Open versus arthroscopic surgery for diffuse tenosynovial giant-cell tumours of the knee: a systematic review

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Diffuse-type tenosynovial giant-cell tumours of the knee (D-TGCT) have a very high complication rate.

The recurrence rate for D-TGCT is mainly dependent on an initially successful resection of the lesion.

The standard of care for this disease involves early surgery with synovectomy. Available surgical techniques may include an arthroscopic or open surgery; however, there is a lack of consensus on which technique should be used, and when.

Arthroscopic excision is effective in minimizing morbidity and surgery-related complications, while an open surgical technique provides a more successful resection with a lower incidence of local recurrence.

We could not conclude with confidence which of the surgical techniques is better at stopping a progression towards osteoarthritis and the need for a total knee arthroplasty.

Keywords: knee; outcomes; pigmented villonodular synovitis; surgical treatment; tenosynovial giant-cell tumour

Introduction

Tenosynovial giant-cell tumour (TGCT) has been previously known as a giant-cell tumour of the tendon sheath or pigmented villonodular synovitis (PVNS), and can also be called a xanthogranuloma, a benign synovioma, or a fibrous xanthoma of the synovium. The term TGCT was finally redefined in the 2013 WHO classification of tumours of soft tissue and bone, Fourth edition, as referring to a group of rare, benign, inflammatory and proliferative neoplastic monoarticular diseases, arising from the tendon sheath, bursae, synovium of the joint or fibrous tissue adjacent to the tendon.

This condition is divided into two different subtypes depending on the presentation: local (L), with a single nodule infiltrating the tendon sheath, or diffuse (D), which affects the synovium of a joint surface with multiple nodules or in an absolutely diffuse fashion. This disease is most frequently seen in adults between 30 and 50 years of age, with a slight predominance among females (1:1.5) and a very low incidence – 10.2 per million/year for L-TGCT and 4.1 per million/year in the D-TGCT type.

Patients with TGCT most commonly present with non-specific symptoms such as pain, repeated non-traumatic joint effusions, stiffness, decreased range of motion, locking, and joint instability. Furthermore, D-TGCT is classically found in large joints such as the knees or other weight-bearing joints like the hips, ankles, shoulders, or elbows, with a more aggressive pattern of growth. On the other hand, L-TGCT usually involves the hands or feet, and has a better prognosis. The knee joint is the most commonly involved articulation, representing 46% of the localized type of TGCT, and up to 75% of the diffuse type. However, we must stress that any joint can be affected and patients are frequently misdiagnosed with rheumatologic diseases, bleeding disorders or septic arthritis.

Given the low incidence of these tumours, and their different biological behaviours, as well as the variety of joints involved, is difficult to establish an absolute standard for treatment. The current consensus for treating a diffuse tenosynovial giant-cell tumour of the knee is surgical resection of the lesional tissue; but there is no consensus about the most appropriate surgical approach – either arthroscopic or with an open synovectomy.
The presence of disease recurrence or residual disease with subsequent surgical intervention can be locally devastating to the joint and surrounding structures, including the underlying bone, muscle, neurovascular structures and skin. Sequelae can include end-stage degenerative joint disease (DJD), which can result in the need for total joint arthroplasty to relieve pain and improve function, with the potential for concomitantly higher morbidity and reduced quality of life.8–11

With all these findings under consideration, the authors present here our findings from the literature and a systematic review regarding the reported outcomes obtained with both open and arthroscopic treatments for D-TGCT.

**Methods**

This study is a systematic comparative review of previously published studies in the English-language literature concerning the outcomes from open and arthroscopic surgery to treat D-TGCT of the knee. Two electronic databases were used: Medline/Pubmed and B-on databases, utilizing searches from 2009 to April 2019. We systematically searched for studies that included the keywords/MeSH terms: “Tenosynovial giant cell tumor [MeSH], OR pigmented villonodular synovitis [MeSH]” AND “surgery” OR “arthroscopic surgery” OR “outcome”. The last search date was 7 April 2019.

For the inclusion criteria, we applied the Population, Intervention, Comparison, Outcome (PICO) strategy. We defined the following as:

1. Population – adult population (>18 years) with D-TGCT/PVNS of the knee;
2. Intervention – open surgery which we compared with arthroscopic surgery;
3. Outcomes:
   a) Primary outcomes:
      • Recurrence of disease
      • Osteoarthrosis
      • The need for knee arthroplasty
   b) Secondary outcomes:
      • 1. Articular effusion
      • 2. Pain
      • 3. Limited range of motion
      • 4. Complications due to surgery: infection or wound dehiscence

For this type of study, we included prospective and retrospective observational studies, randomized controlled trials, case-controlled studies and cohort studies. We excluded the following: review articles and case report studies; articles with only abstracts available; and articles where the full text was not accessible.

**Results**

**Selected studies**

A total of 302 articles (255 from Pubmed/Medline and 47 from B-on databases) were initially examined by title and abstract (Fig. 1). The selection of the articles followed rigorous analysis and confirmation of the MeSH keywords searched, and the inclusion and exclusion criteria. After excluding any overlapping articles between both databases, we selected 19 articles that fulfilled the previously defined criteria (Fig. 1). After an initial reading of the selected articles we excluded another 11 due to a lack of clarity and rigor, limited or unclear information about the outcomes, the subgroup of disease studied, treatment within groups or recurrence for the selected surgical technique (arthroscopic versus open) (Fig. 1). In the final selection we included eight articles, presented in Table 1: two prospective and six retrospective studies.

**Primary outcomes**

**Local recurrence**

Akinci et al observed a group of 15 patients in a prospective study. They had diffuse tenosynovial giant-cell tumour (D-TGCT) of the knee treated with open synovectomy, with a recurrence rate of 26% (five subjects). The authors still considered open total synovectomy to be the gold standard.
standard for surgery even though this conclusion was skewed by the sample size.\textsuperscript{12} Authors Xie et al analysed a group of 175 cases of D-TGCT of the knee where patients were treated with either an arthroscopic synovectomy (118 cases) or an open resection (57 cases) with a global recurrence rate of 24%. They did not identify a significant recurrence difference between patients who were treated with open versus arthroscopic

### Table 1. Characteristics of the studies included and summary of the results

| Author et al. | Year | Type of study | Number of patients | Average follow-up (months) | Age (median years) | Technique | Recurrence rate | Osteoarthrosis | TKA | Secondary outcomes (patients) |
|---------------|------|---------------|-------------------|---------------------------|-------------------|-----------|-----------------|---------------|-----|-------------------------------|
| Akinci et al\textsuperscript{12} | 2011 | prospective | 15 | 80.2 | 42.8 | open synovectomy | 26.3% | NR | 39% | Stiffness (3), KSS perfect (8–42.2%), good (9–47.3%), bad (2–10.5%) NR |
| Xie et al\textsuperscript{13} | 2015 | retrospective | 175 | 108.0 | 35.70 ± 16.12 | open synovectomy 57 arthroscopic synovectomy (118 patients) | 16/57 = 28% | 26/118 = 22% | NR | NR |
| Jabalameli et al\textsuperscript{14} | 2014 | prospective | 15 | 55.2 | 28.2 ± 12.37 | 1 arthroscopic anterior and open posterior synovectomy 7 staged posterior and anterior open synovectomy 2 all arthroscopic synovectomy 1 subtotal arthroscopic synovectomy 4 subtotal open synovectomy | 1/1 recurrence | Moderate to severe (2), Bone erosions 33–56% | 7% NR to which treatment | KSS 63.1 ± 6.7 pre operation, 77.8 ± 9.9 post operation |
| Aurégan et al\textsuperscript{15} | 2013 | retrospective | 7 | 84.0 | 41.0 | Arthroscopic total synovectomy | 29% | NR | NR |
| Jain et al\textsuperscript{16} | 2013 | retrospective | 29 | – | 44.0 | Arthroscopic synovectomy | 57% (12 patients) | NR | NR |
| Colman et al\textsuperscript{17} | 2012 | retrospective | 48 | 40.0 | NR | 11 open posterior and open anterior synovectomy 11 open posterior synovectomy and anterior arthroscopic synovectomy 26 all arthroscopic synovectomy | 64% | 0% | 0% | Wound infection (9%) |
| Vivek and Sharma \textsuperscript{18} | 2009 | retrospective | 37 | 74.4 | 35.2 (10–73) | 16 open/open 8 anterior arthroscopic synovectomy/open posterior synovectomy 13 all arthroscopic subtotal synovectomy | 19% | 25% | NR | NR |
| Patel et al\textsuperscript{19} | 2017 | retrospective | 102 | 25.0 | 39.0 | 84 open synovectomy 4 arthroscopic/open synovectomy 12 arthroscopic synovectomy | 44.8% | NR | NR | Wound infection (6), Haemarthrosis (3), Stiffness (2), DVT (1) |

Note. DVT, deep venous thrombosis; KSS, Knee Society Score; NR, not reported; TKA, total knee arthroplasty.
surgery (p = 0.78), and they recognized that limitations for their study included the sample size, the absence of case controls in their study, and a recurrence rate which was only calculated via electronic medical records.\textsuperscript{13}

In another comparative prospective study (open versus arthroscopic surgery) Jabalameli et al investigated 15 subjects with D-TGCT with a mean age of 28 years, who were followed for four-and-a-half years. Five patients underwent subtotal synovectomy – four in the arthroscopic arm of the study, and one on the open synovectomy side. The other 10 cases were divided as follows: two totally arthroscopic synovectomies, seven staged posterior-and-anterior open synovectomies, and one arthroscopic-anterior and open-posterior synovectomy. They observed two cases of recurrence (7%): one with the arthroscopic-and-open synovectomy and the other with a totally arthroscopic technique. Therefore, from this data they concluded that the treatment of choice for D-TGCT should be staged open-posterior total synovectomy followed by open-anterior synovectomy.\textsuperscript{14}

Aurégan et al conducted a prospective study which involved a group of seven patients with D-TGCT, with a mean age of 41 years, all managed with arthroscopic synovectomy. They were able to follow the group over seven years; during that time two patients had recurrence of disease for a recurrence rate of 29%. The authors assumed that arthroscopic synovectomy enabled an effective excision of the primary lesion with good function, low complication rates, and satisfactory disease control. They stressed that the first arthroscopic approach would allow secondary management with open synovectomy in case of recurrence.\textsuperscript{15}

Jain et al analysed a group of 29 cases in a retrospective study, with a mean age of 44 years and a mean follow-up of seven years. In this group, totally arthroscopic excisions were performed and the authors reported a five-year recurrence-free rate of 57%. Twelve patients developed recurrences between three months and two years postoperatively. However, no recurrence was noted after two years. The authors concluded that arthroscopic excision provided as good a result as open synovectomy, but with lower morbidity.\textsuperscript{16}

Colman et al retrospectively studied 103 cases where 48 cases of D-TGCT of the knee were treated with: (1) a totally arthroscopic surgery, or (2) an open-posterior and anterior-arthroscopic synovectomy, or (3) an open-anterior and open-posterior synovectomy, or (4) a totally open synovectomy. The overall recurrence rate was 50% within a median time of 27 months. A lower recurrence rate was observed in the open-posterior with anterior-arthroscopic synovectomy group (9%), when compared with the totally arthroscopic (62%) or open surgery group (64%, p = 0.008). However, this study had limitations due to the number of patients, with only 11 patients in the group where an open-posterior plus anterior-arthroscopic synovectomy was performed.\textsuperscript{17}

In another study, Sharma and Cheng reached a conclusion similar to Colman et al when evaluating 37 D-TGCT patients over six years. They had 13 patients with D-TGCT treated with totally arthroscopic synovectomy as the initial treatment, a second group of eight patients who underwent anterior-arthroscopic and open-posterior synovectomy, and a third group of 16 patients treated with open-anterior and open-posterior surgery. They calculated the overall recurrence rate at 19% for the open/open synovectomy group versus 25% for the open/arthroscopic group (eight patients) versus 92% in the totally arthroscopic group. They concluded that the totally open synovectomy group had the best recurrence-free rate at two and five years of follow-up.\textsuperscript{17,18}

Patel et al retrospectively analysed 114 D-TGCT cases over a mean observation time of 25 months, where 102 arthroscopic or open synovectomies were performed. These authors observed a statistically higher recurrence rate in the arthroscopic technique group when compared with the open technique (83% vs. 44%, p = 0.0004).\textsuperscript{19}

Osteoarthritis and the need for total knee arthroplasty

During the follow-up of 80.2 months in the Akinci et al study, 39% of patients needed a total knee arthroplasty (TKA) after open synovectomy. Jabalameli et al also reported arthrofibrosis following anterior-open synovectomy in four patients (27%), and in two of those patients (50%) moderate-to-severe osteoarthritis was identified.\textsuperscript{12,14}

Concerning arthritic progression from baseline, Colman et al identified a global rate of 15% — open synovectomy (0%) versus open-plus-arthroscopic synovectomy (9%) versus totally arthroscopic technique (23%) — with a specific rate of 8% of patients who needed a TKA within the follow-up period. However, this was without statistically significant differences between groups (p = 0.16). Also of note, in the Colman et al study, all patients needing a TKA due to knee arthritis had had a previous totally arthroscopic synovectomy. But again, this was without any statistically significant differences compared with other patient groups.\textsuperscript{17}

Jain et al mentioned in their series that no progression toward osteoarthritis was observed during the follow-up period.\textsuperscript{16} Additionally, Sharma and Cheng also did not report any data regarding progression to arthritis or progression to the need for TKA; however, these authors did not report any complications.\textsuperscript{18}

Secondary outcomes

Articular effusion, pain and limited range of motion

Akinci et al observed three open synovectomy patients (20%), with post-operative knee-joint stiffness; however,
None of the patients developed infection or haemarthrosis. According to the Knee Society Score (KSS), eight patients (42.2%) had a perfect outcome, nine (47.3%) had a good outcome, and two patients (10.5%) had bad clinical outcomes. In six patients with staged surgery (posterior and anterior-open synovectomy), Jabalameli et al reported that the KSS score improved significantly post-operatively with no complications regarding knee instability. Aurégan et al also reported a significant improvement in global clinical outcomes after arthroscopic synovectomy, using the Tegner Lysholm score. The improvement was from 68 points (pre-operatively) to 90 points (post-operatively) – \( p = 0.0004 \). This also included cases of L-TGCT.

Patel et al had two cases (1%) of stiffness that required manipulation under anaesthesia (MUA) and three (2%) patients with a neurological injury and foot drop. However, the authors did not specify in which of the TGCT variants these cases were observed. Additionally, this was a single-centre retrospective observational study with a low mean follow-up time (25 months) without a report on functional outcomes.

Complications directly related to surgery
Jabalameli et al observed no infections or neurovascular injuries in any groups studied. Aurégan et al observed a rate of post-operative complication after the arthroscopic procedure as low as 0%, while Colman et al reported lower post-operative complication levels with open-posterior followed by anterior-arthroscopic synovectomy. The most common complication was haemarthrosis (6%), with no significant differences between groups. There were no complications such as infection, neurovascular damage, deep vein thrombosis (DVT) or wound healing in the group studied by Jain et al where totally arthroscopic synovectomy was performed. Patel et al, on the other hand, observed an overall low complication rate (9.8%). However, of these complications 88.9% were due to an open surgery. There were six patients with wound infections, three post-operative haemarthroses, and one case complicated with DVT.

Discussion
TGCT was first described by Chassaignac in 1852 and there is still no consensus about the aetiology and pathogenesis for these lesions; they could be considered neoplastic, inflammatory, traumatic, metabolic, or viral according to various theories. New evidence suggests a clonal neoplastic origin for TGCT that include specific genetic changes, frequently associated with a specific translocation: t(1;2) CSF1:COL6A3. Also under consideration is the ‘paracrine landscape effect’ which is a reactive process with proliferation and recruitment of colony-stimulating factor 1 receptor (CSF1R)-expressing cells that include macrophages, giant cells and osteoclasts. There are also correlations between the onset of this disease and trauma, lipometabolism, and even surgical aggression.

A tenosynovial giant-cell tumour frequently presents as a firm, slow-growing, multilobular, non-tender mass adjacent to the tendon sheath synovium, with similar clinical and histological features between the two different subtypes: localized and diffuse. According to the 2013 WHO classifications, each subgroup can be evaluated radiologically for a growth pattern. Thus, to characterize and estimate the extent of tumour growth for pre-operative assessment, magnetic resonance imaging (MRI) is the standard for evaluation and is the mainstay form of imaging for all of the studies we reviewed. Radiographically, the majority of these tumours present with a poorly defined, peri-articular mass, associated with degenerative joint disease and cystic lesions in the adjacent bone. The L-TGCT typically exhibits a conspicuous nodular form with low signal on T1 weighted imaging (WI) and T2WI due to the presence of haemosiderin. On the other hand, D-TGCT, as a villous proliferation of the synovium, results in a more heterogeneous image with larger areas of hypointensity on T1WI and T2WI. The diffuse type also presents with enhanced heterogeneity on contrast-enhanced T1WI when compared with the localized form (Fig. 2).

Since L-TGCT usually consists of a small, circumscribed, benign mass (usually 0.5 to 4 cm), it has a more favourable course after total mass excision with an overall relatively low recurrence rate of 0–6%. Meanwhile, given that D-TGCT extensively involves the synovial membrane and infiltrates adjacent structures, and has a lack of clear-cut boundaries, this subtype has a much more significant morbidity with a more impaired quality of life, even after proper treatment (Fig. 3 and Fig. 4).

Total synovectomy is the standard of care established for either L-TGCT or D-TGCT. It can be performed via different surgical approaches such as open, arthroscopic, or combined techniques with or without the complement of adjuvant therapies. According to the literature, after arthroscopic synovectomy for D-TGCT the condition can recur as often as 40% to 92% of the time, while the recurrence rate can be less following open synovectomy – 14% to 67%. Nonetheless, there is no clear consensus for which surgical technique offers the best general outcome after treating D-TGCT. For this reason, in this systematic review, we compared outcomes from the different surgical modalities, specifically open and arthroscopic synovectomy techniques. We compared the reported outcomes as discussed in the ‘Methods’ section above; however, we must stress that there are major limitations in this analysis, since a simple definition for ‘recurrence’ is not standardized in these selected studies.
Diffuse TGCT of the knee has a high overall recurrence rate regardless of treatment when compared with the localized variant.\textsuperscript{17} When the extent of disease affects extra-articular tissues, arthroscopic synovectomy will more likely be subtotal with a higher relapse rate.\textsuperscript{16,18} For this reason, Jabalameli et al, Sharma and Cheng, and Patel et al favour open synovectomy techniques when approaching diffuse TGCT.\textsuperscript{14,18,19} Those findings are also supported by Akinci et al, who observed a similar low recurrence rate with open synovectomies.\textsuperscript{12} However, this phenomena was not observed by Xie et al, where no statistically significant differences were found between open and arthroscopic techniques.\textsuperscript{13} In another study, Colman et al observed a significantly lower recurrence rate when a staged open-posterior with anterior-arthroscopic synovectomy was performed. That tends to favour this different approach to D-TGCT of the knee joint.\textsuperscript{17} Despite this finding, Aurégan et al and Jain et al both observed (in their non-comparative studies) low recurrence rates with totally arthroscopic synovectomies.\textsuperscript{15,16}

The recurrence rate in D-TGCT is mainly influenced by residual disease due to subtotal synovectomies.\textsuperscript{16} A non-successful procedure usually requires additional surgical intervention, which is devastating to the joint and all other surrounding structures. These sequelae can ultimately result in end-stage degenerative joint disease, which in most cases ends in the need for total joint arthroplasty to relieve pain and improve function. But, at the same time, this can come with higher morbidity and an impaired quality of life.\textsuperscript{8,10}

A progression to increased osteoarthritis due to the presence of this disease is difficult to measure. Nonetheless, Colman et al observed lower rates of arthritic progression with a totally open synovectomy (0%), when compared with open-plus-arthroscopic synovectomy (9%), or for a totally arthroscopic technique (23%). This
outcome is important because it represents an indirect measure which correlates with the need for TKA.\textsuperscript{17,24} Despite this, in the studies evaluated herein, the rate of progression to osteoarthritis and the need for TKA was not reported by most authors. However, given the results obtained by Akinci et al and Colman et al, it seems there is no significant difference between open synovectomy and arthroscopy when it comes to progression to osteoarthritis and TKA.\textsuperscript{12,17}

Regarding secondary outcomes, we evaluated the presence of articular effusions, pain, limited range of motion, and complications directly related to the surgical procedure itself such as wound infection or dehiscence. Akinci et al looked into open synovectomy results and did not report any infections or haemarthrosis. However, 20\% of patients developed post-operative knee-joint stiffness. The measured KSS in the same group was bad for 10.5\% of patients compared with good and perfect outcomes in 42.2\% and 47.3\%, respectively.\textsuperscript{12} Jabalameli et al also observed no complications in the form of knee instability, infection, or neurovascular injury, and patients showed significant improvement in KSS scores after surgery in those who underwent staged open-posterior and anterior-arthroscopic surgery.\textsuperscript{14}

Aurégan et al reported one case of haemarthrosis after total arthroscopic synovectomy. The overall post-operative Ogilvie-Harris score was correlative/good after partial arthroscopic synovectomy or with complete arthroscopic synovectomy.\textsuperscript{15} Additionally, Colman et al reported an overall low peri-operative complication rate, with no significant differences between the open and arthroscopic groups.\textsuperscript{17} Given the size of the sample and different methods used to assess the risks of local recurrence and complication rates respectively, it was not possible to conclude with significant confidence there was any ‘grand total’ risk from each individual technique.

Taking all this into consideration, it is understandable that other treatment options are being explored every day. Various forms of radiation therapy (radiosynovectomy and external-beam radiotherapy) have been used to try to reduce the risk of local recurrence and to improve recurrence-free survival, and as an alternative to surgery or complementary therapies.\textsuperscript{18} These therapies can include instillation of 90-Yttrium (90Y)-labelled colloid inside the affected joint. This has shown positive results as an adjuvant treatment after surgical synovectomy, and as monotherapy in treating D-TGCT for initial, recurrent or residual large primary disease.\textsuperscript{14,25} However, like any other treatment modality, radiation is not free from complications. The potential for serious toxicity, radionecrosis, and harmful effects on bone and joint cartilage with high iatrogenic morbidity, makes this a questionable option, especially for a benign condition.\textsuperscript{9} Therefore, novel treatment methods for TGCT are being investigated, including immunotherapy agents.\textsuperscript{9}

Historically, conventional chemotherapy has not been proven effective in TGCT, but the finding that D-TGCT cells overexpress colony-stimulating factor 1 (CSF1), resulting in recruitment of CSF1 receptor (CSF1R)-bearing macrophages that are polyclonal and constitute the majority of the tumour, has led to considering clinical trials with CSF1R inhibitors.\textsuperscript{6,25}

The deregulated expression of CSF1 in TGCT seems to result from translocation of the small arm of chromosome 1p11-13 to the chromosome 2q37 region. The gene CSF1 is located precisely at the chromosome 1p13 breakpoint, and here, the promoter element of collagen 6A3 (COL6A3) is fused to the gene CSF1.\textsuperscript{5,25} Moreover, an autocrine loop seems to be involved, given that not only macrophages and monocytes but also the tumour cells express the CSF1 receptor. This suggests that a ‘paracrine landscape’ effect between CSF1/CSF1R may be responsible for TGCT mass growth.\textsuperscript{25} The CSF inhibitors that could disrupt the ‘paracrine landscape’ effect include less potent drugs such as nilotinib and imatinib (tyrosine kinase inhibitors), and more specific inhibitors such as the monoclonal antibodies: emactuzumab, pexidartinib or cabiralizumab.\textsuperscript{25} For the moment, long-term efficacy has not yet been reported with these newer agents.

Within this present era of systemic targeted and multimodality therapies in clinical trials, specifically for the diffuse and more aggressive form of TGCT, surgical resection alone may not be regarded as the gold standard in the near future.

**Conclusions**

Surgical treatment methods for D-TGCT and L-TGCT in the knee are complicated and still controversial in the medical community due to the unusual characteristics of the disease. In our systematic review, we aimed to determine which surgical techniques (arthroscopic or open synovectomy and variations) had a better end result given the primary and secondary outcomes established in the ‘Methods’ section.

Following our review we can conclude that the recurrence rate for D-TGCT is mainly dependent on successful resection of the initial lesion, which we found to be better with an open surgical technique. Nonetheless, arthroscopic techniques were superior when it came to morbidity and surgery-related complications. We could not come to any firm conclusions about the influence of surgical technique on progression toward osteoarthritis and the need for TKA, but a better outcome after open synovectomy seemed to be the rule. We would, therefore, recommend open synovectomy for D-TGCT in the
knee, considering that the lowest recurrence rate is the main goal for intervention.

Once again, we need to stress the limitations of this systematic review due to the number and quality of articles included, which is a consequence of the rarity of this disease. The development of multicentric prospective studies regarding D-TGCT management should be promoted, in order to obtain better answers for the questions presented here.

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