4%), wrist (14.6)	Radical synovectomy + postoperative external beam radiotherapy (30–50 Gy)	0.0%	NA	NA	None reported; excellent tolerance to radiotherapy	29 (3–112)	
Bernthal et al. ⁷⁰	2022	Prospective	176	Mostly large joints: knee (68%)	Surgery only (open resection/ one stage synovectomy), surgery and other treatment systemic therapy (Pexidartinib, imatinib), radiotherapy, or watchful waiting	Observed in 10/75 surgery-only, 7/53 surgery+ other treatment, and 2/27 untreated patients = 10,8% total. No recurrence was observed in patients with systemic therapy only	Systemic therapy (mostly Pexidartinib or imatinib), additional surgery	Not explicitly detailed	Not mentioned	24	
Bernthal et al. ²	2021	Prospective	166	Knee (69%), ankle (11%), hip (7%), others (13%)	Surgery (77.1%) ± systemic therapy: imatinib or Pexidartinib (31.3%), radiation (9%)	42.80%	Repeat surgery (arthroscopic or open), some received systemic therapy or radiation	25.7% of recurrent patients had ≥2 recurrences	Not systematically reported; focus on disease burden and QoL	24	

Brahmi et al. ³⁵	2020	Retrospective	39	Knee (44%), ankle (23%), foot (10%), elbow (8%), hip (5%), wrist (5%), hand (3%), finger (2%)	CSF1R inhibitors (imatinib, nilotinib, Pexidartinib, Emactuzumab)	NA	NA	NA	Not mentioned	67	Tumor progression was reported in 87%; worsening symptoms 13%; progression free 56% at 30 months; 83% who received a second line treatment received a 3rd line for a median duration of 5 months; median time to progression of 9 months, 60% progressed: 40% during treatment (imatinib & pazopanib for 1 patient each). 2 patients received 4th line (both imatinib) and one received a 5th line treatment (Sunitinib). First line treatment for a median duration of 7 months; 15 patients had recurrent disease after first line CSF1R inhibitor: 12 (80%) received a 2nd line treatment for a median duration of 6 months and a median time to progression of 12 months. Progression-free at 30 months in 25% after line 2 and 20% after line 3.
Brien et al. ⁷¹	2004	Retrospective	11	Foot and Ankle (10 ankle; 1 case in metatarsophalangeal joint)	Surgical excision, or synovectomy	63.70%	Re-excision or synovectomy ± postoperative radiotherapy (36–40 Gy)	NR	1 ankle fusion due to joint destruction; 1 transient nerve deficit; no RT-related complications	Primary lesions: 112 (36–180); Recurrent lesions: 42 (18–81)	
Cao et al. ²⁸	2023	Retrospective	90	Spine	Gross total resection (81.1%) or subtotal resection (18.9%); perioperative radiotherapy (13%)	17.8% (8,2% with GTR and 58,8% with STR)	Radiotherapy or reoperation ± radiotherapy	50% of patients treated with reoperation alone	Surgical complications in 55.6% of hospital group; higher in GTR (60%) than STR (33%)	36 (3–528)	
Capellen et al. ⁷²	2018	Retrospective	105	Knee (55%), feet (15%), hand (11%), ankle (9%), hip (4%), elbow (2%), sacroiliac (1%), shoulder (1%), others (2%)	Open synovectomy (anterior and posterior for knee); 2 received external beam radiotherapy, 27 radiosynoviorthesis	18% (0% on those who did RT and 32% on those who did radiosynoviorthesis, 17% on those who underwent surgery)	Repeat resection	6 patients (5%) had persistent tumor at last follow-up	Femoral condyle necrosis, nerve palsy, infection, instability of the collateral ligament at the knee, 2 hematomas	71 (13–238)	
Cassier et al. ⁵⁸	2015	Prospective	28	Knee (52%), hip (14%), foot/ankle (28%), wrist (7%)	Emactuzumab, IV every 2 weeks	NA	NA	NA	Facial edema (64%), asthenia (56%), pruritus (56%), rash (40%); 5 serious AEs including subacute lupus, erythema and dermo-hypodermatitis.	12 (10–23)	Objective response in 86%: partial response in 68% after 6 weeks (three cycles of treatment) Vs 7% complete response and 79% partial response.

Chien et al. ⁵⁰	2021	Retrospective	24	Knee	Open or arthroscopic synovectomy ± adjuvant radiotherapy (30–40 Gy)	41.70%	Repeat surgery; 4 eventually required total knee arthroplasty	Not detailed	No significant RT-related complications	72 (24–180)	
Chin et al. ⁵⁴	2002	Retrospective	40	Knee	Combined anterior + posterior open synovectomy ± intra-articular (75%) or external radiotherapy (12,5%)	18% (17% of those treated with intra-articular RT and 40% with external beam RT)	Repeat surgery + intra-articular RT; one progressed to ipsilateral hip and lung involvement	NR	Stiffness (7.5%), wound issues (10%), reflex sympathetic dystrophy (2.5%), OA leading to Total Knee replacement (2.5%)	60 (18–96)	
de Carvalho et al. ⁷³	2012	Prospective	8	Knee	Subtotal arthroscopic and open synovectomy + adjuvant external-beam radiotherapy	12.50%	2 reinterventions for recurrence of effusion, synovitis, and pain	Not specified	3 minor: peripatellar pain, articular effusion, persistent quadriceps atrophy	103.2 (36–168)	
Desai et al. ³⁴	2025	Prospective	32	Mostly lower joints (knee most common)	Pexidartinib (400, 600 or 800 mg/day), Phase 4	55% on those who discontinued Pexidartinib (at mean 22.8 months) and 0% on those who remained on treatment	Rechallenge with Pexidartinib at the dosage level at which the patient completed the prior trial (3/11)	All those who restarted Pexidartinib achieved disease stabilization	CPK increase, COVID-19, AST/ALT elevation, hypertension (66.7% in the treatment continuation and 100% in retreatment)	24	Disease progression: 55% on those who discontinued Pexidartinib (at mean 22.8 months) and 0% on those who remained on treatment / without restarting Pexidartinib; no significant decrease in EQ-5D-5L VAS scores from baseline; one patient had a 10-point decrease in the PROMIS-PF score at the 24-month visit vs. 2 of 3 who restarted Pexidartinib due to symptomatic progression improved PROMIS-PF or EQ-5D-5L VAS scores from baseline.
Dharmani et al. ⁵²	2024	Retrospective	345	Not specified	82 Pexidartinib, 263 other systemic therapies: non-FDA approved agents: imatinib, nilotinib, sunitinib, sorafenib	NA	NA	NA	34.1% required dose reduction; usage limited by REMS program (hepatotoxicity concerns)	12 Pexidartinib, 10 others	Discontinued treatment anytime / Probability remaining on treatment at 12 months: Pexidartinib 40.2% / 54% vs Imatinib 55.0% / 36.4% vs Sorafenib 57.1% / 31.7% vs Sunitinib 66.7% / 17.1% vs Nilotinib 87.5% / Not estimable. Restarted after discontinuation: 6.3% (Sunitinib) to 21.2% (Pexidartinib).
Dürr et al. ⁷⁴	2019	Retrospective	32	Knee	Open synovectomy ± adjuvant radiosynoviorthesis (in 70,3%)	24.00%	Repeat surgery; some underwent second or third resections	11% had recurrence at final follow-up (all had RSO)	None reported; well-tolerated RSO protocol	49 (14–193)	

Elattar et al. ³⁹	2020	Prospective	12	Knee	Staged synovectomy (arthroscopic anterior + open posterior) + low-dose external radiotherapy (25–30 Gy)	0.00%	NA	NA	Limited range of motion and 3 mild complications: superficial wound infection, repeated effusion, transient neuropraxia	47 (25–72)	
Gelderblom et al. ⁴⁶	2021	Prospective	130	Knee (56%), ankle (23%), hip (10%), others	Pexidartinib	12.00%	NA	NA	Hair color change (75%), fatigue (61%), nausea (47%), liver abnormalities (92% aminotransferase elevations), 3% mixed/cholestatic hepatotoxicity	39 (32–82)	Complete or partial response 60% (95% confidence interval, 51.4%-68.0%), stable disease 20%, and progressive disease 1%. / 65% complete or partial TVS response / initial response at 3.4 months (range, 1.6-38.3 months) via RECIST and 2.8 months (range, 1.6-33.6 months) via TVS, with most responses 77% within the first 6 months / 41% RECIST response by 3 months, 62% by 6 months, and 92% by 18 months / TVS response 60% by 3 months, 77% by 6 months, and 98% by 12 months. / RECIST complete response in 26%, 44% by 8 months 76% by 20 months 1 patient at 42 months 11% progressed on treatment, and 2% progressed after treatment, 1% underwent surgery for residual TGCT after a response to Pexidartinib therapy.
Gelderblom et al. ³⁷	2018	Prospective	56	Knee (52%), ankle/foot (23%), hip (13%), wrist (4%), hand (5%), ulna (2%), other (2%)	Nilotinib (400 mg BID) for up to 1 year phase 2	NA	NA	NA	96% AEs (most common: headache, nausea and increased ALT concentrations); 11% grade 3 (dizziness, hepatic disorder, pruritus, toxidermia, diarrhea); no grade 4–5	48	Progression-free survival at 12weeks Vs. 48 months: 92.6% vs. 57.1% ; after 1year treatment 30% turned operable.

Gelderblom et al. ⁶⁰	2024	Prospective	123	Knee (67%), ankle (11%), hip (13%), other	83 with Vimseltinib 30 mg twice weekly vs 40 with placebo for 24 weeks (MOTION phase 3 RCT)	Not reported (40% response rate in the Vimseltinib group; 0% in the placebo group)	NA	NA	Mostly grade 1–2. Most common: periorbital oedema (45%), fatigue (33%), facial edema (31%), pruritus (29%), CPK elevation (24%)	6 (Week 25 primary endpoint); extension ongoing	RECIST 40% (5% complete response vs 35% partial response) vs 0% placebo (difference 40% [95% CI 29–51]; p<0.0001). Tumor volume score at week 25 was significantly higher in the Vimseltinib group (difference 67% [95% CI 56 to 77]; p<0.0001) with 5% having a complete response and 63% a partial response. Vimseltinib significantly improved physical function as measured by PROMIS-PF (difference 3.3 [1.4 to 5.2]; p=0.0007). The difference in PROMIS-PF response rate was 18% (p=0.046). Additionally, the improvement in stiffness was significantly greater with Vimseltinib than placebo (difference –1.8 [–2.5 to –1.1]; p<0.0001), and the difference in worst stiffness NRS response rates was 24% (8 to 39; nominal p=0.0080). The least squares mean change from baseline for EQ-VAS was significantly higher with Vimseltinib than placebo (difference 7.4 [1.4 to 13.4]; p=0.016). Although the proportion of patients who had an EQ-VAS response did not differ significantly, the result numerically favored Vimseltinib (difference 12% [–5 to 29]; nominal p=0.16). The difference in BPI worst pain response rate for patients receiving Vimseltinib placebo was 26% (4 to 42; p=0.0056).
Gortzak et al. ⁴⁹	2018	Retrospective	56	Knee	Surgical synovectomy ± adjuvant 90Y radiosynovectomy	44.1% (with 90Y), 50% (without 90Y)	Further synovectomy; some received second 90Y injection	9 patients in 90Y group had third surgery; none in control group	Very low; one infection, one skin ulcer (both in non-90Y group)	87.6 (30–304)	
Griffin et al. ¹⁵	2012	Retrospective	50	Knee (40%), hip (8%), ankle (18%), foot (14%), wrist (8%), hand (12%)	Surgery + external beam radiotherapy	6.00%	Excisional biopsy (2), open/arthroscopic synovectomy of the knee + postoperative radiation	NR	Avascular necrosis (4 cases), osteoarthritis leading to total hip arthroplasty (2), septic arthritis (1)	94 (19–330)	

Healey et al. ³³	2023	Prospective	120	Lower extremities (92%); knee (61%), ankle (18%)	Pexidartinib (1000 mg/d/ 800 mg/d), randomized + open-label extension (ENLIVEN)	NA	NA	NA	Hepatotoxicity (13% discontinued), hair color changes, fatigue, nausea	12 (part 1 + part 2 combined)	Decreased in worst-weekly pain: 31% [95% CI 21% to 44%] versus 15% [95% CI 8% to 27%] Placebo; Worst pain 26% [95% CI 17% to 38%] for Pexidartinib versus 10% [95% CI 5% to 20%] for placebo; or the MCID (≥2 points) (31%[95% CI 21% to 44%] for Pexidartinib versus 14% [95% CI 7% to 25%] for placebo; (p=0.02). Difference both groups: baseline to week 25 -2.5 [95% CI -3.0 to -1.9] versus -0.3 [95% CI -0.9 to 0.3]; (p < 0.001) / change w25 to w50 -3.3 6 1.7 Vs. -2.8 6 3.4 Placebo
Heyd et al. ²⁹	2010	Retrospective	41	Knee (61%), ankle (19.5%), hip (7.3%), wrist (7.3%), shoulder (2.4%)	Open or arthroscopic synovectomy + postoperative radiotherapy (30–50.4 Gy; median 36 Gy)	4.90%		Radiotherapy (36.0 Gy)	NR	Mostly mild (≤RTOG Grade II); erythema (26.8%), hyperpigmentation and skin fibrosis (9.7%), 1 lymphedema	6 to >120
Horoschak et al. ⁷⁵	2009	Retrospective	17	Knee (67%), ankle (17%), hand (11%), spine (6%)	Cytoreductive surgery + postoperative external beam radiotherapy (mean dose 34 Gy)	25.00%		Repeat resection; all achieved disease control	NR post-resection	No grade III/ IV toxicity; no radiation-associated malignancy	46 (8–181)
Kat et al. ⁴⁸	2000	Prospective	11	Knee (73%), Hip (27%)	Surgical synovectomy + radiosynovectomy (Y-90 or Re-186)	18.00%		Repeat radiosynovectomy	NR after second RS	None reported; well-tolerated	12
Koca et al. ⁴²	2013	Prospective	15	Knee	Arthroscopic synovectomy ± posterior open synovectomy + adjuvant 90Y radiosynovectomy	0.00%		NA	NA	None reported; no leakage or radiation-related side effects	48 (12–86)
Kodiyan et al. ³¹	2017	Retrospective	9	Knee (89%), hip (11%)	Postoperative external-beam radiotherapy or radiotherapy alone (19–45 Gy, median 36 Gy)	33.00%		Surgery (e.g., synovectomy, hip replacement); Radiotherapy	Not clearly detailed	None reported (no acute or long-term RT-related toxicity)	66 (25–312)
Kotwal et al. ⁷⁶	2000	Prospective	48	Hand: 96% fingers and 4% palm	Surgical excision ± radiotherapy (29% received RT)	4% (0% in the RT group)		NR	NR	No complications from radiotherapy	52 (24–132)

Lee et al. ³⁰	2005	Prospective	7	Foot and ankle	Open synovectomy + postoperative radiotherapy (35 Gy in 20 fractions)	0.00%	NA	NA	None reported	24 (18–36)	
Li et al. ⁷⁷	2015	Retrospective	28	Knee	Arthroscopic synovectomy + postoperative external beam radiotherapy (26/28 diffuse cases), 2 only surgery	7.1 % (those who did not complete post-operative RT).	Repeat arthroscopic resection + post-operative radiotherapy	NR	None reported	54 (24–72)	
Li et al. ⁵¹	2023	Retrospective	37	Hip	Total hip arthroplasty (n=17) or Arthroscopy (n=20)	20% (arthroscopy group only)	All required total hip arthroplasty after failed arthroscopy	NR	THA: 64.7% had ≥1 complications, 3 cases of aseptic loosening; Arthroscopy: 5 patients had complications (including necrosis, OA)	51 (24–94)	
Lin et al. ²⁶	2024	Retrospective	83	Knee (61%), ankle (12%), hip (12%), foot (8.4%), others	Pexidartinib (mean starting dose 622 mg/d; range 200–800 mg/d)	Not reported as recurrence rate (70.4% of the patients had previous surgery and 25.9% previous systemic therapy)	Pexidartinib	NA	Hair color change (8.4%), liver enzyme changes (6%), fatigue (6%), others mild	6 (0–12)	Stiffness 3.0 vs. 6.2 and worst pain 2.7 vs. 5.7 (p < 0.05). The majority of patients reported clinically meaningful improvement in overall symptoms and physical function during treatment with Pexidartinib.
Lin et al. ⁵⁵	2020	Retrospective	48	Knee (71%), ankle (15%), hip (8%), elbow (4%), shoulder (2%)	Surgery + postoperative RT (83.3%) or definitive RT (16.7%)	14.6% (all from the Surgery+ RT group)	Salvage surgery (14.3%), surgery + RT (14.3%), observation (71.4%)	Not specified	Mild RT toxicities: dermatitis (25%), joint effusion (23%), ROM decrease (4%); no surgical complications	52 (14–197)	

Mastboom et al. ⁷⁸	2019	Retrospective	966	Knee (64%), hip (10%), ankle (14%), foot (5%), others (7%)	Arthroscopic (14%) or open synovectomy: one (54%) or two-staged (16%) , excluding prosthesis/amputation cases. 14% received adjuvant therapy	44% (34% of those who underwent open and 46% of those who underwent arthroscopic)	Re-synovectomy; some progressed to prosthesis or multiple surgeries (up to 6)	17% had ≥3 recurrences; location not specified	12% had surgical complications: joint stiffness, infections, hemorrhage, etc. (11% of the open synovectomies and 8% of the arthroscopic)	54
Mollon et al. ⁵³	2016	Retrospective	15	Knee	Combined open and arthroscopic synovectomy ± postoperative radiotherapy	13.00%	Repeat synovectomy; one progressed to total knee arthroplasty	NR	Avascular necrosis (1), lymphedema (1), wound dehiscence (1)	81
Nassar et al. ⁷⁹	2009	Retrospective	12	Knee	Combined anterior and posterior open synovectomy + postoperative external beam radiotherapy (26–30 Gy)	0.00%	NA	NA	None; no infection, thrombosis, wound issues, or radiation-related complications	27 (20–36)
Ottaviani et al. ⁹	2011	Retrospective	122	Knee (75%), ankle (16%), hip (6%), others	Surgical synovectomy ± isotopic synoviorthesis (Y-90 or Re-186) (knee:57%; other locations: 74%)	30% (knee), 9% (other locations)	Repeat surgery (some with synoviorthesis); varying approaches	33% of retreated knees recurred again	None reported with low-dose Y-90 under radioscopy control	70 (18-122)
Palmerini et al. ⁸⁰	2023	Prospective	176	Knee (68%), ankle (14%), hip (10%), others (8%)	Watchful waiting (44.9%), surgery (23.9%), systemic radiotherapy (3.4%); future surgery (2.8%)	NA	NA	NA	NR	24 Systemic therapy at 1-year FU: BPI Pain Interference (2.79 vs. 5.93), BPI Pain Severity (3.63 vs. 6.38), Worst Pain (4.5 vs. 7.5), and Worst Stiffness (4.0 vs. 7.5) / From 1-year to 2-year FU, EQ-5D VAS scores (77.5 vs. 65.0) systemic treatment Vs. different treatment strategy
Park et al. ⁸¹	2012	Retrospective	23	Knee	Synovectomy: arthroscopic (74%) or open (26%)+ low-dose external beam radiotherapy (median 20 Gy)	17.00%	Salvage synovectomy in 75%; 25% refused further treatment	0% after salvage treatment	No grade ≥III toxicity, no radiation-induced malignancy	108 (10–144)

Rodriguez Blanco et al. ⁵⁷	2001	Prospective	22	Knee	Partial anterior arthroscopic synovectomy + external beam radiotherapy (26 Gy)	14.00%	Repeat anterior arthroscopic synovectomy	NR	Residual stiffness and swelling in 3 patients; no infections or thromboembolism	33 (26–76)	
Shabat et al. ⁴¹	2002	Retrospective	10	Knee (6), ankle (3), hip (1)	Debulking surgery + intra-articular yttrium-90 (15–25 mCi) injection (6–8 weeks post-op)	0.00%	NA	NA	None; no systemic leakage or adverse events related to 90Y or surgery	72 (30–144)	
Spierenburg et al. ⁸²	2022	Retrospective	48	Knee (48%), hip (12.5%), ankle (12.5%), foot (10.4%), ulna (2.1%), wrist (4.2%), hand (6.3%), TMJ (2.1%)	Nilotinib (400 mg twice daily) for up to 1 year	NA	Synovectomy (19), other CSF1R inhibitors (6)	NA	No long-term adverse events reported	102 (12–129)	52% progression. Progression-free survival was 77 months. 33% clinical worsening after 11 months 58% received additional treatment, after which 41% had a second relapse. 67% with subsequent treatment (22.2% other CSF1R inhibitors, 70% synovectomy). 64.6% were operable after systemic treatment
Tap et al. ²⁷	2019	Prospective	120	Knee (61%), ankle (18%), hip (11%), wrist (3%), foot (3%), shoulder (2%), spine (2%), elbow (1%), finger (1%)	Pexidartinib 1000 mg/d loading dose/ 800 mg/d maintenance (ENLIVEN)	NA	NA	NA	Hair depigmentation (67%), elevated liver enzymes (AST/ALT), fatigue, dysgeusia; 13% discontinued due to AEs (mostly hepatic)	22 (0–25)	Week 25 tumor shrinkage RECIST 39 vs 0% Placebo (p<0.0001)
Tap et al. ³⁶	2015	Prospective	23	Mostly knee	PLX3397 (Pexidartinib) 1000 mg/d	NA	NA	NA	Hair color change (74%), fatigue (65%), nausea (39%), dysgeusia (26%), periorbital edema (26%); ALT/AST elevation (9%), hyponatremia (9%)	8 (0.5–19.5)	Partial overall response of 52%; 7/23 stable disease; disease control (complete, partial or stable response) of 83% (95% CI, 67 to 98) median 8 months; reduction in tumor volume of 50% or more in 11/14 patients.

Tie et al. ⁴⁰	2023	Retrospective	18	Knee	Complete arthroscopic synovectomy + low-dose external radiotherapy (20 Gy)	0.00%	NA	NA	None during or after surgery or radiotherapy	68 (35–120)	
Van de Sande et al. ³²	2021	Prospective	120	Lower extremities (92%): knee (61%), ankle (18%)	Pexidartinib (1000 mg/d / 800 mg/d); randomized placebo-controlled phase III (ENLIVEN)	NA	NA	NA	Hepatotoxicity (7%); overall AE-related discontinuation 13%	25 (part 1 + part 2 open-label extension)	w25: PROMIS-PF: 3.5 (CI 1.3–5.8) vs. –0.9 (CI –3.0 to 1.3) Placebo; Stiffness: –2.2 (CI –2.8 to –1.6) vs. –0.3 (CI –0.9 to 0.4) Placebo / w25 to w50 improvement: PROMIS-PF: 5.8 (CI 4.1–7.5); stiffness –3.1 (CI –3.9 to –2.3) / PROMIS-PF improvement after w25 correlated with reduction of tumor size (RECIST 1.1) (r = –0.5, p = 0.0008)
van der Heijden et al. ⁴⁵	2016	Retrospective	272	Knee (73%), hip (9%), ankle (11.5%), others	Arthroscopic synovectomy (43.4%), open (35.7%), combined (3.7%), others/unknown (17.3%)	58% (arthroscopic), 36% (open), 50% (combined)	Open or arthroscopic re-synovectomy, total knee or hip arthroplasty. Adjuvant therapy with radiation, radioactive colloid instillation with Yttrium, CSFR targeted tyrosine kinase inhibitor, cryosurgery or methotrexate	Not detailed	Not systematically reported	70 (12–374)	
van der Heijden et al. ⁴⁴	2014	Retrospective	30	Knee	Arthroscopic synovectomy (53%) or open synovectomy (47%)	93% arthroscopic, 29% open	Multiple synovectomies (up to 9 in arthroscopic group)	7% open, 63% arthroscopic	OA in 13%, 10% needed TKR; more functional loss in arthroscopy group	64 (24–393)	
Verspoor et al. ⁵⁹	2019	Retrospective	58	Knee (56%), ankle (11%), hip (10%), foot (4%), shoulder (1%), elbow (1%), wrist (2%), head/neck (2%)	Imatinib mesylate (400–600 mg daily) for locally advanced or recurrent TGCT	NA	NA	NA	Edema (48%), fatigue (50%), nausea (34%), skin rash and dermatitis (12%); grade III–IV toxicities in 11% (neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue)	52 (18–83)	4 presented metastatic disease and were excluded. 29% achieved complete response or partial response. One- and five-year progression-free survival rates were 71% and 48%, respectively. 66% patients discontinued Imatinib Mesylate after a median of 7 months.

Yao et al. ⁸³	2024	Retrospective	178	Knee	Multiportal arthroscopic synovectomy ± posterior open synovectomy ± adjuvant radiotherapy	12% (at 5 years, Kaplan-Meier estimate)	Repeat surgery in 86% of the recurrences	Not specified	1 vascular injury (no functional loss), 8 joint stiffness, that resolved with rehabilitation	80 (26–149)
Zhang et al. ⁴⁷	2024	Retrospective	33	Ankle	Multiportal arthroscopy-assisted synovectomy (15) or combined with open resection (18); 14/33 received postoperative radiotherapy	15.00%	Re-operation and postoperative radiotherapy	NR	None reported (no stiffness, infection, neurovascular damage)	77 (28–142)
Zook et al. ⁴³	2011	Retrospective	9	Knee (88.9%), Hip (11.1%)	Surgical resection + intra-articular injection of chomic phosphate (32P)	30.00%	Repeat 32P injection in 2 patients	Not detailed	None reported	20 (2–48)

N, number of patients in each study; **NA**, Not Applicable; **NR**, Not Reported; **EQ-5D-5L VAS**, EuroQol 5-Dimensions 5-Levels Visual Analogue Scale, self-rated health score from 0 (worst) to 100 (best); **PROMIS-PF**, Standardized Measure of Self-Reported Physical Function; **TVS**, Tumor Volume Score; **RECIST**, Response Evaluation Criteria in Solid Tumors; **NRS**, Numeric Rating Scale, self-reported pain scale; **BPI**, Brief Pain Inventory; **w**, week; **MCID**, Minimal Clinically Important Difference; **FU**, Follow-Up; **GTR**, Gross Total Resection; **STR**, Subtotal Resection; **RT**, Radiotherapy; **AE**, Adverse effects; **OA**, Osteoarthritis; **TKA**, Total Knee Arthroplasty; **RSO**, Radiosynoviorthesis; **BID**, twice a day; **CPK**, Creatine Phosphokinase; **ALT**, Alanine Aminotransferase; **AST**, Aspartate Aminotransferase; **RCT**, Randomized Controlled Trial; **RTOG**, Radiation Therapy Oncology Group; **THA**, Total Hip Arthroplasty; **ROM**, Range Of Motion.

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