Current Oncology Reports (2020) 22: 63
https://doi.org/10.1007/s11912-020-00926-7

SARCOMAS (SR PATEL, SECTION EDITOR)

Management of Pigmented Villonodular Synovitis (PVNS): an Orthopedic Surgeon's Perspective

Nicholas M. Bernthal[1] · Chad R. Ishmael[1] · Zachary D. C. Burke[1]

Published online: 4 June 2020

Abstract

Purpose of Review Pigmented villonodular synovitis (PVNS) or tenosynovial giant cell tumor (TGCT) encompasses a wide spectrum of disease and is divided into localized and diffuse variants. Surgical resection remains the principal treatment for nearly all localized type disease and most diffuse type. Recent mechanistic understanding of the disease led to drug discovery that has opened new avenues for patients with recalcitrant disease. In this manuscript, we review the current treatment options for TGCT, presenting outcomes from traditional surgical approaches as well as those from nonsurgical approaches.

Recent Findings Arthroscopic and/or open surgery remains the mainstay of treatment for TGCT for the vast majority of patients. While radiosynoviorthesis and external beam radiation have been used for recalcitrant disease, recent understanding of the colony stimulating factor 1 receptor (CSF1R) pathway and its paracrine and autocrine role in TGCT has led to the development of targeted inhibitors. Their optimal role and efficacy are unclear due to limited number of high-quality studies and contradictory results; however, recent and ongoing studies suggest there may be a role for their use, especially in diffuse and/or refractory disease.

Summary Surgery remains the most common treatment for TGCT, however, there may be an increasing role for adjuvant therapies, including the new targeted agents. Weighing the side effects of these treatments against the symptomatic benefit on a patient-by-patient basis in this benign disease remains critical.

Keywords Pigmented villonodular synovitis (PVNS) · Tenosynovial giant cell tumor (TGCT) · Orthopedic surgery · Radiosynoviorthesis · External beam radiotherapy · Oncology

Introduction

Pigmented villonodular synovitis (PVNS) or tenosynovial giant cell tumor (TGCT) encompasses a wide spectrum of disease including localized and diffuse variants. It is a locally aggressive but usually benign neoplasm that affects joints, tendon sheaths, and bursae [1, 2]. Patients generally present complaining of pain, swelling, stiffness, and limited range of motion in the affected joints. TGCTs were originally classified by their site of origin—including synovium, bone or tendon sheaths. These groups included PVNS, diffuse type giant cell tumors (DTGCT), nodular tenosynovitis and giant cell tumor of tendon sheath (GCTTS). In 2013, the World Health Organization (WHO) reclassified TGCTs into localized and diffuse types, with localized TGCT including nodular tenosynovitis and GCTTS, and diffuse TGCT including PVNS and DTGCT [1]. Diffuse TGCT commonly occurs in younger patients than localized, affecting more females than males [1]. These are relatively rare tumors—with a recent Dutch registry study reporting a standardized global incidence of 4 cases per million for diffuse TGCT, 10 per million for localized TGCT, and 29 for TGCT affecting digits [3•]. While surgery remains the mainstay of therapy, recurrence rates are high, especially in diffuse TGCT, where recurrence after surgery was 2.6 times higher than those for localized type.

TGCT has been linked to an over-expression of colony stimulating factor 1 (CSF1)—leading to recruitment of CSF-1 receptor (CSF1R) inflammatory cells including giant cells, macrophages, and osteoclasts [2]. This over-expression has been connected to a chromosomal translocation—t(1;2)(CSF-1;COL6A3), however, there is also a group of TGCTs where there appears to be some other source resulting

This article is part of the Topical Collection on *Sarcomas*

✉ Nicholas M. Bernthal
nbernthal@mednet.ucla.edu

[1] Department of Orthopaedic Surgery, David Geffen School of Medicine, UCLA, Los Angeles, CA 90055, USA

in over-expression of CSF1R and recruitment of inflammatory cells without this translocation [4, 5].

Currently, there is no agreement on the ideal treatment for patients with TGCT, particularly for those with diffuse or recurrent disease. The majority of patients are treated by arthroscopic and/or open surgical excision with synovectomy; however, the ideal surgical approach is unclear and recurrence rates are as high as 50% in those with diffuse or recurrent disease [6]. Given these high rates of recurrence, there is great interest in exploring alternative and/or adjuvant therapies. Radiosynoviorthesis and external beam radiation have been suggested as adjuvants to surgery or as primary treatments for inoperable disease [7], however, there are real concerns regarding the efficacy and possible side effects. Recent advances have led to the development of targeted agents inhibiting the CSF1R pathway, and clinical trials have demonstrated efficacy. Nonetheless, the systemic therapies do have significant side effect profiles and therefore a patient-specific approach weighing risks and benefits is needed. In this manuscript, we review current treatment options for patients with TGCT, including new modalities and systemic therapies, noting persistent limitations in therapeutic options and providing our own institutional management philosophy.

Management

While the epidemiology of TGCT is challenging to establish, especially with the aforementioned 2013 WHO change in classification of the disease, estimates suggest that there are approximately 10 cases of localized TGCT per million and approximately 4 cases of diffuse TGCT per million [3•]. The majority of patients are treated surgically with good results: more than 90% of localized type disease is cured with a simple excision. Some diffuse disease is readily resectable with little morbidity but the recurrence rate is reported to be approximately 50% when all surgical approaches and anatomic locations are included [3•]. Those with recurrent, anatomically-challenging diffuse, and/or recalcitrant disease pose a significant treatment challenge [8]. Management options have been discussed and several groups have suggested and published treatment recommendations; however, the best standard of care remains unclear. A combined group from the UK and the Netherlands suggested a cohesive and multidisciplinary treatment protocol for diffuse-type TGCT patients in 2012 [9]. In 2016, an Italian publication stated open surgical resection was the gold-standard management for diffuse TGCT [2]. In that same year, a UK guideline was published stating that most patients with TGCT are treated with surgery alone, however, occasionally imatinib or radiotherapy may be used in addition to or instead of surgery [10]. In practice, most patients with diffuse TGCT are treated surgically, with either arthroscopic or open resection and synovectomy.

Surgery

Surgical resection is the primary treatment for patients with both localized and diffuse TGCT. This includes arthroscopic and open excision, with partial or extensive synovectomy. Several studies have sought to compare the efficacy of open versus arthroscopic synovectomy, with varying results. In a retrospective study, Gu et al. noted no statistically significant difference in rate of recurrence in 41 patients with diffuse PVNS treated via arthroscopic versus open surgery (6% vs 22%; $p \geq 0.05$). They use this data to advocate for arthroscopy based on the lower morbidity (blood loss, operative time, hospital stay) and improved functional scores [11]. However, this study certainly suffers from selection bias as it is presumed that the patients selected for open surgery had more infiltrative, challenging disease burden. In a larger cohort retrospectively reviewed, Colman et al. report a statistically significant lower rate of recurrence in diffuse TGCT of the knee when a combined anterior arthroscopic/open posterior approach was used rather than an all-arthroscopic or open anterior/posterior synovectomy was employed (9% vs 64% vs 62%; $p = 0.008$) [12]. Palmerini et al. found no significant difference in 5-year local failure-free survival for arthroscopic versus open resection in patients with localized (84% vs 72%, $p = 0.4$) or diffuse disease (59% vs 61%; $p = 0.8$), with a median follow-up of 4.4 years.[13] Recently, Mastboom et al. published a multicenter, pooled cohort, database study of patients with both localized, and diffuse PVNS [14••, 15••]. The authors noted a statistically significant higher rate of local relapse-free survival after open versus arthroscopic surgery (87% vs 80%, $p = 0.04$) in patients with localized disease, though this significance was lost during multivariate analysis. They also noted similar results in patients with diffuse PVNS—observing again a statistically significant relapse-free survival after open versus arthroscopic surgery (66% vs 54%, $p = 0.03$), though this was again lost after multivariate analysis. In their 2017 retrospective cohort study of 44 patients with localized PVNS, Georgiannos et al. found no statistical difference in Lysholm and Ogilvie-Harris scores as well as lesion recurrence rate, after arthroscopic excision versus arthroscopically assisted mini-open partial synovectomy [16]. Given these mixed results, it is unclear what the most appropriate surgical approach is, and perhaps varies by tumor size and location. Our institutional experience mirrors that of the University of Pittsburgh reported by Colman [12], where a single session of arthroscopic anterior surgery performed by an experienced sports medicine arthroscopist and open posterior surgery performed by an experienced orthopedic oncologist have yielded the best oncologic and functional outcomes for patients with diffuse-type resectable disease in the knee. Of note, due to space limitations, this discussion omits the data on arthroplasty for downstream arthritic change in the setting in long-standing TGCT.

Systemic Therapy

The recent development and investigation of systemic therapies targeting the CSF1 pathway represent an important advancement in the treatment of TGCT. In particular, these therapies may play a major role in the treatment of advanced, recurrent, and recalcitrant diseases for which surgery carries more morbidity than expected benefit. The efficacy of four different tyrosine kinase inhibitors (TKI) of the CSF1 receptor (CSF1R) have recently been tested in high-quality studies [17–19, 20••, 21••]. This includes two drugs previously approved for use in other malignancies (nilotinib [18] and imatinib [21••] and two novel drugs (emactuzumab [17] and pexidartininb [19, 20••]).

Nilotinib

In a phase 2 trail of oral nilotinib for progressive, recurrent, or inoperable diffuse TGCT ($n = 56$), no patients showed partial or complete response at 12 weeks [18]. Ninety percent of patients had stable disease. Ninety-six percent of patients experienced adverse events, with 11% experiencing grade 3 adverse events.

Imatinib

The efficacy of imatinib—currently indicated for use in both hematologic and solid tumors—was evaluated in a multicenter retrospective cohort of patients with advanced or recurrent diffuse TGCT ($n = 62$) [21••]. At a mean follow-up of 52 months (IQ 18–83), oral imatinib resulted in an overall response rate (ORR) of 31% (95% CI 19–43). Four percent of patients experienced a complete response (CR) and 27% showed partial response (PR). Sixty-five percent had stable disease (SD). The adverse events were consistent with those already known to be associated with imatinib including fatigue (50%), edema/fluid retention (48%), and nausea (34%). Of note, a majority of patients in this trial (59%) discontinued therapy within 1 year due to toxicity or non-specific medical reasons, and 9% experienced serious adverse events (grade 3–4). Four patients with metastatic TGCT showed rapid progression on imatinib therapy and were excluded from the study for secondary analysis.

Emactuzumab

Emactuzumab showed promising results in a phase 1 study of biweekly infusions for advanced diffuse TGCT ($n = 28$) [17]. The ORR was 86% at a mean follow up of 12 months [IQR 10–23 months], with 7% of patients demonstrating complete response, and 79% demonstrating partial response. The most common adverse events were asthenia (56%), pruritis (56%), and facial edema (64%). Twenty percent of patients experienced serious adverse events (grade 3). No new data have been reported since this phase one trail in 2015.

Pexidartinib

Pexidartinib is the only drug approved for use in TGCT at the time of this publication. This approval was based on efficacy demonstrated in a phase I trial [19] and subsequent ENLIVEN study, a placebo-controlled randomized controlled trail (RCT) of oral pexidartinib administered for a 24-week period in patients with advanced diffuse TGCT [20••]. Compared to placebo ($n = 61$), the study group ($n = 59$) experienced a significantly greater ORR (39% vs 0%; $p < 0.0001$) by RECIST. Furthermore, the study group experienced improved functional outcomes, with a significant increase in range of motion (ROM) from baseline when compared to controls ($+8.9 \pm 3.0$; $p = 0.0043$). As with other CSF1 inhibitors, minor adverse events were relatively common. The most common adverse events were hair color changes (67% vs 3%), fatigue (54% vs 36%), and increased serum aminotransferase levels (AST; 39% vs 0% and ALT; 28% vs 2%). Serious adverse events occurred in 13% of patients receiving pexidartinib, compared to 2% of placebo patients. Notably, three patients (5%) experienced serum aminotransferase levels more than three times the upper limit of normal, as well as substantial increases in serum bilirubin and alkaline phosphatase. Enrollment was stopped six patients short of the planned total of 126 patients due to this mixed or cholestatic hepatotoxicity observed in the ENLIVEN study as well as non-TGCT cohorts. There was one death, which occurred in a patient with cardiovascular disease and was not related to the study drug. In 2019, the United States Food and Drug Administration (FDA) approved pexidartinib for treatment of adults with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery with a boxed warning for risk of serious and potentially fatal liver injury. Currently, it is only available via a risk evaluation and mitigation strategy administered by the manufacturer [22].

Imatinib, emactuzumab, and pexidartinib have shown promising early results as systemic treatments of advanced diffuse TGCT with ORRs of 31, 86, and 39% respectively. Pexidartinib showed significantly greater ORR than placebo in a recent RCT, and is the only FDA-approved systemic therapy for TGCT. While Nilotinib showed a high rate of patients with stable disease (90%), no patients experience partial or complete response. Adverse events associated with these drugs are relatively common, although serious adverse events are relatively rare (9–20%). The most recent National Comprehensive Cancer Center clinical guidelines include pexidartinib (category 1) and imatinib (category 2A) as the

only systemic therapies recommended for the treatment of TGCT [8]. The status of emactuzumab development and approval is unknown at the time of this publication.

The development of these systemic therapies marks a turning point in the treatment of advanced and inoperable diffuse TGCT. How they will be integrated into current treatment alogrithms remains to be seen. While complete responses have been observed, they have been relatively uncommon. The relatively high rate of observed partial responses gives hope for the possibility of surgical downstaging in order to facilitate resection in previously inoperable cases or to decrease the morbidity of planned resections in advanced disease (i.e., neoadjuvant use). However, more study is needed to determine the ideal timing and dose of these drugs, as well as the optimal treatment protocols in combination with other therapies such as surgery and radiation. Providers will need to exercise caution when prescribing these therapies and monitor closely for evidence of serious adverse events. A collaborative and multidisciplinary approach, similar to that used in the treatment of malignant tumors, will be essential in managing TGCT in the era of systemic therapies.

Radiosynoviorthesis/External Beam Radiotherapy

Radiosynoviorthesis (RSO) and external beam radiotherapy (EBR) can be used alone or as an adjuvant to surgery, especially in refractory cases. RSO involves the local administration of radioactive agents (most commonly ^{90}yttrium RSO) to restore the synovium as an alternative or adjuvant to surgery [23]. While promising, RSO's efficacy remains unclear due to a limited number of studies and poor-quality data. Recent studies have shown no significant difference in rates of recurrence in patients with diffuse PVNS of the knee with and without RSO treatment [24•, 25•]. Furthermore, Gortzak et al. [25•], found no significant difference in perception of pain, overall physical or mental health scores, or patient satisfaction at a mean follow-up of 7.3 years with or without RSO treatment. A 2015 meta-analysis by Mollon et al. examined individual patient data from 35 observation studies and reported that perioperative EBRT may reduce the rate of recurrence in patients with diffuse disease [26]. They did however note that much of this evidence was low-quality and further study is required. Additional concerns surrounding the use of RSO include potential risks of early-onset arthritis, avascular necrosis, and increased risks of wound healing issues and other surgical complications associated with the use of adjuvant radiotherapy. Perhaps most concerning is the risk of secondary radiation-induced sarcoma and malignant transformation [26].

Conclusion

Diffuse TGCT is a neoplastic, inflammatory disease with a benign but aggressive course that often leads to significant morbidity and poor function for patients. In the majority of cases, it is driven by a chromosomal translocation, t(1;2)(CSF-1;COL6A3), resulting in the overexpression of CSF1, and recruitment of CSF1 receptor (CSF1R) macrophages, giant cells, and osteoclasts [6]. Currently there is no consensus on the ideal treatment for diffuse TGCT and recurrence rates are as high as 50% [6]. Surgical synovectomy remains the primary treatment for diffuse TGCT; however, the ideal surgical approach is unclear. Recent data comparing open, arthroscopic, and combined approach synovectomy has yielded mixed results [11–13, 14••, 15••, 16]. The ideal surgical technique may depend on the location and extent of disease. Many centers including ours have adopted a hybrid arthroscopic anterior and open posterior approach to diffuse TGCT of the knee that has been supported in recent studies.[12, 27, 28]. This is the preferred approach at the author's institution for disease determined to be resectable by a multidisciplinary tumor board. Unlike localized disease, recurrence is frequent and all patients must be appropriately counseled about the rapidly evolving landscape.[11–13, 14••, 15••, 16] Radiosynoviorthesis and external beam radiation therapy have been proposed as adjuvants to reduce recurrence rates after surgery, or as primary treatment for inoperable disease [24•, 25•, 26], however, there is little evidence to support efficacy in reducing recurrence at this time, and the concern for complications such as early arthritis, AVN, wound healing complications, and secondary sarcoma remain high [26]. Radiotherapy is very rarely used in our institution as the efficacy is less concretely demonstrated and the risk profile is viewed as higher than that of systemic options and surgery.

The development of systemic therapies for treatment of advanced diffuse TGCT [17–19, 20••, 21••] and the recent FDA approval for use of pexidartinib in a subset of patients is a major advancement in the treatment of this disease. At present, CSF1R inhibition is being used for patients for whom surgery is highly morbid or unlikely to achieve cure, in an effort to improve symptoms and potentially reducing morbidity in advanced disease. There is clearly much to be learned. Dosing alterations are ongoing to see if a more optimal risk/benefit profile can be achieved, and we continue to investigate questions around drug holidays/cessation of drug/duration of treatment. Systemic therapy with the intent of cure or long-term maintenance may also be feasible, but further study is needed on the ideal treatment algorithm for these drugs, including dosing and combination with other treatment modalities.

In the era of targeted therapeutic options, a multidisciplinary approach with surgeons, radiation oncologists, and medical oncologists collaborating for the treatment of refractory TGCT will be essential. Armed with new therapies and

treatment paradigms, clinicians have the opportunity to provide improved outcomes for patients long affected by the recalcitrant form of this disease. It is essential to remember, however, that the majority of TGCT patients can be cured with simple surgical excision. Understanding the spectrum of disease and identifying patients who require more complex, multidisciplinary approaches is therefore essential.

Compliance with Ethical Standards

Conflict of Interest Nicholas M. Bernthal has received research funding from the National Institutes of Health (NIH), and has received compensation from Zimmer Biomet, Daiichi Sankyo, and Onkos Surgical for service as a consultant. Chad R. Ishmael and Zachary D.C. Burke have no potential conflicts of interest to disclose.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. de Saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone, vol. 5. 4th ed: International Agency for Research on Cancer (IARC); 2013. p. 100–3.
2. Staals EL, Ferrari S, Donati DM, Palmerini E. Diffuse-type tenosynovial giant cell tumour: current treatment concepts and future perspectives. Eur J Cancer. 2016;63:34–40.
3.• Mastboom MJL, Verspoor FGM, Verschoor AJ, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta Orthop. 2017;88:688–94 **Prior to this study, there was limited epidemiologic data regarding TGCTs. This study found that the incidence of TGCT was higher than thought, affects more females than males, and recurrence is common**.
4. Cupp JS, Miller MA, Montgomery KD, Nielsen TO, O'Connell JX, Huntsman D, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. Am J Surg Pathol. 2007;31:970–6.
5. West RB, Rubin BP, Miller MA, Subramanian S, Kaygusuz G, Montgomery K, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A. 2006;103:690–5.
6. Staals EL, Ferrari S, Donati DM, Palmerini E. Diffuse-type tenosynovial giant cell tumour: current treatment concepts and future perspectives. Eur J Cancer. 2016;63:34–40.
7. Mollon B, Lee A, Busse JW, et al. The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee: an individual patient meta-analysis. Bone Joint J. 2015;97-b:550–7.
8. NCCN. NCCN clinical practice guidelines in oncology: soft tissue sarcoma - version 3. 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed 12/9/2019, 2019.
9. van der Heijden L, Gibbons CL, Dijkstra PD, et al. The management of diffuse-type giant cell tumour (pigmented villonodular synovitis) and giant cell tumour of tendon sheath (nodular tenosynovitis). J Bone Joint Surg (Br). 2012;94:882–8.
10. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. Clin Sarcoma Res. 2016;6:20.
11. Gu HF, Zhang SJ, Zhao C, Chen Y, Bi Q. A comparison of open and arthroscopic surgery for treatment of diffuse pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2014;22:2830–6.
12. Colman MW, Ye J, Weiss KR, Goodman MA, McGough RL 3rd. Does combined open and arthroscopic synovectomy for diffuse PVNS of the knee improve recurrence rates? Clin Orthop Relat Res. 2013;471:883–90.
13. Palmerini E, Staals EL, Maki RG, Pengo S, Cioffi A, Gambarotti M, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. Eur J Cancer. 2015;51:210–7.
14.•• Mastboom MJL, Staals EL, Verspoor FGM, et al. Surgical treatment of localized-type tenosynovial giant cell tumors of large joints: a study based on a multicenter-pooled database of 31 international sarcoma centers. J Bone Joint Surg Am. 2019;101:1309–18 **This study examined outcomes after surgical treatment of localized TGCT. Investigators found that larger tumor size and initial surgical treatment with arthroscopy (versus open resection) were associated with recurrence after resection. Open resection was associated with relatively low complication rates and good functional outcomes, and thus led the authors to recommend an open approach and complete resecection over arthroscopy to minimize the risk of recurrence**.
15.•• Mastboom MJL, Palmerini E, Verspoor FGM, et al. Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. Lancet Oncol. 2019;20:877–86 **This international, multi-center, retrospective cohort study assessed outcomes after surgical management of patients with diffuse-type TGCT. Surgical treatment was associated with recurrence in 44% of patients and 12% of patients had complications**.
16. Georgiannos D, Boutsiadis A, Agathangelidis F, Papastergiou S, Karataglis D, Bisbinas I. Arthroscopically-assisted mini open partial synovectomy for the treatment of localized pigmented villonodular synovitis of the knee. A retrospective comparative study with long-term follow up. Int Orthop. 2017;41:925–30.
17. Cassier PA, Italiano A, Gomez-Roca CA, le Tourneau C, Toulmonde M, Cannarile MA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. Lancet Oncol. 2015;16:949–56.
18. Gelderblom H, Cropet C, Chevreau C, Boyle R, Tattersall M, Stacchiotti S, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2018;19:639–48.
19. Tap WD, Wainberg ZA, Anthony SP, Ibrahim PN, Zhang C, Healey JH, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. N Engl J Med. 2015;373:428–37.
20.•• Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet. 2019;394:478–87 **This study investigated the efficacy and safety of a CSF1R tyrosine kinase inhibitor, nilotinib in locally advanced and non-resectable TGCT. 92.6% of patients attained disease control after 10 weeks of treatment – though 96% had a treatment-related adverse event. No grade 4 or 5 adverse events were reported and the authors concluded that CSF1R tyrosine kinase inhibitors have anti-tumor activity, and manageable toxicity in patients with inoperable diesase**.

21.•• Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. Sci Rep. 2019;9:14551 **This international, multi-institutional, retrospective study aimed to assess the efficacy of imatinib mesylate in treating patients with advanced TGCT. They report one- and five-year progression-free survival of 71 and 48% respectively**.

22. DSI: Turalio (pexidartinib), prescribing information. Available at: https://dsi.com/prescribing-information-portlet/getPIContent?productName=Turalio&inline=true. Accessed 12/9/2019, 2019.

23. Modder G. Radiosynoviorthesis (radiation Synovectomy). In: Biersack HJ, Freeman LM, editors. Clinical Nuclear Medicine. Berline, Heidelberg: Springer; 2007.

24.• Durr HR, Capellen CF, Klein A, et al. The effects of radiosynoviorthesis in pigmented villonodular synovitis of the knee. Arch Orthop Trauma Surg. 2019;139:623–7 **This study examined the local recurrence rates of TGCT after open surgical synovectomy with or without adjuvant radiosynoviorthosis. The authors report a 23% recurrence rate in the radiosynoviorthosis group and 27% recurrence rate in the control group. The investigators conclude that surgery remains the mainstay of therapy, however radiosynoviorthosis may help reduce recurrence rates after surgical resection**.

25.• Gortzak Y, Vitenberg M, Frenkel Rutenberg T, et al. Inconclusive benefit of adjuvant ^{90}yttrium hydroxyapatite to radiosynovectomy for diffuse-type tenosynovial giant-cell tumour of the knee. Bone Joint J. 2018;100-b:984–8 **This research investigated the long-term outcomes of patients with diffuse-type TGCT treated with synovectomy with or without intra-articular injection of ^{90}Yttrium hydroxyapatite**. There was no significant difference in outcome.

26. Mollon B, Lee A, Busse JW, et al. The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee: an individual patient meta-analysis. Bone Joint J. 2015;97-b:550–7.

27. Patel KH, Gikas PD, Pollock RC, Carrington RW, Cannon SR, Skinner JA, et al. Pigmented villonodular synovitis of the knee: a retrospective analysis of 214 cases at a UK tertiary referral centre. Knee. 2017;24:808–15.

28. Mollon B, Griffin AM, Ferguson PC, Wunder JS, Theodoropoulos J. Combined arthroscopic and open synovectomy for diffuse pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2016;24:260–6.