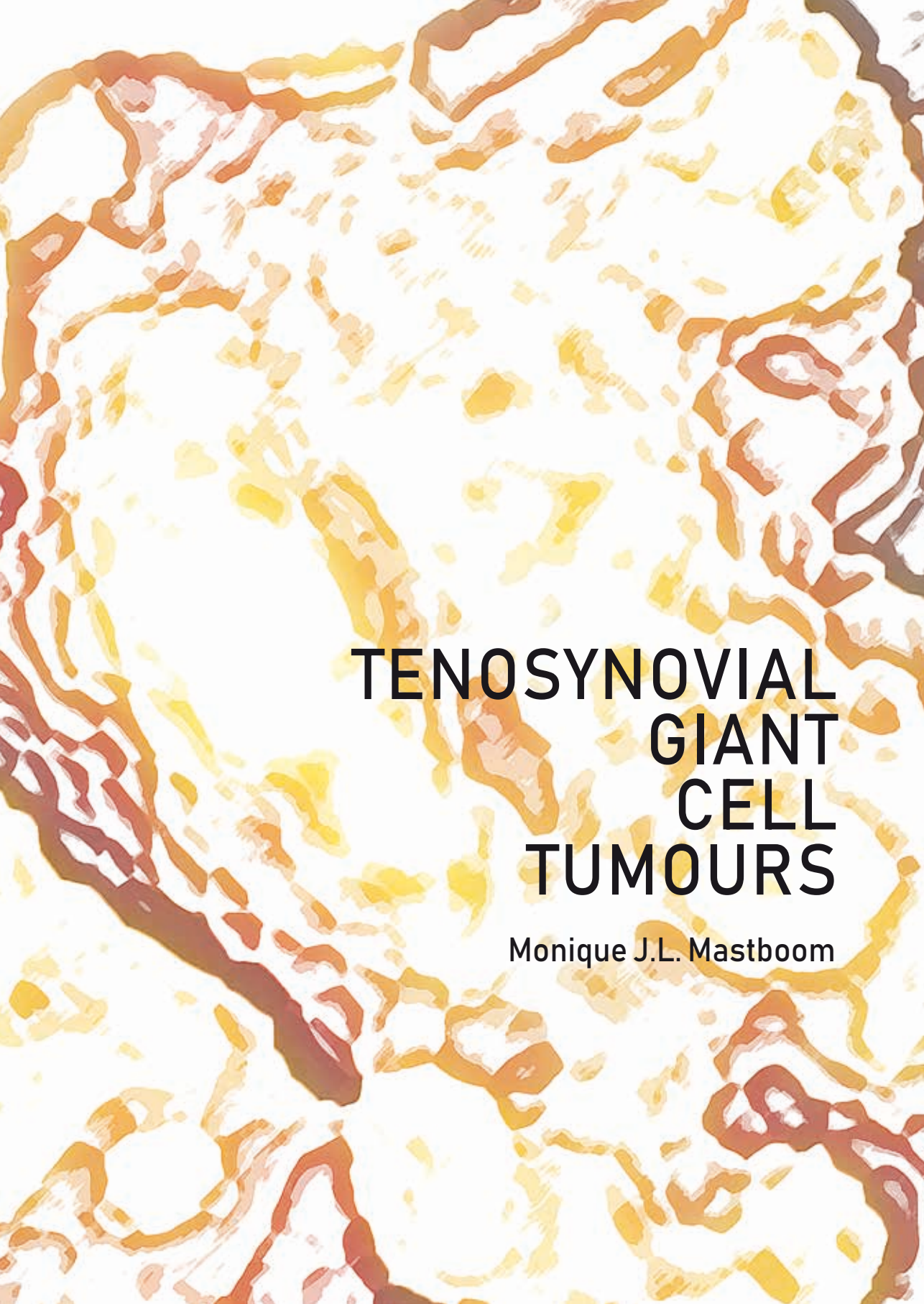


TENOSYNOVIAL GIANT CELL TUMOURS

Monique J.L. Mastboom

TENOSYNOVIAL GIANT CELL TUMOURS

Monique J.L. Mastboom

Although it's rare, it still needs care

TENOSYNOVIAL GIANT CELL TUMOURS

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit van Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 13 november 2018
klokke 16.15 uur

door

Monique J.L. Mastboom

geboren op 19 oktober 1988
te Nijmegen, Nederland

Cover design and thesis layout Lisanne de Koster

ISBN 978-94-9301-479-4

Printed by Gildeprint, Enschede, the Netherlands

The conduction of the research included in this thesis was carried out at the Department of Orthopaedics of the Leiden University Medical Centre, Leiden, the Netherlands.

The printing of this thesis was financially supported by Universiteit Leiden, Daiichi Sankyo, Implantcast Benelux, Anna-Fonds, ChipSoft, MoElBaDa, Consul-TENT, Bedrijfestijn. All funding is gratefully acknowledged.

Promotores

Prof. dr. P.D.S. Dijkstra

Prof. dr. A.J. Gelderblom

Co-promotor

Dr. M.A.J. van de Sande

Leden promotiecommissie

Prof. dr. J.V.M.G. Bovee	
Prof. dr. W.T.A. van der Graaf	*The Royal Marsden NHS Foundation Trust, London*
Dr. I.C.M. van der Geest	*Radboud Universitair Medisch Centrum, Nijmegen*

Table of contents

Chapter 1. General introduction and outline of this thesis 11

Chapter 2. Incidence 28

Higher incidence rates than previously known in Tenosynovial Giant Cell Tumours

M.J.L. Mastboom, F.G.M. Verspoor, A.J. Verschoor, D. Uittenbogaard, B. Nemeth, W.J.B. Mastboom, J.V.M.G. Bovee, P.D.S. Dijkstra, H.W.B. Schreuder, H. Gelderblom, M.A.J. van de Sande, TGCT study group.

Acta Orthop. 2017 Dec;88(6):688-694

Chapter 3. Diagnostics 48

Does *CSF1* over-expression or rearrangement influence biological behaviour in Tenosynovial Giant Cell Tumours of the knee?

M.J.L. Mastboom, D.M. Hoek, J.V.M.G. Bovee, M.A.J. van de Sande*, K. Szuhai* (*Shared last authorship).

Histopathology 2018 Aug. doi: 10.1111/his.13744

Chapter 4. Disease severity 70

Severity classification of Tenosynovial Giant Cell Tumours on MR imaging

M.J.L. Mastboom*, F.G.M. Verspoor*, D.F. Hanff, M.G.J. Gademan, P.D.S. Dijkstra, H.W.B. Schreuder, J.L. Bloem, R.J.P. van der Wal, M.A.J. van de Sande (*Shared first authorship).

Surg Oncol. 2018 Sept;27(3):544-550

Chapter 5. Hormones 94

Can increased symptoms of Tenosynovial Giant Cell Tumours during pregnancy be explained by a change in female sex hormones?

M.J.L. Mastboom, F.G.M. Verspoor, R. Planje, H.W.B. Schreuder, M.A.J. van de Sande.

Submitted

Chapter 6. Children 114

Tenosynovial Giant Cell Tumours in children: a similar entity compared with adults

M.J.L. Mastboom, F.G.M. Verspoor, D. Uittenbogaard, G.R. Schaap, P.C. Jutte, H.W.B. Schreuder, M.A.J. van de Sande.

Clin Orthop Relat Res. 2018 Sept;476(9):1803-1812

Chapter 7. Localized-TGCT 134

Surgical treatment of localized-type Tenosynovial Giant Cell tumours of large joints

M.J.L. Mastboom, E. Staals, F.G.M. Verspoor, A.J. Rueten-Budde, S. Stacchiotti, E. Palmerini, G.R. Schaap, P.C. Jutte, W. Aston, A. Leithner, D. Dammerer, A. Takeuchi, Q. Thio, X. Niu, J.S. Wunder, TGCT study group, M.A.J. van de Sande.

Submitted

Chapter 8. Diffuse-TGCT 162

Outcome of surgical treatment for patients with diffuse-type Tenosynovial Giant Cell Tumours

M.J.L. Mastboom, E. Palmerini, F.G.M. Verspoor, A.J. Rueten-Budde, S. Stacchiotti, E. Staals, G.R. Schaap, P.C. Jutte, W. Aston, H. Gelderblom, A. Leithner, D. Dammerer, A. Takeuchi, Q. Thio, X. Niu, J.S. Wunder, TGCT study group, M.A.J. van de Sande.

Submitted

Chapter 9. Treatment 190

Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumour

M.J.L. Mastboom*, F.G.M. Verspoor*, G. Hannink, R.G. Maki, A. Wagner, E. Bompas, J. Desai, A. Italiano, B.M. Seddon, W.T.A. van der Graaf, J.Y. Blay, M. Brahmi, L. Eberst, S. Stacchiotti, O. Mir, M.A.J. van de Sande, H. Gelderblom, P.A. Cassier (*Shared first authorship).

Submitted

Chapter 10. Quality of life 208

The effect of surgery in Tenosynovial Giant Cell Tumours as measured by patient reported outcomes on quality of life and joint function

M.J.L. Mastboom*, F.G.M. Verspoor*, G. Hannink, W.T.A. van der Graaf, M.A.J. van de Sande, H.W.B. Schreuder (*Shared first authorship).

Accepted in Bone Joint J

Chapter 11. Impact on daily living 232

The patient perspective on the impact of Tenosynovial Giant Cell Tumours on daily living: Crowdsourcing study on physical function and quality of life

M.J.L. Mastboom, R. Planje, M.A.J. van de Sande.

Interact J Med Res. 2018 Feb 23;7(1):e4.

Chapter 12. Limb amputation 258

Limb amputation after multiple treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch cases

M.J.L. Mastboom, F.G.M. Verspoor, H. Gelderblom, M.A.J. van de Sande.

Case Rep Orthop. 2017;7402570.

Chapter 13. Summary of this thesis 274

Chapter 14. General discussion & Future perspectives 284

Chapter 15. Summary in Dutch (Nederlandse samenvatting) 304

Chapter 16. Appendices 316

List of publications

Acknowledgements

Curriculum vitae

chapter one

INTRODUCTION

General introduction and outline of this thesis

Background

Tenosynovial Giant Cell Tumour (TGCT) is an orphan, mono-articular disease, arising from the synovial lining of joints, bursae or tendon sheaths[1, 2]. TGCT is divided into a lobulated well circumscribed lesion (localized-type) and a more locally aggressive lesion (diffuse-type) (*figure 1*). In general, the disease is considered a benign entity, but the diffuse-type can invade surrounding tissues and is regarded as locally invasive[1, 2]. The best treatment modality for this disease is a highly discussed topic. Literature about this disease is scarce. However, the impact of the disease can be severe: a deteriorated joint function threatens the quality of life in the relatively young patient population[3-5]. Therefore, it is of upmost importance to gain insight in the pathophysiology and severity of the disease to improve treatment strategies.

Historical vignette

In the 2013 WHO classification, giant cell tumour of the tendon sheath and pigmented villonodular synovitis (PVNS) were unified in one overarching name: tenosynovial giant cell tumours (TGCT) (*table 1*)[1, 2]. Historically, different terms have been used for this entity, including synovial xanthoma, xanthogranuloma, synovial fibroendothelioma or endothelioma, xanthomatous giant cell tumour of the tendon sheath, myeloplaxoma, chronic haemorrhagic villous synovitis, giant cell fibrohaemangioma, fibrohaemosideric sarcoma, sarcoma fusigiganocellulare, benign or malignant polymorphocellular tumour of the synovial membrane, and fibrous xanthoma of the synovial membrane[6-9].

In 1852, Chassaignac reported a nodular lesion of the synovial membrane affecting the flexor tendons of the fingers[10]. Simon was the first to describe the localized form[11] and Moser the first to define the diffuse form affecting the knee[12]. At that time, the disorder was considered a malignant condition. Dowd was the first person to question this[13]. Jaffe elucidated the clinical, radiological and pathological characteristics of the yellow-brown tumor-like tenosynovial lesions and suggested a reactive or inflammatory origin of the disease as both nodular synovitis and pigmented villonodular synovitis (PVNS) showed similar histological features and both showed a benign course[6]. The authors also merged both localized- and diffuse-forms to PVNS. However, the condition was considered neoplastic after the discovery of numerical

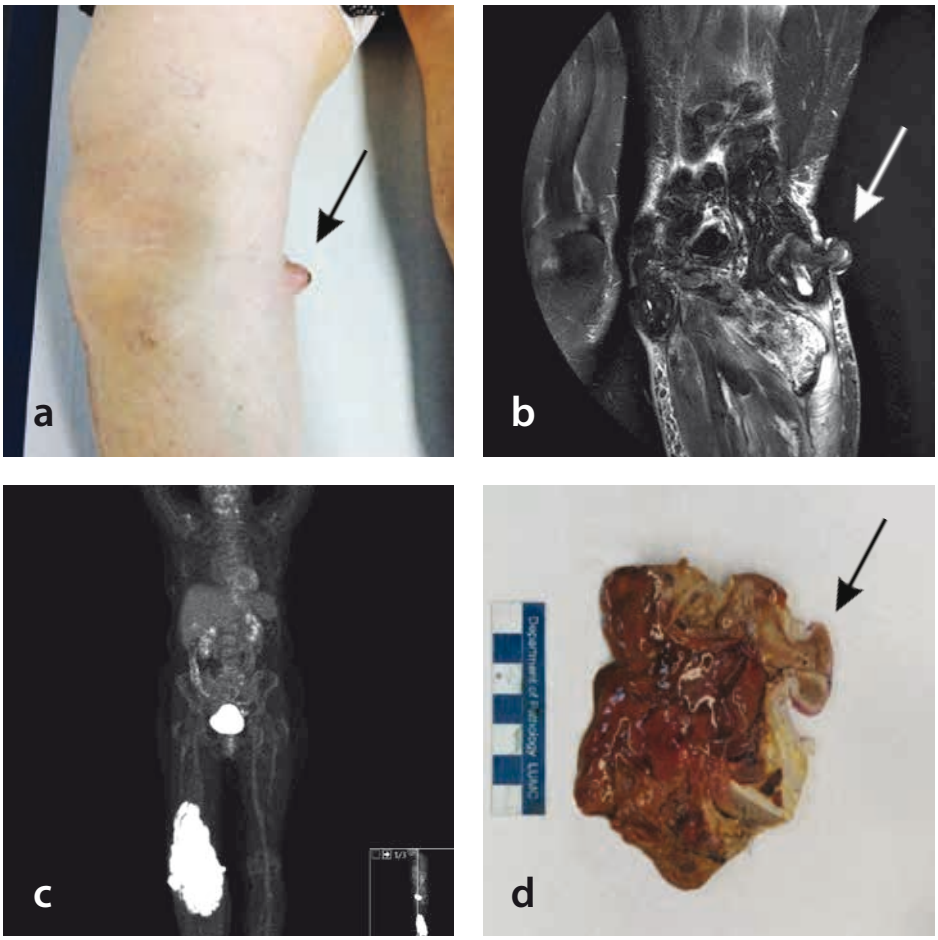


Figure 1 A 65-year-old female patient with a large medical history, consisting of multiple mutilating diffuse-type TGCT-related surgeries of her right knee. **a.** Swollen right knee in bonnet position. On the posterior, medial side is TGCT growing outside the operation-scar (arrow-head). **b.** Sagittal Short-TI Inversion Recovery metal clear MR image, revealing extensive tumour growth, also extending superficially into the skin (arrow-head). Characteristic TGCT blooming effect is seen attributed to scattered areas of low signal intensity, typical for iron deposition. **c.** Positron emission tomography–computed tomography (PET-CT): enhancement around total knee replacement, suspect for recurrent TGCT. **d.** Macroscopic aspect of this tumour after surgical removal, including the typical red-brownish colours and villous appearance. This section shows the extensive TGCT with a polypus bulge growing into the skin (arrow-head).

and structural chromosomal aberrations[14-20]. At present, an inflammatory disease component remains, as only a small part of TGCT encompassing cells are considered neoplastic or tumour cells (2-16%). These neoplastic cells express elevated levels of *CSF1*, resulting in an increase of neoplastic cells by an autocrine-loop as well as the recruitment of multiple non-neoplastic cells by a paracrine loop. This phenomenon is coined as 'the landscape effect'[21, 22].

Aetiology

Chromosomal aberrations, in both localized- and diffuse-TGCT, include trisomy for chromosomes 5 and 7 and translocations involving 1p11-13, most commonly partnering with 2q37 emerging in a t(1;2)(p13,q37) translocation (*figure 2*). At the 1p13 breakpoint, the Colony Stimulating Factor 1 (*CSF1*) gene is located. In both TGCT subtypes, *CSF1* is fused to the collagen 6A3 (COL6A3) promotor. As a result, the fusion leads to deregulated expression of *CSF1*[21] (*figure 3*).

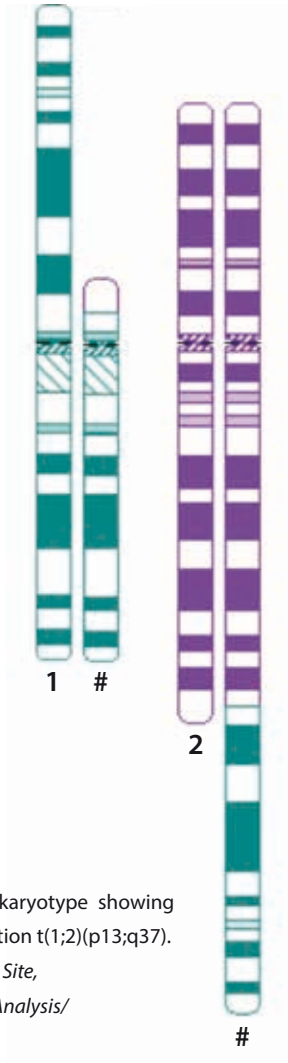


Figure 2 Systemic partial karyotype showing characteristic TGCT translocation t(1;2)(p13;q37). *Source: CyDAS Online Analysis Site, http://www.cydas.org/OnlineAnalysis/*

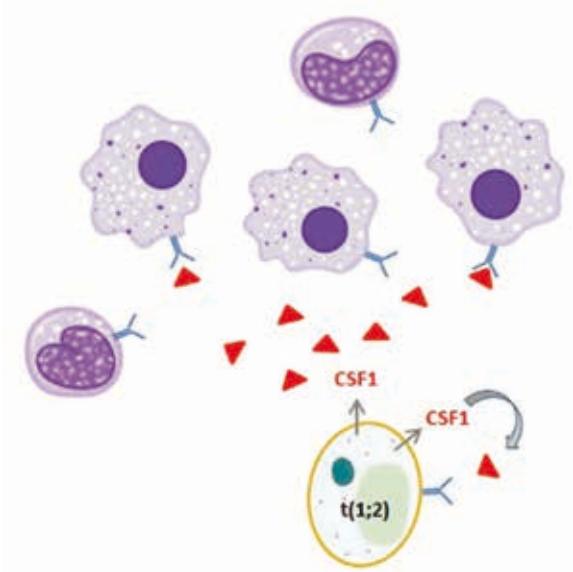


Figure 3 Etiopathogenesis of TGCT, neoplastic cells carrying the translocation (t(1;2)(p13;q37)), express elevated levels of *CSF1* (red triangles). This results in an increase of neoplastic cells through an autocrine loop. In addition, the recruitment of inflammatory cells of the monocyte/macrophage lineage expressing the *CSF1* receptor (paracrine loop), results in the tumour-landscape effect. *Source: permission obtained from designer drs. D.M. Hoek*

Table 1 Chronological literature overview on acquaintance of Tenosynovial Giant Cell Tumours

Study	Jaffe (1941)[6]	Fletcher (1992)[14]	Cin (1994)[15]
Name	Pigmented Villonodular Synovititis (PVNS)		
Types	***Circumscribed form*** affected membrane ≥1 yellow-brown sessile/stalked tumor-like nodular outgrowths ***Diffuse form*** brownishly pigmented membrane, covered by villous and coarse nodular outgrowths		
Definition	Mono-articular, regarded synovium of tendon sheath, bursa, and joint.		
Histopathological features	Multinuclear giant cells, hemosiderinladen macrophages and lipophages, alternate with areas of intercellular collagen and hyalin		
Tumourigenesis	Inflammatory response, unknown to what agent	Numerical changes (trisomy) in chromosome 5 and 7	Structural aberrations (short arm) 1p11-13
Tumour characteristics	Different parts of individual lesions vary widely. A considerable number of blood vessels and much blood pigment		

West (2006)[21]	Cupp (2007)[22]	WHO (2013)[1, 2]	Panagopoulos (2014)[56]
		Tenosynovial Giant Cell Tumour (TGCT)	
		Localized-type well circumscribed, small (0.5-4 cm) and lobulated tumour ***Diffuse-type*** Large (>5 cm) firm or sponge-like tumour, typical villous pattern and multi-nodular appearance with variegated colours	
Mononuclear and multinucleated cells, both showing high levels of *CSF1*R	Perinuclear *CSF1* protein expression within mononuclear cells in a diffuse, punctate pattern	Synovial like mononuclear cells, multinucleated osteoclast-like giant cells, foam cells, siderophages, inflammatory cells	
Neoplastic (*CSF1* rearrangement, including strong promotor region COL6A3 gene) and non-neoplastic	Central mechanism of tumorigenesis is the signaling pathway initiated by *CSF1* and *CSF1*R interaction		
Landscape effect; a minority of neoplastic cells (*CSF1* overexpression) create a tumour landscape comprised of non-neoplastic cells	***Two groups:*** ***1:*** both *CSF1* translocation and high expression of *CSF1* RNA (61%). ***2:*** no detectable translocation, but high expression of *CSF1* RNA or *CSF1* protein (39%)		Case-report: inversion t(1;1)(q21;p11), resulting in *CSF1*-100A10 fusion gene, indicates replacement of 3'-UTR of *CSF1* in abirritations targeting *CSF1* gene

Empty fields remained unchanged.

CSF1: Colony Stimulating Factor 1; *CSF1*R: Colony Stimulating Factor 1 Receptor.

Macroscopy and microscopy

Definite diagnosis of TGCT is established on microscopy.

Macroscopically, localized-TGCT is an encapsulated or pedunculated, small (<5 cm) lesion with a white to grey aspect and alternating yellow and brown areas. In contrast, diffuse-TGCT involves a large part or all of the synovial lining with either a typical villous pattern (intra-articular) or a multi-nodular appearance (extra-articular), including a diverse colour pattern, varying from white-yellow to brown-red areas. The diffuse-type shows an infiltrative growth pattern. Microscopically, both types contain an admixture of mononuclear cells (histiocyte-like and larger cells) and multinucleated giant cells, lipid-laden foamy macrophages (also known as xanthoma cells), siderophages (macrophages including hemosiderin-depositions), stroma with lymphocytic infiltrate and some degree of collagenization (*figure 4*)[1, 2].

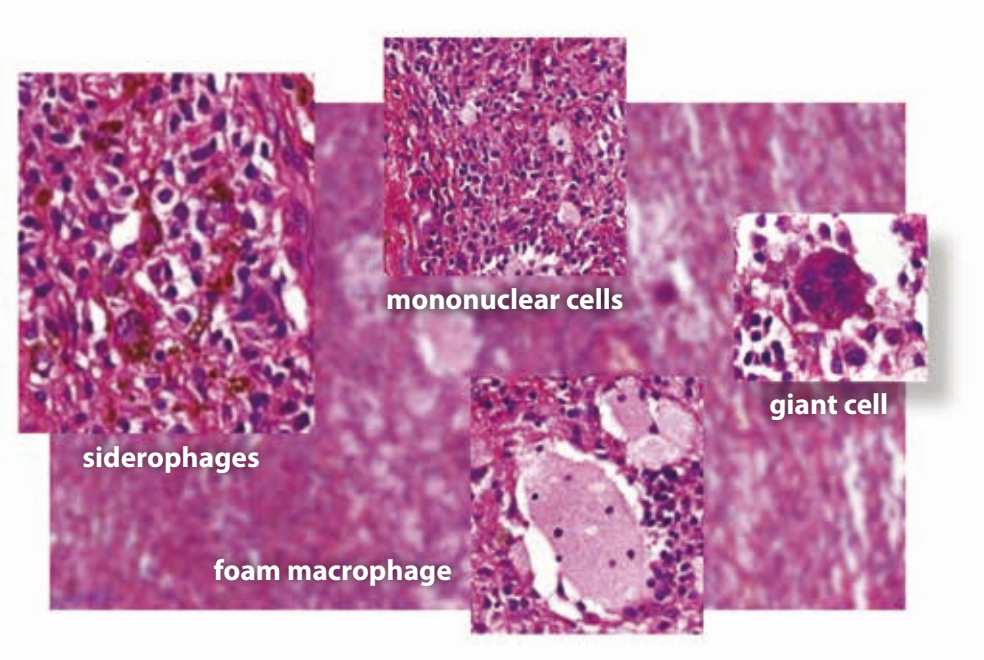


Figure 4 Tenosynovial Giant Cell Tumours contain an admixture of mononuclear cells, multinucleated giant cells, foam macrophages and siderophages.

Clinical presentation

TGCT affecting small joints, both fingers and toes, usually presents as localized-TGCT. In large joints, excluding digits, both localized- and diffuse-TGCT are seen. The diffuse-type mainly affects weight-bearing joints, predominantly the knee (75%)[1, 2, 4]. TGCT incidence is based on one single US-county study in 1980, that reported an incidence of 9 and 2 per million person-years for localized- (including digits) and diffuse-TGCT, respectively[23]. Male:female ratio is about 1:1.5 for both types. The mean age at the time of diagnosis lies between 30 and 50 years[1, 2, 4]. Typically, patients primarily present with pain and swelling of the associated joint (*figure 1a*). Additional symptoms might be limited range of motion, stiffness, instability, giving way and locking complaints[5]. Time to definitive diagnosis is often prolonged, on average 4.4 years, due to these unspecific symptoms and the rarity of the disease[4, 24, 25]. As TGCT is not lethal, overall survival is similar to the general population. Diffuse-TGCT frequently becomes a debilitating chronic illness; therefore joint function and quality of life should be assessed as disease-outcome[3, 5, 26, 27].

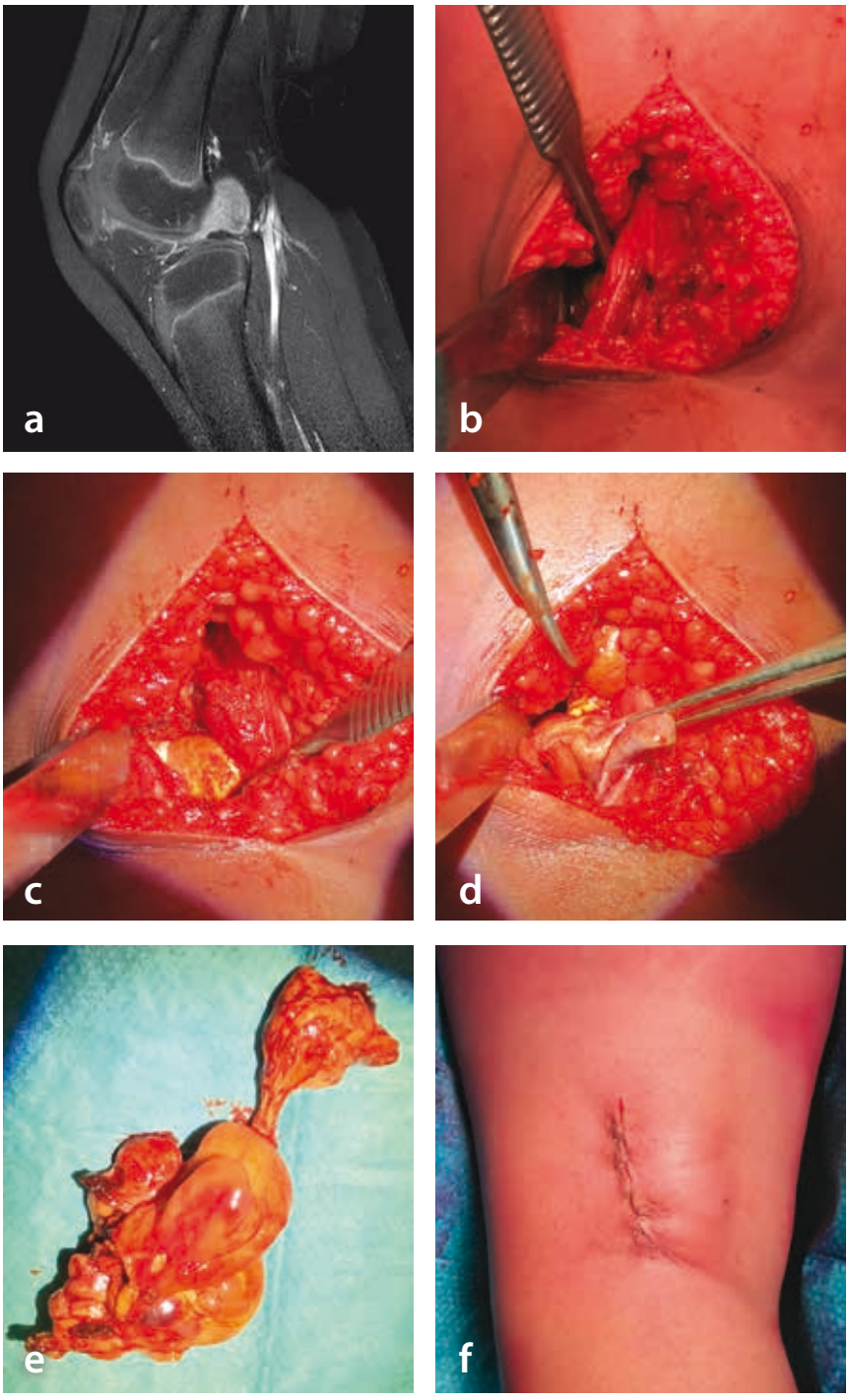
Radiology

In daily practice, an X-ray imaging of the affected joint is frequently performed as a first line imaging. Degenerative changes and effusion may be present but are nonspecific, and could also be noticed on computed tomography (CT). Magnetic resonance (MR) imaging is the most distinctive imaging technique[7, 8, 28-30]. MR imaging reveals nodular (localized-type) or villous (diffuse-type) proliferation of synovium, including associated joint effusion. On T1- and T2-weighted fast spin echo and other fluid sensitive sequences, lesions demonstrate predominantly intermediate to low signal intensity (dark). After intravenous administration of Gadolinium-chelate, TGCT shows heterogeneous enhancement. Hemosiderin deposits are frequently seen, but occur also in other entities[31]. This degraded hemoglobin deposits cause local changes in susceptibility ('blooming effect') on gradient echo sequences, resulting in low signal intensity areas that are larger than the anatomical substrate (*figure 1b*). No substantial change in signal intensity is detected when comparing the localized- and diffuse-types[7, 28]. Differential diagnosis based on MR imaging includes hemophilia, synovial hemangioma, rheumatoid pannus, amyloid arthrophy and desmoid fibromatosis.

Treatment modalities

The current standard of care is still surgical resection of the tumour, either arthroscopically or with an open resection (*figure 5*), in order to: 1. reduce pain, stiffness, and joint destruction caused by the disease process; 2. improve function; and 3. minimize the risk of recurrence. Depending on the extensiveness of the disease, complete resection is frequently impossible, especially in diffuse-TGCT. Some reports consider arthroscopic management of TGCT superior to open surgery, because of less morbidity and a shorter recovery period[32-36]. Standard arthroscopy of the knee using the anteromedial and anterolateral approaches however, does not allow surgical access to all areas where diseased tissue could be present. A systematic review showed lower recurrence rates for open synovectomy (average 14%, maximum 67%) compared to arthroscopic synovectomy (average 40%, maximum 92%) in diffuse-TGCT[37]. A randomized controlled trial for arthroscopic synovectomy versus open synovectomy or surgical treatment versus targeted therapy is not (yet) performed.

Figure 5 ***(right page)*** Example of the surgical technique of an open synovectomy in localized-TGCT. An 8-year-old boy presented at the outpatient clinic with intermittent complaints of pain and swelling of his left knee of more than 12 months. These progressive debilitating symptoms were not sufficiently reduced by paracetamol and have led to school absenteeism. In the outpatient clinic, swelling was not objectified without limitation in range of motion and palpation was diffusely pressure painful. X-ray imaging did not show abnormalities. **a.** A sagittal T1-weighted MR imaging after intravenous administration of Gadolinium-chelate, revealed a well-circumscribed lesion on the posterior knee compartment. The T1-weighted and Proton Density MR scan (not shown here) revealed a lesion of low intensity. Despite the young age of the boy, a localized-TGCT was suspected. An open resection was planned, because of debilitating symptoms. **b.** A small lazy-C-incision was performed on the posterior, lateral side of the left knee. This approach and surgical window was chosen because of the lateral tumour localization. After opening the crural fascia, the saphena parva vene, the suralis cutaneous medius nerve, the tibialis nerve and the peroneus nerve were identified. Lateral gastrocnemius muscle was partially released, because of lateral localization of the tumour, without compromising the neurovascular bundle. **c & d.** The capsule overlying the tumour was partially released. A yellow-brown tumourous aspect showed and could be resected en bloc from the posterior cruciate ligament where it generally pedicles from. **e.** The entire localized-TGCT was excised. **f.** Minimal invasive techniques can be used to prevent post-operative complaints such as stiffness. After histological examination, TGCT diagnosis was confirmed.


a
b
c
d
e
f

In patients with extensive and/or recurrent TGCT, other available treatment modalities include radiation synovectomy with 90yttrium[38], external beam radiation therapy[39-41], and cryosurgery[42]. Their therapeutic value has only been assessed in retrospective, mostly single center series and their long-term side effects and complications are poorly described.

Discovery of the *CSF1-CSF1*R pathway in the pathogenesis of the tumour contributed to trials with targeted therapy. At present extensive or recurrent diffuse-TGCT is also treated with non-selective *CSF1* inhibitors such as nilotinib and imatinib[43, 44]; selective *CSF1* inhibitors such as pexidartinib, emactuzumab, cabrilazimab; or monoclonal antibody such as MSC110[45-48]. Long-term efficacy data have not yet been reported with these newer agents. Emactuzumab showed an overall response rate of 86% and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months)[45]. The preliminary results for cabiralizumab are consistent, with radiographic response and improvement in pain and function in five out of 11 patients (45%)[46]. Pexidartinib had an overall response rate of 52% (all patients had a partial response) and a rate of disease control of 83%. Responses were associated with an improved joint function (median duration of response exceeded eight months)[48].

TGCT in animals

TGCT affects both humans and animals. Case-reports of cats, dogs, horses, a European lynx and a reticulated giraffe are described[49-55]. Adequate diagnosis is animals is even more challenging, due to its rarity, unspecific symptoms and the absence of a verbal patient history. MR scans are infrequently performed. When animals present with debilitating symptoms of this tumour, extreme measures as joint amputation or euthanasia are more common.

Aim of thesis

Treatment of the often debilitating chronic illness, tenosynovial giant cell tumours (TGCT) of large joints, is challenging. This thesis aims to find better treatment modalities for this disease by evaluating the pathophysiology, biological behavior, diagnosis and quality of life. Sufficient data for evaluation of the rare disease TGCT was established through collaboration with the RadboudUMC and additionally with 31 international sarcoma centers.

Foremost, this thesis aims to create awareness for TGCT and to improve medical care. It evaluates different aspects of this heterogeneous neoplasm and addresses currently existing lacunas concerning disease incidence, histopathologic- and hormonal characteristics, disease severity stratification and pediatric disease burden. Moreover, this thesis addresses long-term effects of systemic targeted treatment and assessment of health-related quality of life after treatment in TGCT patients. Lastly, this thesis presents the largest global individual data study of TGCT for both localized- and diffuse-type TGCT.

Outline of thesis

In **chapter 2** we performed nationwide incidence calculations upon TGCT, since no incidence study was reported past 1980. Radiologically and clinically, localized- and diffuse-TGCT are two different entities. However, genetically and histopathologically they are identical. **Chapter 3** correlates the biological behaviour of TGCT in the knee at a molecular level.

In the patient-population of localized- and diffuse-TGCT, different disease extent exist. Therefore, **chapter 4** focuses on the establishment of a TGCT severity classification, sub-classifying both localized- and diffuse-type TGCT into two more distinct subtypes.

The clinical behaviour between TGCT patients differs greatly. In **chapter 5** we explore the influence of female sex hormones on the experienced TGCT-related symptoms.

Many case-series of TGCT in adults are described, whereas TGCT is only incidentally reported in children. **Chapter 6** evaluates differences in TGCT presentation between adults and children.

Relatively small and heterogeneous case-series emphasize the importance of a large-scaled study. In **chapter 7** and **chapter 8**, an international multicentre study in 31 international sarcoma centres is described. This study explores risk factors for TGCT of large joints in 941 localized- and

1192 diffuse-type TGCT patients. Results of this study are crucial to the treatment possibilities and prognosis of this rare entity.

Since a decade, targeted therapies are used in TGCT; however long-term results are still lacking. In **chapter 9**, we evaluated the long-term efficacy of imatinib mesylate, a targeted therapy blocking the Colony Stimulating Factor 1 (*CSF1*) receptor, in patients with advanced TGCT.

In a benign disease, not only oncologic outcomes are of interest. Of utmost importance is quality of life for patients bearing this chronic disease. **Chapter 10** evaluates the quality of life and joint function after surgical treatment and **chapter 11** assesses the patient perspective on daily life with TGCT by crowdsourcing.

To emphasize the impact of a disease considered benign, extreme measures like above knee amputation are described in **chapter 12** as final treatment for TGCT.

Finally, a summary of this thesis is provided in **chapter 13**. Conclusions, clinical implications and future perspectives for the subject of this thesis are discussed in **chapter 14**.

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
4. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
5. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
6. Jaffe HL, Lichtenstein L, Sutro CJ: Pigmented villonodular synovitis, bursitis, tenosynovitis. Arch Pathol 1941; 31:731-65.
7. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
8. Hughes TH, Sartoris DJ, Schweitzer ME, Resnick DL. Pigmented villonodular synovitis: MRI characteristics. Skeletal radiology. 1995;24(1):7-12.
9. Flandry F, Hughston JC. Pigmented villonodular synovitis. J Bone Joint Surg Am. 1987;69(6):942-9.
10. Chassaignac EP. Cancer de la gaîne des tendons. Gazette des hôpitaux civils et militairs 1852; 185-6. *French*
11. Simon G. Exstirpation einer sehr grossen, mit dickem Stiele angewachsenen Kniegelenkmaus mit glücklichem Erfolge. Arch Klin Chirurgie. 1865;6:573.
12. Moser E. Primares sarkom der fussgelenkkapsel. Deutsche Ztschr f Chir. 1909;98:306-10.
13. Dowd CN. Villous arthritis of the knee (Sarcoma). Annals of Surgery. 1912;56:363.
14. Fletcher JA, Henkle C, Atkins L, Rosenberg AE, Morton CC. Trisomy 5 and trisomy 7 are nonrandom aberrations in pigmented villonodular synovitis: confirmation of trisomy 7 in uncultured cells. Genes, chromosomes & cancer. 1992;4(3):264-6.
15. Dal Cin P, Sciot R, Samson I, De Smet L, De Wever I, Van Damme B, et al. Cytogenetic characterization of tenosynovial giant cell tumors (nodular tenosynovitis). Cancer research. 1994;54(15):3986-7.
16. Mertens F, Orndal C, Mandahl N, Heim S, Bauer HF, Rydholm A, et al. Chromosome aberrations in tenosynovial giant cell tumors and nontumorous synovial tissue. Genes, chromosomes & cancer. 1993;6(4):212-7.
17. Ohjimi Y, Iwasaki H, Ishiguro M, Kaneko Y, Tashiro H, Emoto G, et al. Short arm of chromosome 1 aberration recurrently found in pigmented villonodular synovitis. Cancer genetics and cytogenetics. 1996;90(1):80-5.
18. Sciot R, Rosai J, Dal Cin P, de Wever I, Fletcher CD, Mandahl N, et al. Analysis of 35 cases of localized and diffuse tenosynovial giant cell tumor: a report from the Chromosomes and Morphology (CHAMP) study group. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 1999;12(6):576-9.
19. Nilsson M, Hoglund M, Panagopoulos I, Sciot R, Dal Cin P, Debiec-Rychter M, et al. Molecular cytogenetic mapping of recurrent chromosomal breakpoints in tenosynovial giant cell tumors. Virchows Archiv : an international journal of pathology. 2002;441(5):475-80.
20. Brandal P, Bjerkehagen B, Heim S. Molecular cytogenetic characterization of tenosynovial giant cell tumors. Neoplasia. 2004;6(5):578-83.

21. 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(3):690-5.
22. 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. The American journal of surgical pathology. 2007;31(6):970-6.
23. Myers BW, Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. Medicine (Baltimore). 1980;59(3):223-38.
24. Bhimani MA, Wenz JF, Frassica FJ. Pigmented villonodular synovitis: keys to early diagnosis. Clin Orthop Relat Res. 2001(386):197-202.
25. Cotten A, Flipo RM, Chastanet P, Desvigne-Noulet MC, Duquesnoy B, Delcambre B. Pigmented villonodular synovitis of the hip: review of radiographic features in 58 patients. Skeletal radiology. 1995;24(1):1-6.
26. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
27. van der Heijden L, Piner SR, van de Sande MA. Pigmented villonodular synovitis: a crowdsourcing study of two hundred and seventy two patients. Int Orthop. 2016;40(12):2459-68.
28. Poletti SC, Gates HS, 3rd, Martinez SM, Richardson WJ. The use of magnetic resonance imaging in the diagnosis of pigmented villonodular synovitis. Orthopedics. 1990;13(2):185-90.
29. Nordemar D, Oberg J, Brosjo O, Skorpil M. Intra-Articular Synovial Sarcomas: Incidence and Differentiating Features from Localized Pigmented Villonodular Synovitis. Sarcoma. 2015;2015:903873.
30. Wang C, Song RR, Kuang PD, Wang LH, Zhang MM. Giant cell tumor of the tendon sheath: Magnetic resonance imaging findings in 38 patients. Oncology letters. 2017;13(6):4459-62.
31. Barile A, Sabatini M, Iannessi F, Di Cesare E, Splendiani A, Calvisi V, et al. Pigmented villonodular synovitis (PVNS) of the knee joint: magnetic resonance imaging (MRI) using standard and dynamic paramagnetic contrast media. Report of 52 cases surgically and histologically controlled. La Radiologia medica. 2004;107(4):356-66.
32. de Carvalho LH, Jr., Soares LF, Goncalves MB, Temponi EF, de Melo Silva O, Jr. Long-term success in the treatment of diffuse pigmented villonodular synovitis of the knee with subtotal synovectomy and radiotherapy. Arthroscopy. 2012;28(9):1271-4.
33. Kubat O, Mahnik A, Smoljanovic T, Bojanic I. Arthroscopic treatment of localized and diffuse pigmented villonodular synovitis of the knee. Collegium antropologicum. 2010;34(4):1467-72.
34. Loriaut P, Djian P, Boyer T, Bonvarlet JP, Delin C, Makridis KG. Arthroscopic treatment of localized pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20(8):1550-3.
35. Rhee PC, Sassoon AA, Sayeed SA, Stuart MS, Dahm DL. Arthroscopic treatment of localized pigmented villonodular synovitis: long-term functional results. American journal of orthopedics. 2010;39(9):E90-4.
36. Noailles T, Brulefert K, Briand S, Longis PM, Andrieu K, Chalopin A, et al. Giant cell tumor of tendon sheath: Open surgery or arthroscopic synovectomy? A systematic review of the literature. Orthop Traumatol Surg Res. 2017;103(5):809-14.
37. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
38. Gortzak Y, Vitenberg M, Frenkel Rutenberg T, Kollender Y, Dadia S, Sternheim A, 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(7):984-8.

39. Heyd R, Seegenschmiedt MH, Micke O. The role of external beam radiation therapy in the adjuvant treatment of pigmented villonodular synovitis. Zeitschrift fur Orthopadie und Unfallchirurgie. 2011;149(6):677-82.
40. Mollon B, Lee A, Busse JW, Griffin AM, Ferguson PC, Wunder JS, 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(4):550-7.
41. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
42. Verspoor FG, Scholte A, van der Geest IC, Hannink G, Schreuder HW. Cryosurgery as Additional Treatment in Tenosynovial Giant Cell Tumors. Sarcoma. 2016:3072135.
43. 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.
44. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
45. Cassier PA, Italiano A, Gomez-Roca CA, Le Tourneau C, Toulmonde M, Cannarile MA, et al. *CSF1*R 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(8):949-56.
46. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-*CSF1*R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). ASCO conference 2017. 35 (15 Supplement 1).
47. Brahmi M, Vinceneux A, Cassier PA. Current Systemic Treatment Options for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis: Targeting the *CSF1*/*CSF1*R Axis. Current treatment options in oncology. 2016;17(2):10.
48. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference Chicago 2018.
49. Ihms EA, Rivas A, Bronson E, Mangus LM. Pigmented Villonodular Synovitis in a Reticulated Giraffe (Giraffa Camelopardalis). Journal of zoo and wildlife medicine : official publication of the American Association of Zoo Veterinarians. 2017;48(2):573-7.
50. Malatesta D, Cuomo A, Mara M, Di Guardo G, Gentile L, Macolino A, et al. Benign giant cell tumour of tendon sheaths in a European Lynx (Lynx lynx). Journal of veterinary medicine A, Physiology, pathology, clinical medicine. 2005;52(3):125-30.
51. Akerblom S, Sjostrom L. Villonodular synovitis in the dog: a report of four cases. Veterinary and comparative orthopaedics and traumatology: VCOT. 2006;19(2):87-92.
52. Dempsey LM, Maddox TW, Meiring T, Wustefeld-Janssens B, Comerford EJ. Computed Tomography Findings of Pigmented Villonodular Synovitis in a Dog. Veterinary and comparative orthopaedics and traumatology: VCOT. 2018.
53. Cotchin E. Further observations on neoplasms in dogs, with particular reference to site of origin and malignancy. Brit Vet J 1954;110:274-86.
54. Hulse EV. A benign giant-cell synovioma in a cat. The Journal of pathology and bacteriology. 1966;91(1):269-71.
55. Davies JD, Little NR. Synovioma in a cat. The Journal of small animal practice. 1972;13(3):127-33.
56. Panagopoulos I, Brandal P, Gorunova L, Bjerkehagen B, Heim S. Novel *CSF1*-S100A10 fusion gene and *CSF1* transcript identified by RNA sequencing in tenosynovial giant cell tumors. International journal of oncology. 2014;44(5):1425-32.

INCIDENCE

chapter two

Higher incidence rates than previously known in Tenosynovial Giant Cell Tumours

A nationwide study in the Netherlands

M.J.L. Mastboom[1], F.G.M. Verspoor[2], A.J. Verschoor[3], D. Uittenbogaard[1], B. Nemeth[4], W.J.B. Mastboom[5], J.V.M.G. Bovée[6], P.D.S. Dijkstra[1], H.W.B. Schreuder[2], H. Gelderblom[3], M.A.J. van de Sande[1], TGCT study-group*

Acta Orthop. 2017 Dec;88(6):688-694

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

[4] Clinical Epidemiology, Leiden University Medical Centre, Leiden, the Netherlands

[5] Oncology Surgery, Medical Spectrum Twente, Enschede, the Netherlands

[6] Pathology, Leiden University Medical Centre, Leiden, the Netherlands

***TGCT study-group:**

G.R. Schaap, W.J. Kleyn Molekamp, S.T. Hokwerda, P. van der Woude, M. Henket, S.E. Brandt, J. van de Breevaart Bravenboer, L.A. Lisowski, P. van der Zwaal, J.M.G.T. Jenner, J.A. Jansen, A. de Gast, H.J. Noten, D.E. Meuffels, T. Gosens, R. Krips, D.T. Mensch, P.H.J. Bullens, R. Onstenk, F.L. Van Erp Taalman Kip, A.P. van Noort-Suijdendorp, C.H. Geerdink, D.M.J. Dorleijn, H.H. Kaptijn, M.W. Bloembergen, O.P.P. Temmerman, W.P. Zijlstra, T.D. Berendes, M. van den Besselaar, U.T. Timur, M.A. Witlox, M.R. Krijnen, P.C. Konings, B.R. Chander, F.C.W. Slootmans, D.J. Wever, D. Haverkamp, R.E.A.M. Zwartelé, E.M. Nelissen, K.G. Auw Yang, R. de Haan, P.C. Jutte, D.B.F. Saris, S.F. de Boer, R.J. de Raadt, C.P. Schönhuth, J.G.A. Amaya, R.J. Hillen, A.J.H. Vochteloo, B.G.W. Daalmans, P.C. Kaijser Bots, W.L.W. van Hemert

Abstract

Background and purpose

Tenosynovial Giant Cell Tumours (TGCT) are rare, benign tumours, arising in synovial lining of joints, tendon sheaths or bursae. 2 Types are distinguished: localized-, either digits or extremity, and diffuse lesions. Current TGCT incidence is based on 1 single US-county study in 1980, with an incidence of 9 and 2 per million person-year in localized- (including digits) and diffuse-TGCT, respectively. We aim to determine nationwide and worldwide incidence rates (IR) in TGCT affecting digits, TGCT localized-extremity and TGCT diffuse-type.

Material and methods

Over a 5-year period, the Dutch Pathology Registry (PALGA) identified 4503 pathology reports on TGCT. Reports affecting digits were solely used for IR-calculations. Reports affecting extremities, were clinically evaluated. Dutch IRs were converted to world population IRs.

Results

2815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. Dutch IR in digits, localized extremity and diffuse-type was 34 (95% CI 33-35), 11 (95% CI 11-12) and 5 (95% CI 4-5) per million person-years, respectively. All 3 groups showed a female predilection and highest number of new cases in age-category 40-59 years. Knee-joint was most often affected: localized-extremity (46%) and diffuse-type (64%), mostly treated with open-resection: localized (65%) and diffuse (49%). Reoperation rate due to local recurrence for localized-extremity was 9%, diffuse-TGCT 23%.

Interpretation

This first nationwide study and detailed analyses of IRs in TGCT estimated a worldwide IR in digits, localized-extremity and diffuse-TGCT of 29, 10 and 4 per million person-years, respectively. Recurrence rate in diffuse-type is 2.6 times higher, compared with localized-extremity. TGCT is still considered a rare disease; however, it is more common than previously understood.

Background

Tenosynovial Giant Cell Tumours (TGCT) are a rare entity, affecting generally young patients (below the age of 40 years), with an equal sex distribution. The World Health Organisation (WHO) classification of Tumours of Soft Tissue and Bone (2013) distinguishes 2 TGCT-types: localized and diffuse lesions[1, 13]. Microscopically the 2 types show no clear difference. However, on Magnetic Resonance Imaging (MRI) discrimination between these types is made[2].

The localized-type was previously described as Giant Cell Tumour of Tendon Sheath, nodular synovitis or localized Pigmented VilloNodular Synovitis (PVNS). The typical macroscopic aspect is a well circumscribed, small (among 0.5 to 4 centimetres) usually lobulated lesion, with white to grey, yellow and brown mottled areas[1]. Based on anatomical site of the localized-type tumour, differentiation is made into a group affecting digits and a group occurring in and around larger joints[3, 4]. TGCT affecting digits is defined as a localization distal to metacarpal or metatarsal bones; localized TGCT-extremity is defined as all sites near joints proximal and including metacarpal- and metatarsal-joints.

In localized-TGCT, most lesions are found in the digits of hand and feet (*Figure 1*). The majority of these lesions arise from the tendon sheath and less frequently from synovial lining of digital joints. Common treatment is marginal excision[5, 6]. A systematic review showed a recurrence rate of 15%, after an average follow-up of 37 to 79 months[7]. Fewer localized TGCT lesions are found around larger joints, they originate from synovial lining, tendon sheaths or bursae (*Figure 2*). The preferred treatment of these lesions is marginal excision by an arthroscopic or by open approach[5, 6]. A systematic review reported an average recurrence rate of 6% after arthroscopic resection and 4% after open resection (with variable follow-up)[8].

The diffuse-type TGCT; previously called diffuse Pigmented VilloNodular Synovitis (PVNS) or Synovitis (Villo)nodularis Pigmentosa (SVP), is a more destructive and locally aggressive tumour (*figure 3*). Diffuse-TGCT is defined by the presence of an infiltrative soft tissue mass along synovial lining, showing villous projections of the proliferated synovial membrane, with or without involvement of the adjacent joint or other structures. Macroscopically, the diffuse-type affects a large part of synovial lining and has a multinodular, multi-coloured appearance, including white, yellow and rust-coloured areas[1]. 75% are located around the knee-joint[8]. Current treatment

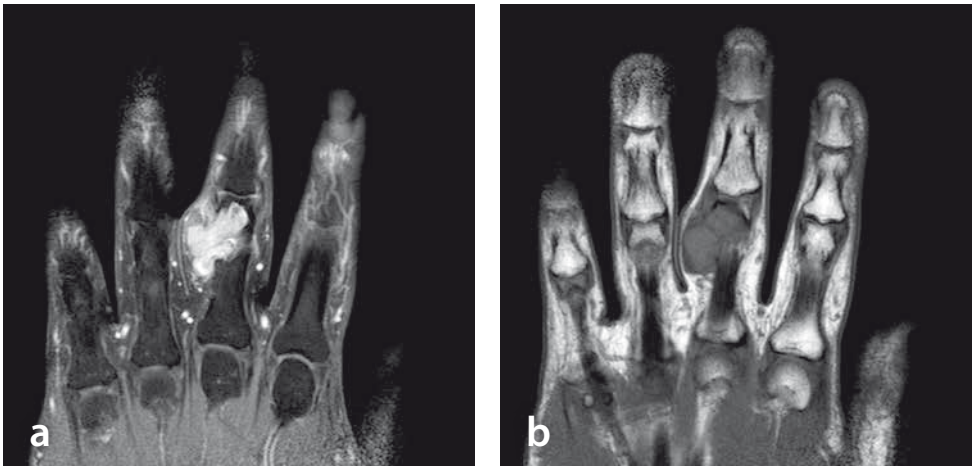


Figure 1 MRI of TGCT localized-type, affecting digits - A 43 year old male patient with a well circumscribed tumour in the proximal phalanx of the third digit of the right hand. **a.** A coronal T1-weighted MRI after intravenous contrast injection. **b.** A clear coronal T1 weighted MRI without intravenous contrast injection.

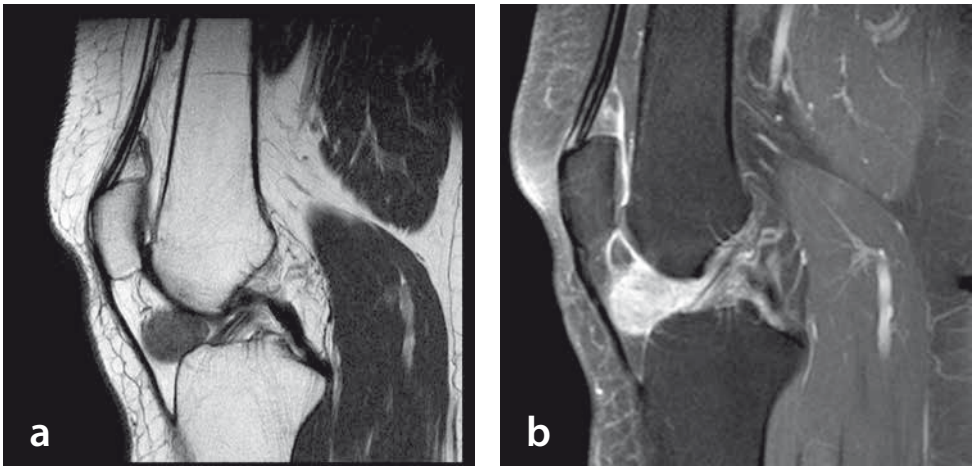


Figure 2 MRI of TGCT localized-type, extremity - Sagittal T1 weighted turbo spin echo MRI of a 47 year old female patient, affecting her right knee. A well circumscribed lesion in Hoffa's fat pad is seen. **a.** Proton density weighted MRI. **b.** Pre-saturation inversion recovery MRI.

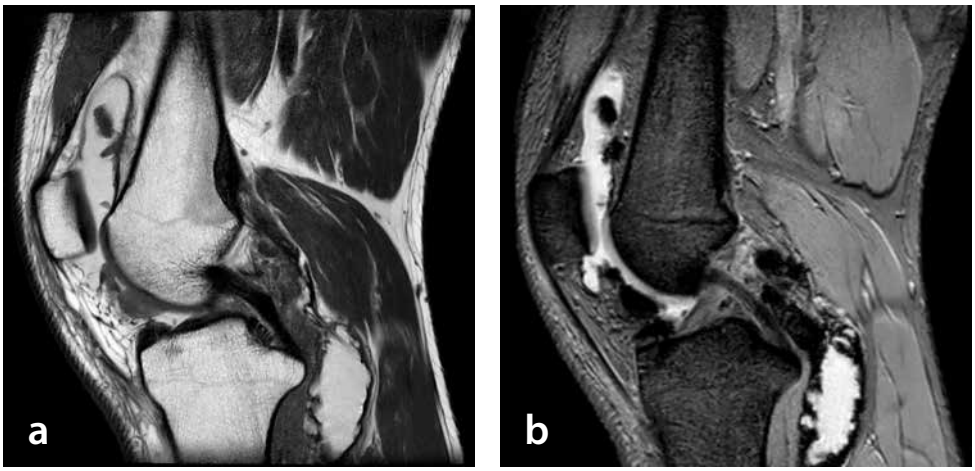


Figure 3 MRI of TGCT diffuse-type. A 23 year old male patient with an extensive proliferative synovial process around both cruciate ligaments, dominating the anterior and posterior knee compartments, intra- and extra-articular. Inside suprapatellar pouch and Baker's cyst a blooming villonodular aspect shows typical iron depositions. **a.** Sagittal proton density weighted turbo spin echo MRI. **b.** Sagittal T2 weighted fast field echo MRI.

is surgical excision[5, 6, 9]. However, it is often difficult to perform a marginal excision. Average recurrence rates after arthroscopy are 40% and after open resection 14%, with variable follow-up times[8]. In extensive disease, peri-operative radiotherapy might reduce recurrence rate[10, 11]. Patients with (multiple) recurrences experience impaired quality of life[12].

According to the WHO-classification of 2002 and 2013, the Incidence Rate (IR) in TGCT is not exactly known[1, 13]. Current TGCT IRs are based on 1 single US-county study completed in 1980, with an IR of 9 and 2 per million person-year in localized- (including digits) and diffuse-TGCT, respectively[14]. Verschoor et al. (2015) performed the initial nationwide registry based study on giant cell containing tumours and calculated an overall IR for TGCT of 50 per million per year. Discrimination between localized and diffuse disease was not possible as additional clinical information was lacking. The difference in biological behaviour, however, demands for further stratification of this general IR in the 3 different TGCT-groups. Therefore, we aimed to estimate the worldwide (WHO-standardized) TGCT IR by investigating clinical data of affected joints, sex differences, 10 year age specific categories, initial treatments, follow-up and recurrences rate at individual patient level through extensive additional data collection at participating hospitals.

Material and methods

A search in PALGA, the non-profit nationwide network and registry of histo- and cytopathology in The Netherlands was performed[15]. To find all patients with Tenosynovial Giant Cell Tumours, between January 2009 and January 2014, search terms 'Tenosynovial Giant Cell Tumour', 'Pigmented Villonodular Synovitis' and a variety of synonyms were used, either as a code or as free text[16], see *supplementary data*. Received pathology-reports provided limited and anonymous information on sex, age, date of tissue removal and conclusion of the pathology report. In these reports, definitive diagnosis was frequently provided, however information on (localized/diffuse) type and affected joint was only sparsely available. Therefore, further investigation of additional clinical and radiological data was necessary. Reports with TGCT affecting digits were solely used for calculating incidence rate (for TGCT-digits) and not further investigated clinically. PALGA interlinked 1941 pathology-reports to 95 original Dutch hospitals. Departments of pathology received a request to collaborate in this nationwide study. After approval, personal hospital identifiers were obtained and concerned departments (mostly orthopaedics and general surgery) were invited to confirm TGCT diagnosis and add detailed information on TGCT-type, affected joint, sex, age at first histologically proven TGCT, primary treatment, total surgeries related to TGCT, date of last follow-up and follow-up status. Clinical and radiographic data were derived from medical files. Data were kept anonymously. 75 of 95 attributed hospitals collaborated, including all specialized and academic centres.

Clinical evaluation started with 1941 eligible TGCT cases. In 1576 (81%) cases, diagnosis was confirmed. 253 Reports were determined to be in digits and amended in digits-group. For included TGCT extremity cases (n 1323), incomplete evaluated clinical data were imputed for unknown data on TGCT-type (n=393), affected joint (n=101), sex (n=52), age (n=54) and treatment (n=484), using multiple imputation techniques. 10 Datasets were imputed, results were pooled according to standard Rubin's rules[17]. All imputed data were checked for errors. Finally, 1323 patients with histological proven TGCT were included (*figure 4*).

In addition to the 2562 patients with TGCT affecting digits which were already identified based on the pathology reports, 253 additional patients with TGCT affecting digits were discovered during clinical data evaluation. 2815 TGCT patients affecting digits were identified (2649 fingers, 119 toes, 47 finger or toe), but not investigated in detail.

Reoperation rate due to local recurrence was defined as surgery for recurrent TGCT, based on additional pathology reports in the same patient, at least 6 months after initial surgery until January 2015 (date of PALGA-search).

Statistics

The Statistical Package for Social Sciences statistics (SPSS) version 23 was used for analyses. The IR was separately estimated for TGCT localized-, either digits or extremity, and diffuse-type TGCT per year, by using the number of histologically proven TGCT as numerator and the sum of individual person-years for The Netherlands as the denominator. IRs were reported for the overall study period, by calendar year, and stratified on type, affected joints, sex and 10-years age categories (age at TGCT diagnosis). The Central Bureau of Statistics (CBS) provided information on Dutch population during the examined period.

Overall worldwide IRs were obtained by standardizing Dutch IRs to global IRs by using the direct method, applying age-specific IRs in each 10-year age group to the world WHO standard population (http://seer.cancer.gov). Estimates of IRs were reported with 95% Confidence Intervals (CI). Patient demographics were reported as counts and percentages for categorical variables and as medians and interquartile ranges (IQR) for continuous variables. The Kaplan Meier method was used to evaluate reoperation due to local recurrence free survival at 2- and at 5-year.

Ethics, funding, and potential conflict of interest

Research is performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. As this study does not involve subject-related research, it is not covered by Dutch law on human subjects research. This study is approved by the Institutional review board (CME) from our institution (registration number G16.024, 22 April 2016). In collaboration of physicians of the TGCT study group, and in special collaboration with Radboud University Medical Centre and Medical Spectrum Twente, data collection was performed. Data capturing and analyses was performed in the Leiden University Medical Centre. No funding or benefits were received, by none of the authors. There is no conflict of interest by any of the authors regarding this manuscript.

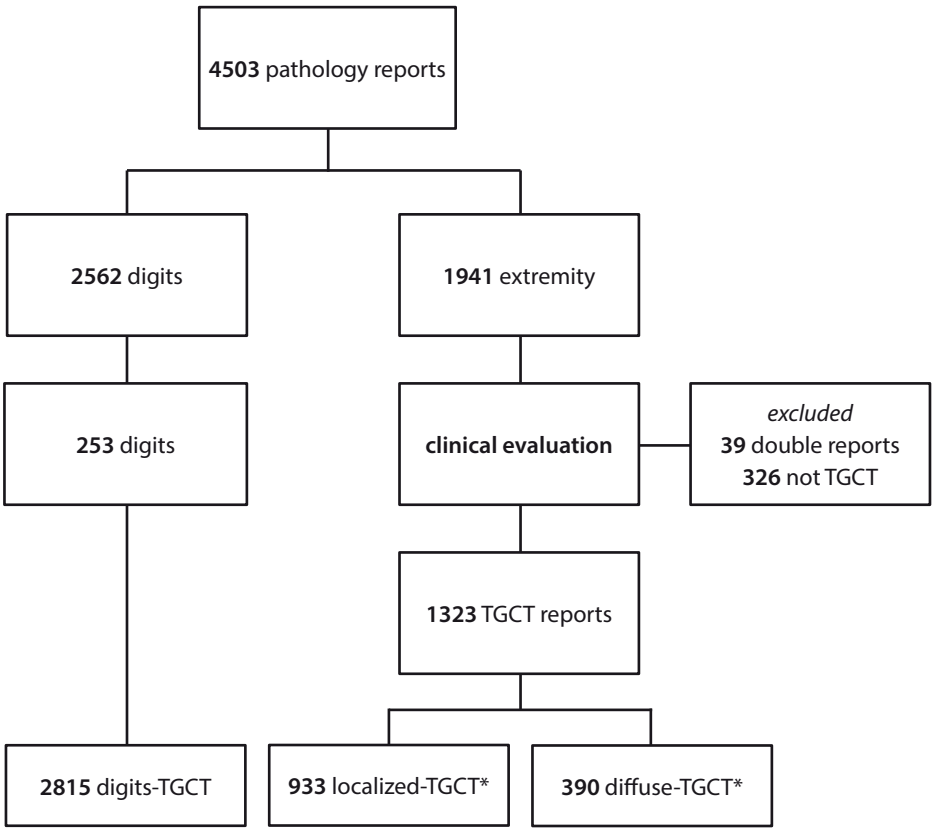


Figure 4 Inclusion flowchart

*Localized-TGCT affecting extremities, excluding digits

Table 1 Incidence rates (IRs) of localized- and diffuse-type TGCT in The Netherlands: overall, by calendar year 2009-2013, sex and age-categories.

		Localized TGCT – digits	
	Person-years	**New cases***	**IR****
Overall	83,226,498	2815	33.8 (33 - 35)
Calendar year			
2009	16,485,787	578	35.1 (32 - 38)
2010	16,574,989	561	33.8 (31 - 37)
2011	16,655,799	580	34.8 (32 - 38)
2012	16,730,348	563	33.6 (31 - 37)
2013	16,779,575	533	31.8 (29 - 35)
Sex			
Female	42,032,934	1698 (60)	40.4 (39 - 42)
Male	41,193,564	1117 (40)	27.1 (26 - 29)
Age at diagnosis			
0-9	9,528,271	13 (0)	1.4 (1 - 2)
10-19	10,012,994	98 (3)	9.8 (8 - 12)
20-29	10,178,289	259 (9)	25.4 (23 - 29)
30-39	10,673,194	411 (15)	38.5 (35 - 42)
40-49	12,894,743	650 (23)	50.4 (47 - 54)
50-59	11,456,662	704 (25)	61.5 (57 - 66)
60-69	9,466,681	503 (18)	53.1 (49 - 58)
70-79	5,680,080	155 (6)	27.3 (23 - 32)
80-89	2,860,556	22 (1)	7.7 (5 - 12)

Localized TGCT – extremity		Diffuse TGCT	
New cases*	**IR****	**New cases***	**IR****
933	11.2 (11 - 12)	390	4.7 (4 - 5)
192	11.7 (10 - 13)	73	4.4 (4 - 6)
183	11.0 (10 - 13)	82	5.0 (4 - 6)
176	10.6 (9 - 12)	78	4.7 (4 - 6)
188	11.2 (10 - 13)	77	4.6 (4 - 6)
194	11.6 (10 - 13)	80	4.8 (4 - 6)
544 (58)	12.9 (12 - 14)	236 (61)	5.6 (5 - 6)
389 (42)	9.4 (9 - 10)	154 (39)	3.7 (3 - 4)
6 (1)	0.6 (0 - 1)	2 (0)	0.2 (0 - 1)
57 (6)	5.7 (4 - 7)	26 (7)	2.6 (2 - 4)
108 (11)	10.6 (9 - 13)	49 (13)	4.8 (4 - 6)
169 (18)	15.8 (14 - 18)	62 (16)	5.8 (5 - 7)
211 (23)	16.4 (14 - 19)	70 (18)	5.4 (4 - 7)
193 (21)	16.9 (15 - 19)	71 (18)	6.2 (5 - 8)
133 (14)	14.0 (12 - 17)	58 (15)	6.1 (5 - 8)
41 (4)	7.2 (5 - 10)	37 (9)	6.5 (5 - 9)
15 (2)	5.2 (3 - 9)	15 (4)	5.2 (3 - 9)

*New cases: number of cases, %. **IR: Incidence rate per million person-years (95% CI).

Results

During a 5-year period; 2815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. TGCT affected digits 3 and 7 times more often compared to localized-extremity and diffuse-TGCT, respectively. Dutch TGCT IRs were 34 (CI 33 - 35) in TGCT affecting digits, 11 (CI 11 - 12) in localized-type extremity TGCT and 5 (CI 4 - 5) in diffuse-type TGCT per million person-years. Median age for TGCT affecting digits was 49 (IQR 38-59) years, for localized-extremity type 45 (IQR 34-56) years and diffuse-TGCT 47 (IQR 32-61) years. Male-female ratio was about 1:1.5 for any type.

Table 1 shows IRs per million person-years by calendar years 2009 up to and including 2013, sex and 10 year age-specific categories of the 3 different TGCT-groups. In these 3 groups: IRs over disaggregated years were quiet similar, female IR were slightly higher compared to male IRs and the majority of new cases were seen in age-categories 40-49 and 50-59 years.

In 2015, The Netherlands counted 16,900,726 inhabitants. According to calculated IR; 571 new TGCT affecting digits, 189 new localized-extremity and 79 new diffuse-TGCT patients were diagnosed in 2015. The estimated standardized worldwide IRs were 29, 10 and 4 per million person-years for respectively localized-digits, localized-extremity and diffuse-TGCT.

As TGCT affecting digits were not clinically investigated, following results were based on localized-extremity and diffuse-type. The majority of TGCT cases affected the knee-joint; 46% and 64% in localized- and diffuse-TGCT respectively (*figure 5*), followed by the hand- and wrist-joint in localized-type and the ankle- and hip-joint in diffuse-type TGCT. Sex distribution per affected joint was comparable.

The initial TGCT treatment plan was open resection in 65% and 49% in localized- and diffuse-lesions, respectively (*figure 6*). TGCT was reported as an incidental finding during endoprosthetic replacement in 60 procedures.

According to the clinical charts, the majority of patients were lost to follow-up in both types (71% in localized- and 55% in diffuse-TGCT). Therefore, we decided to base recurrence rates on additional surgeries (defined by a second pathology report documenting recurrence of TGCT in PALGA). By evaluating the municipal personal records database (Gemeentelijke BasisAdministratie (GBA)) for

all patients, 8 patients (7 localized- and 1 diffuse-TGCT) deceased at time of evaluation and were censored at time of death when no second surgery was performed.

Reoperation rate due to local recurrence, calculated as a percentage from all TGCT patients, in localized-TGCT was 9% and in diffuse-TGCT 23%. Reoperation free survival curves for localized- and diffuse-TGCT are shown in *figure 7*. In localized-extremity, reoperation free survival at 2- and at 5-years was 90% and 83%, respectively. In diffuse-type, reoperation free survival at 2- and at 5-years was 77% and 49%, respectively. Only a minority (12%) of TGCT patients were primarily treated in a tertiary oncology centre: 9% of localized-type (excluding digits) and 18% of diffuse-type.

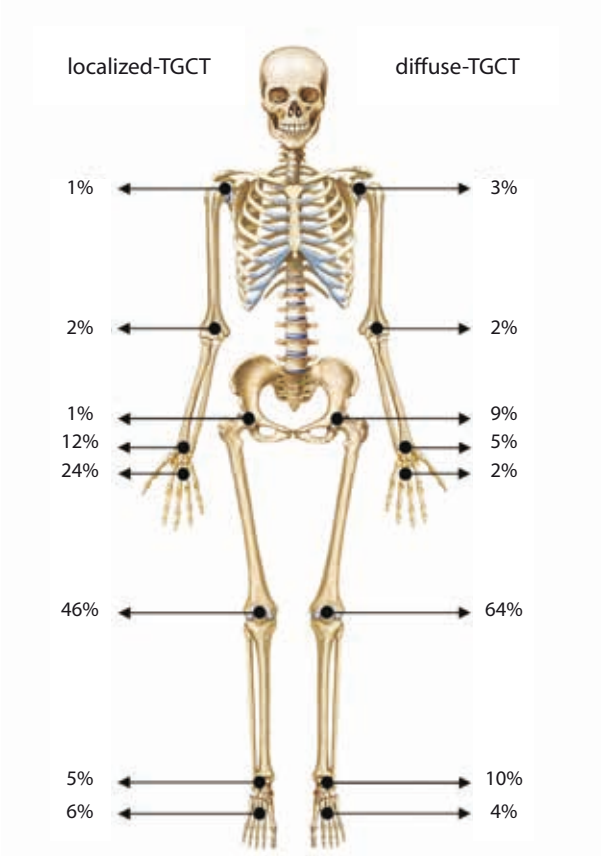


Figure 5 Skeleton, showing affected TGCT localization (fingers and toes excluded). 3% in localized-type and 1% in diffuse-type is classified as 'other'.

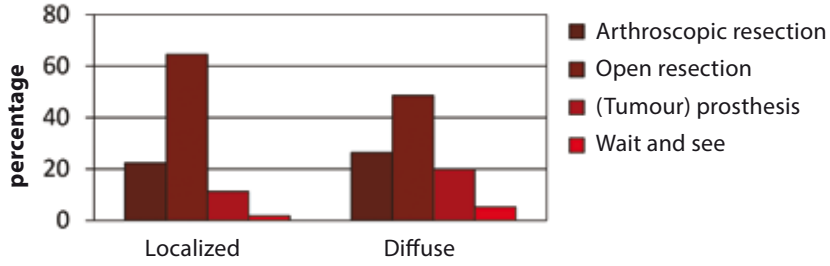


Figure 6 Bar graph initial treatment for TGCT affecting extremities in The Netherlands, excluding digits.

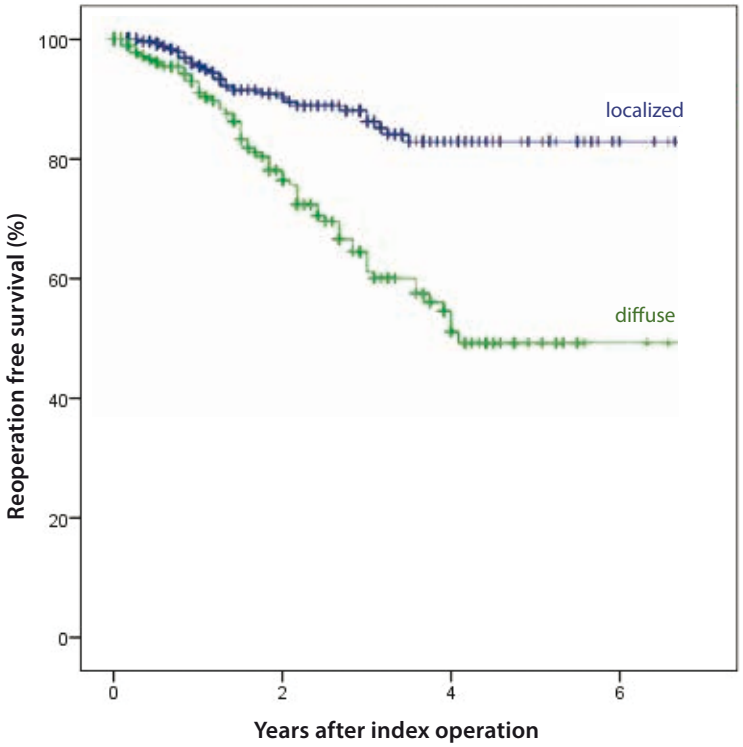


Figure 7 Reoperation due to local recurrence free survival curve in localized-extremity and diffuse-TGCT (Kaplan Meier), excluding digits. Time zero is time of primary surgery. 8 Patients died and were censored at time of death if a reoperation had not occurred.

Discussion

Microscopically localized-extremity and diffuse-TGCT are identical[1]. A distinction is made between localized-digits and localized-extremity, based on anatomical location and histological differences[3, 4]. TGCT affecting digits are characterized as multiple, small (average 1 centimetres) nodules surrounded by a thin fibrous capsule, originating in synovial tissue of tendon sheaths or small joints of digits, with a small number of cleft-like spaces and thick bundles of collagenous tissue, showing rarely inflammatory cells. On the contrary, TGCT localized-extremity lesions are typically single, relatively large (average 2 centimetres) lesions covered by 1 or more layers of synovial cells, intra-articular, showing large or numerous pseudoglandular spaces sometimes filled with foam cells and showing more inflammatory cells than digits[3].

Because of the rarity of the disease, current TGCT literature contains predominantly retrospective, relatively small cohort studies, including heterogeneous data[4]. 2 previous studies described TGCT incidence: Myers and Masi (1980) reported 117 new cases of localized- (including digits) and 49 new cases of diffuse-type TGCT between 1960 and 1976, resulting in an IR of 9 per million person-years for localized- and 2 per million person years for diffuse-type TGCT. A single hospital study was performed by Monoghan et al. (2001) and showed an IR of 20 new cases per million per year between 1990 and 1997 for localized-type TGCT (including digits). Compared to the initial US-county study[14], our study showed a 5-fold higher IR in localized-type (combining localized-digits and localized-extremity), and a more than 2.6 fold higher IR in diffuse-type. This difference could be attributed to our nationwide coverage, our registry based-clinically verified character and because of increased knowledge about the disease.

Localized- and diffuse-lesions are distinguished clinically and on MRI. To investigate these lesions separately, clinical and radiological confirmation is of utmost importance. Treatment in localized-TGCT affecting digits or extremity is mostly 1 single excision. In contrast, multiple mutilating surgeries are often required for diffuse-type TGCT, with a continuous risk of recurrences. In an effort to find all TGCT patients, our search included specific pathology codes for TGCT and both TGCT and synonyms of TGCT as free text (*Appendix*). Therefore, cases with 'synovitis' or differential diagnostic TGCT were represented in our search. In addition, PALGA data is based on input of physicians and sometimes lacks specificity. For instance affected joint:

'upper extremity', 'hand' or 'wrist' could all turn out, after clinical evaluation, to be affected digits. In our search, 1941 patients were clinically evaluated and 1323 ascertained histologically proven TGCT extremity cases were included. Consequently, only 68% of eligible TGCT patients had histologically proven TGCT of the large joints. Without clinical TGCT-confirmation, the estimated IR would have been much higher.

Despite our large number of patients with lack of follow-up, reoperation rates due to local recurrence were described, based on additional surgeries, defined by a second pathology report documenting recurrence of TGCT in PALGA (up to January 2015, date PALGA-search was performed). Recurrences without treatment (no additional pathology report) were not included, therefore reoperation rate due to recurrence is not identical to recurrence rate. However, compared to literature, we found comparable average recurrence rates for localized-TGCT-extremity (9%) and for diffuse-type (23%)[8]. As local recurrence might develop years after initial surgery[18], and PALGA provided pathology reports with a maximum of 7 years after initial surgery, underestimation of the true recurrence free survival is likely.

There are some limitations to this study. Determined IR may be exposed to under- or overestimation. Primarily, our calculated IR could be slightly underestimated, because our study is based on a search in PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands[15]. TGCT patients without a biopsy or treatment are not represented in this pathology based cohort.
Second, our IR in localized-extremity and diffuse-type could be marginally over- or underestimated, because 21% of eligible TGCT patients was not clinically evaluated and therefore imputed. Analyses with and without imputed data were comparable. PALGA identified 1941 eligible TGCT patients, scattered over 95 Dutch hospitals. Regarding different hospital-boards, different concerning departments (pathology, orthopaedics, general surgery) and different local legislations, it was challenging to evaluate all eligible TGCT patients.
Third, clinical distinction between localized-extremity and diffuse-type TGCT is difficult, especially for clinicians not familiar with this rare disease[19].
Subsequently, an overestimation of IR in TGCT localized-digits might be present. IR of digits is solely based on PALGA-registry numbers, in contrast to localized-extremity and diffuse-TGCT IRs

which were clinically evaluated.

Global IRs were estimated by using a direct standardization approach (http://seer.cancer.gov). Even though this is a widely accepted method, there is no adjustment for other influences in global structure or possible risk factors in TGCT.

To calculate prevalence rates, follow-up time and status is important. Majority of our investigated patients lacked in clinical chart follow-up. It seemed unfair to estimate TGCT prevalence rates as the proportion of TGCT patients alive at the end of 2013 and diagnosed with TGCT: this assumes TGCT to not resolve and not to be cured.

In The Netherlands, traditionally, larger orthopaedic clinics have been treating TGCT or diagnosed TGCT as an incidental finding during arthroscopy or endoprosthetic replacement. When (severe) complaints occur, patients are commonly referred to specialized tertiary sarcoma centres. In this study, we investigated primary patients to calculate incidence rate. No centralization of care of TGCT in these primary patients is shown, with only a minority of 12% primarily treated in a tertiary oncology centre. Remarkably, only 18% of diffuse-TGCT was primarily treated in tertiary oncology centres.

In summary, this study is the first nationwide study and detailed analyses of IRs in TGCT. IRs for TGCT of digits, localized-type-extremity and diffuse-type were calculated using additional hospital record evaluation of patients originally selected from a nationwide pathology registry. The worldwide estimated incidence rate in digits, localized-extremity and diffuse-TGCT is 29, 10 and 4 per million person-years, respectively. Despite high clinical variability in localized-extremity and diffuse-lesions, both types show a predilection for the knee-joint, slight predisposition in female patients, median age around 47 years at first treatment and primarily treated with an open resection. Recurrence rate in diffuse-type is 2.6 times higher, compared to localized-type extremity. TGCT is still considered a rare disease, however, more common than previously understood.

Supplementary data

An appendix is available as supplementary data in the online version of this article, http://dx.doi.org/10.1080/17453674.2017.1361126

References

1. de St. Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, localized type/diffuse type. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4th ed. Lyon: IARC Press; 2013. p. 100-3.
2. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
3. Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. Cancer. 1986;57(4):875-84.
4. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
5. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
6. Verspoor FG, van der Geest IC, Vegt E, Veth RP, van der Graaf WT, Schreuder HW. Pigmented villonodular synovitis: current concepts about diagnosis and management. Future oncology. 2013;9(10):1515-31.
7. Fotiadis E, Papadopoulos A, Svarnas T, Akritopoulos P, Sachinis NP, Chalidis BE. Giant cell tumour of tendon sheath of the digits. A systematic review. Hand (N Y). 2011;6(3):244-9.
8. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
9. Gonzalez Della Valle A, Piccaluga F, Potter HG, Salvati EA, Pusso R. Pigmented villonodular synovitis of the hip: 2- to 23-year followup study. Clin Orthop Relat Res. 2001(388):187-99.
10. Mollon B, Lee A, Busse JW, Griffin AM, Ferguson PC, Wunder JS, 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(4):550-7.
11. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
12. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
13. de St. Aubain Somerhausen N, Dal Cin P. Gaint cell tumour of tendon sheath/Diffuse-type giant cell tumour. In: Fletcher CD, Unni KK, Mertens F, editors. World Health Organization Classification of Tumours Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002. p. 109-14.
14. Myers BW, Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. Medicine (Baltimore). 1980;59(3):223-38.
15. Casparie M, Tiebosch AT, Burger G, Blauwgeers H, van de Pol A, van Krieken JH, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol. 2007;29(1):19-24.
16. Verschoor A, Bovee J, van de Sande M, Gelderblom H. Incidence and demographics of giant cell containing tumors in the Netherlands: a nationwide pathology database study. Annual Meeting of the Connective Tissue Oncology Society; November 4-7; Salt Lake City, Utah, USA2015.

17. Rubin DB. Multiple imputation after 18+ years. Journal of the American Statistical Association. 1996;91(434):473-89.
18. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
19. Flandry F, Hughston JC, McCann SB, Kurtz DM. Diagnostic features of diffuse pigmented villonodular synovitis of the knee. Clinical orthopaedics and related research. 1994(298):212-20.

DIAGNOSTICS

chapter three

Does *CSF1* over-expression or rearrangement influence biological behaviour in tenosynovial giant cell tumours of the knee?

M.J.L. Mastboom[1], D.M. Hoek[2], J.V.M.G. Bovee[3], M.A.J. van de Sande[*1], K. Szuhai[*2]

Histopathology 2018 Aug. doi: 10.1111/his.13744

[1] Orthopaedic Surgery, Leiden University Medical Center, Leiden, the Netherlands

[2] Cell and Chemical biology, Leiden University Medical Center, Leiden, the Netherlands

[3] Pathology, Leiden University Medical Center, Leiden, the Netherlands

*Authors contributed equally to this work.

Abstract

Introduction

Localized- and diffuse-type tenosynovial giant cell tumours (TGCT) are regarded different clinical and radiological TGCT-types. However, genetically and histopathologically they seem indistinguishable. We aimed to correlate *CSF1*-expression and *CSF1*-rearrangement with the biological behaviour of different TGCT-types with clinical outcome (recurrence).

Methods

Along a continuum of extremes, therapy naïve knee TGCT patients with >3 year follow-up, mean age 43(range 6-71)years and 56% female were selected. Nine localized-(two recurrences), 16 diffuse-type(nine recurrences) and four synovitis as control were included. Rearrangement of the *CSF1*-locus was evaluated with split-apart Fluorescence In Situ Hybridization (FISH) probes. Regions were selected to score after identifying *CSF1*-expressing regions, using mRNA ISH with the help of digital correlative microscopy. *CSF1*-rearrangement was considered positive in samples containing >2 split signals/100 nuclei.

Results

Irrespective of TGCT-subtype, all cases showed *CSF1*-expression and in 76% *CSF1*-rearrangement was detected. Quantification of *CSF1*-expressing cells was not informative, due to the extensive intra tumour heterogeneity. Of the four synovitis cases, two also showed *CSF1*-expression, without *CSF1*-rearrangement. No correlation between *CSF1*-expression or rearrangement with clinical subtype and local recurrence was detected. Both localized- and diffuse-TGCT cases showed a scattered distribution in the tissue of *CSF1*-expressing cells.

Conclusion

In diagnosing TGCT, *CSF1* mRNA-ISH in combination with *CSF1* split-apart FISH; using digital correlative microscopy, is an auxiliary diagnostic tool to identify rarely occurring neoplastic cells. This combined approach allowed us to detect *CSF1*-rearrangement in 76% of the TGCT-cases. Neither *CSF1*-expression nor presence of *CSF1*-rearrangement could be associated with the difference in biological behaviour of TGCT.

Introduction

Tenosynovial giant cell tumour (TGCT), previously known as pigmented villonodular synovitis (PVNS) and giant cell tumour of tendon sheath, is a rare, neoplastic lesion arising from the synovial lining of joints, bursae or tendon sheaths in predominantly young adults. Excluding digits, this mono-articular disease is most commonly diagnosed around the knee or other weight bearing joints[1-3].

Initially, TGCT was believed to be an inflammatory disease[4]. After genomic aberrations were discovered, TGCT was evidently considered neoplastic[5-10]. Chromosomal aberrations include trisomy for chromosomes 5 and 7 and translocations involving the short arm of chromosome 1p11-13, most commonly translocated to chromosome 2q37 region. At the 1p13 breakpoint, Colony Stimulating Factor 1 (*CSF1*) gene is located. The translocation leads to a classical promoter fusion event in which collagen 6A3 (COL6A3) promoter element is fused to *CSF1*. As a result, the fusion leads to deregulated expression of *CSF1*[11]. The excessive *CSF1* secretion attracts inflammatory cells that express the *CSF1* receptor (*CSF1*R) (i.e. monocytes and macrophages). Consequently, in TGCT tissue, only a small percentage of cells (2-16%) are neoplastic, carrying the t(1;2) translocation. This phenomenon is coined as "the landscape effect"[11, 12]. Based on *CSF1* rearrangements (translocation), two groups are described. The first group is defined by both *CSF1* over-expression and *CSF1* translocation, whereas the second group lacks the classical translocation. The latter group likely carries other rearrangements altering *CSF1* regulation leading to high *CSF1* mRNA and *CSF1* protein levels[12].

According to the 2013 WHO classification, TGCT is subdivided in a lobulated well circumscribed lesion (localized-type) and a more locally aggressive lesion, involving a large part or all of the synovial lining (diffuse-type)[1, 2, 13] (*figure 1*). Standard choice of treatment was surgical resection of the lesional tissue, either arthroscopically or with an open resection[14-17]. The localized-type TGCT is known with a favourable course after resection (average recurrence rates <6%), while the diffuse-type TGCT generally causes significant morbidity due to the high risk of local recurrence (>50% depending on surgical procedure and follow-up time)[15, 18, 19]. Therefore, at present diffuse-type TGCT is also treated with *CSF1* inhibitors, such as nilotinib, imatinib, pexidartinib, emactuzumab, cabrilazimab and MSC110[20]. Long term efficacy data have not yet been reported with these newer agents.

Recurrent TGCT is rarely lethal, but a chronic illness with substantial morbidity to the joint leading to functional and quality of life impairment, caused by the course of the disease itself and multiple treatments[21]. Clinically, localized- and diffuse-TGCT are clearly two very different diseases. However, histopathologically they seem indistinguishable with both subtypes containing an admixture of mononuclear cells (histiocyte-like and larger cells) and multinucleated giant cells, lipid-laden foamy macrophages (also known as xanthoma cells), siderophages (macrophages including hemosiderin-depositions), stroma with lymphocytic infiltrate and some degree of collagenisation[1, 2].

It remains unclear why localized- and diffuse-TGCT are microscopically and genetically identical, but clinically distinct. Moreover, predictors for progressive disease or local recurrence are lacking. In this study, we investigate whether *CSF1* over-expression and rearrangement are correlated with tumour characteristics (localized-/diffuse-TGCT) and clinical outcome (recurrence). We hypothesize that diffuse-type TGCT, compared with localized-type TGCT, would have a higher load of neoplastic cells. We expect that a higher tumour load is associated with recurrent disease.

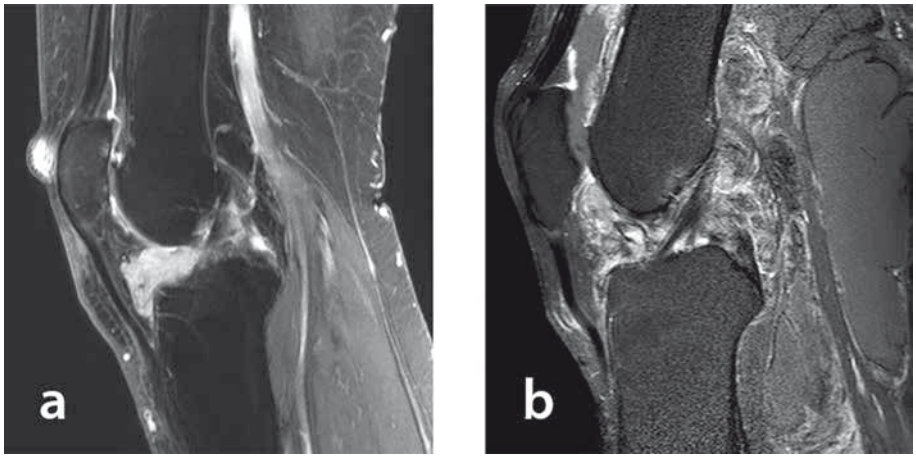


Figure 1 Localized- and diffuse-TGCT sagittal T1-weighted MR image after intravenous contrast injection with fat suppression. Tumour region enhances by contrast injection. **a.** A localized-TGCT involving Hoffa's fat pad in the anterior part of the left knee in a 55-year-old female patient (L4835). **b.** Left knee in a 61-year-old male patient with extensive recurrent diffuse-TGCT located intra- and extra-articular with an additional posterior large Baker's cyst including tumour (L3496).

Methods

Case acquisition and study design

Subtypes of TGCT (localized- or diffuse) were defined based on clinical features and radiological imaging according to 2013 WHO[1, 2]. Along a continuum of extremes, 25 patients with TGCT affecting the knee were carefully selected: patients with small or very large localized or diffuse lesions, with and without recurrent disease. All cases showed all characteristic histological features of TGCT (mononuclear cells, giant cells, macrophages, siderophages, foam cells or lymphocyte-clusters). Included patients were therapy naïve (one diagnostic arthroscopy elsewhere was allowed) and treated with open synovectomy at the Leiden University Medical Centre (LUMC). A clinical follow-up of at least three years was required for inclusion. For comparison, we used tissue specimens of four patients with non-TGCT synovitis. Written informed consent was obtained from all patients. This study was performed in accordance with the Code of Conduct for responsible use in The Netherlands (Dutch Federation of Medical Scientific Societies) and approved by the local medical ethical committee (P13.029).

Inclusion selected cases and tissue specimens

Nine localized- and 16 diffuse-type TGCT patients were included, mean age at surgery of 43 (range 6-71) years, mean follow-up of 57 (range 36-121) months (*table 1*), with a slight female predominance (56%). Two localized- and nine diffuse-type TGCT patients had recurrent disease, after mean 26 (range 14-53) months. The mean age at surgery of the four patients with non-TGCT synovitis was 53 (range 44-65) years, including two (50%) females.

For each patient, multiple formalin-fixed paraffin-embedded (FFPE) tissue blocks and corresponding Haematoxylin and Eosin stained (H&E) 4 µm slides of the primary resected specimen were reviewed by an expert bone and soft tissue pathologist (JVMGB) to confirm TGCT diagnosis and to select representative areas of the tumour with highest proportion of suspected neoplastic cells.

A large tissue heterogeneity was observed between the different blocks. As a control for the landscaped *CSF1* mRNA expression, multiple blocks were selected for three cases (L4046, L3496 and L4954) representing various tissue compositions.

Table 1 Descriptives of study population

	Localized	Localized recurrence	Diffuse	Diffuse recurrence	No TGCT
Total number	7	2	7	9	4
Mean age at surgery (R), y	33 (6-55)	41 (20-62)	54 (33-71)	42 (17-63)	53 (44-65)
Male:female	5:2	0:2	2:5	4:5	2:2
Mean time to recurrence (R), m	na	31 (18;44)	na	24 (14-53)	na
Mean follow up (R), m	61 (39-100)	81 (40;121)	54 (39-97)	51 (36-70)	na

Localized: localized-TGCT; Diffuse: diffuse-TGCT; R: range; y: years; m: months

CSF1 mRNA expression

The RNAscope 2.5 High Definition(HD)-RED assay (Advanced Cell Diagnostics, 322350) was used to detect *CSF1* mRNA expression. This assay visualizes single RNA molecules per cell by a novel method of in situ hybridization (ISH). The double Z probe design allowed simultaneous signal amplification and background suppression[22]. Positive (PPIB (Cyclophilin B)) and negative controls (bacillus subtilis strain SMY) ensured reliable results. mRNA hybridisation were performed according to manufacturer's protocols.

CSF1 rearrangement

To identify the presence of *CSF1* rearrangements at region 1p13, DNA Fluorescence In Situ Hybridisation (FISH) analysis was performed on all tissue specimens using bacterial artificial chromosome (BAC) clones: RP11-354C7 (centromeric to *CSF1*) and RP11-96F24 (telomeric to *CSF1*)) bracketing *CSF1* locus, to identify both translocation and inversion. Probe labelling and hybridisation were done according to previously described protocols[23]. An index case outside of the study population (L4018) was included with a COBRA-FISH molecular karyotyping proven inv(1)(p13;q23) as reference for the detection of the chromosome inversion in tissue section[24]. Detailed description of mRNA ISH and FISH procedures are presented in *supplementary material*.

Scoring and correlative analysis

All slides were scanned in brightfield and/or fluorescence on a Pannoramic P250 or MIDI digital scanner (3DHistech, Budapest, Hungary). Scanned images were visualized using the Pannoramic Viewer (V2.1; 3DHistech). Interpretation was performed manually by a senior FISH expert (KS), blinded towards TGCT-type and clinical outcome. Because *CSF1* expressing regions were expected to contain neoplastic cells, three of these regions were selected. With the use of digital correlative microscopy, regions with *CSF1* mRNA expressing (supposed neoplastic) cells were identified and the same areas were scored after FISH analysis. If the distance between the two signals was larger than the size of a single hybridization signal, cells were recorded *CSF1* split positive. All nuclei within the selected area with a complete set of signals were evaluated. Nuclei with an incomplete set of signals were excluded from counting. Samples containing >2/100 nuclei with a *CSF1* split were considered *CSF1* split positive.

Results

CSF1 mRNA expression

Specimens of all localized- and diffuse-TGCT cases showed a scattered, tissue infiltrating distribution of *CSF1* expressing cells (*figure 2*). Corresponding to the landscape effect, heterogeneous distribution of *CSF1* expressing cells were observed when sections from multiple bock were analysed, meaning that regions completely devoid *CSF1* expressing cells were seen in regions containing large proportion of foam cells or regions with lymphocytic infiltrates. *CSF1* mRNA pattern expression was not observed in multinucleate giant cells, siderophages or foam cells. Consequently, due to the great heterogeneity between different blocks derived from one tumour and within regions in one section, quantification of *CSF1* expressing cells, meaning the expression of the proportion of *CSF1* positive cells, was not informative and was not further analysed (*supplementary material figure 1*). Selecting the block with the highest possible neoplastic cell component, we did not observe a clear difference in distribution of *CSF1* between different TGCT cases. Cells with *CSF1* mRNA expression were distributed diffusely and showed an infiltrating scattered pattern throughout the sections with some clustering at various regions within a tissue element (*figure 2*, *supplementary material figure 2 and 3*).

For the control cases, two of the four cases with synovitis showed expression of *CSF1* (L5619, L5620). However, in these two cases *CSF1* expression was restricted to cells localised in the synovial lining, which was different from the scattered distribution seen in TGCT (*figure 3*). The other two cases with synovitis showed no expression of *CSF1* (L3715, L5622).

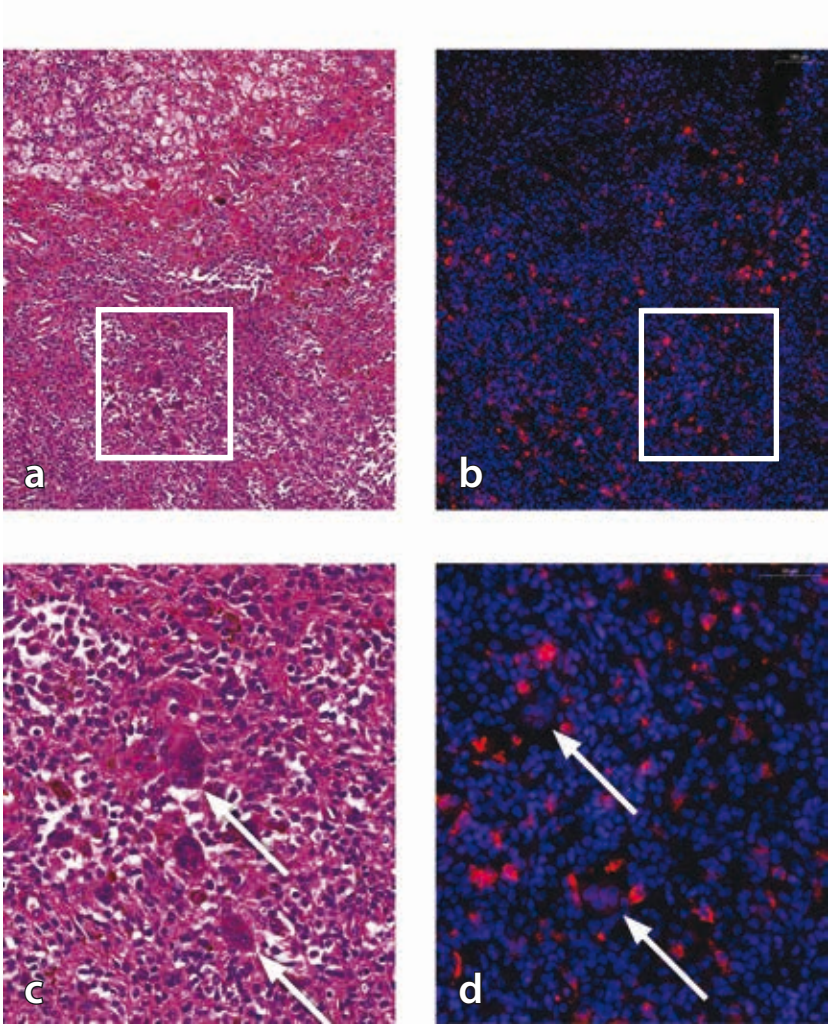


Figure 2 Conventional histology and mRNA ISH from 61-year-old male patient (L3496), with extensive recurrent diffuse-TGCT. This is the same patient as figure 1 right. Left panel H&E stained section (A; C) with matching *CSF1* mRNA ISH (B; D) on the right panel. White box in panel A and B show regions at higher resolution in panel C and D. Heterogeneous cellular composition of TGCT is visible including foam cells, inflammatory cells, synovial-like cells, siderophages and characteristic giant cells (A; C). mRNA ISH shows a scattered distribution of *CSF1* expressing cells with granular cytoplasmic signals (red signal), identifying *CSF1* expressing cell-nuclei (blue signal after DAPI staining). Green arrowheads shows giant cells without *CSF1* expression. Scale bars are in the right top corner 100µm for panel A and B and 50µm for panel C and D.

CSF1 rearrangement

The *CSF1* probe set showed a clear split-apart signal even for detection of chromosome inversion using our molecular karyotyping proven index case with an inv(1)(p13;q23) indicating that cases with no split signal are unlikely to have similar inversion. Due to great heterogeneity, *CSF1* split scoring was done on selected areas based on presence of *CSF1* expressing cells identified by mRNA ISH using correlative digital microscopy. Using this approach, *CSF1*-gene rearrangement was detected in 76% of all TGCT cases: in localized-type 77% and in diffuse-type 75% (*figure 4, supplementary material figure 2*). Further stratification of positive cases, rearrangement of the *CSF1* locus was present in 78% of localized-TGCT without recurrence, 100% of localized-TGCT with recurrent disease, 86% of diffuse-TGCT without recurrence and 67% of diffuse-TGCT including recurrent disease (*table 2, supplementary material table 1 patient and tumour characteristics*). There was no *CSF1* gene rearrangement in all four synovitis control cases.

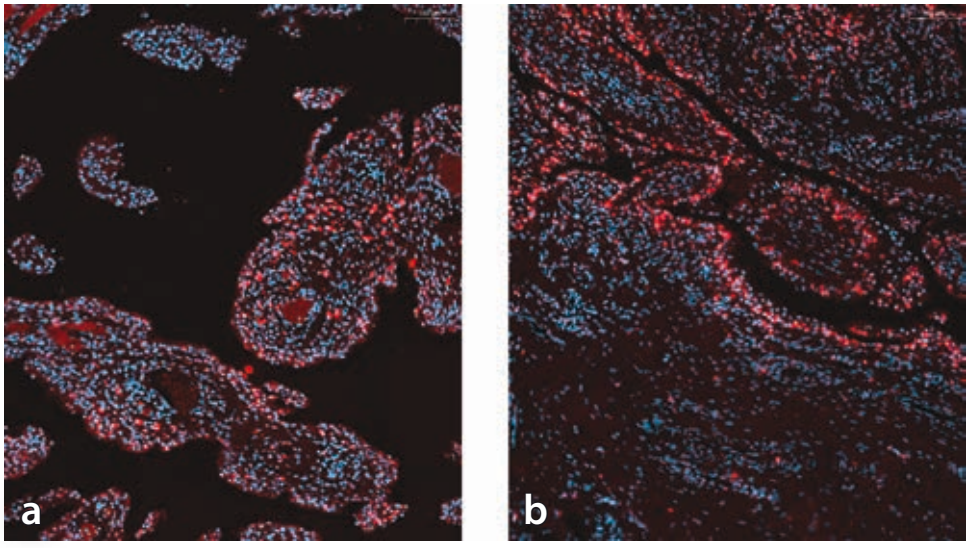


Figure 3 Distribution of synovial lining *CSF1* mRNA ISH positive cells in TGCT and reactive synovitis.
a. 61-year-old male patient (L3496) with diffuse-type TGCT. Cells with red cytoplasmic staining after mRNA ISH, show a deep infiltrating pattern in synovial villi with rare occurrence at the synovial lining parts. This is the same patient as figure 1 right and figure 2. **b.** 45-year-old female patient (L5620) with synovitis, showing *CSF1* expressing cells (red cytoplasmic signal) restricted to cells localised in the synovial lining. Nuclei are displayed in blue after DAPI staining, scale bars are in the right top corner (100µm).

Table 2 Proportion of cases with *CSF1* mRNA expression and *CSF1* gene rearrangement*

	N	*CSF1* **over-expression**	*CSF1* **gene rearrangement**
Localized	7	7 (100%)	5 (78%)
Localized recurrence	2	2 (100%)	2 (100%)
Diffuse	7	7 (100%)	6 (86%)
Diffuse recurrence	9	9 (100%)	6 (67%)
Synovitis	4	2 (50%)	0 (0%)

Localized: Localized-TGCT; Diffuse: Diffuse-TGCT

*Comprehensive patient and tumour characteristics are shown in *supplementary material table 1*.

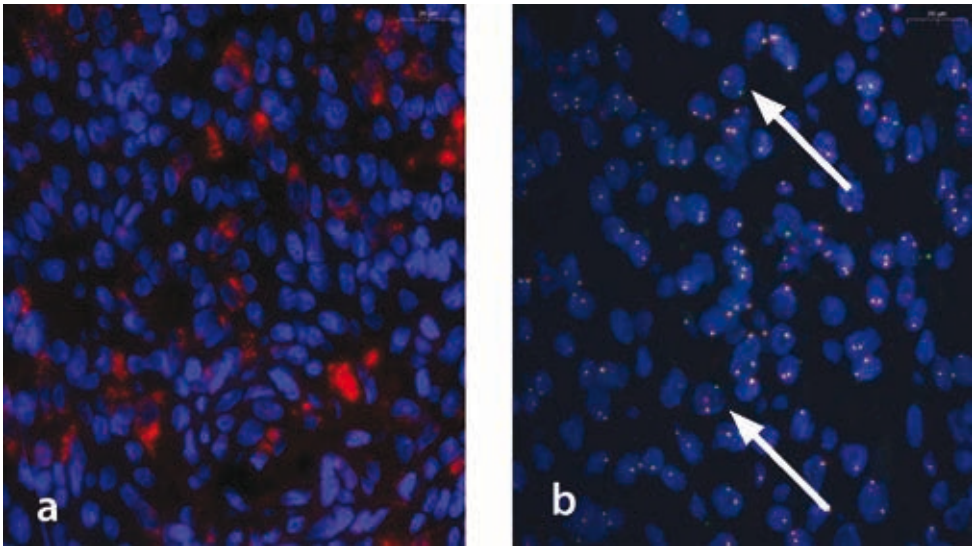
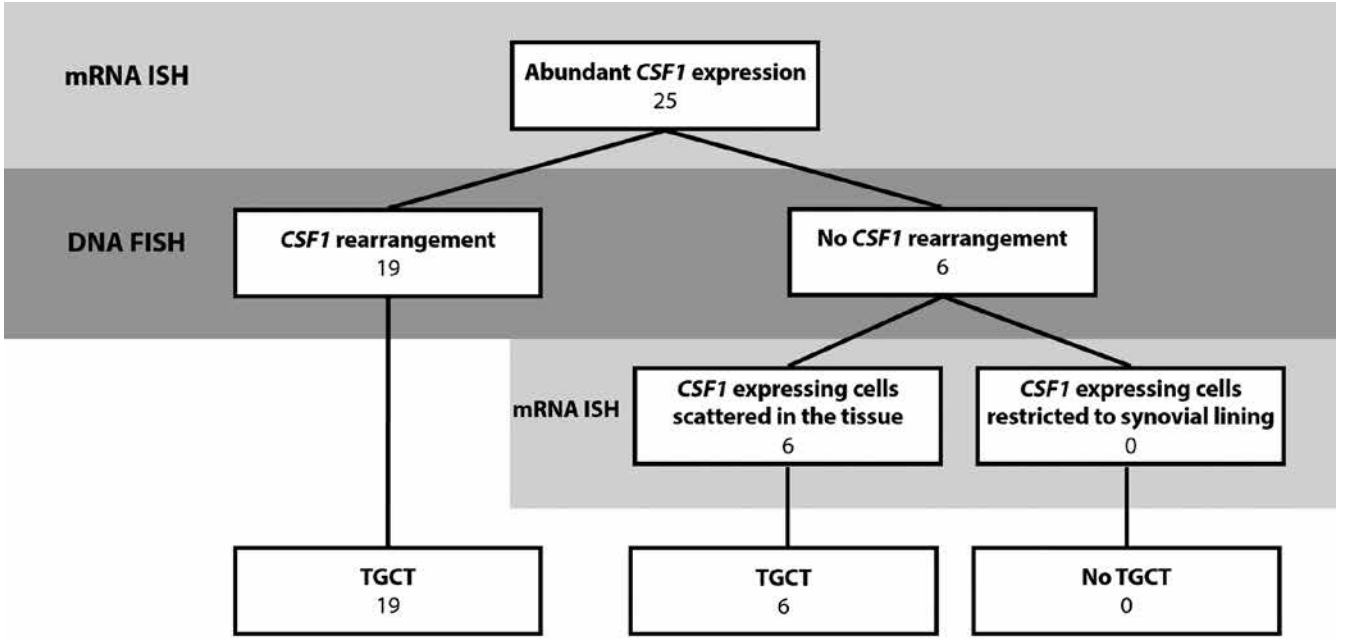


Figure 4 Correlative microscopy used to identify neoplastic cells. **a.** mRNA ISH helps to identify regions with cells overexpressing *CSF1* mRNA (red signal), blue nuclei after DAPI staining. **b.** *CSF1* locus specific split-apart probe set using BAC probes: centromeric (red) and telomeric (green) probes. Yellow signal represent co-localization of the signal meaning no rearrangement. White arrowheads indicate cells with split-apart signal, indicating rearrangement of the *CSF1* gene. Samples are from a 61-year-old male patient (L3496), with extensive recurrent diffuse-TGCT, the same patient as figure 1 A, figure 2, figure 3A. Scale bars are in the right top corner (20µm)

Figure 5 Proposed workflow for molecular pathology work up of TGCT cases

Numbers represent TGCT cases in this study

CSF1, Colony Stimulating Factor1; mRNA ISH, mRNA In Situ Hybridization; DNA FISH, DNA Fluorescence In Situ Hybridisation



Discussion

Localized- and diffuse-type TGCT are histopathologically identical and carry the same chromosomal translocation, leading to uncontrolled over-expression of *CSF1* due to a gene fusion between COL6A3 and *CSF1* genes. Undeniably, localized- and diffuse-type TGCT are clinically different diseases. In a well-defined TGCT population with >3 years follow-up, molecular differences in primary resected tissue between both subtypes and clinical outcome (recurrence) were evaluated. We were unable to find a clear association between *CSF1* over-expression or *CSF1* rearrangement and the biological behaviour in TGCT of the knee.

In this study, 76% *CSF1* rearrangement was detected when lumping all our 25 cases together, compared with 61% of the evaluated cases by Cupp et al.[12]. Further subdivided, our study revealed no difference in *CSF1* rearrangement for localized-TGCT (77%) and diffuse-TGCT (75%). On the contrary, West et al. reported a large difference between these two types; 87% rearrangement in localized- and 35% in diffuse-TGCT[11]. The relatively high percentage of rearrangement in our study, could be attributed to our scoring on preselected areas, based on high *CSF1* expression. In addition, our DNA FISH analysis, using bacterial artificial chromosome (BAC) clones (RP11-354C7 and RP11-96F24) bracketing *CSF1* locus, identifies not only a translocation, but also an inversion for *CSF1* rearrangements. Panagopoulous et al. revealed a *CSF1*-S100A10 fusion gene, with translocation t(1;1)(q21;p11) as the sole karyotypic abnormality[25]. Nilsson et al. found that 30% of the TGCT specimens did not have a rearrangement involving the 1p13 locus, where *CSF1* is located using split-apart interphase FISH approach, similar to ours[8]. Next to the translocation, Panagopoulos et al. reported the replacement of the 3'-UTR of *CSF1*, resulting in over-expression or a longer lifetime of *CSF1* mRNA due to loss of the 3-UTR controlling region[25]. Similar cryptic changes leading to loss of smaller gene region involving the 3'-UTR segment of *CSF1* are beyond the detection level of our FISH probes. Next to this, other, yet not identified alterations leading to deregulated *CSF1* expression cannot be ruled out in cases with *CSF1* mRNA expression without *CSF1* rearrangement of the *CSF1* locus.

Up to date, clinically reliable antibodies working on FFPE tissue sections to detect *CSF1* or *CSF1*R are lacking. Therefore, mRNA ISH was the best regarded option to identify *CSF1* over-expressing cells. Consistent with previous reports, all 25 evaluated cases showed *CSF1* up-regulation[11]. Exact

determination of the proportion of *CSF1* expressing cells was considered not meaningful, since in all tumours considerable intratumoural heterogeneity was observed between selected blocks and with individual tissue sections, reflecting the "landscape effect"[11]. This heterogeneity prevents any conclusion on the true neoplastic cell load in the tumour and a possible correlation to clinical outcome.

Deregulated *CSF1* expression is believed to be the central mechanism of tumourigenesis for TGCT. *CSF1*, also called macrophage colony-stimulating factor, is a cytokine, produced by many different cell types including macrophages, fibroblasts, endothelial cells and osteoblasts (and other cancer types, especially in bone metastasis)[26]. *CSF1* is expressed in neoplastic cells infiltrating throughout the lesion. Secreted *CSF1* recruits non-neoplastic macrophages into the tumour. By binding to its receptor *CSF1*R (type III receptor tyrosine kinase), *CSF1* promotes survival, proliferation and differentiation of cells of the mononuclear phagocyte lineage (e.g. monocytes, macrophages and osteoclasts)[27, 28]. Besides its general biological function, *CSF1* is also involved in inflammatory or reactive synovitis (rheumatoid arthritis, chronic artritis) and cancer (breast, endometrial, ovarian, lung, kidney)[12, 27]. When *CSF1* is expressed in reactive synovitis, its expression is restricted to cells in the synovial lining[12, 29], as was confirmed in our synovitis control cases.

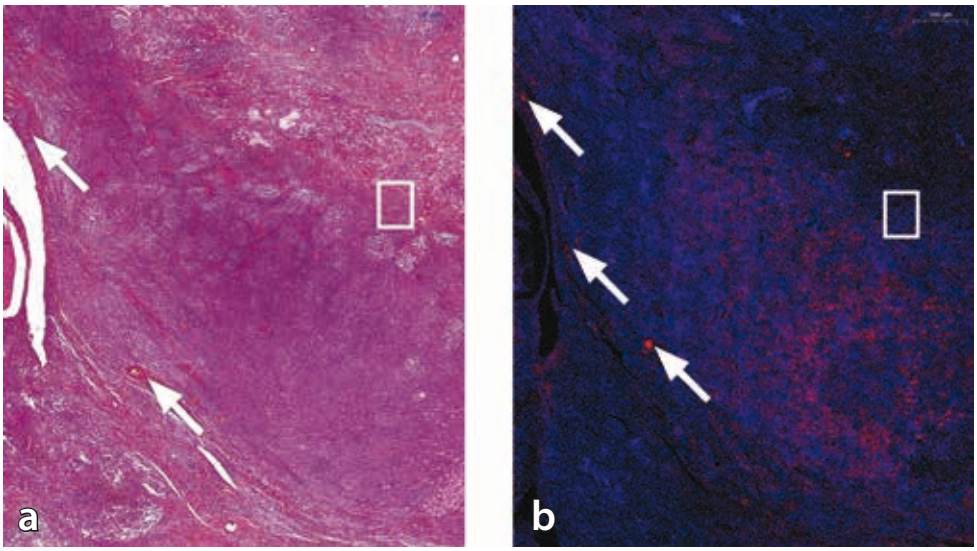
Inhibition of signalling between *CSF1* and *CSF1*R targets the underlying cause of the disease[29, 30]. The involvement of this pathway contributed to the introduction of systemic therapies for extensive diffuse-TGCT[20]. Primarily, imatinib[31] or related drugs as nilotinib[32] showed efficacy in the treatment. Recently, new *CSF1*R blockers were developed and are investigated in clinical trials; Emactuzumab and Cabiralizumab (FPA008) both monoclonal antibodies directed against *CSF1*R[33-35]; Pexidartinib (PLX3397; retains *CSF1*R in inactive state)[29], and MSC110 (an antagonist of the *CSF1* ligand)[35]. Emactuzumab (N=29) showed an overall response rate of 86% (two patients with a complete response) and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months)[33]. The preliminary results for cabiralizumab (N=22) are consistent, with radiographic response and improvement in pain and function in five out of 11 patients (45%)[34]. In a randomized, placebo-controlled phase 3 study, pexidartinib showed an improved overall response rate by RECIST: 39% in the pexidartinib-group (N=61) and 0% of placebo-group (N=59), after median six months follow-up[36]. However, long term results still need to be evaluated with these newer agents.

Within our well-defined patient cohort, all patients had a minimum follow-up of three years. However, patients without recurrent disease at the time of analysis could still develop this in due course, since it is known that local recurrence might develop years after initial surgery[1, 2, 15, 19, 37]. Verspoor et al. calculated an overall recurrence rate of 72% in 75 patients with diffuse-TGCT of the knee with a mean follow-up from index treatment of 13.9 years. They suggested a trend towards the longer the follow-up, the greater the number of recurrences[19].

In conclusion, DNA FISH analysis, using bacterial artificial chromosome (BAC) clones (RP11-354C7 and RP11-96F24) bracketing *CSF1* locus, can identify both chromosomal rearrangement caused translocation or inversion of the *CSF1* locus. *Figure 5* summarizes the workflow in the current study and the proposed workflow for molecular pathology work up of TGCT cases. The use of *CSF1* mRNA ISH in combination with *CSF1* split-apart FISH is an auxiliary diagnostic tool to confirm the diagnosis of TGCT. This combined approach allowed us to detect *CSF1*-gene rearrangement in 76% of the TGCT cases. At the molecular level, localized- and diffuse-type TGCT are indistinguishable when evaluating *CSF1* expression and the presence of the pathognomonic translocation involving the *CSF1* gene.

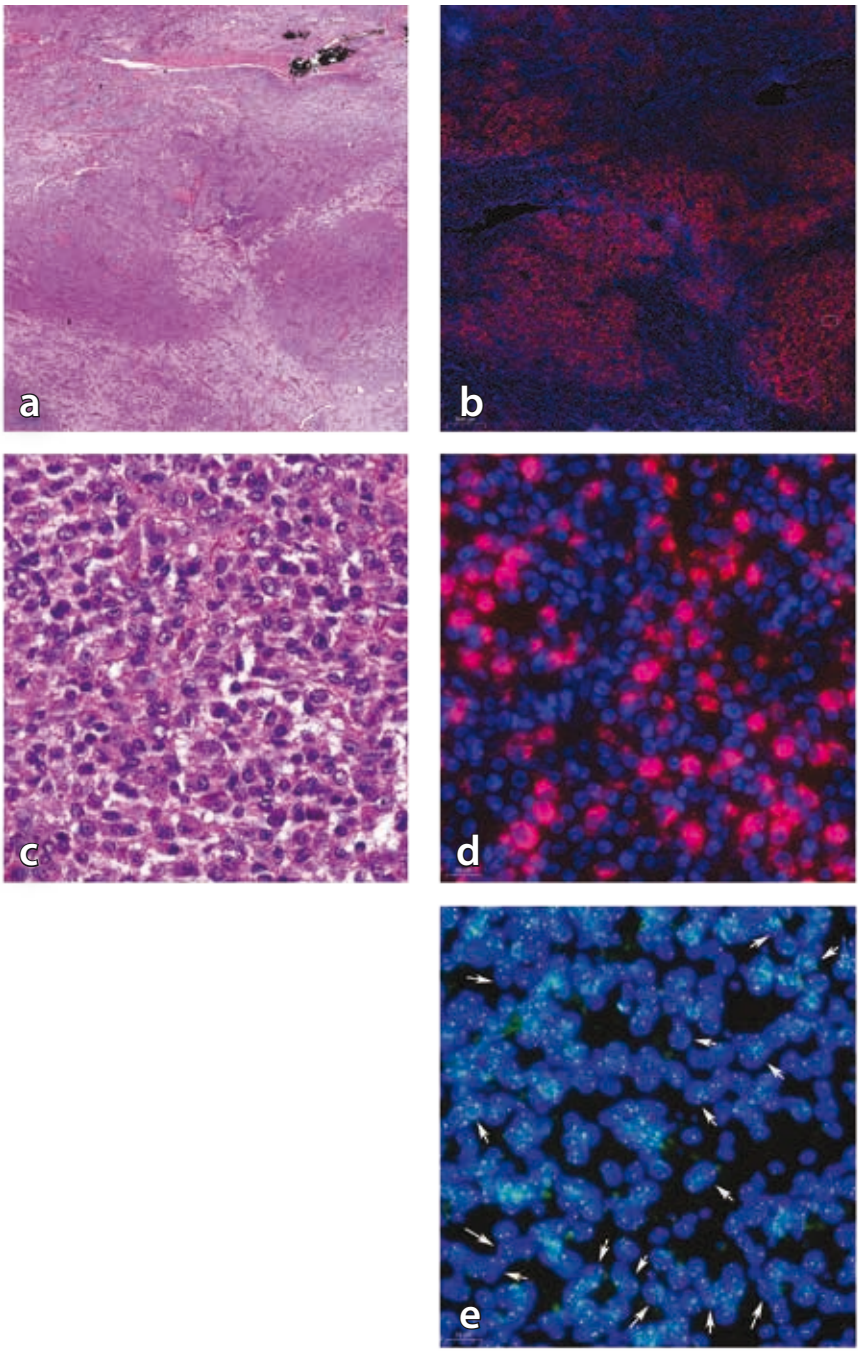
Supplementary data

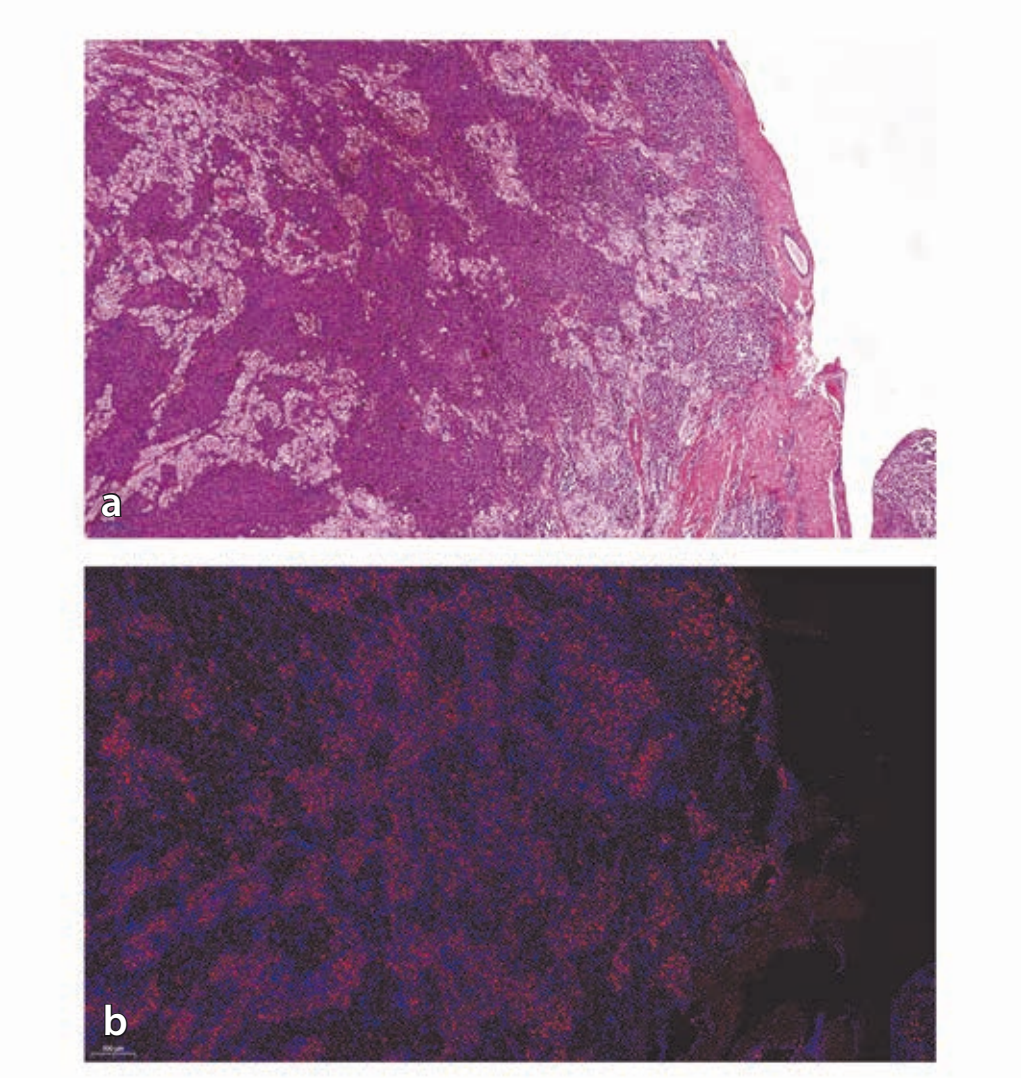
Supplementary data are available in the online version of this article, doi: 10.1111/his.13744



Supplementary figure 1 Low power magnification overview of TGCT case from a 61-year-old male patient (L3496), the same patient as figure 1 A, figure 2, figure 3A, figure 4. **a.** Hematoxyllin-eosin staining. **b.** *CSF1* mRNA ISH (red) of the same case depicting identical regions, nuclei are stained with DAPI (blue). White arrowheads indicate blood vessels with erythrocytes, giving a strong red fluorescing signal. A heterogeneous distribution of *CSF1* expressing cells with remarkable variation in their distribution in the tissue is clearly visible. White squared inset, indicates regions in high power magnification shown in details in figure 2. Scale bars are in the right top corner (500 µm).

Supplementary figure 2 ***(right page)*** Overview of TGCT localized case without recurrence from a 55-year-old female patient (L4385), presented in figure 1A. **a & b.** Hematoxillin-eosin staining low and high power overview. **b & d.** *CSF1* mRNA ISH (red) of the same case depicting identical regions, nuclei are stained with DAPI (blue). In panel B a white squared inset indicate the region shown in high power magnification in panel D. **e.** Using correlative microscope areas with more neoplastic cells (mRNA ISH positive cells) were identified and scored for *CSF1* locus specific split-apart probe set using BAC probes. Yellow signal represent co-localization of the signal meaning no rearrangement. White arrowheads indicate cells with split-apart signal, indicating rearrangement of the *CSF1* gene. Scale bars are at the bottom left corners and 500 and 20 µm for low and high power images, respectively.


a
b
c
d
e



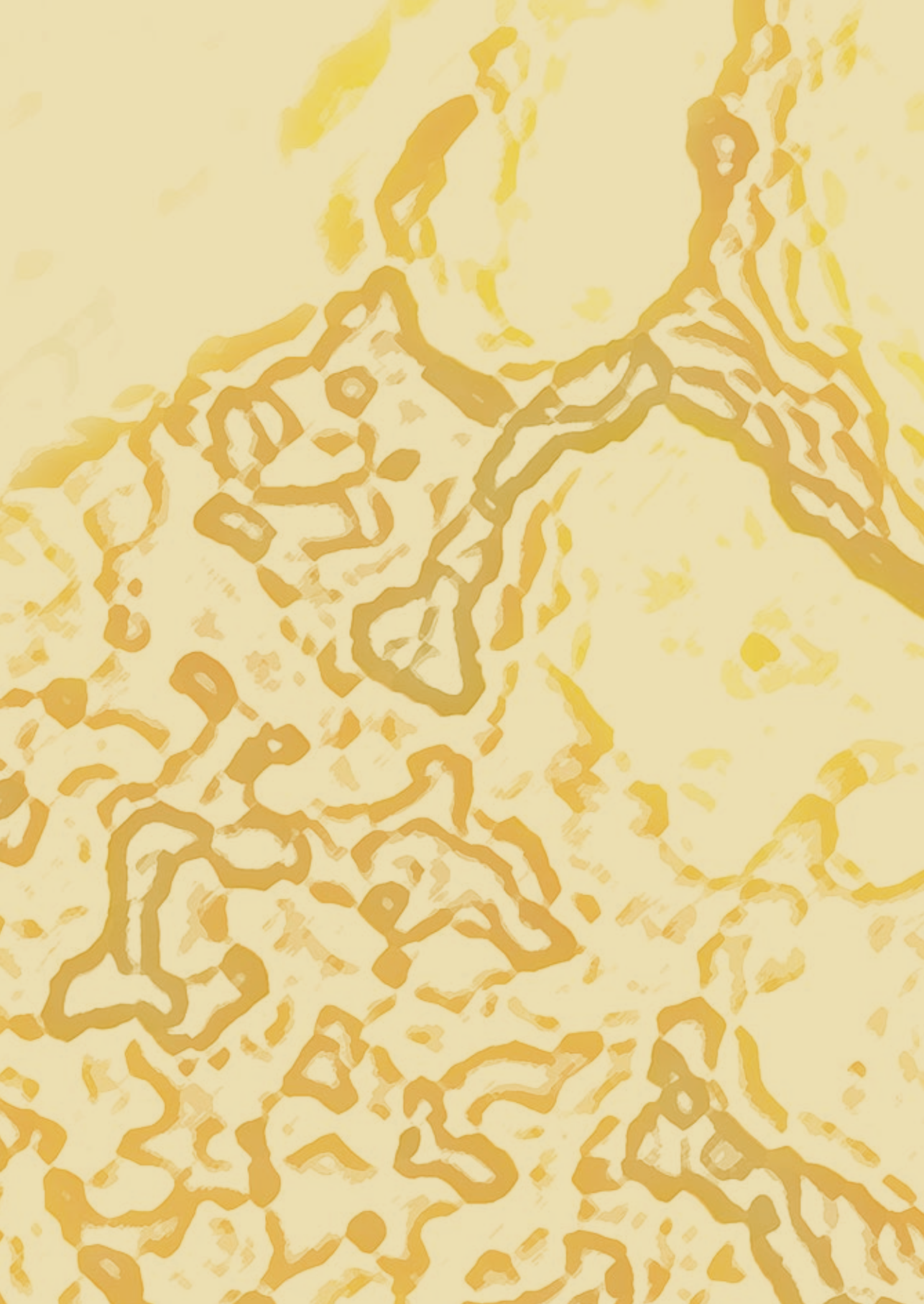
Supplementary figure 3 Correlative microscope image comparing sections after hematoxillin-eosin staining (**a**) and *CSF1* mRNA ISH (**b**) of a diffuse, non-recurrent TGCT case from a 50-year-old male patient (L3697). Diffuse infiltrating *CSF1* expressing cells are present throughout the section. Scale bars are at the left bottom corner (200 µm).

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
4. Jaffe HL LL, Sutro CJ. Pigmented Villonodular Synovitis, Bursitis and Tenosynovitis. Arch Pathol. 1941(31):731-65.
5. Fletcher JA, Henkle C, Atkins L, Rosenberg AE, Morton CC. Trisomy 5 and trisomy 7 are nonrandom aberrations in pigmented villonodular synovitis: confirmation of trisomy 7 in uncultured cells. Genes, chromosomes & cancer. 1992;4(3):264-6.
6. Mertens F, Orndal C, Mandahl N, Heim S, Bauer HF, Rydholm A, et al. Chromosome aberrations in tenosynovial giant cell tumors and nontumorous synovial tissue. Genes, chromosomes & cancer. 1993;6(4):212-7.
7. Ohjimi Y, Iwasaki H, Ishiguro M, Kaneko Y, Tashiro H, Emoto G, et al. Short arm of chromosome 1 aberration recurrently found in pigmented villonodular synovitis. Cancer genetics and cytogenetics. 1996;90(1):80-5.
8. Nilsson M, Hoglund M, Panagopoulos I, Sciot R, Dal Cin P, Debiec-Rychter M, et al. Molecular cytogenetic mapping of recurrent chromosomal breakpoints in tenosynovial giant cell tumors. Virchows Archiv : an international journal of pathology. 2002;441(5):475-80.
9. Sciot R, Rosai J, Dal Cin P, de Wever I, Fletcher CD, Mandahl N, et al. Analysis of 35 cases of localized and diffuse tenosynovial giant cell tumor: a report from the Chromosomes and Morphology (CHAMP) study group. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 1999;12(6):576-9.
10. Brandal P, Bjerkehagen B, Heim S. Molecular cytogenetic characterization of tenosynovial giant cell tumors. Neoplasia. 2004;6(5):578-83.
11. 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(3):690-5.
12. 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. The American journal of surgical pathology. 2007;31(6):970-6.
13. Mastboom MJL, Verspoor FGM, Hanff DF, Gademan MGJ, Dijkstra PDS, Schreuder HWB, Bloem JL, van der Wal RJP, van de Sande MAJ. Severity classification of Tenosynovial Giant Cell Tumours on MR imaging. Surg Oncol. 2018;27(3):544-550.
14. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
15. 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(2):210-7.
16. 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(4):808-15.
17. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.

18. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
19. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
20. Brahmi M, Vinceneux A, Cassier PA. Current Systemic Treatment Options for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis: Targeting the *CSF1*/*CSF1*R Axis. Current treatment options in oncology. 2016;17(2):10.
21. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
22. Wang F, Flanagan J, Su N, Wang LC, Bui S, Nielson A, et al. RNAscope: a novel in situ RNA analysis platform for formalin-fixed, paraffin-embedded tissues. The Journal of molecular diagnostics : JMD. 2012;14(1):22-9.
23. Szuhai K, Bezrookove V, Wiegant J, Vrolijk J, Dirks RW, Rosenberg C, et al. Simultaneous molecular karyotyping and mapping of viral DNA integration sites by 25-color COBRA-FISH. Genes, chromosomes & cancer. 2000;28(1):92-7.
24. Szuhai K, Tanke HJ. COBRA: combined binary ratio labeling of nucleic-acid probes for multi-color fluorescence in situ hybridization karyotyping. Nature protocols. 2006;1(1):264-75.
25. Panagopoulos I, Brandal P, Gorunova L, Bjerkehagen B, Heim S. Novel *CSF1*-S100A10 fusion gene and *CSF1* transcript identified by RNA sequencing in tenosynovial giant cell tumors. International journal of oncology. 2014;44(5):1425-32.
26. Hung JY, Horn D, Woodruff K, Prihoda T, LeSaux C, Peters J, et al. Colony-stimulating factor 1 potentiates lung cancer bone metastasis. Laboratory investigation; a journal of technical methods and pathology. 2014;94(4):371-81.
27. Achkova D, Maher J. Role of the colony-stimulating factor (CSF)/CSF-1 receptor axis in cancer. Biochemical Society transactions. 2016;44(2):333-41.
28. Barreda DR, Hanington PC, Belosevic M. Regulation of myeloid development and function by colony stimulating factors. Developmental and comparative immunology. 2004;28(5):509-54.
29. Tap WD, Wainberg ZA, Anthony SP, Ibrahim PN, Zhang C, Healey JH, et al. Structure-Guided Blockade of *CSF1*R Kinase in Tenosynovial Giant-Cell Tumor. The New England journal of medicine. 2015;373(5):428-37.
30. Peyraud F, Cousin S, Italiano A. CSF-1R Inhibitor Development: Current Clinical Status. Current oncology reports. 2017;19(11):70.
31. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
32. 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.
33. Cassier PA, Italiano A, Gomez-Roca CA, Le Tourneau C, Toulmonde M, Cannarile MA, et al. *CSF1*R 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(8):949-56.

34. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, Ravi V, Cassier PA, Rutkowski P, Sankar N, Qazi I, Sikorski RS, Collins H, Zhang C, Shocron E, Gelderblom H. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-*CSF1*R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). Am. Soc. Clin. Oncol. 2017;Conference: 2017 Annual Meeting ASCO. United States. 35 (15 Supplement 1).
35. Hung M, Stuart AR, Higgins TF, Saltzman CL, Kubiak EN. Computerized Adaptive Testing Using the PROMIS Physical Function Item Bank Reduces Test Burden With Less Ceiling Effects Compared With the Short Musculoskeletal Function Assessment in Orthopaedic Trauma Patients. Journal of orthopaedic trauma. 2014;28(8):439-43.
36. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference; 2018; Chicago.
37. Mastboom MJL, Verspoor FGM, Gelderblom H, van de Sande MAJ. Limb Amputation after Multiple Treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch Cases. Case reports in orthopedics. 2017;2017:7402570.



SEVERITY

chapter four

Severity classification of Tenosynovial Giant Cell Tumours on MR imaging

M.J.L. Mastboom*[1], F.G.M. Verspoor*[2], D.F. Hanff[3], M.G.J. Gademan[4], P.D.S. Dijkstra[1], H.W.B. Schreuder[2], J.L. Bloem[3], R.J.P. van der Wal[1], M.A.J. van de Sande[1]

Surgical oncology. 2018 Sept;27(3):544-550

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Radiology, Leiden University Medical Centre, Leiden, the Netherlands

[4] Clinical Epidemiology, Leiden University Medical Centre, Leiden, the Netherlands

*Authors contributed equally to this work.

Abstract

Aim

Current development of novel systemic agents requires identification and monitoring of extensive Tenosynovial Giant Cell Tumours (TGCT). This study defines TGCT extension on MR imaging to classify severity.

Methods

In part one, six MR parameters were defined by field-experts to assess disease extension on MR images: type of TGCT, articular involvement, cartilage-covered bone invasion, and involvement of muscular/tendinous tissue, ligaments or neurovascular structures. Inter- and intra-rater agreement were calculated using 118 TGCT MR scans. In part two, the previously defined MR parameters were evaluated in 174 consecutive, not previously used, MR-scans. TGCT severity classification was established based on highest to lowest Hazard Ratios (HR) on first recurrence.

Results

In part one, all MR parameters showed good inter- and intra-rater agreement (Kappa≥0.66). In part two, cartilage-covered bone invasion and neurovascular involvement were rarely appreciated (<13%) and therefore excluded for additional analyses. Univariate analyses for recurrent disease yielded positive associations for type of TGCT HR12.84(95%CI4.60-35.81), articular involvement HR6.00(95%CI2.14-16.80), muscular/tendinous tissue involvement HR3.50(95%CI1.75-7.01) and ligament-involvement HR4.59(95%CI2.23-9.46). With these, a TGCT severity classification was constructed with four distinct severity-stages. Recurrence free survival at 4 years (log rank p<0.0001) was 94% in mild localized (n56, 1 recurrence), 88% in severe localized (n31, 3 recurrences), 59% in moderate diffuse (n32, 12 recurrences) and 36% in severe diffuse (n55, 33 recurrences).

Conclusion

The proposed TGCT severity classification informs physicians and patients on disease extent and risk for recurrence after surgical treatment. Definition of the most severe subgroup attributes to a universal identification of eligible patients for systemic therapy or trials for novel agents.

Introduction

Tenosynovial Giant Cell Tumour (TGCT) affecting large joints is an orphan, mono-articular, potentially locally aggressive disease with high recurrence rates. According to the 2013 WHO classification of tumours of soft tissue and bone, at the base of growth pattern, a radiological distinction is made between single nodule (localized-TGCT) and multiple lesions (diffuse-TGCT). These types differ in their clinical presentation, response to treatment and prognosis, but histologically, they seem identical[1-4].

Localized-type TGCT is classified as a circumscribed benign small (between 0.5 and 4 cm) mass[1, 5]. Standard treatment of choice is excision. Subsequently, overall reported recurrence rates are relatively low: 0-6%[6]. On the contrary, diffuse-type TGCT, previously named Pigmented VilloNodular Synovitis (PVNS), extensively involves the synovial membrane and infiltrates adjacent structures[6, 7]. Reported recurrence rates of diffuse-TGCT following open synovectomy are 14% up till 67% and after arthroscopic synovectomy 40% up till 92%[6]. Recurrent or residual disease, frequently requiring multiple, sometimes mutilating operations, may result in total joint arthroplasties, morbidity and loss of quality of life[8-12]. With this large variety in disease presentation and recurrence rates, a more comprehensive and outcome-based classification is asked for. The emerging era of systemic targeted and multimodality therapies (available in trial settings) increases the need for a method to select eligible patients in order to create comparable patient cohorts[13-15].

In diagnosing and treating TGCT, magnetic resonance (MR) imaging is the most distinctive imaging technique[4, 16-19]. MR imaging reveals conspicuous nodular (localized-type) or villous proliferation of synovium (diffuse-type). However, current literature lacks specific MR discriminating features to describe or quantify tumour extent in relation to clinical outcome. Uniform MR descriptions are of utmost importance for clinical and research purposes. Therefore this study aims to sub-classify tumour severity especially in diffuse-type TGCT. First, a group of radiologists and orthopaedic surgeons identified and defined potentially distinguishing parameters. Second, these MR parameters were applied on a different study-population to establish TGCT severity subgroups.

Methods

Part I: Identification and evaluation of TGCT specific MR parameters

Using case discussions in expert meetings with two dedicated musculoskeletal radiologists and three oncological orthopaedic surgeons, six MR parameters were selected in relation to anatomical or surgical landmarks. These parameters were 1 type of TGCT (based on 2013 WHO classification[1,2]), 2 articular involvement, 3 cartilage-covered bone invasion, 4 involvement of muscular/tendinous tissue, 5 involvement of ligaments and 6 involvement of neurovascular structures (*figure 1*) (*Appendix*).

To evaluate usability and reproducibility, 118 MR scans of TGCT patients, treated at the Leiden University Medical Centre (LUMC), were randomly retrieved (MM). The six MR parameters were evaluated in a heterogeneous group of TGCT cases as scans included cases of various large joints (knee (79; 67%), ankle (13; 11%), foot (10; 9%)), severity subtypes and treatment phases. MR scans were conducted using a 1.5 or 3.0 Tesla unit Philips (Best, The Netherlands) Ingenia MR with dedicated coils. Standard musculoskeletal scan-protocol included: T1- and T2-weighted fast spin echo, T1-weighted fat-suppressed post Gd-chelate contrast and optionally T2* gradient-echo sequences in two planes (transversal and either sagittal or coronal). To assess inter- and intra-rater agreement, all MR scans were evaluated by one dedicated musculoskeletal radiologist (DH) and by two dedicated orthopaedic surgeons (RW, MS). MR evaluation was blinded to patient characteristics.

Inter-rater agreement and accompanying 95% confidence interval (95% CI) between three physicians was calculated for all 118 cases by Fleiss-Kappa (dichotomous outcomes in all parameters, except for articular involvement with three outcomes). To evaluate intra-rater agreement with the accompanying 95% CI (linear weighted kappa), 36 randomly chosen MR scans (31%) were again evaluated three months after initial evaluation by the senior orthopaedic surgeon (MS).

Part II: Application of TGCT MR parameter

None of the MR scans in part I were used in part II. The combined TGCT-database of two sarcoma centres in The Netherlands (LUMC and Radboud University Medical Centre (RUMC)) was used to include consecutive MR scans conducted between 2005 and 2015 (n=283). MR scan inclusion criteria were: pre-treatment MR scan of histologically proven TGCT of large joints, conducted in two planes (transversal and either sagittal or coronal), and open resection as primary treatment

Figure 1 Definition of six TGCT specific MR parameters

TGCT-type

a. Localized-type on a sagittal PD-weighted FSE MR image of a 49 year old female patient. Localized-TGCT is defined according to WHO as a well circumscribed nodular lesion at synovial lining of bursa, joint or tendon sheath.

b. Diffuse-type on a sagittal PD-weighted FSE MR image of a 24 year old male patient. Diffuse-TGCT is defined as a multinodular lesion involving a larger part or multiple compartments of the synovial lining.

Articular involvement

c. Intra-articular well circumscribed lesion on posterior cruciate ligament on a PD-weighted FSE MR image of a 18 year old female patient. Intra-articular involvement is defined as TGCT involvement inside synovial lining of joint.

d. Extra-articular involvement, along gastrocnemius muscle insertion, on a sagittal T1-weighted FSE MR image of a 33 year old male patient. Extra-articular involvement is defined as TGCT involvement outside synovial lining of the joint.

e. Both intra- and extra-articular involvement on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 63 year old female patient with TGCT. Extensive tumour growth anterior and posterior.

Cartilage-covered bone invasion

f. Cartilage covered bone invasion on a sagittal T1-weighted FSE MR image of a 59 year old male patient. Square presents cartilage covered bone, defined as clear invasion of bone through cartilage; not only touch cartilage. Circle presents not-cartilage covered bone invasion.

Muscular/tendinous tissue involvement

g. Muscular/tendinous tissue involvement, anterior vastus medialis muscle and posterior hamstrings tendon, on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 63 year old female patient with TGCT. Muscular/tendinous tissue is defined as involvement of muscular/tendinous tissue or >180 degrees encagement of tendon/muscle.

Ligament involvement

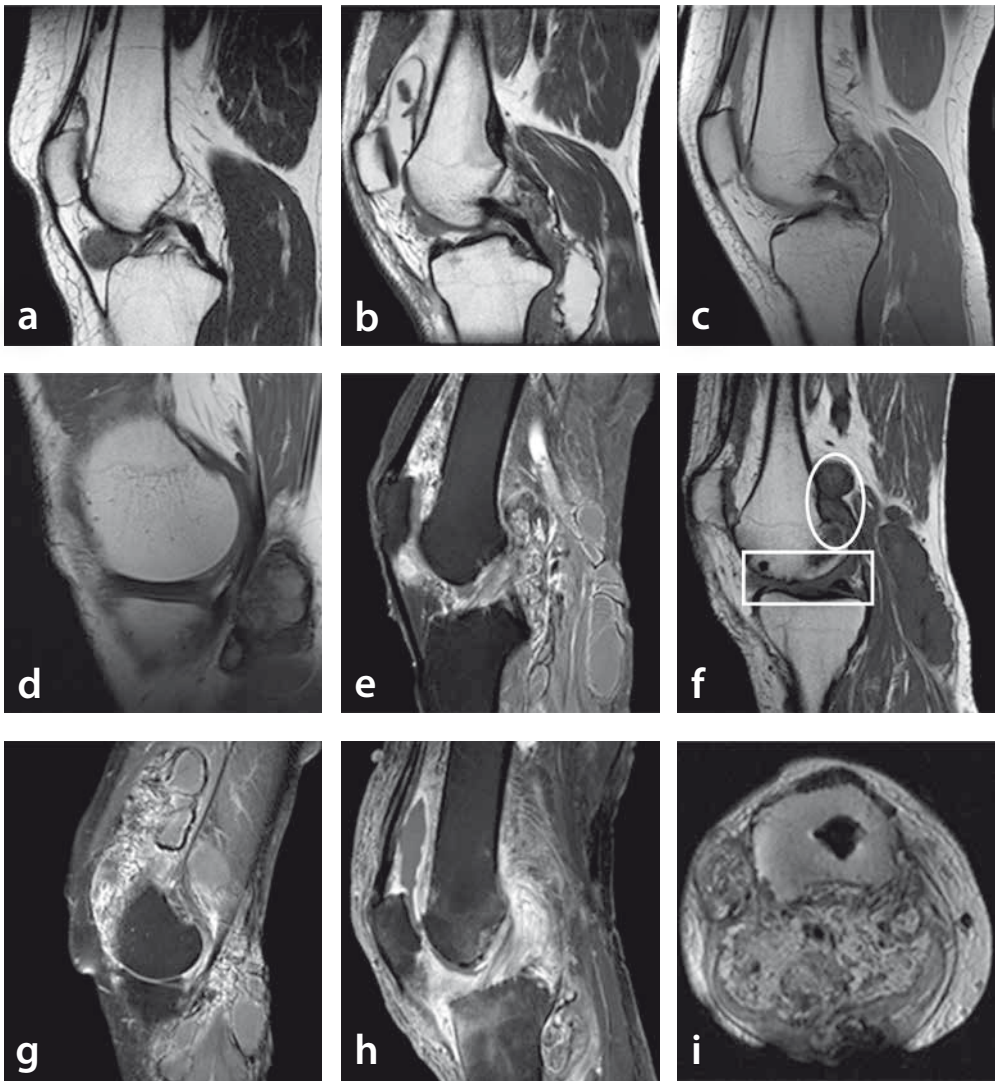
h. Cruciate ligament enhancement on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 64 year old male patient. Ligament involvement is defined as involvement of ligament or >180 degrees encagement of ligament.

Neurovascular structures involvement

i. Popliteal artery encagement on an axial PD-weighted FSE MR image of a 62 year old female patient, referred to a tertiary sarcoma centre with extensive TGCT. Neurovascular involvement is defined as > 180 degrees encagement of the artery or nerve.

FSE, Fast Spin Echo; PD, Proton Density

Figure e & g is the same female patient.


a
b
c
d
e
f
g
h
i

in one of the two participating centres. Large joints were defined as all joints proximal to and excluding metatarsophalangeal and metacarpophalangeal joints. When TGCT affected the knee, one diagnostic arthroscopy prior to open resection was allowed, since tumour extent would not be affected. Open synovectomy was defined as gross total resection of disease, either one- or two-staged, without adjuvant therapy. 174/283 Patients met the inclusion criteria (*figure 2*). Median follow-up was 36 (IQR 21-60) months, maximum follow-up 12 years after primary surgery.

The senior author (MS) evaluated the six defined MR parameters (part I) on these pre-treatment scans (77 LUMC, 97 RUMC). MR evaluation was blinded to patient characteristics and clinical outcome. Patient and tumour characteristics were gathered: gender, localization (affected joint), age at time of the MR scan, date of open synovectomy, first local recurrence and date of first recurrence (on MR imaging), and date of last follow-up. Median follow-up was calculated from date of primary surgery to date of last clinical follow-up, including interquartile range (IQR). Recurrence free survival was calculated from date of surgery to recurrent disease or last contact.
As outcome, first recurrence was defined as new disease presence after synovectomy or growing residual disease (diagnosed on follow-up MR scan). Proposed risk factors were gender, localization (knee versus other joints) and age at the time of the MR scan (below or above 40 years). Hazard ratios (HRs) and their corresponding 95% CI were estimated for risk factors and MR parameters

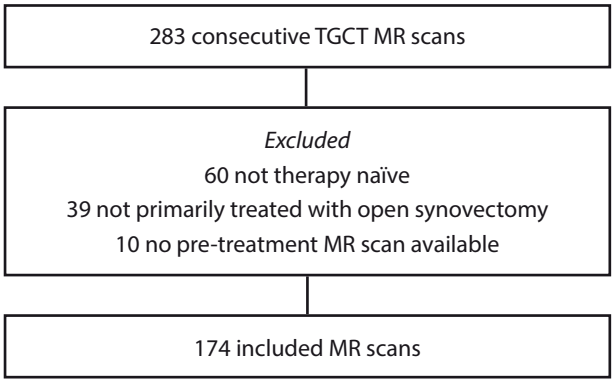


Figure 2 Inclusion flowchart part II TGCT severity classification.

(part I) by univariate and multivariate Cox regression analyses to estimate the relation on recurrent disease. Since estimating HR is unreliable for rarely present MR parameters, only parameters with an adequate number of presence (minimum of 20%) were used for additional analyses. Recurrence free survival close to median time of follow-up was calculated by Kaplan Meier analyses and log rank test. Time zero was defined as date of primary open synovectomy.

At the base of HRs with positive associations of risk factors and MR parameters on first recurrences, the TGCT severity classification was established. The TGCT subgroup flow chart started with the MR parameter with highest HR, followed by descending HRs. Statistical Package for Social Statistics (SPSS) version 23 was used for analyses.

Ethical statement

This study was approved by the institutional review board from our institution (registration number P13.029). No funding was received.

Results

Part I: Evaluation of TGCT specific MR parameters

Inter-rater agreements for type of TGCT, articular involvement, cartilage-covered bone invasion, and involvement of muscular/tendinous tissue, ligaments or neurovascular structures were 0.71; 0.68; 0.66; 0.67; 0.75 and 0.73, respectively. Intra-rater agreements for these parameters were between 0.72 and 1.00 (*table 1*). Since inter- and intra-rater agreements were good[20] for these six MR features, all parameters were considered viable to use for TGCT subgroup analyses.

Part II: Application of TGCT MR parameters

Out of 174 MR scans, the knee was affected most (122; 70%), followed by the ankle (20; 12%) (*table 2*). In univariate analyses, none of the proposed risk factors were associated with recurrent disease ($p>0.37$) (*table 3*) and consequently not used for further analyses. Both MR parameters cartilage-covered bone invasion and involvement of neurovascular structures were rarely seen on MR images (< 13%) and in accordance with our exclusion criteria not used for additional analyses. In univariate analyses, the remaining four MR parameters were associated with recurrent disease ($p<0.002$) (*table 3*); strongest association was seen in diffuse-type compared with localized-type

Table 1 Inter- and intra-rater agreement (kappa) in six MR parameters

Agreement	Type of TGCT	Articular involvement	Cartilage-covered bone invasion	Muscular/ tendinous tissue involvement	Ligament involvement	Neurovascular involvement
Inter-rater	0.71 (0.60-0.81)	0.68 (0.58-0.78)	0.66 (0.56-0.76)	0.67 (0.56-0.77)	0.75 (0.57-0.93)	0.73 (0.62-0.83)
Intra-rater	0.94 (0.82-1.06)	0.89 (0.74-1.04)	0.79 (0.39-1.19)	0.72 (0.50-0.94)	0.86 (0.68-1.04)	1.00 (1.00-1.00)

Inter-rater, Agreement between three physicians (one musculoskeletal radiologist, two orthopaedic surgeons).

Intra-rater, Agreement for 31% of MR scans initially evaluated and re-evaluated 3 months thereafter by the senior orthopaedic surgeon.

Interpretation of inter- and intra-rater agreement (K-value) [20]

Agreement value	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

(HR 12.84 (95%CI 4.60-35.81)), subsequently intra- and extra-articular involvement compared with extra-articular (HR 6.00 (95%CI 2.14-16.80)) and involvement of muscular/tendinous tissue or ligaments compared with no involvement (HR 3.50 (95%CI 1.75-7.01), HR 4.59 (95%CI 2.23-9.46), respectively).
Multivariate analyses for MR parameters did not show individual positive association, except for parameter type of TGCT (*supplementary material I*).

Four TGCT severity subtypes were established using a flowchart that begins with the parameters with highest HR (parameter type of TGCT), followed by parameters with descending HRs. These four subtypes showed a clinically relevant or significant prognostic value for recurrent disease and were classified as: mild localized (n56, 1 recurrence), severe localized (n31, 3 recurrences), moderate diffuse (n32, 12 recurrences) and severe diffuse (n55, 33 recurrences).

1. **Mild localized** contained localized-type, either intra- or extra-articular involvement without involvement of muscular/tendinous tissue/ligaments.
2. **Severe localized** included localized-type, either intra- or extra-articular lesions and either or both involvement of muscular/tendinous tissue/ligaments.
3. **Moderate diffuse** comprised diffuse-type with intra- and/or extra-articular disease without involvement of muscular/tendinous tissue/ligaments.
4. **Severe diffuse** was diffuse-type including intra- and extra-articular involvement and involvement of at least one of the three structures (muscular/tendinous tissue/ligaments) (*figure 3*).

Recurrence free survival at 4 years (close to median follow-up diffuse-type) for the four patient groups according to the new MR subtypes descended from 94% in mild localized, to 88% in severe localized, to 59% in moderate diffuse and to 36% in the least favorable subtype, severe diffuse. Median time to local recurrence in moderate diffuse and severe diffuse subtypes was 29.5 (IQR 14.5-48.0) and 22.0 (IQR 11.8-33.5) months, respectively. Majority of recurrent disease cases were already treated with a re-operation (32/49, 65%). One patient, classified as severe diffuse, died of another disease, after four months and was censored at that time. Novel MR based TGCT severity and associated Kaplan Meier survival curves presented significant difference between the four patient groups (log rank $p<0.0001$) and additional differentiation compared with solely sub-classifying in localized- and diffuse-TGCT (*figure 4 and supplementary material II*).

Table 2 TGCT MR scan demographics

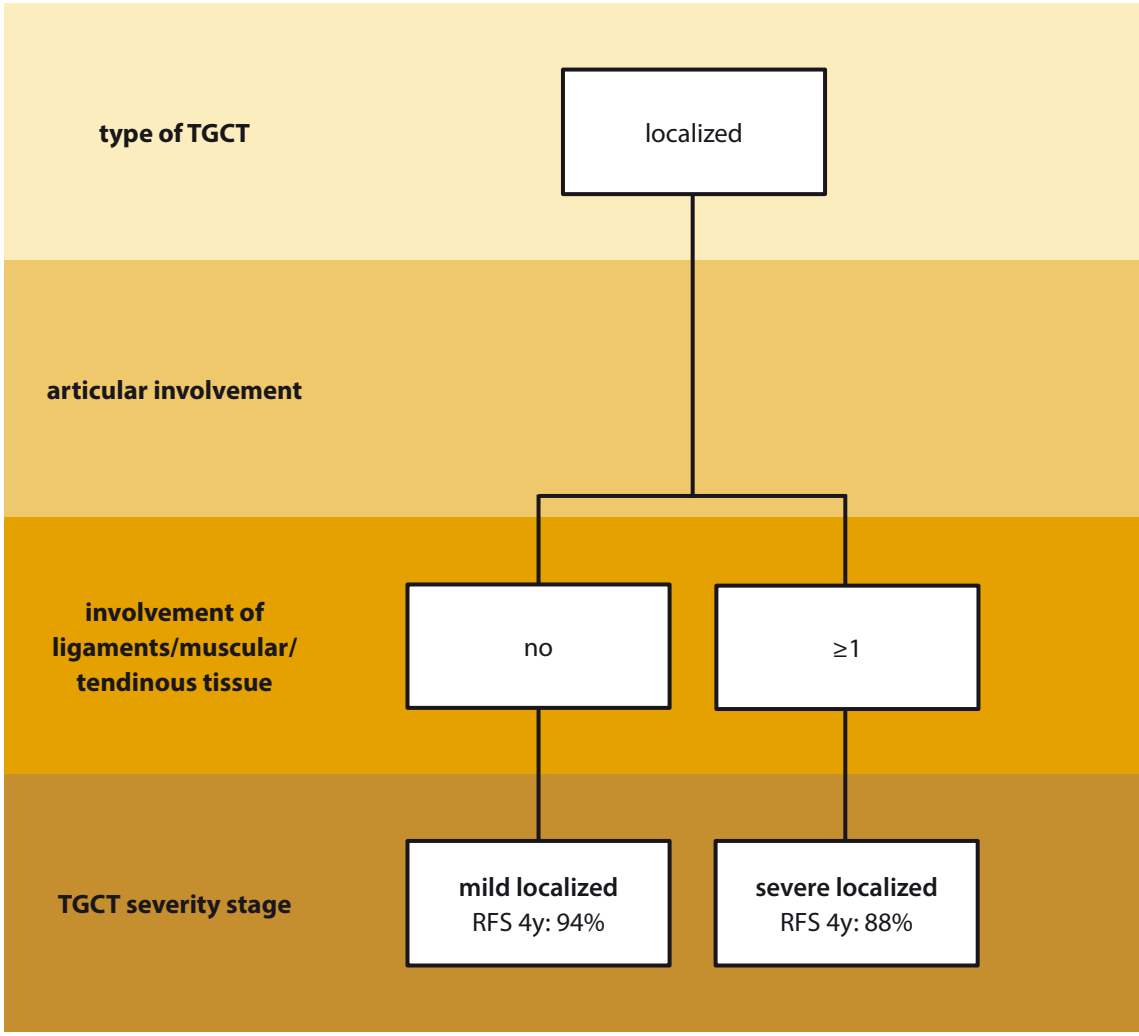
	Cases (%)	Cases localized TGCT (%)	Cases diffuse TGCT (%)
Total number of MR scans	174	87	87
Gender			
Female	105 (60)	33 (38)	36 (41)
Male	69 (40)	54 (62)	51 (59)
Median age at MR scan (IQR)	37 (26-48) years	37 (24-47) years	36 (26-49) years
Localization			
Knee	122 (70)	63 (72)	59 (68)
Hip	8 (5)	0 (0)	8 (9)
Ankle	20 (12)	10 (11)	10 (11)
Foot	9 (5)	5 (6)	4 (5)
Elbow	6 (3)	4 (5)	2 (2)
Other	9 (5)	5 (6)	4 (5)
Median follow-up (IQR)	36 (21-60) months	32 (17-56) months	41 (24-63) months
Total number of recurrences			
Recurrent disease	49 (28)	4 (5)	45 (52)
No recurrent disease	125 (72)	83 (95)	42 (48)

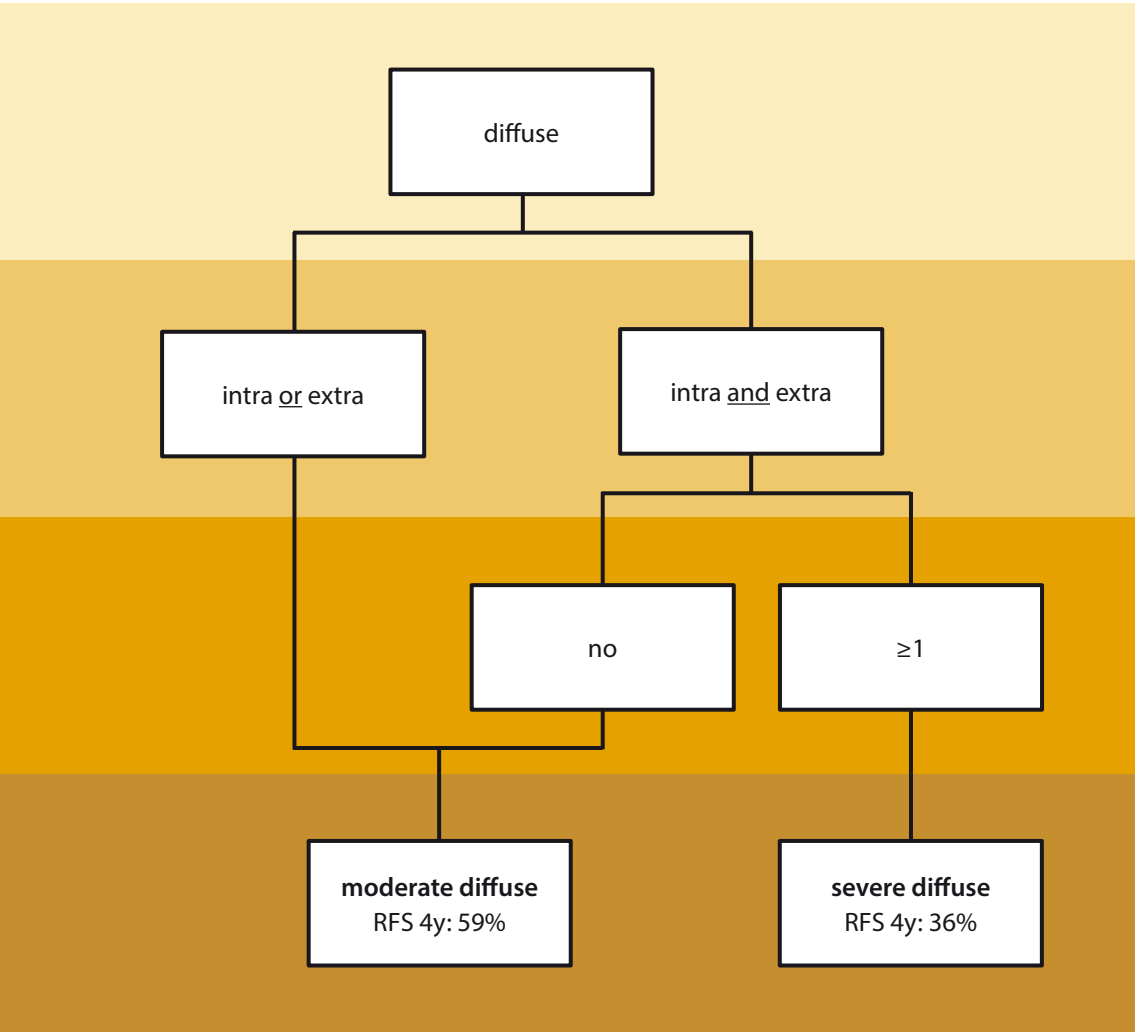
IQR, interquartile range

Table 3 Risk of recurrence on MR imaging;
univariate analyses in proposed risk factors and four MR parameters.

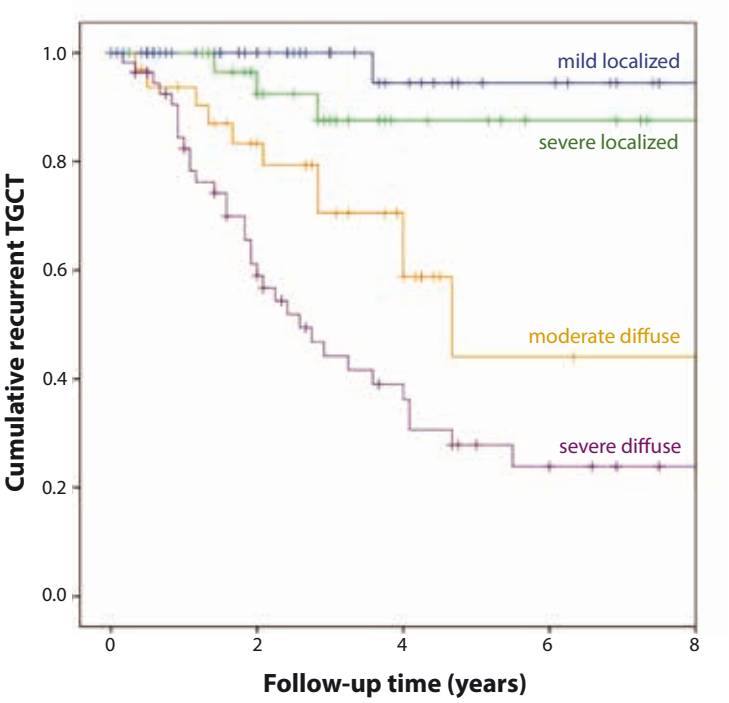
	n (%)	Hazard ratio (95% CI)	P
Gender			
Male	69 (40)	1.29 (0.74-2.27)	0.37
Female	105 (60)	1	
Age			
<40 years	91 (52)	1.15 (0.66-2.02)	0.63
>40 years	83 (48)	1	
Localization			
Knee	122 (70)	1.15 (0.63-2.12)	0.65
Other joint	52 (30)	1	
TGCT-type			
Diffuse	87 (50)	12.84 (4.60-35.81)	<0.000
Localized	87 (50)	1	
Articular involvement			
Intra-articular	59 (34)	1.11 (0.31-3.95)	0.87
Intra- and extra-articular	75 (43)	6.00 (2.14-16.80)	0.001
Extra-articular	40 (23)	1	
Muscular/tendinous tissue involvement			
Yes	90 (52)	3.50 (1.75-7.01)	<0.000
No	84 (48)	1	
Ligament involvement			
Yes	86 (49)	4.59 (2.23-9.46)	<0.000
No	88 (51)	1	

Figure 3 TGCT severity classification, containing four severity subtypes: mild localized, severe localized, moderate diffuse and severe diffuse.





RFS 4y, Recurrence Free Survival at 4 years



Time (years)	0	2	4	6	8
Number at risk	174	105	51	24	10

Figure 4 TGCT recurrence free survival curve for four TGCT severity subtypes, affecting large joints, estimated with Kaplan Meier method. Time zero was date of primary open synovectomy. One patient, classified as severe diffuse died of another disease after 4 months and was censored at that time.

Discussion

This is the first study to define severity subtypes in Tenosynovial Giant Cell Tumours (TGCT) based on a combination of four MR imaging parameters. These subtypes correlate with a spectrum of disease severity ranging from low to high risk of local recurrence after surgical intervention.

Within this present era of systemic targeted and multimodality therapies (available in trial settings) in TGCT, standalone surgical resection cannot be regarded the gold standard anymore for more severe cases[21]. Because of the lack of clear-cut boundaries in diffuse-TGCT, complete resection is difficult and at times technically impossible or undesirable with joint function preservation and quality of life in mind. In patients with locally advanced TGCT or (multiple) recurrence(s), systemic therapies targeting the *CSF1/CSF1*R axis have been investigated; less potent drugs as nilotinib and imatinib[22, 23], and more specific inhibitors as emactuzumab (RG7155), pexidartinib (PLX3397) and cabiralizumab (FPA008). Emactuzumab (N=29) had an overall response rate of 86% (two patients with a complete response) and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months)[24]. In a randomized, placebo-controlled phase 3 study, pexidartinib showed an improved overall response rate by RECIST: 39% in the pexidartinib-group (N=61) and 0% of placebo-group (N=59), after median six months follow-up[25]. The preliminary results with cabiralizumab (N=22) are consistent, with radiographic response and improvement in pain and function in five out of 11 patients 28[15]. However, long term efficacy data have not yet been reported with these newer agents.

Patient inclusion for these trials is very heterogeneous. A strict patient selection is desirable, to accurately evaluate effect of these treatments. At present, patient selection for trial inclusion is established by preference of treating physician and might differ per centre. Defining more aggressive TGCT subtypes and including these uniformly defined patients into trials would more adequately investigate the effect and toxicities of treatment[26]. In this study, we propose to include patients defined with 'severe diffuse' TGCT subtype. Monitoring the effect of systemic therapy also benefits from clear agreements on parameters.

Uniform MR descriptions are of utmost importance for clinical and research purposes. Thus far, no well-defined tumour parameters exist. Definition of unambiguous MR criteria is challenging,

because of the rarity of the tumour and small number of heterogeneous cases, variety of joints involved, different disease severity as well as several treatment modalities[2, 27]. So far, MR imaging has shown to be the best discriminating method to evaluate TGCT[4, 28]. In our study, six objective clinically relevant MR parameters were defined in relation to anatomical or surgical landmarks. According to our exclusion criteria for the development of the severity classification, parameters cartilage covered bone invasion and neurovascular involvement showed inadequate number of presence and were therefore not used. However, in larger case series these two parameters might correlate with more aggressive disease and hence a higher recurrence rate.

To date, no radiology-based TGCT severity classification exists. Subdividing between localized- and diffuse-TGCT seems an oversimplification that fails to estimate differences in recurrent rates for individual patients. Murphey et al. presented an extensive review of different TGCT features on several imaging techniques, without relating these features to disease severity, treatment or recurrences[4]. Van der Heijden et al. further sub-classified diffuse-TGCT affecting the knee in 30 patients into mild or severe, without linking to recurrent disease. Mild diffuse-TGCT was defined as involvement of either anterior or posterior compartment of the knee, with the cruciate ligaments as boundary. Severe diffuse-TGCT was defined as involvement of both compartments, with or without extra-articular extension[9]. In contrast to most literature, we selected a homogeneously treated patient population to develop four severity subtypes, by only including patients initially treated with an open synovectomy.

In line with most papers, especially papers on trial medication, and based on clinical practice, we included all large joints to sub-classify disease severity for TGCT. Prior research did not show a (significant) difference in recurrence rates for both localized and diffuse disease when comparing the knee with other joints[6, 27, 29, 30]. A recent TGCT incidence calculation study showed a predominance of the knee in 46% in localized- and 64% in diffuse-type (excluding digits)[5], in line with our overrepresentation of the knee of 70%. In the future, a TGCT severity classification focused on the knee would contain more detailed knee-specific MR parameters and equal treatment approaches.

Limitations to this study: primary, the resulting HRs had wide confidence intervals, indicating low

precision in the estimates. This is likely related to the relatively small sample size, given that the patients were divided into several groups based on the MR parameters. Secondly, because of the relatively small number of recurrences in severity subtypes mild localized (n 1) and severe localized (n 3), Hazard Ratios may be unreliable. Therefore, it was not feasible to estimate a cox model and to generate a true prediction model. Additionally, localized-TGCT is known to have few recurrences and often remains without clinical complaints after resection. In both sarcoma centres, patients are therefore discharged from follow-up after the first follow-up post-surgery and requested to return again when clinical complaints present. In our analyses, 31 localized-type patients were censored at date of last clinical follow-up within the first two years in survival curve (*figure 4*). Less often, patients with diffuse-type have also lacked follow-up (13 censored first two years). It could be assumed that these patients did not have complaints and recurrent disease. Furthermore, in study part two (establishing TGCT subtypes), newest included MR scans originated from 2015. These cases had a maximum follow-up of two years. Since it is known that local recurrence might develop years after initial surgery[2, 11, 29], in our study a median of 29.5 in moderate diffuse and 22.0 months in severe diffuse-TGCT subtypes, underestimation of recurrence free survival could be present. Finally, even though quite a large number of MR scans (174) were used in development of the severity classification, in larger case-series including long follow-up time, it might be possible to differentiate further in disease severity and assess additional subtypes.

To conclude, in reporting TGCT affecting large joints on MR imaging, six parameters are helpful in discriminating disease extent. Patients can be accurately monitored by using these MR parameters. With respect to recurrence, a combination of four MR parameters classifies patients into one of four severity subtypes, presented with distinct recurrence free survival rates. In the era of personalized medicine, treatment is individualized for each patient depending on the extent of disease. Because histopathological prognostic factors are lacking, sub-classification of TGCT on MR imaging is a potential tool to stratify future patient prognosis and identify candidates for targeted therapies, thereby aiding with the decision in daily practice.

Supplementary data

Supplementary data related to this article can be found at
https://doi.org/10.1016/j.suronc.2018.07.002

Appendix

TGCT MR parameters, affecting large joints, in therapy naïve primary TGCT patients

Agreement:

- Involvement of a structure: when signal intensity is changed to TGCT signal intensity, this structure is considered to be involved with TGCT and to be scored.
- When involvement of a structure is unclear: choose **'structure involved'** (when in doubt; over-scoring, not under-scoring).

MI parameters

1. **TGCT-type**
   - ***Localized-type***[†]: well circumscribed nodular lesion at synovial lining of bursa, joint or tendon sheath
   - ***Diffuse-type***[††]: multinodular lesion involving a larger part or all of the synovial lining
2. **Articular involvement**
   - ***Intra-articular***[$]: inside synovial lining of joint
   - ***Extra-articular***[$$]: outside synovial lining of joint
   - ***Both intra- and extra-articular***
3. **Cartilage-covered bone invasion**
   - ***Yes***: clear invasion of bone *invading* cartilage; *not only* touch cartilage
   - ***No***: no bone invasion or solely bone-usuration or bone invasion *not* cartilage-covered
4. **Muscular/tendinous tissue involvement***
   - ***Yes***: involvement of muscular/tendinous tissue or >180 degrees encasement of tendon/muscle
   - ***No***: no involvement or encasement of tendon/muscle
5. **Ligament involvement****
   - ***Yes***: involvement of ligament or >180 degrees encasement of ligament
   - ***No***: no involvement or encasement of ligament

6. **Neurovascular structure involvement**[#]
    - ***Yes***: encasement >180 degrees of important nerves and/or vessels
    - ***No***: no encasement of nerves or vessels

[†] **Localized-type**: be careful to always classify one nodular lesion as localized-type. Also when one nodular lesion is reeved by another structure (it might seem like additional nodules).

[††] **Diffuse-type**: be careful to always classify diffuse-type when two or more tendon sheaths or muscles are involved. Do not classify these cases as one large nodule.

[$] **Intra-articular**: concerning the knee: cruciate ligaments are counted as intra-articular structures as the synovial lining of the ligaments should be considered intra-articular.

[$$] **Extra-articular**: concerning the knee: Hoffa

* **Muscular/tendinous tissue involvement:** concerning the knee: also account parameter when solely popliteus muscle involvement is present.

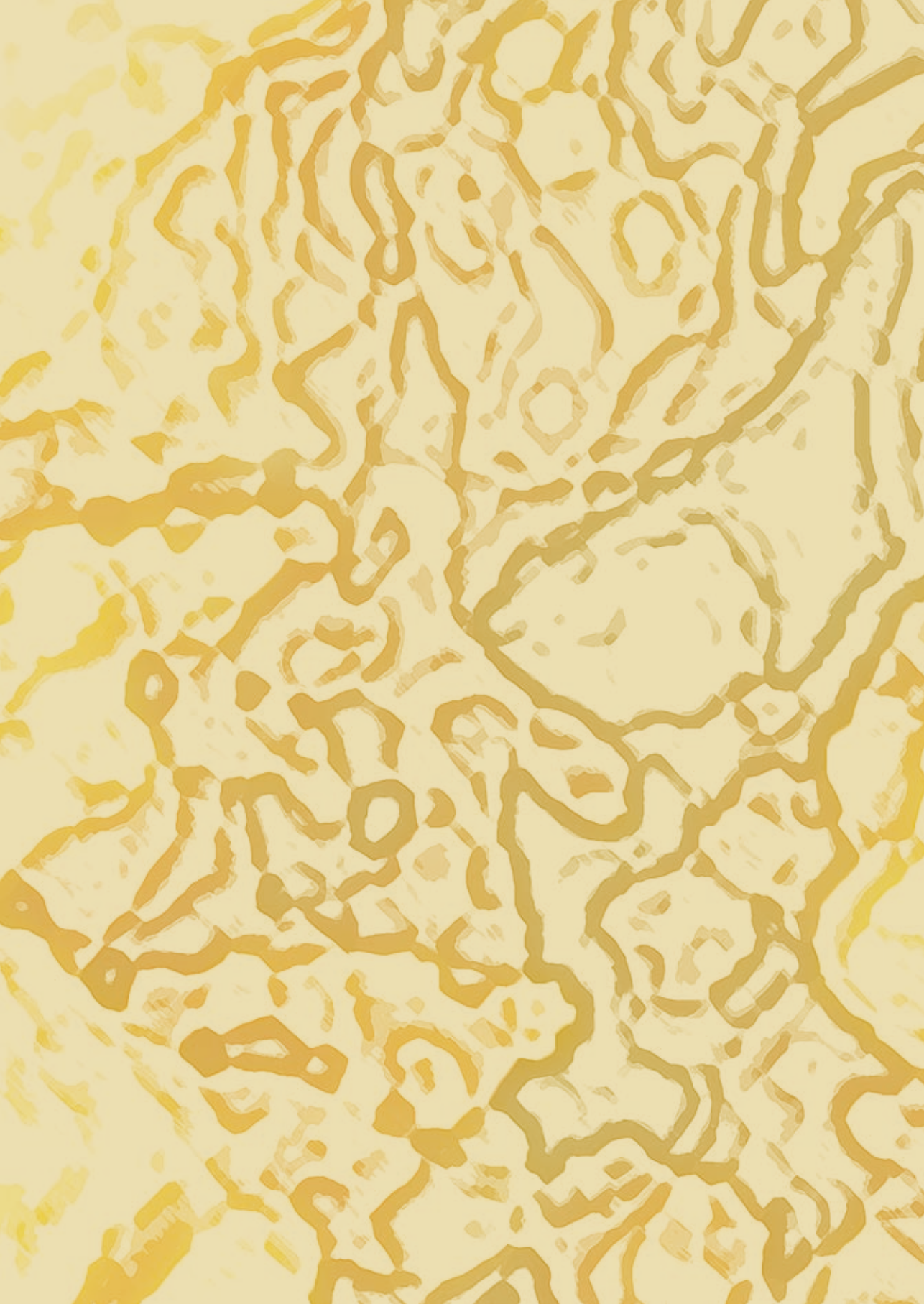
** **Ligament involvement:** TGCT involvement of ligament, in hand or foot: account parameter when intra-tarsal/digital ligaments, ankle syndesmose and plantar fascia are involved. TGCT concerning the knee with ligament involvement: anterior and/or posterior cruciate ligament, and/or medial/lateral collateral ligament.

[#] **Neurovascular involvement**: in hand or foot: also digital or sensible nerves

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. Frassica FJ, Khanna JA, McCarthy EF. The role of MR imaging in soft tissue tumor evaluation: perspective of the orthopedic oncologist and musculoskeletal pathologist. Magnetic resonance imaging clinics of North America. 2000;8(4):915-27.
4. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
5. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
6. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
7. Tyler WK, Vidal AF, Williams RJ, Healey JH. Pigmented villonodular synovitis. The Journal of the American Academy of Orthopaedic Surgeons. 2006;14(6):376-85.
8. Mastboom MJL, Verspoor FGM, Gelderblom H, van de Sande MAJ. Limb Amputation after Multiple Treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch Cases. Case reports in orthopedics. 2017;2017:7402570.
9. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
10. Verspoor FG, Hannink G, Scholte A, Van Der Geest IC, Schreuder HW. Arthroplasty for tenosynovial giant cell tumors. Acta orthopaedica. 2016;87(5):497-503.
11. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
12. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
13. Tap WD, Wainberg ZA, Anthony SP, Ibrahim PN, Zhang C, Healey JH, et al. Structure-Guided Blockade of *CSF1*R Kinase in Tenosynovial Giant-Cell Tumor. The New England journal of medicine. 2015;373(5):428-37.
14. Ries CH, Cannarile MA, Hoves S, Benz J, Wartha K, Runza V, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer cell. 2014;25(6):846-59.
15. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-*CSF1*R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). ASCO conference 2017. 35 (15 Supplement 1).
16. Hughes TH, Sartoris DJ, Schweitzer ME, Resnick DL. Pigmented villonodular synovitis: MRI characteristics. Skeletal radiology. 1995;24(1):7-12.
17. Nordemar D, Oberg J, Brosjo O, Skorpil M. Intra-Articular Synovial Sarcomas: Incidence and Differentiating Features from Localized Pigmented Villonodular Synovitis. Sarcoma. 2015;2015:903873.

18. Poletti SC, Gates HS, 3rd, Martinez SM, Richardson WJ. The use of magnetic resonance imaging in the diagnosis of pigmented villonodular synovitis. Orthopedics. 1990;13(2):185-90.
19. Wang C, Song RR, Kuang PD, Wang LH, Zhang MM. Giant cell tumor of the tendon sheath: Magnetic resonance imaging findings in 38 patients. Oncology letters. 2017;13(6):4459-62.
20. Altman D. Practical Statistics for Medical Research. Hall/CRC Ca, editor 1990.
21. 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.
22. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
23. 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.
24. Cassier PA, Italiano A, Gomez-Roca CA, Le Tourneau C, Toulmonde M, Cannarile MA, et al. *CSF1*R 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(8):949-56.
25. Tap WD GH, Stacchiotti S, Palmerini P, Ferrari S, Desai J, Bauer S, Blay JY, Alcindor T, Ganjoo KN, Martin Broto J, Ryan CW, Edward Shuster DE, Zhang L, Wang Q, Hsu H, Lin PS, Tong S, Wagner AJ, editor Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference; 2018; Chicago.
26. Gounder MM, Thomas DM, Tap WD. Locally Aggressive Connective Tissue Tumors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(2):202-9.
27. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
28. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res. 2017;103(1S):S91-S7.
29. 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(2):210-7.
30. Barile A, Sabatini M, Iannessi F, Di Cesare E, Splendiani A, Calvisi V, et al. Pigmented villonodular synovitis (PVNS) of the knee joint: magnetic resonance imaging (MRI) using standard and dynamic paramagnetic contrast media. Report of 52 cases surgically and histologically controlled. La Radiologia medica. 2004;107(4):356-6.



Can increased symptoms of Tenosynovial Giant Cell Tumours during pregnancy be explained by a change in female sex hormones?

M.J.L. Mastboom[1], F.G.M. Verspoor[2], R. Planje[1], H.W.B. Schreuder[2], M.A.J. van de Sande[1]

Submitted.

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

Abstract

Objective

Tenosynovial Giant Cell Tumours (TGCT), both localized- and diffuse-type, are rare, mono-articular neoplasms, with a slight female predominance. The clinical behaviour between patients differs greatly. This study aims to evaluate the increase in TGCT-related symptoms during pregnancy and the influence of female sex hormones thereon.

Methods

In a prospective-cohort-study, TGCT-related symptoms before and during pregnancy were evaluated in two Dutch centres and by use of the largest online TGCT patient-support group. Second, as a proxy for disease activity the combined TGCT-database of two sarcoma-centres in the Netherlands (N=455) was used to compare recurrence free survival rates between the sexes (during and after fertile-age). Finally, female hormonal receptor status was evaluated with immunohistochemistry on TGCT-specimens from eight women (18-50 years).

Results

Forty percent (8/20) of women with diffuse-TGCT of lower extremity reported an increase in TGCT-related symptoms during pregnancy, predominantly an increase in swelling (62%). Mean VAS-score on symptoms increased between 5.9 (SD 2.1) before pregnancy to 6.6 (SD 1.7) during pregnancy. Similar results were reported in the patient-support group.

No differences were found in recurrence free survival rates, between both sexes, (localized- ($p=0.206$ ≤50 years, $p=0.935$ >50 years); diffuse-type ($p=0.664$ ≤50 years, $p=0.140$ >50 years)), neither in pre- versus post-menopausal women (localized- ($p=0.106$); diffuse-type($p=0.666$)). In all examined localized- and diffuse-TGCT tissue-samples, oestrogen or progesterone hormone-receptor staining was negative.

Conclusion

An increase in TGCT-related symptoms during pregnancy was reported. This could not directly be linked to female sex hormones as hormone receptors were missing histopathologically. Recurrence free survival rates were comparable, making a relation with female sex hormones improbable.

Background

Tenosynovial Giant Cell Tumour (TGCT), previously known as Pigmented Villonodular Synovitis (PVNS), is a rare, benign neoplasm arising from synovial joints, tendon sheaths and bursae. It affects a relatively young population aged 30-50 years and has a slight female predominance (male:female 1:1.5)[1-3]. Two subtypes are distinguished. The localized-type is defined as a single nodule, affecting only a distinct area of the synovium with an incidence rate of 10.2 per million person-years (excluding digits). The diffuse-type is known to be more aggressive and involves a larger part or the entire synovial lining. It has an incidence rate of 4.1 per million person-years[4, 5]. TGCT is a mono-articular disease predominantly affecting weight-bearing joints; knee (46% and 64%), hip (1% and 9%), and ankle (5% and 10%) for localized- and diffuse-type, respectively[3, 4]. Pain, swelling, limited range of motion and stiffness of the affected joint are the most common symptoms[6-9]. Rapid diagnosis is difficult due to these unspecific symptoms and since most physicians are unfamiliar with the disease[5, 10-12]. Arthroscopic or open synovectomy is the standard of care[1, 2, 5, 8]. After surgical treatment, localized-type in the knee generally follows a favourable course with an average recurrence rate of 4 to 6% after resection (with variable follow-up). In contrast, diffuse-type in the knee presents with multiple recurrences, on average 14% to 40% after surgical treatment[5].

In TGCT, answers on everyday questions are lacking: e.g. do hormone-based anticonceptiva influence my disease? Does pregnancy influence the clinical behaviour of TGCT? In the outpatient clinic and on online TGCT patient fora, an increase in TGCT-related symptoms during pregnancy is observed. In healthy pregnant women, joint pain in the knee and hip are frequently reported[13, 14]. This pain is not only attributed to the additional weight. Elevated female sex hormones (oestrogen, progesterone and the oestrogen-dependent relaxin) are known to weaken soft tissue structures, resulting in increased joint laxity during pregnancy, joint instability and lower extremity dysfunction[13, 15, 16]. To our knowledge, only two case-reports of two pregnant women with both localized-TGCT exist (*supplementary material*). The first case report described a patient diagnosed with TGCT six months after pregnancy completion, as the patient was misdiagnosed with chondromalacia patellae[17]. The second patient presented with an acute onset of knee pain during first semester of pregnancy. It was hypothesized that pregnancy-related changes triggered torsion or bleeding of the tumour, leading to this acute presentation[18]. Elevated levels of oestrogen

and progesterone receptors have been identified in giant cell tumour of bone, dermatofibroma protuberans and malignancies of breast, endometrium, ovary, prostate, colon. Hormone receptor positive tumours show a better prognosis[19-24]. The presence of female sex hormone receptors in TGCT is unknown.

This study aims to evaluate patient reported TGCT-related symptoms before and during pregnancy in two different patient populations. Influences of sex specific hormones and female fertile life phase specific hormones are determined by comparing recurrence free survival rates between the sexes and pre- versus post-menopausal women. Finally, presence of female sex hormonal receptor-status in available tumour tissue is assessed.

Methods

Questionnaires in two sarcoma centres and a patient-support group

Patients with diffuse-TGCT were included, since diffuse-TGCT is a more widespread and extensive disease, including more clinical complaints and higher recurrence rates, compared with localized-TGCT.

Two sarcoma centres

One-hundred sixty-two female patients with histopathologically proven diffuse-TGCT were extracted from the combined Dutch TGCT-database (Leiden University Medical Centre (LUMC) N=92 and Radboud University Medical Centre (RUMC) N=70) (*figure 1*)[25]. Excluded were seventy-four patients <18 years or >50 years, non-weight bearing upper-extremity TGCT (elbow, wrist) or temporomandibular localization. The remaining 88 patients were invited to complete the TGCT-questionnaire. Incomplete questionnaires were unsuitable for analysis (N=26). Finally, sixty-two questionnaires of patients with diffuse-TGCT of lower extremities were included.

The comprehensive TGCT-hormone questionnaire contained questions on patient- and tumour-characteristics, initial TGCT-symptoms (prior to primary treatment), current TGCT-symptoms (symptoms at time of questionnaire completion) and TGCT-symptoms before and during pregnancy. To quantify TGCT-related symptoms, Visual Analogue Scale (VAS) questions were included, ranging from 0 (no symptoms) to 10 (worst symptoms) (*supplementary material*). The pregnancy questions were completed for the first pregnancy (>6 months) after TGCT-diagnosis

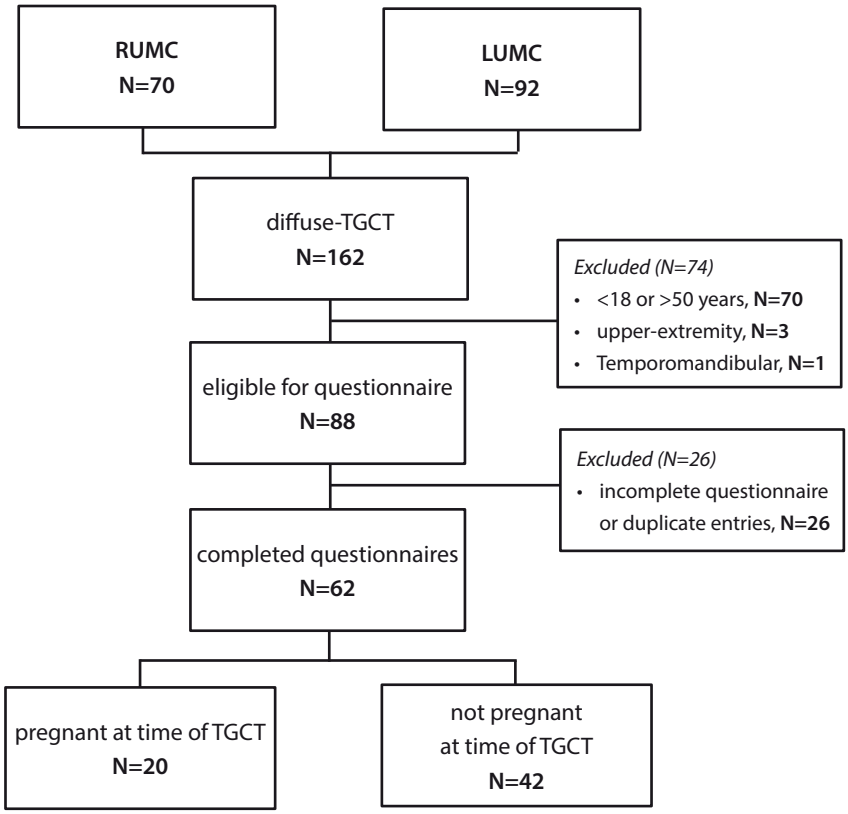


Figure 1 Inclusion flowchart of diffuse-TGCT women, treated in one of two sarcoma centres.
RUMC, Radboud University Medical Centre; LUMC, Leiden University Medical Centre.

and questions were answered regarding the TGCT affected joint.

Patient-support group

Previously, an international crowdsourcing study was conducted in 337 patients to evaluate impact of TGCT on daily living[26]. An e-survey was distributed in the largest, online support group for TGCT-patients: the closed Facebook group 'PVNS is pants!!'. This study contained 129 women with diffuse-TGCT of lower extremity, aged between 18 and 50 years (*figure 2*). Besides patient- and tumour characteristics, the e-survey contained validated questionnaires on physical function and quality of life. Furthermore, questions on TGCT-related symptoms and intensity of symptoms,

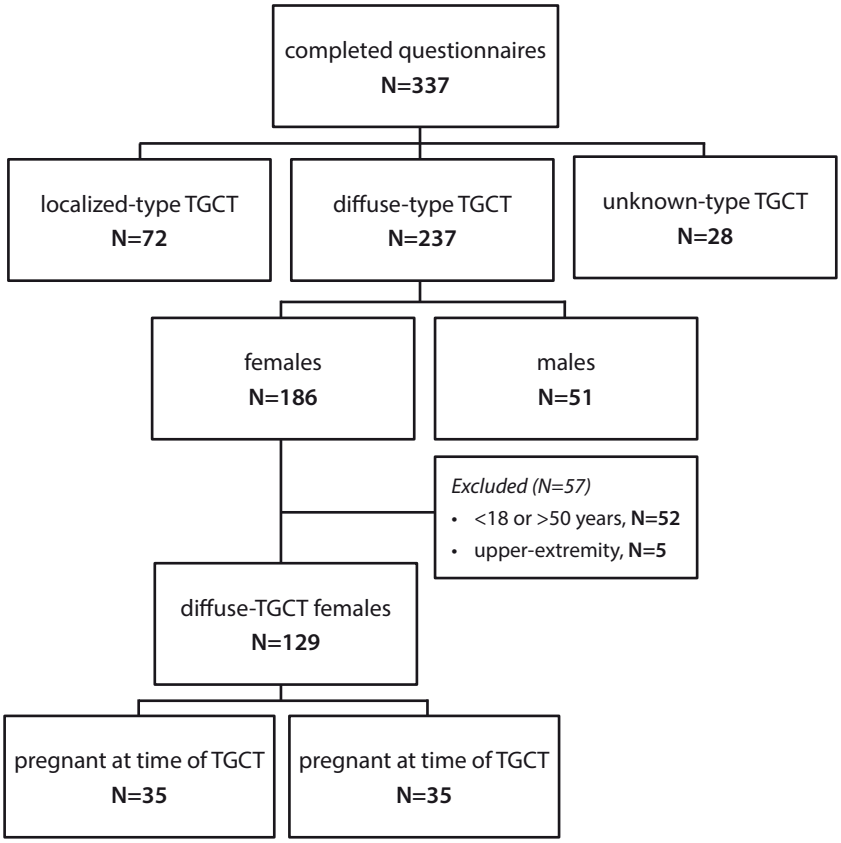


Figure 2 Inclusion flowchart of the patient-support group.

before and during pregnancy were included for women only. These questions were not previously published (*supplementary material*). In more than one pregnancy, questions were answered for the pregnancy that most affected the TGCT-related symptoms.

NetQuestionnair (NetQ), an online, professional survey software supported by the LUMC, was used to distribute and complete the questionnaires for the two sarcoma centers (eight months available) and the patient-support support group (six months available). Both questionnaires were approved by the institutional review board from the LUMC (comprehensive TGCT-questionnaire study registration number P13.029 and patient support group e-survey study P16.232). NetQ

automatically captured questionnaire-answers into an SPSS 23 file (Statistical Package for Social Sciences statistics (SPSS®) Version 23 (Chicago, IL, USA)), only accessible to TGCT researchers. Unique site visitors were determined by IP addresses. When duplicate entries were detected, the most recent one was included. Statistical analyses were mainly descriptive. To verify that diffuse-type women with increased TGCT-symptoms during pregnancy were comparable with diffuse-type women not pregnant during TGCT in the patient support group, chi-square tests were used for TGCT localization (knee versus hip, ankle and foot), initial surgery (arthroscopy versus open synovectomy), recurrence (yes versus no) and total number of surgeries (1 surgery versus ≥2 surgeries). Independent t-tests were used to compare continuous scores of validated questionnaires on physical function and quality of life.

Comparison of recurrence free survival rates

Recurrence was defined as new disease presence after synovectomy or growing residual disease (diagnosed on follow-up MR scan). To determine influences of sex specific hormones and female fertile life phase specific hormones, recurrence free survival rates between the sexes and pre- versus post-menopausal in women were assessed as a proxy. The combined database of two sarcoma centres (LUMC and RUMC) in The Netherlands (N=455, 262 diffuse-TGCT) was used[25]. This dataset contained all consecutive patients surgically treated for histopathologically proven TGCT between 1990 to 2017. Fertile life phase was defined between 16 and ≤50 years at primary diagnosis, since median age at natural menopause ranges between 49 and 52 years[27].

Using SPSS®, recurrence free survival rate after index operation was calculated through Kaplan-Meier survival method and log rank test in male and female patients ≤50 years and >50 years for localized- and diffuse-type separately. Similarly, recurrence free survival rates in pre- versus post-menopausal women were compared.

Female hormone-receptors in TGCT

Immunohistochemistry was performed on paraffin-embedded pathological specimens of histopathologically proven TGCT tissue, obtained from eight randomly selected women between 18 and 50 years to determine female hormone receptor status. All samples were of primary resected localized- (N=4) or diffuse-TGCT (N=4), located in the lower extremity (hip, knee, ankle). Monoclonal Rabbit Anti-Human Oestrogen receptor α and monoclonal mouse anti-human

progesterone receptor were used (*supplementary material*). Hormone receptor status was assessed in the LUMC by a dedicated pathologist, specialized in bone and soft tissue tumours. Slides were verified with positive controls of women with oestrogen or progesterone receptor positive breast cancer.

Results

Questionnaires in two sarcoma centres and a patient-support group

Two sarcoma centres

Sixty-two women with diffuse-TGCT of the lower extremities ((knee 50 (81%), hip 6 (9%) and ankle/foot 6 (9%)) with a median age at diagnosis of 30 (IQR 25-38) years completed the comprehensive Dutch questionnaire (*Table 1*). Twenty (32%) patients were pregnant after being diagnosed with TGCT. Eight (40%) of these patients self-reported an increase, two (10%) a decrease of symptoms and 10 (50%) continued at the same level (*Table 2*). TGCT-related symptoms included pain, swelling and limited range of motion of the affected joint, swelling was predominantly increased (62%) (*Table 3*). In patients with increasing symptoms, mostly during second or third trimester (5/8 (63%)) of pregnancy, mean VAS score increased from 5.9 (SD 2.1) before pregnancy to 6.6 (SD 1.7) during pregnancy.

Patient-support group

In 129 women, median age at time of diagnosis was 30 (IQR 24-39) years and TGCT was mostly located in the knee (93 (72%)) (*Table 1*). Thirty-five (27%) women had TGCT during pregnancy. Twenty-three (66%) pregnant women stated an increase, 3/35 (9%) a decrease and 9/35 (26%) did not experience a difference in symptoms during pregnancy. Of all reported symptoms, swelling (57%) of the associated joint increased the most. Additional symptoms included pain, limited range of motion and stiffness (*Table 3*). Self-reported intensity of TGCT-related symptoms after pregnancy was compared with reported intensity of symptoms before pregnancy; in 10/26 (38%) intensity increased, 6/26 (23%) intensity decreased and in 10/26 (38%) intensity continued at a comparable level. No differences were detected in patient- and tumour-characteristics in women with increased TGCT-symptoms during pregnancy compared with women not pregnant during TGCT (*Supplementary material; Table 1*).

Table 1 Tumour- and patient-characteristics of female diffuse-TGCT patients, from two sarcoma centres* and a patient-support group**.

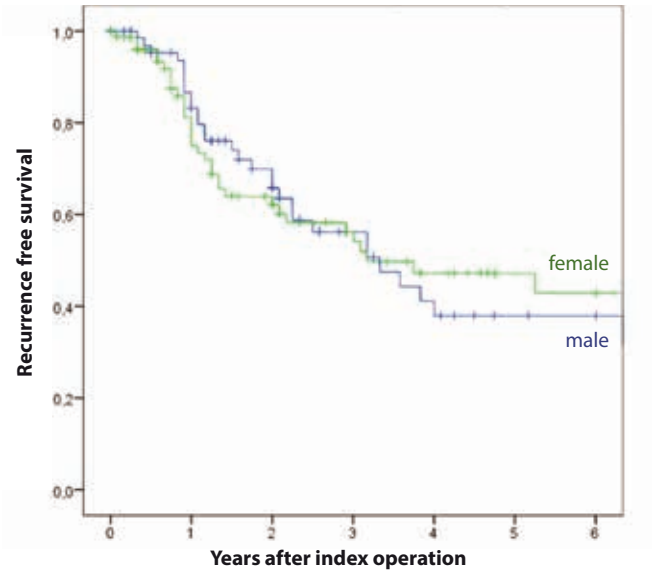
	Sarcoma centres n (%)	Support group n (%)
Total number of women	62 (100)	129 (100)
TGCT-localization		
Knee	50 (81)	93 (72)
Hip	6 (9)	18 (14)
Ankle/Foot	6 (9)	18 (14)
Initial symptoms		
Pain	38 (61)	109 (85)
Swelling	50 (81)	103 (80)
Limited range of motion	32 (52)	83 (64)
Stiffness	22 (36)	74 (57)
Current symptoms		
Pain	36 (58)	98 (76)
Swelling	23 (37)	76 (59)
Limited range of motion	31 (50)	88 (68)
Stiffness	22 (36)	84 (65)
Pregnant >6 months		
Total	20 (32)	35 (27)
Increased symptoms	8/20 (40)	23/35 (66)
Decreased symptoms	2/20 (10)	3/35 (9)
	Median (IQR)	**Median (IQR)**
Age at time of diagnosis (years)	30 (25-38)	30 (24-39)
Age at time of questionnaire (years)	38 (32-43)	38 (30-45)

Initial symptoms, symptoms of the affected joint prior to primary treatment; Current symptoms, symptoms at time of questionnaire completion. *Leiden University Medical Centre (LUMC) and Radboud University Medical Centre (RUMC). **Largest, online patient support group for TGCT-patients: the closed Facebook group 'PVNS is pants!!'

Table 2 Patient- and tumour characteristics of eight women with increased diffuse-TGCT related symptoms during pregnancy.

Patient	Joint	Age at pregnancy (years)	Time of TGCT diagnosis before pregnancy[$] (months)	TGCT treatments prior pregnancy	Most prominent increasing symptom during pregnancy	TGCT treatments after pregnancy	Last follow-up status[++]
1	Hip	23	84[+]	OS + ^{90}Yttrium, OS + cryosurgery	Limited ROM		Residual disease
2	Knee	29	36	2x OS two-staged, OS one-staged + nilotinib + RT 56 Gy	Swelling	EPR	NED
3	Knee	30	24[$$]	AS	Swelling	AS	NED
4	Knee	31	96		Limited ROM	AS, OS*	NED, osteo-arthritis
5	Knee	34	12[$$$]	AS	Swelling	PLX, OS two-staged	Too shortly after OS
6	Knee	34	84	AS	Swelling	2012 OS	Residual disease
7	Ankle	37	2		Pain	OS during pregnancy	Residual disease
8	Knee	38	6		Swelling	OS	NED

TGCT, tenosynovial giant cell tumour; AS, arthroscopic synovectomy; OS, open synovectomy; PLX, PLX3397/ pexidartinib; EPR, endoprosthetic reconstruction; Limited ROM, limited range of motion; NED, no evidence of disease. [$]Pregnancies were uncomplicated, unless otherwise specified. [+]Pregnancy was prematurely terminated because of major pain complaints of hip. [++]Last follow-up >2 years since last treatment, unless otherwise specified. [$$]B12 deficiency, right after pregnancy locking of affected knee. [$$$]Had to stop TNF-α-inhibitor (indicated for oligoarthritis and Crohn's disease). *Complication: abscess and sepsis.



numbers at risk

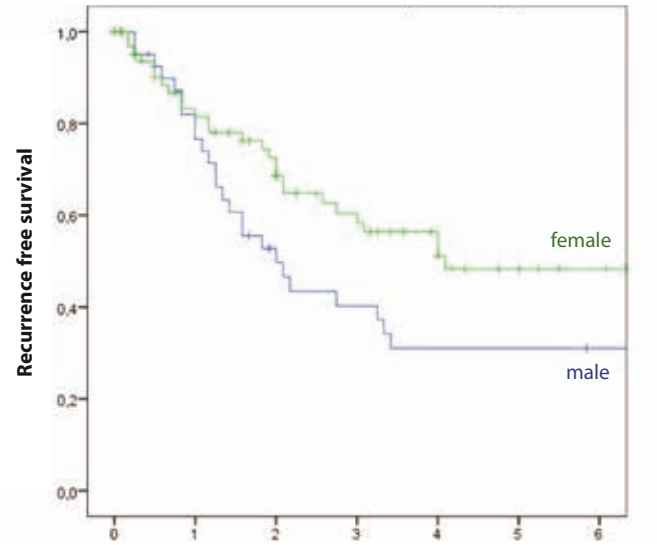
male	71	49	32	20	12	8	6
female	84	51	34	25	18	11	9

Figure 3 Recurrence free survival curve in 155 diffuse-TGCT patients ≤50 years* (p=0.664).
*Age at primary diagnosis

Table 3 Most prominent increased TGCT-related symptoms during pregnancy.

	Sarcoma centres n (%)	Support group n (%)
Pain	1 (13)	5 (22)
Swelling	5 (62)	13 (57)
Limited range of motion	2 (25)	3 (13)
Stiffness	0	2 (8)
Total increased symptoms	8 (100)	23 (100)

All patients were requested to indicate which TGCT-symptom increased most during pregnancy. This table presents self-reported increased symptoms in 8/20 (40%) and 23/35 (66%) women with diffuse-TGCT from two Dutch sarcoma centres and the patient-support group, respectively. In both populations swelling was the most prominent symptom.



numbers at risk

male	42	30	17	13	10	10	9
female	65	47	37	28	21	13	11

Figure 3 (*continued*) Recurrence free survival curve in 107 diffuse-TGCT patients >50 years* (p=0.140).
*Age at primary diagnosis

Comparison of recurrence free survival rates

Female recurrence free survival rates were comparable to male rates for localized-type (log rank p=0.206 ≤50 years, p=0.935 >50 years) and diffuse-type (log rank p=0.664 ≤50 years, p=0.140 >50 years) (*figure 3*). Similarly, in women during and after fertile age, recurrence free survival rates were comparable for localized-type (log rank p=0.106) and diffuse-type (log rank p=0.666).

Female hormone-receptors in TGCT

All eight localized- and diffuse-TGCT tissue samples were oestrogen or progesterone hormone receptor negative. Further evaluation of additional patient samples was therefore deemed unnecessary.

Discussion

This is the first study to evaluate hormonal influences on the clinical presentation of Tenosynovial Giant Cell Tumour (TGCT). An increase in TGCT-related symptoms during pregnancy was reported, in particular swelling of the affected joint. Recurrence free survival rates were comparable for both sexes as well as for pre- versus postmenopausal women. Oestrogen and progesterone-receptors were not present with immunohistochemistry in TGCT tissue.

In the current study, 56% (31/55) of pregnant patients reported an increase in TGCT-related symptoms and a minority reported a decrease in these symptoms (9%; 5/55). Swelling of the affected joint was self-reported as the most prominent symptom during pregnancy. Since TGCT is a mono-articular disease, this swelling is not comparable with the clinical (bilateral) oedema accompanying a majority of (healthy) pregnancies[14]. The increase in symptoms was mainly present during second and third trimester of pregnancy. Similar, healthy pregnancy is associated with an increase in lower extremity symptoms during these trimesters[14]. A valid question would be why an increase in mono-articular TGCT swelling during pregnancy would present in these later stages of pregnancy. Since growth hormone is already present five weeks after conception, the question is whether growth hormone influences TGCT-related joint swelling. The experienced increase in disease burden might be caused by progressive disease, but is more likely based on increased effusion. Although pregnancy seems to provoke an increase in TGCT-related symptoms, this might be coincidental according to subjective complaints, recall bias and focus on the affected joint.

In general, a multifactorial aetiology is responsible for lower-extremity symptoms during healthy pregnancy[28]. First; biomechanical changes, including the anterior shift of the center of gravity[13], the extra bodyweight[29] and a different gait-pattern due to an increased pressure on the lateral side of the foot[30], are responsible for lower limb and functional knee pain in pregnant women. As a consequence, a decrease in physical functioning is reported during progression of pregnancy, also in healthy women[15]. Second; relaxation of joints is a physiologic process associated with pregnancy. This increased joint-laxity and weakened soft tissue structures is mainly based on the pregnancy initiated elevated levels of the hormone relaxin[31]. Third; discontinuation of medication considered unsafe for the unborn child, for instance non-steroidal anti-inflammatory drugs (NSAID's) or tumour necrosis factor-blockers (TNF-α-inhibitors), might affect the experience of TGCT-symptoms. Additional factors of possible influence on TGCT-related symptoms are nausea/fatigue, stress, emotional/personal problems and anxiousness for additional tasks after pregnancy. The increased TGCT-related symptoms during pregnancy might also be attributed to this multifactorial aetiology for lower extremity symptoms during healthy pregnancy. One (1/8(13%)) patient with increased symptoms interrupted her TNF-α-inhibitor (indicated for oligoarthritis and Crohn's disease) (*Table 2; patient 5*).

To test the hypothesis that female sex hormones influence TGCT, we compared recurrence rates for both sexes. Since oestrogen and progesterone in women decline after fertile age, recurrence free survival rate analyses were performed for both sexes ≤50 and >50 years, without revealing a difference. In accordance with literature no differences in recurrence rates between male and female TGCT-patients were found[32]. To our knowledge, pre- versus post-menopausal analyses had not been performed before and yielded also no difference.

In all eight primary resected TGCT-tissues, oestrogen or progesterone receptors were completely absent. This is a small sample size, although it is unlikely that positive female sex hormone status will be detected by evaluating additional specimens. Hormone-based anticonceptica or female hormone based treatments do not seem to influence the clinical behaviour of TGCT. Future research is recommended to find the cause of increased symptoms in TGCT during pregnancy and to contribute to possible new treatment modalities, e.g. growth-factor, ED-A fibronectin (expressed during embryogenesis) or changes in the auto-immune system.

Evaluation of hormonal influences in TGCT is challenging because of the rarity of the tumour and the heterogeneous patient population. Main limitation in our two questionnaire studies was participant recall bias. Information provided on a recall basis diminishes the accuracy of results. Preferably, an observational study would be performed, including a control group and radiographic evaluation of tumour severity before and after pregnancy. Furthermore, answers from the e-survey in the patient support group could be influenced by multicultural differences. Finally, while previous surgeries provoke deteriorated clinical outcome, treatments before pregnancy and treatment phase during pregnancy were not taken into consideration.

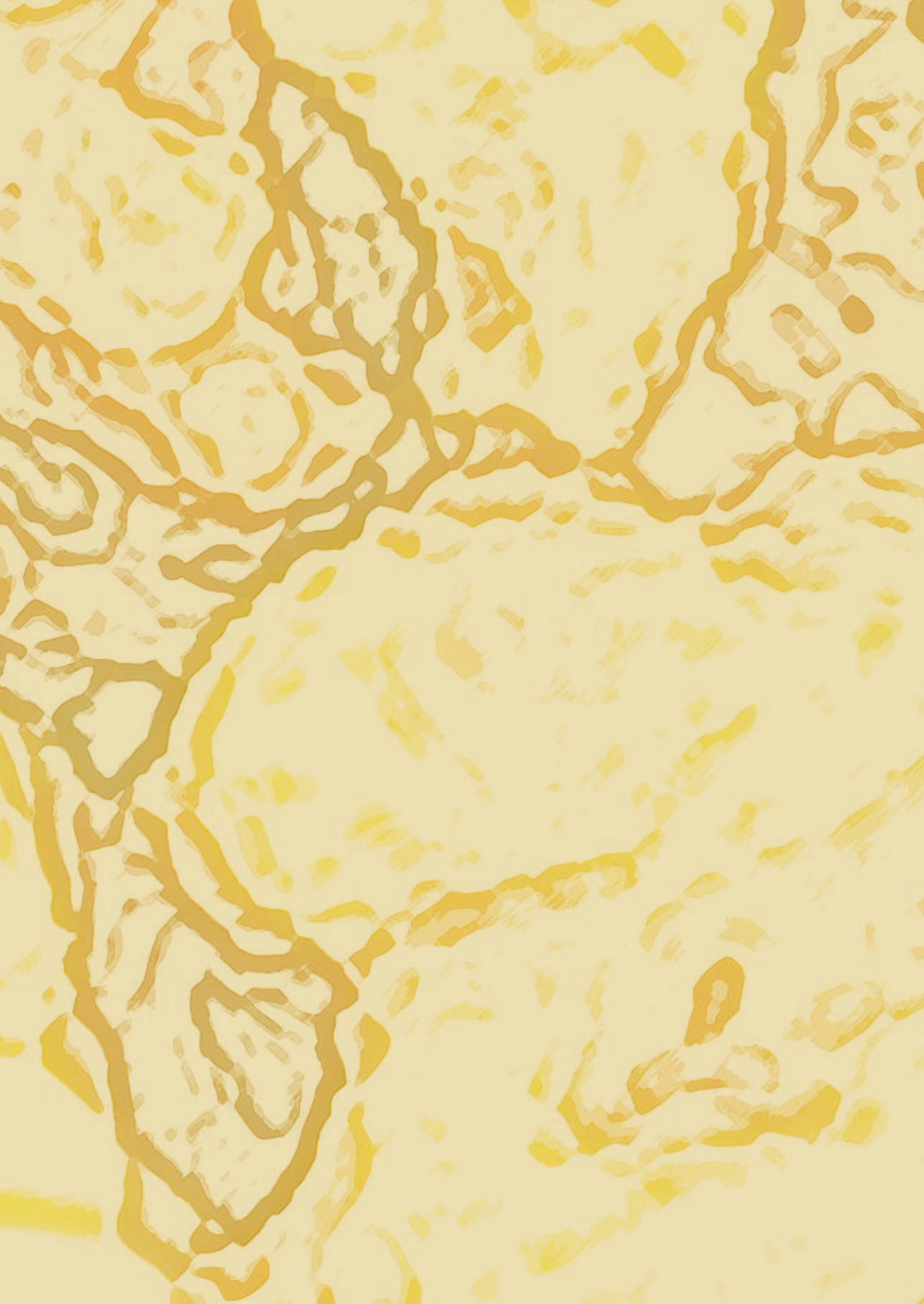
Conclusion

In conclusion, an increase in TGCT-related symptoms during pregnancy was reported in two different patient cohorts. This could not directly be linked to female sex hormones as hormone receptors were missing histopathologically. Recurrence free survival rates between both sexes and between pre- versus post-menopausal women were also comparable, making a causal relation with female sex hormones even more unlikely.

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
4. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
5. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
6. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
7. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
8. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
9. Zvijac JE, Lau AC, Hechtman KS, Uribe JW, Tjin ATEW. Arthroscopic treatment of pigmented villonodular synovitis of the knee. Arthroscopy. 1999;15(6):613-7.
10. Hufeland M, Gesslein M, Perka C, Schroder JH. Long-term outcome of pigmented villonodular synovitis of the hip after joint preserving therapy. Arch Orthop Trauma Surg. 2017.
11. Vastel L, Lambert P, De Pinieux G, Charrois O, Kerboull M, Courpied JP. Surgical treatment of pigmented villonodular synovitis of the hip. J Bone Joint Surg Am. 2005;87(5):1019-24.
12. Gonzalez Della Valle A, Piccaluga F, Potter HG, Salvati EA, Pusso R. Pigmented villonodular synovitis of the hip: 2- to 23-year followup study. Clin Orthop Relat Res. 2001(388):187-99.
13. Marnach ML, Ramin KD, Ramsey PS, Song SW, Stensland JJ, An KN. Characterization of the relationship between joint laxity and maternal hormones in pregnancy. Obstet Gynecol. 2003;101(2):331-5.
14. Vullo VJ, Richardson JK, Hurvitz EA. Hip, knee, and foot pain during pregnancy and the postpartum period. J Fam Pract. 1996;43(1):63-8.
15. Ostensen M, Fuhrer L, Mathieu R, Seitz M, Villiger PM. A prospective study of pregnant patients with rheumatoid arthritis and ankylosing spondylitis using validated clinical instruments. Ann Rheum Dis. 2004;63(10):1212-7.
16. Bridges AJ, Smith E, Reid J. Joint hypermobility in adults referred to rheumatology clinics. Ann Rheum Dis. 1992;51(6):793-6.
17. Edwards MR, Tibrewal S. Patello-femoral joint pain due to unusual location of localised pigmented villonodular synovitis-a case report. Knee. 2004;11(4):327-9.
18. Uslu M, Cetik O, Atasoy P, Eksioglu F, Engin M. Localized pigmented villonodular synovitis of the knee: acute onset in pregnancy. Rheumatol Int. 2006;26(11):1054-6.
19. Berger U, McClelland RA, Wilson P, Greene GL, Haussler MR, Pike JW, et al. Immunocytochemical determination of estrogen receptor, progesterone receptor, and 1,25-dihydroxyvitamin D3 receptor in breast cancer and relationship to prognosis. Cancer research. 1991;51(1):239-44.

20. Campbell-Thompson M, Lynch IJ, Bhardwaj B. Expression of estrogen receptor (ER) subtypes and ERbeta isoforms in colon cancer. Cancer research. 2001;61(2):632-40.
21. Ciocca DR, Puy LA, Fasoli LC. Study of estrogen receptor, progesterone receptor, and the estrogen-regulated Mr 24,000 protein in patients with carcinomas of the endometrium and cervix. Cancer research. 1989;49(15):4298-304.
22. Demertzis N, Kotsiandri F, Giotis I, Apostolikas N. Giant-cell tumors of bone and progesterone receptors. Orthopedics. 2003;26(12):1209-12.
23. Kieback DG, Press MF, Atkinson EN, Edwards GL, Mobus VJ, Runnebaum IB, et al. Prognostic significance of estrogen receptor expression in ovarian cancer. Immunoreactive Score (IRS) vs. Composition Adjusted Receptor Level (CARL). Anticancer research. 1993;13(6b):2489-96.
24. Parlette LE, Smith CK, Germain LM, Rolfe CA, Skelton H. Accelerated growth of dermatofibrosarcoma protuberans during pregnancy. Journal of the American Academy of Dermatology. 1999;41(5 Pt 1):778-83.
25. Mastboom MJL, Verspoor FGM, Uittenbogaard D, Schaap GR, Jutte PCH, Schreuder HWB, et al. Tenosynovial Giant Cell Tumors in Children: A Similar Entity Compared With Adults. Clinical Orthopaedics and Related Research. 2018.
26. Mastboom MJL, Planje R, van de Sande MAJ. The patient perspective on the impact of Tenosynovial Giant Cell Tumors on daily living. Crowdsourcing study on physical function and quality of life in 337 patients from 30 countries. Interactive Journal of Medical Research. 2018.
27. Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol. 1998;148(12):1195-205.
28. Ponnapula P, Boberg JS. Lower extremity changes experienced during pregnancy. J Foot Ankle Surg. 2010;49(5):452-8.
29. Spahn G, Lesser A, Hofmann GO, Schiele R. [Knee-related Pain Problems during Pregnancy Correlate with an Increase in Body Weight. Results of a Prospective Study]. Z Geburtshilfe Neonatol. 2015;219(5):213-9.
30. Nyska M, Sofer D, Porat A, Howard CB, Levi A, Meizner I. Planter foot pressures in pregnant women. Isr J Med Sci. 1997;33(2):139-46.
31. MacLennan AH, Nicolson R, Green RC, Bath M. Serum relaxin and pelvic pain of pregnancy. Lancet. 1986;2(8501):243-5.
32. 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(2):210-7.



chapter six

CHILDREN

Tenosynovial Giant Cell Tumours in children

a similar entity compared with adults

M.J.L. Mastboom[1], F.G.M. Verspoor[2], D. Uittenbogaard[1],
G.R. Schaap[3], P.C. Jutte[4], H.W.B. Schreuder[2], M.A.J. van de Sande[1]

Clin Orthop Relat Res. 2018 Sept;476(9):1803-1812

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Radboud, the Netherlands

[3] Orthopaedic Surgery, Academic Medical Centre Amsterdam, Amsterdam, the Netherlands

[4] Orthopaedics Surgery, University Medical Centre, Groningen, Groningen, the Netherlands

Abstract

Background

Tenosynovial Giant Cell Tumour (TGCT) is a rare, benign, monoarticular entity. Many case-series in adults are described, whereas TGCT is only incidentally reported in children. Therefore, its incidence rate and natural history in children are unknown.

Questions/purposes

(1) How many cases have been reported of this condition, and what were their characteristics?

(2) What is the standardized paediatric incidence rate for TGCT?

(3) Is there a clinical difference in TGCT between children and adults?

(4) What is the risk of recurrence after open resection in children compared with adults?

Methods

Data were derived from three sources: (1) a systematic review on TGCT in children, seeking sources published between 1990 and 2016, included 17 heterogeneous, small case-series; (2) the nationwide TGCT incidence study: the Dutch paediatric incidence rate was extracted from this nationwide study by including patients younger than 18 years of age. This registry-based study, in which eligible patients with TGCT were clinically verified, calculated Dutch incidence rates for localized and diffuse-type TGCT in a 5-year timeframe. Standardized paediatric incidence rates were obtained by using the direct method; (3) from our nationwide bone and soft tissue tumour data registry, a clinical data set was derived. Fifty-seven children with histologically proven TGCT of large joints, diagnosed and treated between 1995 and 2015, in all four tertiary sarcoma centres in The Netherlands, were included. These clinically collected data were compared with a retrospective database of 423 adults with TGCT. Chi square test and independent t-test were used to compare children and adults for TGCT type, sex, localization, symptoms before diagnosis, first treatment, recurrent disease, followup status, duration of symptoms, and time to followup. The Kaplan-Meier method was used to evaluate recurrence-free survival at 2.5 years.

Results

TGCT is seldom reported because only 76 paediatric patients (39 female), 29 localized, 38 diffuse, and nine unknown type, were identified from our systematic review. The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively. From our clinical data set, symptoms both in children and adults were swelling, pain, and limited ROM with a median time before diagnosis of 12 months (range, 1-72 months). With the numbers available, we did not observe differences in presentation between children and adults in terms of sex, symptoms before diagnosis, first treatment, recurrent disease, followup status, or median time to followup. The 2.5-year recurrence-free TGCT survival rate after open resection was not different with the numbers available between children and adults: 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%) in localized, respectively ($p = 0.527$) and 53% (95% CI, 35%-79%) versus 56% (95% CI, 49%-64%) in diffuse type, respectively ($p = 0.691$).

Conclusions

Although the incidence of paediatric TGCT is low, it should be considered in the differential diagnosis in children with chronic monoarticular joint effusions. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies being developed, future research should define the most effective treatment strategies for this heterogeneous disease.

Introduction

Tenosynovial Giant Cell Tumour (TGCT) is a benign, monoarticular entity. Two histologically identical but clinically different types are distinguished: localized and diffuse lesions[1]. This distinction can be made either on MRI or at the time of surgery. The localized type is defined by the World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone of 2013[2] as a well-circumscribed benign small lesion (*figure 1*). By contrast, the diffuse type, previously named pigmented villonodular synovitis (PVNS), shows unclear boundaries with extensive involvement of the entire synovial membrane and infiltrative growth through adjacent structures[1] (*figure 2*). The knee is the most common large joint affected by TGCT with 46% of localized and 64% of diffuse-type TGCTs affecting that joint; the hand and wrist are the next most common joints affected by the localized form, and the ankle and hip are the next most common joints affected by diffuse TGCT[3]. Delayed diagnosis is not uncommon as a result of different nonspecific clinical signs and symptoms[4, 5], and the definitive diagnosis must be made histologically. The standard treatment remains surgical resection, but recurrence occurs in 4% to 6% patients with localized and 14% to 40% of diffuse TGCT affecting the knee[5]. Histologic or radiologic risk factors for recurrent disease are unknown.

All described case-series on TGCT concern adults, whereas TGCT is only incidentally reported in children. Owing to the rarity of the disease, the available evidence base on TGCT contains predominantly retrospective, relatively small cohort studies, including heterogeneous data[6]. Sufficient data on paediatric patients with TGCT are lacking.

We therefore combined a systematic review with analysis from a nationwide paediatric TGCT incidence study in The Netherlands[3] and clinical data on TGCT in children and adults from four tertiary sarcoma centres in The Netherlands to answer the following questions: (1) How many cases have been reported of this condition, and what were their characteristics? (2) What is the standardized paediatric incidence rate for TGCT? (3) Is there a clinical difference in TGCT between children and adults? (4) What is the risk of recurrence after open resection in children compared with adults?

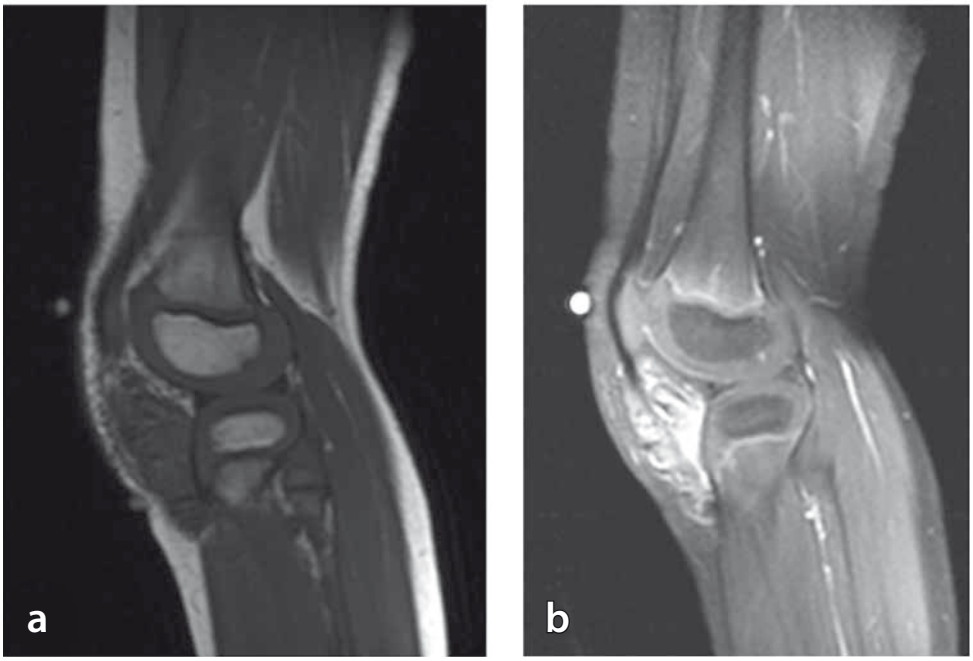


Figure 1 Localized type TGCT: MRI of a 6-year-old boy with TGCT in his left knee. **a.** Sagittal T1-weighted image showing a well-circumscribed nodular lesion at the synovial lining of the anterior knee compartment. **b.** Sagittal T1-weighted spectral presaturation with inversion recovery (SPIR) image after IV gadolinium administration shows heterogeneous enhancement.

Patients and Methods

Children were defined as patients younger than 18 years at presentation. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints. Data were derived from three sources: a systematic review, the nationwide TGCT incidence study, and from our bone and soft tissue tumour data registry.

A systematic review on TGCT in children was performed, seeking sources published between 1990 and 2016. Search terms and MeSh headings were "tenosynovial giant cell", "diffuse type giant cell", "giant cell tumors", "PVNS", "pigmented villonodular synovitis", and "synovitis, pigmented villonodular" combined with "infant", "child", "neonat", "pediatric", "paediatric", "toddler", "teen", "teenager", "juvenile", "adolescent", "girl", and "boy". A total of 619 articles were identified in PubMed,

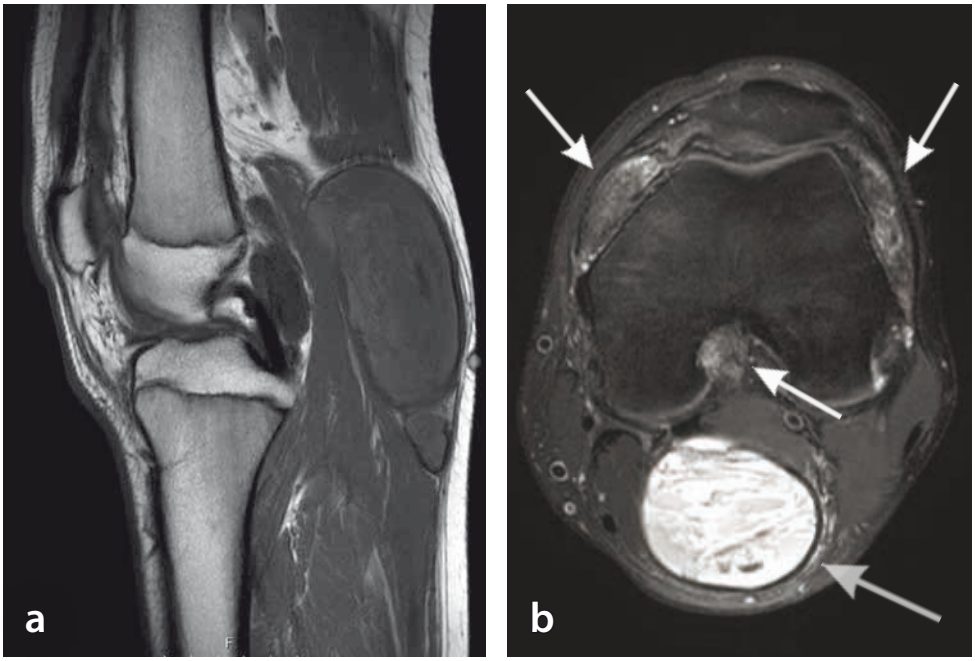


Figure 2 Diffuse type TGCT: MRI of a 16-year-old boy with TGCT in his left knee. **a.** Sagittal T1-weighted turbo spin echo (TSE) image shows extensive intra- and extra-articular villous proliferation of synovium. Posterior is a large Baker's cyst. **b.** Transversal T2-weighted TSE image with heterogeneous low to intermediate signal of the TGCT anterior and posterior (white arrows). Baker's cyst is shown posteriorly (bigger grey arrow).

EMBASE, and Cochrane library. All titles and abstracts were screened by two independent reviewers (MJLM, DU) including case-series with at least two TGCT paediatric patients and published in English. Case-series without detailed data on children were excluded, resulting in a data set of 17 heterogeneous, mostly small case-series of two to six patients (*Table 1*). The largest study included 11 patients with localized TGCT of large joints[7].

The Dutch paediatric incidence rate was extracted from the nationwide TGCT incidence study by including patients < 18 years of age[3]. Standardized incidence rates were obtained by using the direct method, applying age-specific incidence rates in each 1-year age group to the WHO standard population (http://seer.cancer.gov). This study by Mastboom et al.[3] was a registry-based study and eligible patients with TGCT were clinically verified. Patients without histologically proven TGCT were not included.

From our national bone and soft tissue tumour data registry (PALGA), a clinical data set was derived, including 57 patients < 18 years with (histologically proven) TGCT in large joints, treated between 1995 and 2015, in one of the four tertiary sarcoma centres in The Netherlands. Clinical, biologic, and imaging data on TGCT type, sex, localization, age at diagnosis, symptoms before diagnosis, treatment(s), recurrence(s), and followup were collected.

A combined retrospective database of two tertiary oncology centres (Leiden University Medical Centre and Radboud University Medical Centre) in The Netherlands has recorded all patients with TGCT since 1990 (455 patients). TGCT data on children were compared with TGCT data on 423 adults (32 children within this database were excluded from the adult group).

Statistical analyses, for our clinical data set, were predominantly descriptive. Chi square test was used to compare children and adults on TGCT type, sex (male versus female), localization (knee versus other large joints), symptoms before diagnosis (pain, swelling, and loss of function: yes versus no), first treatment (arthroscopic resection versus open resection), recurrent disease (no recurrence versus recurrence), and followup status. Independent t-test was used to compare median duration of symptoms and median time to followup. All reported p values were two-tailed. Statistical significance level was defined at $p < 0.05$. The recurrence-free survival curve was assessed with Kaplan-Meier methods.

This study was approved by the institutional review board from the Leiden University Medical Centre (medical ethical approved protocol P13.029). Data capturing and analyses were performed at Leiden University Medical Centre. SPSS Version 23 (Chicago, IL, USA) was used for analyses.

Results

Our systematic review identified 17 case-series involving 76 children (39 female) with TGCT, 29 localized, 38 diffuse, and nine unknown type (*Table 1*). The paediatric group ranged from 3 to 18 years of age. The knee was most frequently affected (44 [58%]). Swelling, pain, and limited ROM were described symptoms before diagnosis (mean duration, 15 months). The majority of patients were primarily treated with synovectomy, either arthroscopic or open. Recurrent disease was described in 10 patients (13%). Only five paediatric studies described function or quality of life after treatment. Patients with (multiple) recurrences experienced impaired function and quality of life, according to van der Heijden et al.[22]. Five children with diffuse TGCT, described by de Visser et al.[13], had fair to

excellent results on the Musculoskeletal Tumour Society (MSTS) score after surgical treatment (MSTS by Enneking). Gholve et al.[7] described 11 children with surgically treated localized TGCT without disabling joint function according to a telephone questionnaire survey. Seven surgically treated children, described by Baroni et al.[4], recovered full ROM and two patients showed impaired joint movement with occasional mild to moderate pain in four children with localized and five children with diffuse type. Nakahara et al.[21] showed three children with diffuse disease of the knee with almost maximum Knee Society Scores and improved postoperative ROM of at least 0° to 145°.

The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively[3]. Between 2009 and 2013, 53 children with localized TGCT (excluding digits) and 24 children with diffuse TGCT were diagnosed in The Netherlands. This resulted in a Dutch incidence rate of 2.86 per million person-years for localized TGCT (excluding digits) and 1.30 per million person-years for diffuse TGCT; this was converted to standardized incidence rates (*Supplemental Table 1 [Supplemental materials are available with the online version of CORR®.]*). In both localized and diffuse types, the knee was most commonly affected (*Figure 3*).

Clinical data of TGCT in children from the four Dutch tertiary sarcoma centres seemed similar to those observed in the combined two Dutch retrospective adult databases (*Table 2*). Fifty-seven children (median age at diagnosis, 16 years; range, 4-18 years) with TGCT of large joints were identified (*Table 2*). Symptoms before diagnosis were swelling, pain, and limited ROM with a median duration of 12 months (range, 1-72 months). These symptoms and the diagnostic delay seemed similar to those observed in adults (*Table 2*). Children showed a localized diffuse ratio of one to one; the knee was predominantly affected (13 of 28 [46%] localized, 19 of 29 [66%] diffuse) and there was a predilection for females (15 of 28 [54%] localized, 18 of 29 [62%] diffuse). In 423 adults, the localized:diffuse ratio was 1:1.6; the knee was predominantly affected (121 of 172 [70%] localized, 189 of 251 [75%] diffuse) with a predilection for females (107 of 172 [62%] localized, 142 of 251 [57%] diffuse).

Recurrence-free survival curves were not different with the numbers available between children and adults at the four involved tumour centres (*Figure 4*). The 2.5-year recurrence-free survival, after surgical treatment, in paediatric patients compared with adults was 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%; p = 0.527) in localized and 53% (95%

Table 1 Literature overview on TGCT affecting all joints in children, including at least two TGCT cases (1990-2016, English language)*

Study	Year	Number	Sex	Mean age (years; range)	Symptoms before diagnosis	Mean duration of symptoms (months; range)
Givon[8]	1991	2	1 M, 1 F	7 (7-7)	S, W, LROM	60 (both patients)
Rosenberg†[9]	2001	2	2 M	12 (10-14)	S	NA
Neubauer‖[10]	2007	5	3 M, 2 F	12 (8-15)	S,P	10 (2-24)
Gholve et al.‖[7]	2007	11	6 M, 5 F	12 (7-16)	S, P	10 (1-24)
Pannier†[11]	2008	6	2 M, 4 F	12‡	NA	NA
Baroni et al.[4]	2010	9	4 M, 5 F	11 (7-15)¶	S, P, LROM	18 (2-48)
Current	2017	57	24 M, 33 F	14 (4-18)	S, P, LROM	16 (1-72)
Also adult cases included						
Abdul-Karim[12]	1992	2	2 M	10 (10-10)	S, P	NA
de Visser et al.[13]	1999	5	4 M, 1 F	16 (12-18)	NA	NA
Perka[14]	2000	2	2 F	12 (8-16)	S, P, LROM	12‡
Somerhausen[15]	2000	4	3 M, 1 F	14 (3-18)	S	7 (6-8)
Gibbons[16]	2002	3	1 M, 2 F	11 (8-15)	S	28 (6-96)§
Bisbinas[17]	2004	5	5 F	14 (12-15)	S	2‡
Brien[18]	2004	3	1 M, 2 F	13 (12-15)	S, P	7 (1-24)§
Sharma[19]	2006	4	2 M, 2 F	14 (8-17)	S, P	2‡
Sharma[20]	2007	3	2 M, 1 F	17 (16-18)	S, P	5 (2-9)
Nakahara et al.[21]	2012	3	2 M, 1 F	11 (8-13)	NA	NA
van der Heijden[22]	2014	7	2 M, 5 F	14 (6-18)	NA	NA
Total		**133**				

TGCT type	Joint	Primary surgeries	Recurrent disease	Mean followup (months; range)
1 L, 1 D	2 knee	1 AS, 1 US	0	24 (12-36)
1 L, 1 D	2 knee	1 OS, 1 US	NA	NA
5 unknown	4 knee, 1 ankle	5 AS	1	36 (12-84)
11 L	2 knee, 3 ankle, 4 foot, 1 hand, 1 wrist	11 OS	0	54 (15-130)
2 L, 4 D	5 knee, 1 ankle	5 US, 1 MT	2	58[‡]
4 L, 5 D	9 knee	4 AS, 5 OS	0	82 (46-143)
28 L, 29 D	32 knee, 11 ankle, 5 foot, 4 hip, 2 hand, 2 other, 1 wrist	9 AS, 47 OS, 1 WS	23	55 (0-260)
2 D	1 foot, 1 ankle	1 US, 1 AP	0	132 (108-156)
5 D	4 knee, 1 ankle	4 US, 1 RS	5 residual disease	30 (21-75)
2 L	2 knee	2 US	0	NA
4 D	1 knee, 1 foot, 1 buttock, 1 thigh	4 US	0/1 NA	44.5 (0-114)
3 L	3 foot	3 US	0	NA
5 L	5 ankle	5 OS	0	46 (12-150)
3 D	2 foot, 1 ankle	3 US	2	NA
4 unknown	4 ankle	4 US	0	37.5 (19-65)
3 D	3 knee	3 OS	1	96 (54-138)
3 D	3 knee	3 OS	0	29 (20-36)
7 D	7 knee	4 AS, 3 OS	4	95 (24-212)
	57 L, 67 D, 9 unknown			

[*]Large joints were defined as all joints proximal to and excluding metatarsophalangeal and metacarpophalangeal joints; large case-series not describing children in detail were not included; [†]language of article was French; included information is based on an English abstract; [‡]range unavailable; [§]including adult cases; [‖]TGCT cases in digits were excluded; [¶]case number 6, a 2-year-old girl, was excluded according to a delayed time to diagnosis of 38 months; TGCT = tenosynovial giant cell tumour; M = male; F = female; NA = information not available; S = swelling; W = warmth; LROM = limited ROM; P = pain; L = localized TGCT; D = diffuse TGCT; AS = arthroscopic synovectomy; OS = open synovectomy; US = unspecified

CI, 35%-79%) versus 56% (95% CI, 49%-64%; p = 0.691) in diffuse type, respectively. In the four involved sarcoma centres, most children and adults alike were primarily surgically treated by open resection: localized TGCT in 25 of 28 children (89%) were thus treated compared with 142 of 172 adults (85%; p = 0.486); for diffuse TGCT in children, the proportion was 22 of 29 (76%) compared with 188 of 251 in adults (75%; p = 0.289). Recurrence risk in children and adults was likewise not different with the numbers available: two of 28 (7%) compared with 22 of 172 (13%; p = 0.365) in localized type and 11 of 29 (38%) compared with 119 of 251 (47%; p = 0.921) in diffuse type, respectively.

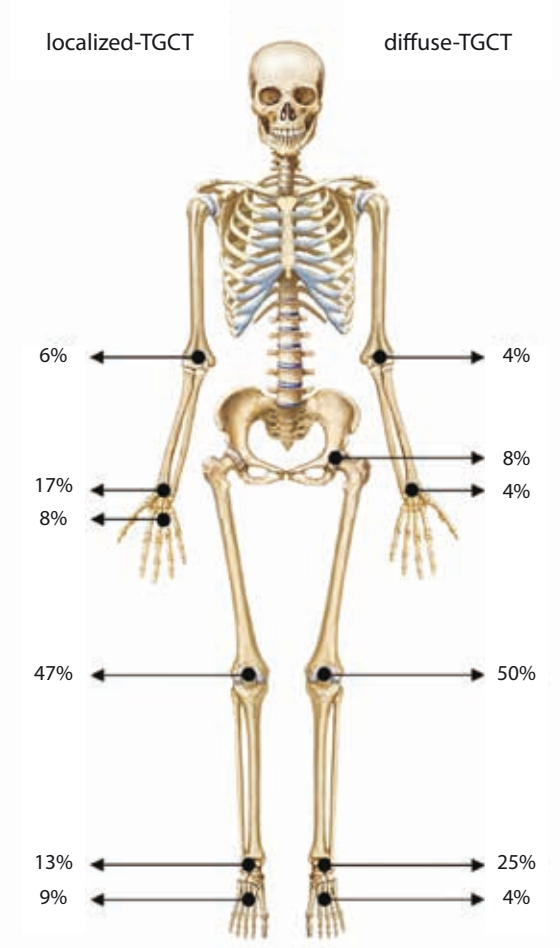


Figure 3 Skeleton showing TGCT localization in children extracted from a Dutch incidence study, excluding digits[3]. In diffuse TGCT, one patient was classified as "other"; he was treated for TGCT in his vertebral column.

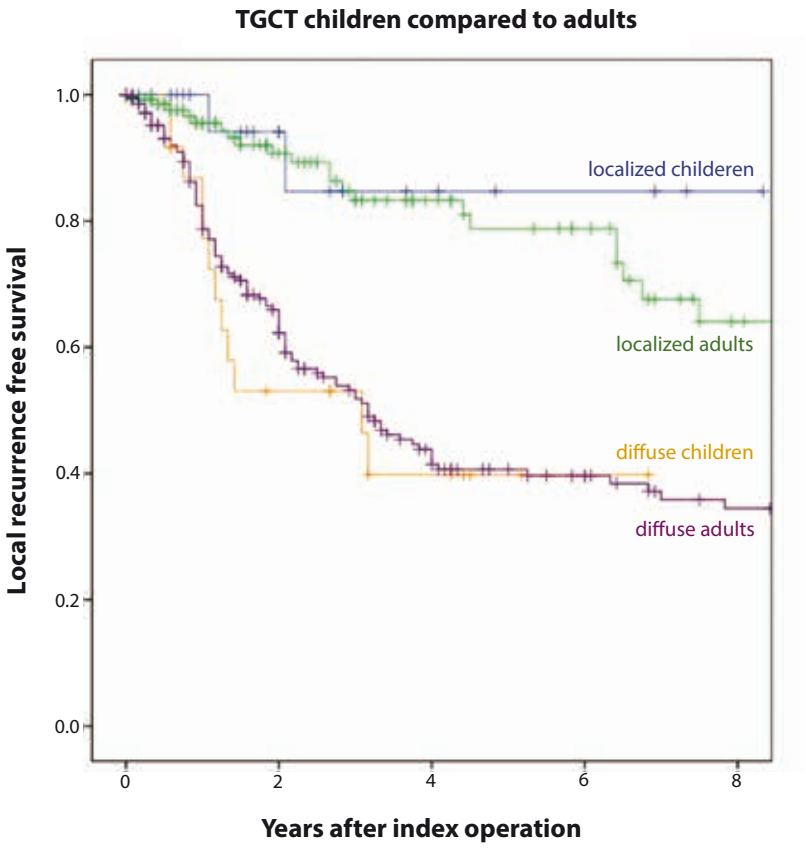


Figure 4 Local recurrence-free survival curve of localized and diffuse TGCT (Kaplan-Meier), excluding digits. Time zero is the time of the primary surgery. All patients were surgically treated; patients treated with wait-and-see treatment are excluded. In the adult graph, two patients died and were censored at the time of death if a recurrence had not occurred.

Table 2 Details of patients with TGCT of large joints in children versus adults, including sex, localization, age, symptoms, first treatment, recurrent disease, and followup[†]

	Children	
Patient variables	**Localized TGCT**	**Diffuse TGCT**
Total number of patients	28	29
Sex		
Male:female ratio	13:15 (1:1.2)	11:18 (1:1.6)
Localization		
Knee	13 (46%)	19 (66%)
Other joints	15 (54%)	10 (34%)
Age		
Median age at diagnosis (years; range)	16 (4-18)	16 (11-18)
Symptoms before diagnosis		
Swelling	24 (86%)	21 (72%)
Pain	12 (43%)	17 (59%)
Limited ROM	3 (11%)	4 (14%)
Median duration of symptoms (months; range)	9 (1-48)	18 (1-72)
First treatment		
Arthroscopic resection	3 (11%)	6 (21%)
Open resection	25 (89%)	22 (76%)
Wait and see	0	1 (3%)
Recurrent disease[†]	**N = 28**	**N = 28**
No recurrence	26 (93%)	17 (61%)
≥ 1 recurrence	2 (7%)	11 (39%)
Followup status		
Disease-free	19 (68%)	16 (55%)
Alive with disease[‡]	4 (14%)	9 (31%)
Death of other disease	0	0
Lost to followup[‡]	5 (18%)	4 (14%)
Median time to followup (months; range)[*]	25 (7-100)	77 (7-144)

Adults		Children versus adults	
Localized TGCT	**Diffuse TGCT**	**p value localized TGCT**	**p value diffuse TGCT**
172	251		
		0.285	0.434
65:107 (1:1.6)	109:142 (1:1.3)		
		0.019	0.207
121 (70%)	189 (75%)		
51 (30%)	62 (25%)		
42 (19-82)	38 (19-72)		
106 (62%)	163 (65%)	0.010	0.510
103 (60%)	157 (63%)	0.129	0.558
13 (8%)	49 (20%)	0.608	0.486
12 (1-240)	24 (1-300)	0.176	0.153
		0.486[+]	**0.289**[+]
7 (4%)	37 (15%)		
147 (85%)	188 (75%)		
18 (11%)	26 (10%)		
N = 154	**N = 225**	**0.280**	**0.407**
132 (86%)	106 (47%)		
22 (14%)	119 (53%)		
		0.840	**0.768**
110 (64%)	121 (48%)		
19 (11%)	94 (37%)		
0	2 (1%)		
43 (25%)	34 (14%)		
36 (6-301)	54 (6-350)	0.127	0.780

[*]Patients lost to followup are excluded for median time to followup; lost to followup is defined as < 6 months followup; [†+]wait and see treatment was not included in calculation of independent t-test; children were included between 1995 and 2015 adults between 1990 and 2015; [‡]patients alive with disease either have wait and see treatment, residual or recurrent disease; TGCT = tenosynovial giant cell tumor.

Discussion

TGCT is most commonly seen in adults in the third and fourth decades of life, but this study confirms that it also affects paediatric patients. The paediatric incidence rate for both localized and diffuse type suggests that it is rare, but we believe it is still common enough to include in the differential diagnosis of both children and adults with nonspecific symptoms like swelling, pain, and limited ROM. We found no differences with the numbers available between children and adults in terms of presenting symptoms, treatments used in the few available case-series, and recurrence-free survival rates. In the era of personalized medicine, future research should define the most effective treatment for TGCT, with its various clinical scenarios, both in children and adults.

There are some limitations to this study. In our systematic review, many case-series included data from children with TGCT in embedded studies that also contained adults' data. When data on children was not separately described, these children were not included in the overview (*Table 1*). The determined incidence rate is a conservative estimate, because our search was based on the nationwide network and registry of histo- and cytopathology in The Netherlands[23]. Patients with TGCT without a biopsy or treatment were not represented in this pathology-based cohort. By standardizing incidence rates, they could be extrapolated to other populations. However, generalizability of the standardized incidence rate depends on the age-specific population structure of the country compared with the WHO population. Included patients had histologically proven TGCT by a dedicated musculoskeletal pathologist (UF, HB, AS, JB). However, patients were not centrally reviewed for this study. Neither functional outcome nor quality of life was evaluated. For TGCT treatment, only surgical treatment was evaluated. Future, comparative studies on treatments should determine what should be done for patients (children and adults) with TGCT. Although surgery is the mainstay, other treatments are used, and future research needs to define what the best approaches are for the various clinical scenarios in which this disease presents. In our patients, children with the localized type frequently lacked longer term followup, mainly as a result of absence of clinical symptoms (17 censored in the first 2.5 years; *Figure 4*). Smaller patient numbers with the diffuse type sometimes lacked longer followup (nine censored in the first 2.5 years).

TGCT does not seem to be an adults-only disease and should be considered in the differential diagnosis in children with (chronic) monoarticular joint effusion. Our systematic review identified mainly small, heterogeneous TGCT case-series in children. Future studies might consider including children with TGCT to allow for optimalization of the treatment protocol in both children and adults.

The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years compared with an overall incidence rate of 10.2 and 4.1 per million person-years in localized and diffuse types, respectively[3]. To date, the incidence rate for chronic monoarthritis in children and adolescents is unknown. Savolainen et al. calculated an incidence rate of 64 per 100,000 for all types of arthritis in children (< 16 years) in a defined population in Finland[24]. Although TGCT in children probably accounts for only a small percentage of all types of arthritis, it should still be considered in the differential diagnosis.

Symptoms in children seemed similar to those in adults (*Table 1*). Nonspecific symptoms accompanied by pain and diffuse joint swelling with thickening of the synovial capsule and/or joint effusion resulted in limited movement in approximately half of the patients. Studies in adults add mechanical symptoms, instability, and stiffness[5, 25].

A systematic review (without age limitations) in 2013[5] reported average recurrence rates for localized TGCT in the knee after open resection (4%) and after arthroscopic resection (6%) in contrast to diffuse type after open resection (14%) and after arthroscopic resection (40%) at a mean followup of 108 months. Patel et al.[25] presented 214 patients with knee TGCT of all ages with a recurrence rate of 9% in 100 localized patients and 48% in 114 patients with diffuse TGCT after a mean followup of 25 months (range, 1-168 months). Palmerini et al.[26] reported 294 patients with TGCT of all ages in all joints with a local failure rate of 14% in localized and 36% in diffuse type after a median followup of 4.4 years (range, 1-20 years). The sole primary disease or patients with a first relapse were included. The current paediatric case-series showed comparable recurrence rates of 7% in localized and 39% in diffuse type after a mean followup of 55 months (range, 7-350 months). TGCT is a rare condition in adults and it is even less common in children. Nonspecific symptoms often contribute to a delay in establishing a diagnosis. TGCT should be considered in chronic monoarthritis both in adults and in children. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies now being developed[27], future research should define the most effective treatment strategies for this heterogeneous disease.

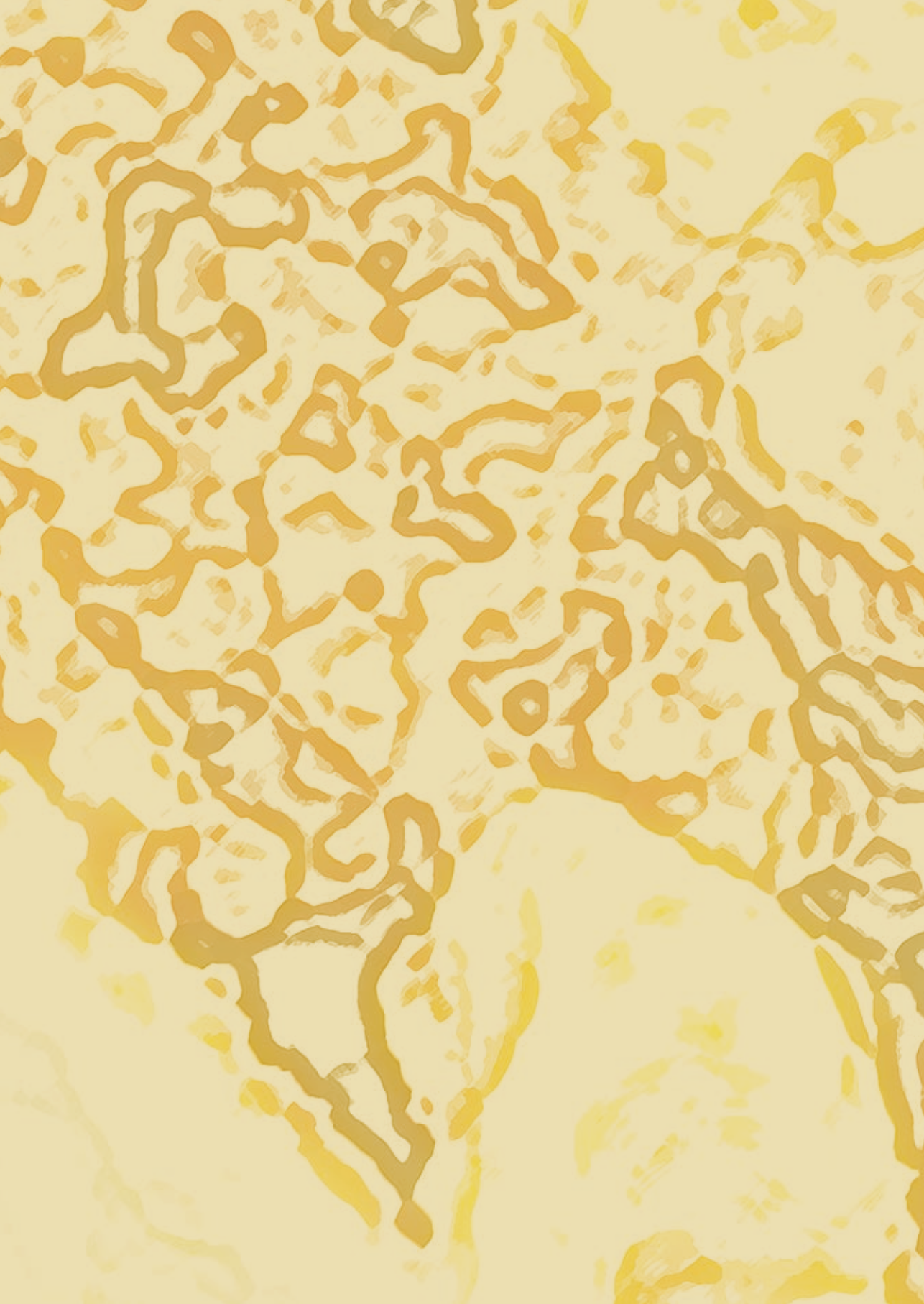
Supplementary data

Supplementary data are available in the online version of this article:
https://dx.doi.org/10.1007/s11999.0000000000000102

References

1. de St. Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, localized type/diffuse type. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4th ed. Lyon: IARC Press; 2013. p. 100-3.
2. Fletcher CDM. WHO Classification of Tumours of Soft Tissue and Bone: IARC Press; 2013.
3. Mastboom MJL, Verspoor, FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, Bovée JVMG, Dijkstra PDS, Schreuder HWB, Gelderblom H, Sande van de MAJ, TGCT study group. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta Orthopaedica. 2017;88.
4. Baroni E, Russo BD, Masquijo JJ, Bassini O, Miscione H. Pigmented villonodular synovitis of the knee in skeletally immature patients. Journal of children's orthopaedics. 2010;4(2):123-7.
5. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
6. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
7. Gholve PA, Hosalkar HS, Kreiger PA, Dormans JP. Giant cell tumor of tendon sheath: largest single series in children. Journal of pediatric orthopedics. 2007;27(1):67-74.
8. Givon U, Ganel A, Heim M. Pigmented villonodular synovitis. Archives of disease in childhood. 1991;66(12):1449-50.
9. Rosenberg D, Kohler R, Chau E, Bouvier R, Pouillaude JM, David L. [Pigmented villonodular synovitis. Diffuse and localized forms in children]. Archives de pediatrie : organe officiel de la Societe francaise de pediatrie. 2001;8(4):381-4.
10. Neubauer P, Weber AK, Miller NH, McCarthy EF. Pigmented villonodular synovitis in children: a report of six cases and review of the literature. The Iowa orthopaedic journal. 2007;27:90-4.
11. Pannier S, Odent T, Milet A, Lambot-Juhan K, Glorion C. [Pigmented villonodular synovitis in children: review of six cases]. Revue de chirurgie orthopedique et reparatrice de l'appareil moteur. 2008;94(1):64-72.
12. Abdul-Karim FW, el-Naggar AK, Joyce MJ, Makley JT, Carter JR. Diffuse and localized tenosynovial giant cell tumor and pigmented villonodular synovitis: a clinicopathologic and flow cytometric DNA analysis. Human pathology. 1992;23(7):729-35.
13. de Visser E, Veth RP, Pruszczynski M, Wobbes T, Van de Putte LB. Diffuse and localized pigmented villonodular synovitis: evaluation of treatment of 38 patients. Archives of orthopaedic and trauma surgery. 1999;119(7-8):401-4.
14. Perka C, Labs K, Zippel H, Buttgereit F. Localized pigmented villonodular synovitis of the knee joint: neoplasm or reactive granuloma? A review of 18 cases. Rheumatology (Oxford, England). 2000;39(2):172-8.
15. Somerhausen NS, Fletcher CD. Diffuse-type giant cell tumor: clinicopathologic and immunohistochemical analysis of 50 cases with extraarticular disease. The American journal of surgical pathology. 2000;24(4):479-92.
16. Gibbons CL, Khwaja HA, Cole AS, Cooke PH, Athanasou NA. Giant-cell tumour of the tendon sheath in the foot and ankle. The Journal of bone and joint surgery British volume. 2002;84(7):1000-3.
17. Bisbinas I, De Silva U, Grimer RJ. Pigmented villonodular synovitis of the foot and ankle: a 12-year experience from a tertiary orthopedic Oncology Unit. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2004;43(6):407-11.
18. Brien EW, Sacoman DM, Mirra JM. Pigmented villonodular synovitis of the foot and ankle. Foot & ankle international. 2004;25(12):908-13.

19. Sharma H, Jane MJ, Reid R. Pigmented villonodular synovitis of the foot and ankle: Forty years of experience from the Scottish bone tumor registry. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2006;45(5):329-36.
20. Sharma H, Rana B, Mahendra A, Jane MJ, Reid R. Outcome of 17 pigmented villonodular synovitis (PVNS) of the knee at 6 years mean follow-up. The Knee. 2007;14(5):390-4.
21. Nakahara H, Matsuda S, Harimaya K, Sakamoto A, Matsumoto Y, Okazaki K, et al. Clinical results of open synovectomy for treatment of diffuse pigmented villonodular synovitis of the knee: case series and review of literature. The Knee. 2012;19(5):684-7.
22. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
23. Casparie M, Tiebosch AT, Burger G, Blauwgeers H, van de Pol A, van Krieken JH, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol. 2007;29(1):19-24.
24. Savolainen E, Kaipiainen-Seppanen O, Kroger L, Luosujarvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. The Journal of rheumatology. 2003;30(11):2460-8.
25. 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(4):808-15.
26. 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(2):210-7.
27. Brahmi M, Vinceneux A, Cassier PA. Current Systemic Treatment Options for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis: Targeting the CSF1/CSF1R Axis. Current treatment options in oncology. 2016;17(2):10.



LOCALIZED

chapter seven

Surgical treatment of localized-type Tenosynovial Giant Cell tumours of large joints

a multicentre-pooled database of 31 international sarcoma centres

M.J.L. Mastboom[1], E.L. Staals[2], F.G.M. Verspoor[3], A.J. Rueten-Budde[4], S. Stacchiotti[5], E. Palmerini[6], G.R. Schaap[7], P.C. Jutte[8], W. Aston[9], A. Leithner[10], D. Dammerer[11], A. Takeuchi[12], Q. Thio[13], X. Niu[14], J.S. Wunder[15], TGCT study-group*, M.A.J. van de Sande[1]

Submitted.

[1] Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands

[2] Orthopaedic Surgery, Musculoskeletal Oncology Department, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[3] Orthopaedic Surgery, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

[4] Mathematical institute, Leiden University, Leiden, The Netherlands

[5] Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[6] Medical Oncology, Musculoskeletal Oncology Department, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[7] Orthopaedic Surgery, Academic Medical Center, Amsterdam, The Netherlands

[8] Department of Orthopaedics, University Medical Center, University of Groningen, Groningen, The Netherlands

[9] Orthopedic surgery, Royal National Orthopedic Hospital, London, the United Kingdom

[10] Department of Orthopaedic Surgery, Medical University Graz, Graz, Austria

[11] Orthopedic surgery, Medical University of Innsbruck, Innsbruck, Austria

[12] Orthopaedic surgery, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

[13] Orthopedic surgery, Massachusetts General Hospital Harvard, Boston, United States of America

[14] Department of Orthopedic Oncology, Beijing Jishuitan Hospital, Beijing, 100035, China

[15] University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, Canada

***TGCT study-group:**

M. Fiocco, H. Gelderblom, P.D.S. Dijkstra, R.J.P. van der Wal, P.A. Daolio, P. Picci, A. Gronchi, S. Ferrari, H. Özger, R.G. Maki, H.W.B. Schreuder, I.C.M. van der Geest, J.A.M. Bramer, M. Boffano, E. Goldenitsch, D. Campanacci, P. Cuomo, P.C. Ferguson, A.M. Griffin, Y. Sun, T. Schubert, K. Patel, M.S.J. Aranguren, A. Blancheton, F. Gouin, H.R. Dürr, C.F. Capellen, J. Schwab, S. Iwata, O. Vyrva, W. Weschenfelder, E.H.M. Wang, M. Wook Joo, Y.K. Kang, Y.G. Chung, W. Ebeid, J. Bruns, T. Ueda

Abstract

Background

Localized-type Tenosynovial Giant Cell Tumour (TGCT) is a rare, neoplastic disease with only limited data supporting treatment protocols. A multicentre-pooled collection of individual patient data resulted in the largest global retrospective cohort of localized-TGCT patients to date. We describe treatment protocols and evaluate their oncological outcome, complications and functional results. A secondary study aim was to identify risk factors for local recurrence after surgical treatment.

Methods

Patients with histologically proven localized-TGCT of large joints were included if treated between 1990-2017 in one of 31 tertiary sarcoma centres. In 941 patients with localized-TGCT, 62% were female, median age at initial treatment was 39 years with a median follow-up of 37 months. 67% affected the knee and the primary treatment at a tertiary centre was one-staged open resection in 73%. Proposed risk factors were tested in a univariate analysis and significant factors subsequently included for multivariate analysis, with an endpoint of first local recurrence after treatment in a tertiary centre.

Results

Recurrent disease developed in 12% of all cases, with local recurrence free survival rates at 3, 5 and 10 years of 88%, 83% and 79%, respectively. The strongest risk factor for recurrent disease was prior recurrence ($p<0.001$). Complications were noted in 4% after surgical treatment of localized-TGCT. Initial symptoms of pain and swelling improved after surgical treatment(s) in 71% and 85%, respectively. For therapy naïve cases, univariate and multivariate analyses yielded positive associations with local recurrence for tumour size ≥5 cm vs <5 cm (HR 2.50; 95%CI 1.32-4.74; $p=0.005$) and initial treatment with arthroscopy vs open resection (HR 2.18; 95%CI0.98-4.84; $p=0.056$).

Conclusions

Risk factors for recurrent disease after resection of localized-type TGCT were larger tumour size and initial treatment with arthroscopy. Relatively low complication rates and good functional outcome warrant an open approach with complete resection when possible, to reduce recurrence rates in high risk patients.

Introduction

In 2013 the WHO defined Tenosynovial Giant Cell Tumours (TGCT), after unification of Giant Cell Tumour of the Tendon Sheath and Pigmented Villonodular Synovitis (PVNS), as a benign mono-articular disease, arising from the synovial lining of joints, bursae or tendon sheaths in predominantly young adults[1, 2].

Clinically and radiographically, TGCT is subdivided into a lobulated often well-bordered lesion (localized-type) that does not involve the surrounding (teno-)synovial lining and a more aggressive lesion, involving a large part or all of the synovial lining (diffuse-type)[1-3]. Despite sharing the same histopathology and genetics, the natural course of disease in localized- and diffuse-TGCT is incomparable and necessitate a separate assessment of treatment protocol and surgical outcome. Based on anatomical site of the localized-type tumour, differentiation is made between disease affecting digits and disease occurring in and about larger joints[4-6]. The present study focuses on localized-TGCT of large joints (*figure 1*), most commonly affecting the knee or other weight bearing joints[1, 2, 6, 7].

The macroscopic appearance of localized-TGCT is typically a well-circumscribed lobulated lesion, with white to grey, yellow and brown mottled areas. According to the WHO, localized-TGCT is a small lesion, with a size range of 0.5 to 4 cm[1, 2]. However, according to the authors' experience, the largest size can frequently exceed 4 cm, especially when compressed in relatively tight joints (e.g. foot and ankle) or situated in the anterior or posterior aspect of the knee.

The main patients complaints related to localized-TGCT include pain, joint effusion, stiffness, locking and limited range of motion[8, 9]. The predominant standard of care for localized-TGCT is surgical resection of the tumour, in order to: (1) reduce debilitating symptoms and prevent joint destruction caused by local compression of cartilage; (2) improve limb function; and (3) minimize the risk of local recurrence. Clinical and oncological outcomes following surgery depend on multiple factors including the localization and extent of disease and possibly the technical experience of the surgeons[3, 7, 10-12].

The current literature mainly consists of relatively small, or larger but heterogeneous case-series,

as localized-TGCT of large joints is an orphan disease, with an incidence of 10.2 per million person-years[6]. A systematic review, including predominantly small case-series up to ten patients, showed comparable recurrence rates after arthroscopic and open resection of the knee (6% versus 4%, respectively)[13]. However, studies included in this review had different follow-up times ranging from not available to 18, up till 112 months. Complications and functional outcomes after surgical treatment are only sparsely reported and surgical treatment by arthroscopic or open resection for localized-TGCT at present remains a matter of debate[7-9, 14-16].

Evaluation of a large number of individual patients is preferred to evaluate the best treatment strategy and possibly identify risk-factors for recurrent disease. Individual participant data meta-analysis offers advantages, above a meta-analyses, as missing data can be accounted for at the individual level, subgroup analyses can be performed (e.g. per affected joint) and follow-up information can be updated[17]. Therefore, we aimed to collaborate with tertiary sarcoma centres all over the world to include individual participant data of TGCT affecting large joints.

The primary aim of this international multicentre cohort study is to provide comprehensive and up to date insights on TGCT surgical treatment as well as oncologic and functional outcomes and complications in this largest global retrospective cohort of patients with localized-TGCT. Secondarily, risk factors for local recurrence after surgical treatment are identified.

Methods

Recruitment and inclusion criteria

Patients with histologically proven TGCT of large joints were included if treated between 1990 and 2017 in one of 31 sarcoma centres globally (*supplementary material*). Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints. Identification and collection of TGCT cases was performed in the centres of origin and data were collected based on the initial treatment at tertiary centres. Data were encrypted and transferred to the international multicentre database at the Leiden University Medical Centre (LUMC). Patient accrual occurred between May 2016 until May 2018.

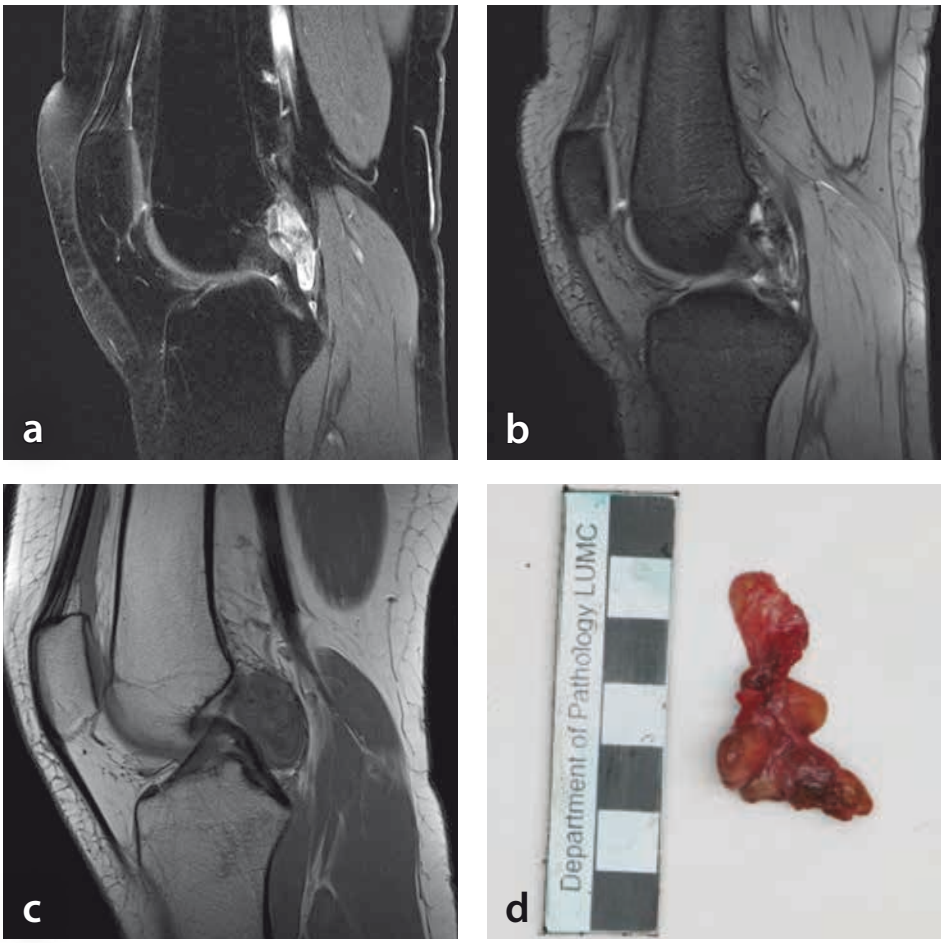


Figure 1 Intra-articular localized-TGCT in the posterior part of the left knee in a 19 year old female. **a.** Sagittal T1-weighted Magnetic Resonance (MR) imaging after intravenous contrast injection with fat suppression. TGCT shows marked enhancement after contrast injection. **b.** TGCT shows an intermediate to low signal intensity on a sagittal T2-weighted MR scan. **c.** On a sagittal proton-density weighted MR imaging, localized-TGCT presents with low signal intensity. **d.** Macroscopic aspect of a well-circumscribed localized-TGCT after complete open resection. Arrow shows brownish areas, representing hemosiderin depositions. On the ruler, 1 block equals 1 cm.

Study parameters

Collected patient-, tumour- and treatment characteristics with corresponding definitions are shown in *appendix table 1*. Complete data on core criteria was necessary for reliable analyses. The following characteristics were defined as core criteria: TGCT-type, admission status, date and type of initial treatment at tertiary centre and first local recurrence.

Patient-, tumour- and treatment characteristics

Thirty-one specialized sarcoma centres spread throughout Europe, North America, Canada and Asia collaborated to provide a total of 2169 TGCT cases. The present study focuses on localized-TGCT (*table 1*), therefore patients with diffuse-TGCT (N=1192) or unknown type TGCT (N=36) were excluded.

Statistical analyses

The endpoint for statistical analysis was local recurrence free survival after initial treatment in a tertiary centre. Recurrent disease was defined as new disease presence after resection performed in a tertiary centre or progressive residual disease (as diagnosed on repeated follow-up Magnetic Resonance (MR) imaging).

To investigate the effect of risk factors on outcome, univariate analyses were performed and significant factors ($p<0.05$) were subsequently included in a multivariate analysis. Proposed risk factors were admission status (therapy-naïve versus recurrent disease), sex (male versus female), age (≤35 years versus >35 years), localization (knee versus hip versus foot and ankle versus upper extremity), bone-involvement (present versus absent), surgical technique (open versus arthroscopic) and size (<5 cm versus ≥5 cm). Patients with treatment 'wait and see' or 'endoprosthetic reconstruction' were excluded from statistical analyses (N=85).

Observed recurrence free survival probabilities at 3, 5, and 10 years were computed for all cases and subgroups based on admission status and localization.

All data were selected for completeness on core criteria (*appendix table 1 and figure 1*). Statistical analyses were carried out using R version 3.4.1. Exact survival information and statistical methods are shown in *supplementary material*.

Purposefully, an estimate of the median time to recurrence was not provided. Calculating such a median, based on patients for whom a recurrence was recorded, would assume that all other patients could not experience a recurrence in the future. The extent of this so-called immortal time bias is unknown. For this reason, such an estimate will always be an underestimation of the true time to recurrence.

Table 1 Patient-, tumour- and treatment characteristics

Characteristics	Overall (%)
Total number	941 (100)
Admission status (N=941)	
Therapy naïve^	897 (95)
≥1 Surgery elsewhere^^	44 (5)
Sex (N=941)	
Male	360 (38)
Female	581 (62)
Median age at initial treatment years (N=882)	39
IQR	27-50
≤35 years	374 (42)
>35 years	508 (58)
Localization (N=941) (figure 2)	
Knee	633 (67)
Hip	37 (4)
Ankle	119 (13)
Foot*	58 (6)
Shoulder	9 (1)
Elbow	14 (2)
Wrist	24 (3)
Hand*	33 (4)
Other	14 (2)
Bone involvement (N=689)	
Present	57 (8)
Absent	632 (92)
Median duration of symptoms# months (N=571)	9
IQR	4-24
Type of (surgical) treatment at tertiary centre (N=930)	
Arthroscopic resection	140 (15)
One-staged open resection	675 (73)
Endoprosthetic reconstruction+	21 (2)
Wait and see$,+	64 (7)
Resection not specified&	30 (3)
Median tumour size initial treatment in cm (N=637)	3.0
IQR	2.0-4.5
<5 cm	496 (78)
≥5 cm	141 (22)
Adjuvant therapy initial treatment (N=787)	
External beam radiotherapy	8 (1)
^{90}Yttrium	21 (3)
Systemic targeted therapy	2 (0.3)
Other	11 (1)
None	745 (95)

^Therapy-naïve or primary admission at tertiary centre are considered similar. ^^≥1 Surgery elsewhere or recurrent admission are considered similar. *Digits are excluded. #Symptoms were defined as either pain, swelling, stiffness or limited range of motion (table 8-9). $Wait and see or conservative treatment are considered similar. +Endoprosthetic reconstruction or wait and see as initial treatment are excluded for risk and survival analyses. &Resection not specified is considered either arthroscopic- or open resection.

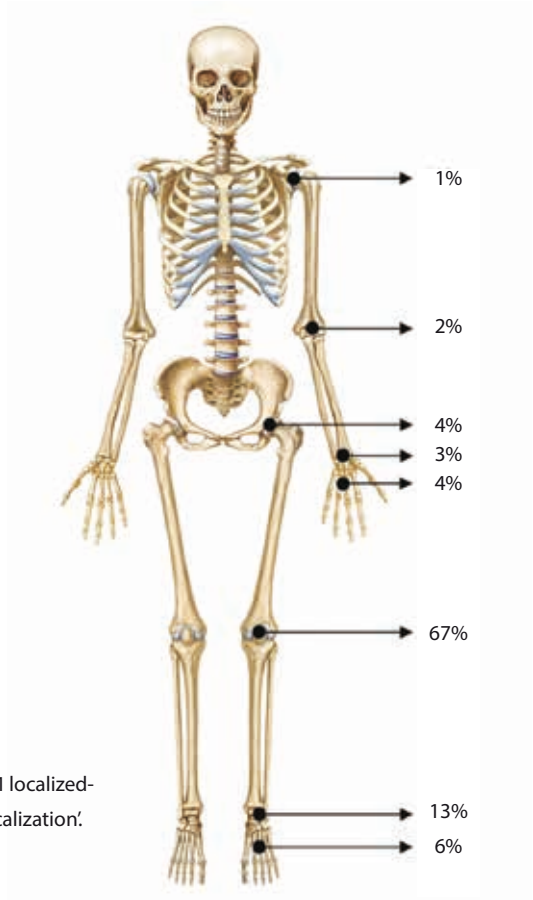


Figure 2 Skeleton showing localization of TGCT in 941 localized-TGCT cases. 14 (2%) cases were classified as 'other localization'.

Ethical consideration

This study is conducted according to the Declaration of Helsinki (October 2013) and approved by the institutional review board (CME) from the Leiden University Medical Centre (LUMC) (May 4th, 2016; G16.015).

Source of Funding

The department of orthopaedics of the Leiden University Medical Centre (LUMC) receives research funding by Daiichi Sankyo.

Results

Oncologic outcome

In 823 patients with localized-TGCT of large joints and complete survival data, 100 (12%) had a recurrence during the follow-up period. Recurrence free survival (RFS) continued to decrease with longer follow-up times (*table 2-3, figure 3-5*).

Univariate- and multivariate analyses for local recurrence

The risk factor admission status was highly associated with significant differences in recurrence risk ($p < 0.001$) in univariate analysis of 823 patients with localized-TGCT and complete core data: RFS at 5 years in patients entering the tertiary hospital with recurrent disease (surgery elsewhere) was 34% (95% CI 17-51), compared with 86% (95% CI 82-89) in therapy naïve patients (*figure 3*). After excluding patients initially treated elsewhere, the risk factors tumour size and surgical technique were found to

Table 2 Oncologic outcome after surgical treatment of localized-TGCT affecting large joints

	Localized-TGCT
First local recurrence after initial treatment at a tertiary centre (N=823)	
Present	100 (12%)
Absent	723 (88%)
Total number of recurrences (N=100)	
1	82 (82%)
2	13 (13%)
≥3	5 (5%)
Mean total number of surgeries (N=657)	1.2 (range 1-5)
Mean total number of surgeries in recurrent disease (N=100)	2.1 (range 1-5)
Median follow-up months (N=823)	37 (95%CI 33-40)
Status last follow-up (N=743)	
No evidence of disease	569 (73%)
Alive with disease - wait and see	29 (9%)
Alive with disease - awaiting treatment	6 (1%)
Death of other disease	2 (0.1%)
Lost to follow-up*	137 (17%)

*Lost to follow-up was defined as follow-up less than 6 months or stratified during follow-up as lost to follow-up

Table 3 Localized-TGCT recurrence free survival (RFS) of all patients and therapy naïve patients treated at a tertiary centre

Year	N all	% RFS all (95%CI)	N therapy naïve	% RFS therapy naïve (95%CI)
3	388	88 (85-91)	372	90 (88-93)
5	231	83 (80-87)	223	86 (82-89)
10	66	79 (75-84)	63	82 (78-87)

N is number of patients at risk at 3, 5, and 10 years

be positively associated with first local recurrence (*table 4-5, figure 3-5*). Younger patients ≤35 years also had fewer recurrences than older patients (82% vs 88%, p=0.04). Similar results were calculated in a subgroup analysis in therapy naïve patients with localized-TGCT affecting the knee.

Observed recurrence free survival according to admission status and localization

As arthroscopic resection is less common in the hip, foot/ankle and upper extremity, arthroscopic and open resection were compared for TGCT affecting the knee (*figure 5*). The highest recurrence rates occurred in therapy naïve patients with tumours located within the knee joint who were initially treated with an arthroscopic resection (18%) (*figure 6*).

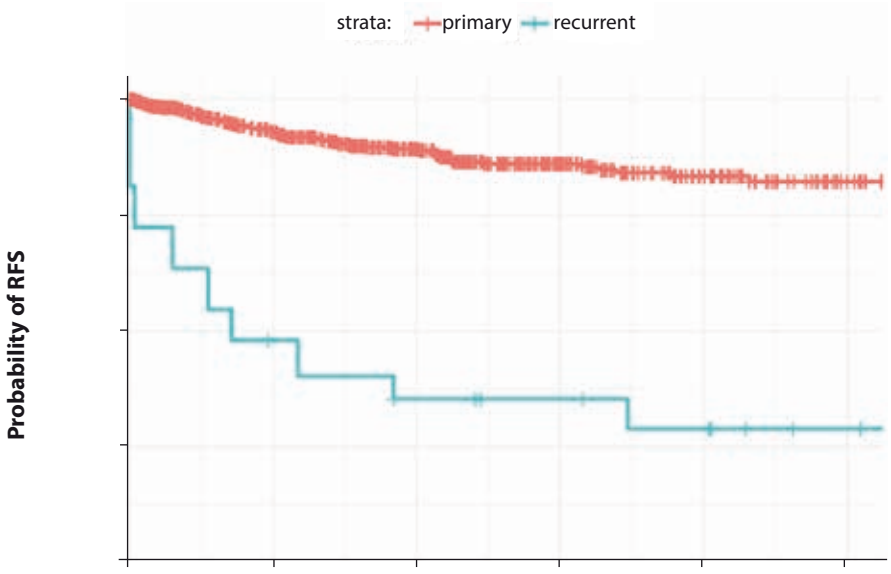
When comparing therapy naïve patients with patients initially treated elsewhere, a declining RFS was observed at 3, 5 and 10 years in subgroup analyses of patients with tumours located in the knee, foot/ankle and upper extremity (*table 6*).

Complications

A total of 34 (4%) complications after surgical treatment of localized-TGCT were reported (*table 7*). The majority of these complications presented after open resection (30/34; 88%). Following arthroscopic resection, two complications were reported (6%).

Functional outcome

Prior to surgical treatment, the majority of patients had symptoms of pain (73%) and swelling (66%) (*table 8*). After surgical treatment, at final follow-up, symptoms of pain, swelling, joint stiffness and limited range of motion were absent in the majority of cases.



number at risk

primary	791	490	298	172	99	53
recurrent	32	14	10	8	5	1
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 3 Local recurrence free survival curve in localized-TGCT stratified for admission status (p<0.001)
Time zero was date of initial resection at tertiary centre. Primary: patient with therapy-naïve disease initially treated at tertiary centre, recurrent: patient initially treated elsewhere

Table 4 Univariate analyses in 791 patients with therapy naïve localized-TGCT

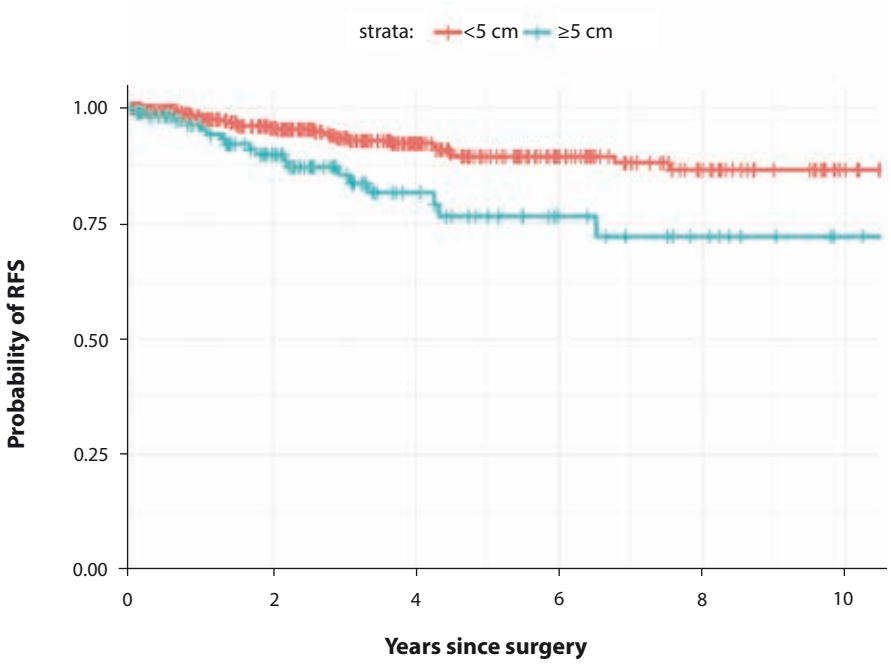
Variable	N	% RFS at 5 years	95%CI	P value
Age				
≤35 years	343	82	77-88	0.04
>35 years	447	88	84-92	
Sex				
male	292	88	82-93	0.56
female	499	85	80-89	
Localization				
knee	529	85	81-89	0.71
foot/ankle	156	84	76-93	
upper extremity	82	90	81-98	
Size				
<5 cm	454	89	85-94	0.009
≥5 cm	124	76	66-87	
Bone involvement				
absent	543	85	81-89	0.70
present	50	74	57-91	
Surgical technique				
open	629	87	83-91	0.04
arthroscopic	132	80	72-88	

RFS: Recurrence free survival, 95%CI: 95% Confidence interval

Table 5 Multivariate analyses in 554 patients with therapy naïve localized-TGCT

Variable		Hazard ratio	95% CI	P value
Age	per year	0.99	0.97-1.01	0.425
Size	<5 cm	1		
	≥5 cm	2.50	1.32-4.74	0.005
Surgical technique	open	1		
	arthroscopic	2.18	0.98-4.84	0.056

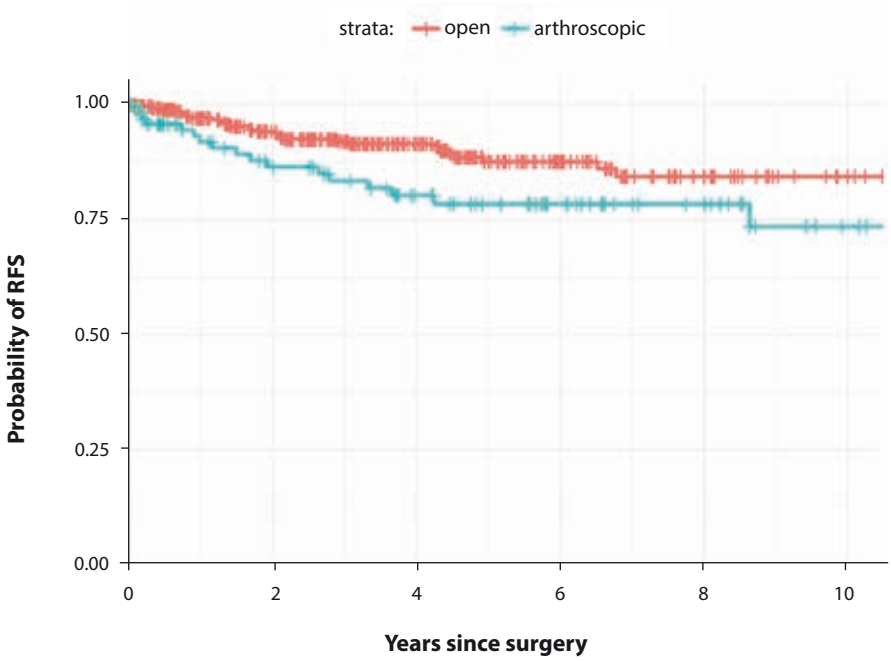
95%CI: 95% Confidence interval



number at risk

<5 cm	454	267	149	91	58	36
≥5 cm	125	75	36	21	13	6
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 4 Local recurrence free survival curve in therapy naïve patients with localized-TGCT stratified for size (p=0.009). Time zero was date of initial resection at tertiary centre.



number at risk

open	400	256	154	77	40	21
arthroscopic	114	70	52	35	22	9
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 5 Local recurrence free survival curve in patients with therapy naïve localized-TGCT affecting the knee stratified for surgical technique (p=0.02). Time zero was date of initial resection at tertiary centre. Open: open resection, arthroscopic: arthroscopic resection

For a mean of 501 (53%) patients with localized-TGCT, complete data were available both prior to treatment and at last follow-up (*table 9*). The majority of patients experienced pain and swelling prior to initial treatment, of which 71% and 85% were resolved after surgery at final follow-up**.** Swelling or stiffness might coincide with recurrent disease as 34% (21/61) and 40% (8/20) of patients with swelling and joint stiffness respectively at final follow-up had recurrent disease. In contrast to pain, limited range of motion or chronic use of analgesics, as 20% (25/124), 30% (8/27) and 29% (7/24), respectively, had recurrent disease.

Chronic analgesic treatment versus complications

Two of 26 patients (8%) with a complication used chronic analgesic treatment compared to five of 429 (3%) patients without a complication.

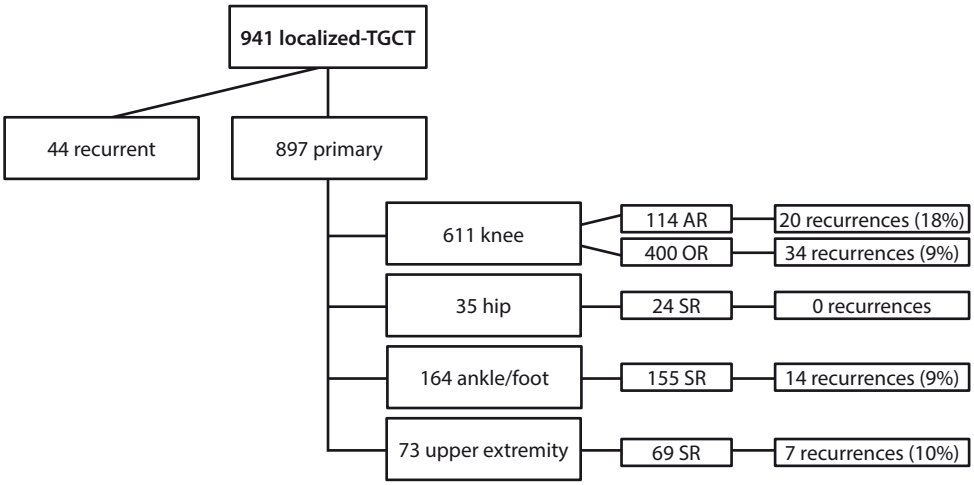


Figure 6 Flowchart localized-TGCT. Primary: patient was first seen at tertiary centre with therapy-naïve disease, recurrent: patient initially treated elsewhere, AR: Arthroscopic resection, OR: Open resection, SR: Surgical resection (either arthroscopic or open resection). Treatments other than surgical resections were not included in this flowchart (e.g. endoprosthetic reconstruction, wait and see treatment or adjuvant therapy). Upper extremity includes shoulder, elbow, wrist and hand. Other localization (N=14) were not included in this flowchart.

Table 6 Recurrence free survival (RFS) probabilities for localized-TGCT

Admission status	Localization	N[+]	%RFS at 3 years	95% CI	%RFS at 5 years	95% CI	%RFS at 10 years	95% CI
primary	knee	529	89	87-93	85	81-89	81	76-87
primary	foot/ankle	156	90	84-96	84	76-93	81	71-91
primary	upper extremity*	82	93	86-100	90	81-98	86	74-97
recurrent	knee	16	44	19-68	44	19-68	**	
recurrent	foot/ankle	11	30	3-57	18	0-41	18	0-41
recurrent	upper extremity*	3	67	13-100	67	13-100	67	13-100

Since the hip was affected sporadically (primary N=24; recurrent N=2) without recurrent disease during follow-up, reliable analyses were not possible. [+]N: number at baseline (time point = 0), *Upper extremity including other localization, **Survival estimates of recurrent knee patients at 10 years could not be estimated (due to lack of follow-up information). Primary: patient was first seen at tertiary centre with therapy-naïve disease, recurrent: patient initially treated elsewhere, 95%CI: 95% Confidence interval.

Table 7 Complications after surgical treatment at tertiary centre (N=763)

Complications after surgical treatment	N (%)
Superficial wound infection	11 (1)
Deep wound infection	1 (0.1)
Joint stiffness[$]	5 (0.7)
Haemorrhage	1 (0.1)
Neurovascular damage	3 (0.4)
Thrombosis	3 (0.4)
Other[+]	10 (1)

As osteoarthritis is either caused by extensive disease or by (multiple) treatments, this was not taken into account for complications. [$]Joint stiffness requiring manipulation under anaesthesia. [+]Other surgical complications after initial treatment included: joint subluxation (hip), compartment syndrome, ligament incision during surgery, complex regional pain syndrome, tourniquet blistering, tendinitis.

Table 8 Symptoms prior to treatment and at final follow-up

Symptom	Pre-treatment	Final follow-up
Pain (PT 767, FF 522)	560 (73%)	128 (25%)
Swelling (PT 675, FF 525)	448 (66%)	64 (12%)
Joint stiffness (PT 663, FF 525)	65 (10%)	21 (4%)
Limited range of motion (PT 667, FF 523)	110 (16%)	27 (5%)
Chronic analgesic treatment* (FF 568)		25 (4%)

Presented numbers indicate presence of symptom. *Chronic analgesic treatment data were only collected at final follow-up, PT: total number pre-treatment, FF: total number final follow-up

Table 9 Comparing symptoms localized-TGCT prior to treatment to last follow-up

	No pain last fu	Pain last fu	Total
No pain initially	122 (24%)	18 (4%)	140
Pain initially	260 (52%)	104 (21%)	364
	No swelling last fu	**Swelling last fu**	
No swelling initially	160 (32%)	11 (2%)	171
Swelling initially	284 (56%)	50 (10%)	334
	No stiffness last fu	**Stiffness last fu**	
No stiffness initially	427 (86%)	16 (3%)	443
Stiffness initially	50 (10%)	4 (1%)	54
	No limited range of motion last fu	**Limited range of motion last fu**	
No limited range of motion initially	385 (77%)	16 (3%)	401
Limited range of motion initially	88 (18%)	9 (2%)	97

fu: follow-up.

Discussion

The results of this international multicentre study offer reliable insight into the outcome of the treatment of patients with the orphan and heterogeneous disease localized-type Tenosynovial Giant Cell Tumour (TGCT). We evaluated oncologic results, complications and functional results after surgical treatment. The greatest strength of this dataset is that it represents the largest collection of localized-TGCTs of large joints in the scientific literature, including a subgroup of patients with long follow-up (>10 years).

Oncologic outcome

Surgical resection of TGCT has been the treatment of choice by either an arthroscopic or open technique, based on the preference of the patient and treating physician, and might also differ by centre. Physicians in favour of arthroscopic resection claim faster recovery, a lower complication rate and less joint morbidity[23-30]. However, opponents of arthroscopic resection point out the risk of inadequate excision, higher recurrence rates and a theoretical risk of joint seeding and portal contamination[13, 16].

In the current study, we identified higher recurrence rates after arthroscopic (18%) compares to open resection (9%) of therapy naïve localized-TGCT affecting the knee joint. This is also presented in the systematic review of van der Heijden et al. (6% after arthroscopic and 4% after open resection)[13]. These higher recurrence rates may be explained by the longer follow-up times on average and the larger sample size of localized-TGCT cases (*table 4-5, figure 3-5*). The single most important and significant risk factor for local recurrence is recurrent disease at presentation. In a subgroup analysis of patients with primary disease treated in a tertiary centre, the greatest risk for first local recurrence was associated with tumour size ≥5 cm and arthroscopic resection at initial treatment. This could be attributed to the fact that arthroscopic en bloc and complete resection is likely only possible in a small percentage of cases with small/pedunculated and accessible lesions, whereas in most cases intralesional removal would be performed arthroscopically thereby potentially leaving residual disease in the joint. Several other studies reported higher rates of recurrences after incomplete resections[10, 23, 31, 32].

Complications

All surgical treatments are associated with complications and data following resection of TGCT are currently lacking in recent literature. The present study reported a complication rate of 4% after surgical treatment for localized-TGCT. The most common complication in localized-TGCT was a superficial wound infection after open resection.

Functional outcome

TGCT related symptoms are mainly joint pain, swelling, stiffness and limited range of motion, but these occur with great variability in extent and severity. Gelhorn et al. concluded that not all patients experience all symptoms to the same extent (e.g. swelling but no pain, or pain and swelling but no stiffness or limited range of motion)[9]. Symptoms prior to initial treatment at a tertiary centre were compared with symptoms at last follow-up. Initial symptoms of pain and swelling improved after surgical treatment(s) in 71-85% of patients. This is comparable with a crowdsourcing study in 337 TGCT patients originating from 30 countries[8]. Stiffness and limited range of motion seemed not to be debilitating symptoms in the majority of patients, either initially or at last follow-up. There was no relationship between symptoms at last follow-up and recurrent disease. Symptoms are subjective for each patient and not all patients were included with complete data. Nevertheless, the main initial TGCT-related complaints are pain and swelling and these could potentially improve after surgical treatment(s).

Joint specific analyses

In daily practise, TGCT patients present as a heterogeneous group. To provide reliable results, homogeneous subgroup analyses are essential. This was possible with our individual participant data meta-analysis. Even though quite a large number of TGCT cases were collected, complete risk factor subgroup analyses were only feasible for TGCT affecting the knee (67%).

Limitations

As a result of increased awareness about TGCT, more patients are now being referred to (tertiary) orthopaedic oncological referral centres as new targeted therapies are being examined in on-going RCTs[33-35]. However, data on patients treated at non-specialized centres are lacking in both the literature and within the present study. Therewith, selection (referral) bias is induced. The

degree of selection bias according to affected joints is negligible, as similar percentages of affected localizations (*figure 2*) were reported in a recent incidence calculation study with nationwide coverage[6]. Non-specialized centres that resect smaller tumours without local recurrence were not present, possibly introducing an overestimation of LR for localized-TGCT in general.

As data were collected by local investigators or physicians according to the multicentre study design, data quality depended on data registry on site. Only data available in the source data file of the patients could be retrieved. In addition, interpretation of individual parameters could differ. No central histopathological review was performed, as it was assumed that each centre provided the correct diagnosis as set by their histopathology department.

Recurrence rates could either be over-estimated or under-estimated. Over-estimation since date of a second operation or follow-up status 'alive with disease' was classified as recurrence (if recurrence data was missing). On the contrary, under-estimation could be present if patients with recurrent disease did not return at all or did not return to their original centre. It should be noted that patients with recurrent disease had a longer follow-up compared with patients without recurrent disease. This could be explained by the fact that patients without symptoms and (assumed) without recurrent disease were dismissed from follow-up and therefore presented with shorter follow-up times. Plausibly, patients without symptoms are not experiencing recurrent disease. In addition, if treatments were recently performed, patients also had shorter follow-up times and are still at risk of recurrence.

Conclusion

We present the largest international study that evaluated the clinical profile, management and outcome for patients with TGCT. Localized-TGCT remains a heterogeneous and orphan disease, with an overall recurrence free survival of 83% at 5 years. Risk factors for recurrent disease were larger tumours, primary treatment with arthroscopy and initial surgical treatment outside of a tertiary centre. Relatively low complication rates and good functional outcomes warrant complete resection, most commonly accomplished by an open surgical approach, to reduce recurrence rates in high risk patients.

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. Mastboom MJL, Verspoor FGM, Hanff DF, Gademan MGJ, Dijkstra PDS, Schreuder HWB, Bloem JL, van der Wal RJP, van de Sande MAJ. Severity classification of Tenosynovial Giant Cell Tumours on MR imaging. Surg Oncol. 2018;27:544-50.
4. Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. Cancer. 1986;57(4):875-84.
5. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
6. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
7. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
8. Mastboom MJ, Planje R, van de Sande MA. The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life. Interactive journal of medical research. 2018;7(1):e4.
9. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
10. 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(2):210-7.
11. 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(4):808-15.
12. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
13. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
14. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
15. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
16. Verspoor FG, van der Geest IC, Vegt E, Veth RP, van der Graaf WT, Schreuder HW. Pigmented villonodular synovitis: current concepts about diagnosis and management. Future oncology. 2013;9(10):1515-31.
17. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. Bmj. 2010;340:c221.
18. Honaker J, King G, Blackwell M. Amelia II: a program for missing data. J Stat Softw. 2011;45:1-54.
19. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc. 1996;91:473-89.

20. Fay MP, Shaw PA. Exact and Asymptotic Weighted Logrank Tests for Interval Censored Data: The interval R package. Journal of statistical software. 2010;36(2).
21. Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. Statistics in medicine. 1996;15(13):1387-95.
22. Anderson-Bergman C. icenReg: Regression Models for Interval Censored Data in R. J Stat Softw. 2017;81(12):1-23.
23. Ogilvie-Harris DJ, McLean J, Zarnett ME. Pigmented villonodular synovitis of the knee. The results of total arthroscopic synovectomy, partial, arthroscopic synovectomy, and arthroscopic local excision. J Bone Joint Surg Am. 1992;74(1):119-23.
24. De Ponti A, Sansone V, Malchere M. Result of arthroscopic treatment of pigmented villonodular synovitis of the knee. Arthroscopy. 2003;19(6):602-7.
25. Jain JK, Vidyasagar JV, Sagar R, Patel H, Chetan ML, Bajaj A. Arthroscopic synovectomy in pigmented villonodular synovitis of the knee: clinical series and outcome. Int Orthop. 2013;37(12):2363-9.
26. de Carvalho LH, Jr., Soares LF, Goncalves MB, Temponi EF, de Melo Silva O, Jr. Long-term success in the treatment of diffuse pigmented villonodular synovitis of the knee with subtotal synovectomy and radiotherapy. Arthroscopy. 2012;28(9):1271-4.
27. Kubat O, Mahnik A, Smoljanovic T, Bojanic I. Arthroscopic treatment of localized and diffuse pigmented villonodular synovitis of the knee. Collegium antropologicum. 2010;34(4):1467-72.
28. Loriaut P, Djian P, Boyer T, Bonvarlet JP, Delin C, Makridis KG. Arthroscopic treatment of localized pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20(8):1550-3.
29. Rhee PC, Sassoon AA, Sayeed SA, Stuart MS, Dahm DL. Arthroscopic treatment of localized pigmented villonodular synovitis: long-term functional results. American journal of orthopedics. 2010;39(9):E90-4.
30. Noailles T, Brulefert K, Briand S, Longis PM, Andrieu K, Chalopin A, et al. Giant cell tumor of tendon sheath: Open surgery or arthroscopic synovectomy? A systematic review of the literature. Orthop Traumatol Surg Res. 2017;103(5):809-14.
31. Schwartz HS, Unni KK, Pritchard DJ. Pigmented villonodular synovitis. A retrospective review of affected large joints. Clin Orthop Relat Res. 1989(247):243-55.
32. Chin KR, Barr SJ, Winalski C, Zurakowski D, Brick GW. Treatment of advanced primary and recurrent diffuse pigmented villonodular synovitis of the knee. J Bone Joint Surg Am. 2002;84-A(12):2192-202.
33. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference. 2018.
34. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). ASCO conference 2017. 35 (15 Supplement 1).
35. 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(8):949-56.

Appendix

Table 1 Collected patient and tumour characteristics with corresponding definitions.

Characteristic	Definition
TGCT-type	Localized-/diffuse-TGCT as defined by the 2013 WHO[1, 2]
Admission status	Previously treated*
Sex	Male/female
Age at initial treatment	Age at initial treatment
Side	Left/right
Localization	TGCT affected joint
Bone involvement	Discontinuation of cortex by tumour ingrowth*
Date first diagnosis	Date first diagnosis
Duration of symptoms	Duration of symptoms in months
Pain, swelling, stiffness and limited range of motion prior to initial treatment and at last follow-up	(Clinically relevant) Pain, swelling, stiffness[+] and limited range of motion prior to initial treatment* and at last follow-up
Total number surgeries	All surgeries related to TGCT, including re-operations for complications
Date initial treatment**	Date initial treatment at tertiary centre and date(s) of consecutive treatment(s)
Initial treatment**	Type of initial treatment and consecutive treatment(s): arthroscopic resection, one-staged open resection, two-staged open resection, (tumour) prosthesis, amputation, wait and see[++], synovectomy not specified
Tumour size	Largest size in any dimension (cm), according to the 2013 WHO classification[1, 2], <5 and ≥5 cm were compared
Adjuvant therapy	Nothing, radiotherapy, ^{90}Yttrium, targeted therapy, cryosurgery, other
Date complication	Date complication related to surgical treatment
Complication	Type of complication related to surgical treatment: no complication, superficial wound infection, deep wound infection, joint stiffness[+], haemorrhage, neurovascular damage, thrombosis, other, unknown
Total number recurrences	Total number local recurrences
Date final follow-up	Date final follow-up
Status last follow-up	No evidence of disease, alive with disease wait and see, alive with disease planned surgery of adjuvant therapy, death of disease, death of other disease, lost (<6 months follow-up)
Chronic analgesic treatment at last follow-up	Chronic analgesic treatment at last follow-up

Characteristics in **bold** were core criteria. *These parameters were answered by present or absent. **(Date) initial treatment, initial treatment in tertiary centre is not necessarily first treatment of the patient. [+]Stiffness requiring manipulation under anaesthesia. [++]Wait and see and conservative treatment are considered similar.

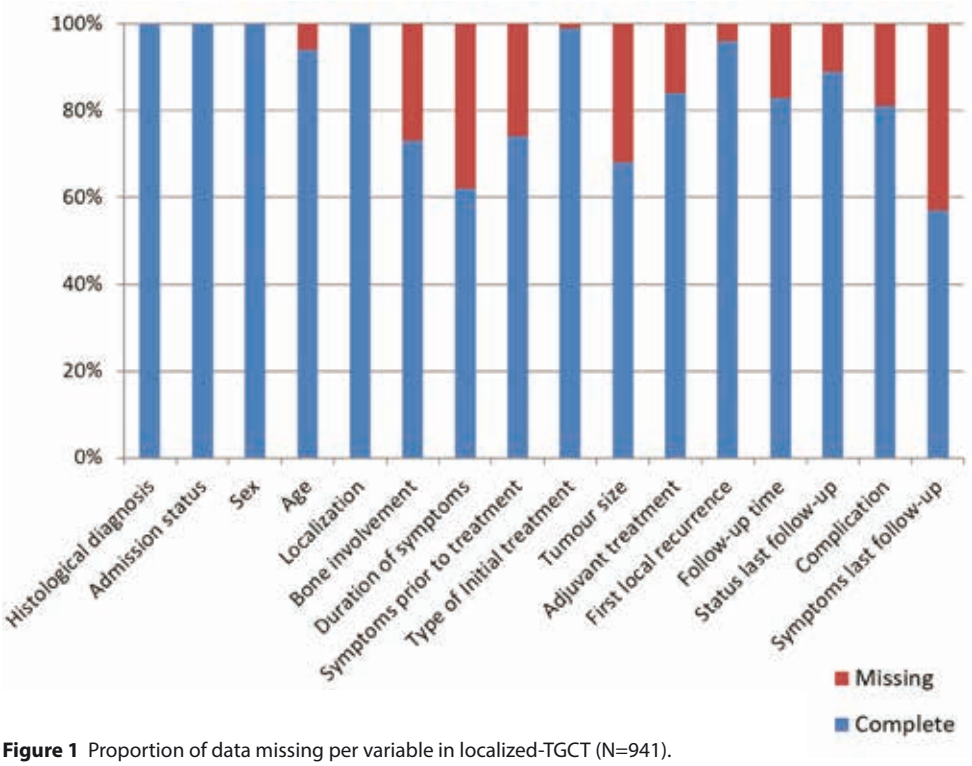


Figure 1 Proportion of data missing per variable in localized-TGCT (N=941).
Symptoms prior to initial treatment at tertiary centre include pain, swelling, stiffness and limited range of motion. Symptoms at last follow-up include pain, swelling, stiffness, limited range of motion and chronic analgesic treatment at last follow-up.

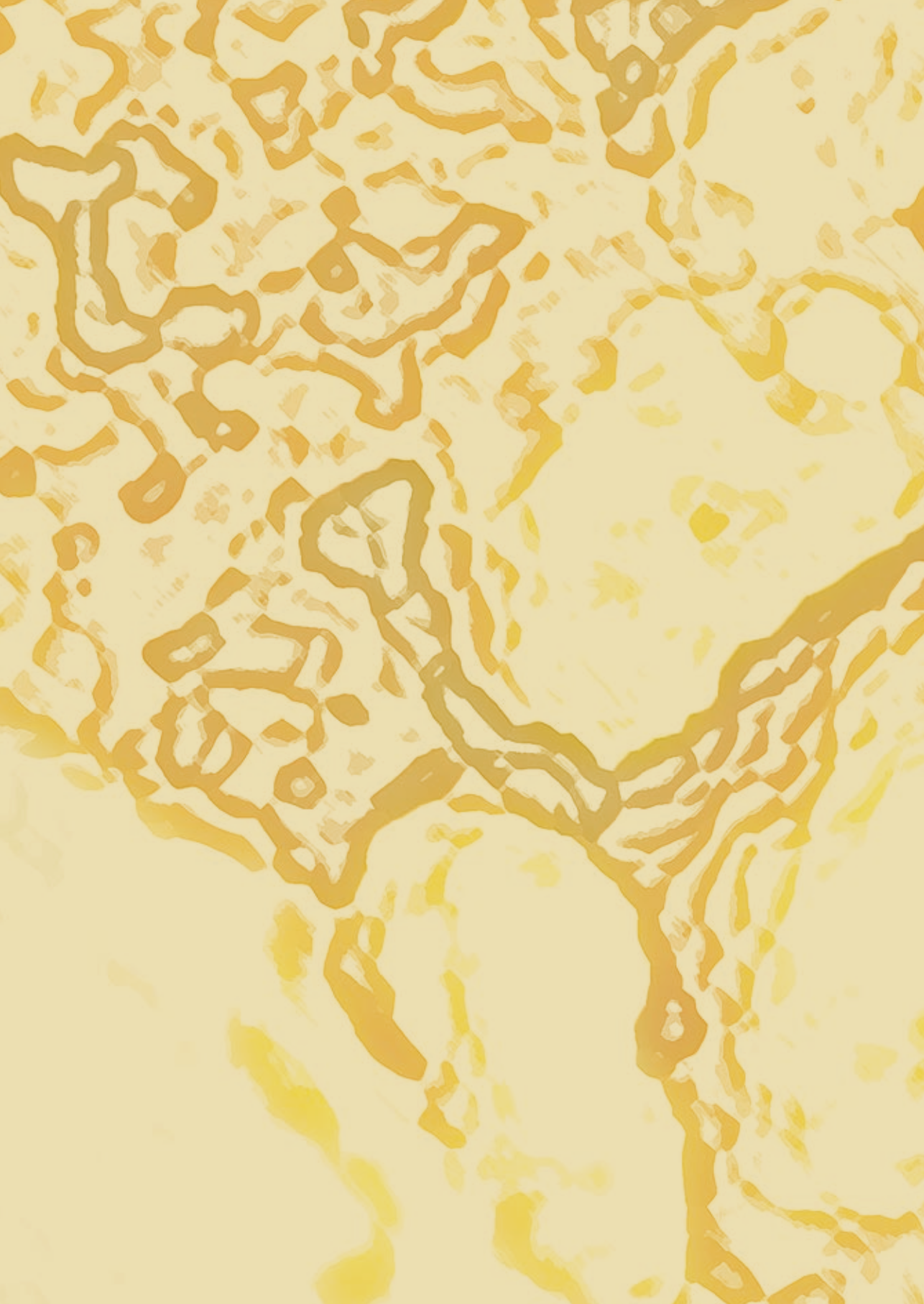
Supplementary material participating international sarcoma reference centres

1. Leiden University Medical Center, **Leiden**, The Netherlands
2. Radboud University Nijmegen Medical Center, **Nijmegen**, The Netherlands
3. IRCCS Istituto Ortopedico Rizzoli, **Bologna**, Italy
4. Fondazione IRCCS Istituto Nazionale dei Tumori, **Milano**, Italy
5. Istituto Ortopedico Gaetano Pini, **Milano**, Italy
6. Mount Sinai School of Medicine, **New York**, USA
7. Medical University Graz, **Graz**, Austria
8. Halen İstanbul Üniversitesi, **Istanbul**, Turkey
9. AOU Città della Salute e della Scienza, **Torino**, Italy
10. Orthopedic Hospital Gersthof, **Vienna**, Austria
11. Careggi University-Hospital, **Firenze**, Italy
12. University Medical Center Groningen, **Groningen**, The Netherlands
13. Academic Medical Center, **Amsterdam**, The Netherlands
14. Mount Sinai Hospital, **Toronto**, Canada
15. Beijing Jishuitan Hospital, **Beijing**, 100035, China
16. Institut Roi Albert II, **Brussels**, Belgium
17. Royal National Orthopedic Hospital, **London**, the United Kingdom
18. Hospital de Navarra, **Pamplona**, Spain
19. Centre hospitalier universitaire de Nantes, **Nantes**, France
20. Ludwig-Maximilians-University Munich, **Munich**, Germany
21. Medical University of Innsbruck, **Innsbruck**, Austria
22. Massachusetts General Hospital Harvard, **Boston**, United States of America
23. Chiba Cancer Center, **Chiba**, Japan
24. National Cancer Center, **Tokyo**, Japan
25. Kanazawa University Graduate School of Medical Sciences, **Kanazawa**, Japan
26. Sytenko Institute of Spine and Joint Pathology, **Kharkiv**, Ukraine
27. Universitätsklinikum Jena, **Jena**, Germany
28. University of the Phil-Phil General Hospital, **Manila**, Philippines
29. Catholic University of Korea, **Seoul**, Korea
30. Cairo University, **Cairo**, Egypt
31. Wilhelmsburger Krankenhaus Groß Sand, **Hamburg**, Germany

Supplementary material exact survival information and statistical methods

For some cases exact survival information was not available (*appendix figure 1*). In 7 out of 61 cases, we could recover the missing recurrence indicator: in 2 cases patients had a second treatment and in 5 cases patients had follow-up status 'alive with disease' and were classified as recurrent disease. If the exact time of recurrence was not recorded, an approximation was sometimes possible. If the date of surgery to treat a local recurrence was known, this was used instead (N=33). If this information was missing as well, then the date of last recurrence was used as an upper bound (N=5). Otherwise the date of last recorded follow-up was used as an upper bound (N=69). If data on recurrence status or date of recurrence was missing and could not be recovered as described, patients were excluded for risk- and survival analyses (N=64).
Some centres did not record follow-up time in patients without recurrent disease. To prevent exclusion of these patients, we imputed their follow-up time (N=97). Multiple imputation technique was applied and 5 complete data sets were imputed using the R-package Amelia II[18]. Statistical analyses were conducted on all data sets and the results were then pooled following Rubin's rule[19].

As a consequence of the approximation of the time of recurrence by upper bounds in some cases, common survival methods (Kaplan-Meier estimate, log rank test) were substituted by methods that allow interval censoring. Observed survival curves and probabilities were computed using non-parametric maximum likelihood estimates for interval censored data with the R-package interval[20]. P-values for the univariate analyses were calculated with the score test of Sun (1996)[21]. Covariates that were found to have a significant association with local recurrence free survival in the univariate analysis were included in a multivariate Cox regression analysis using the icenReg R-package, which allows for interval censored data[22].



DIFFUSE

chapter eight

Outcome of surgical treatment for patients with diffuse-type Tenosynovial Giant Cell Tumours

Largest cohort of individual participant data meta-analysis of 31 international sarcoma centres

M.J.L. Mastboom[1], E. Palmerini[2], F.G.M. Verspoor[3], A.J. Rueten-Budde[4], S. Stacchiotti[5], E.L. Staals[6], G.R. Schaap[7], P.C. Jutte[8], W. Aston[9], H. Gelderblom[10], A. Leithner[11], D. Dammerer[12], A. Takeuchi[13], Q. Thio[14], X. Niu[15], J.S. Wunder[16], TGCT-study group*, M.A.J. van de Sande[1]

Submitted.

[1] Orthopaedic Surgery, Leiden University Medical Center, Leiden, the Netherlands

[2] Medical Oncology, Musculoskeletal Oncology Department, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[3] Orthopaedic Surgery, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands

[4] Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, the Netherlands

[5] Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[6] Orthopaedic Surgery, Musculoskeletal Oncology Department, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[7] Orthopaedic Surgery, Academic Medical Center, Amsterdam, the Netherlands

[8] Department of Orthopaedics, University Medical Center, University of Groningen, Groningen, the Netherlands

[9] Orthopedic surgery, Royal National Orthopedic Hospital, London, the United Kingdom

[10] Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands

[11] Department of Orthopaedic Surgery, Medical University Graz, Graz, Austria

[12] Orthopedic surgery, Medical University of Innsbruck, Innsbruck, Austria

[13] Orthopaedic surgery, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

[14] Orthopedic surgery, Massachusetts General Hospital Harvard, Boston, United States of America

[15] Department of Orthopedic Oncology, Beijing Jishuitan Hospital, Beijing, 100035, China

[16] University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, Canada

***TGCT study-group**

M. Fiocco, P.D.S. Dijkstra, R.J.P. van der Wal, P.A. Daolio, P. Picci, A. Gronchi, S. Ferrari, H. Özger, R.G. Maki, H.W.B. Schreuder, I.C.M. van der Geest, J.A.M. Bramer, M. Boffano, E. Goldenitsch, D. Campanacci, P. Cuomo, P.C. Ferguson, A.M. Griffin, Y. Sun, T. Schubert, K. Patel, M.S.J. Aranguren, A. Blancheton, F. Gouin, H.R. Dürr, C.F. Capellen, J. Schwab, S. Iwata, O. Vyrva, W. Weschenfelder, E.H.M. Wang, M. Wook Joo, Y.K. Kang, Y.G. Chung, W. Ebeid, J. Bruns, T. Ueda

Abstract

Objective

Diffuse-type Tenosynovial Giant Cell Tumour (TGCT) is a rare, locally aggressive and difficult to treat disease. An international multicentre-pooled retrospective study of individual patient data was developed to describe global treatment protocols, evaluate oncological outcome, complications and functional results. A secondary study aim was to identify risk factors for local recurrence after surgical treatment.

Methods

Patients treated in 31 sarcoma reference centres between 1990 and 2017, with histologically proven diffuse-TGCT of large joints were included. Of 1192 cases of diffuse-TGCT, 58% were female with a median age 35 years. 64% affected the knee and in 54% primary treatment was one-staged open synovectomy. Risk factors were tested in a univariate analysis and significant factors subsequently included for multivariate analysis, with first local recurrence after surgical treatment in a tertiary centre as the primary outcome.

Results

At a median follow-up of 54 (95%CI 50-58) months, recurrent disease developed in 44% of all surgically treated cases, with local recurrence free survival (RFS) at 3, 5, 10 years of 62%, 55% and 40%, respectively. The strongest risk factor for recurrent disease was prior recurrence (HR 3.5 95%CI 2.8-4.4, $p<0.001$) with a 5-year RFS of 64% in surgery naïve patients compared with 25% in patients operated for recurrent disease. Complications were noted in 12% of patients. Pain and swelling improved after surgical treatment(s) in 59% and 72% of patients respectively. In a subgroup analysis including only naïve cases affecting the knee, neither sex (male;female), age (≤35years;>35years), bone-involvement (present;absent), surgical technique (open;arthroscopic) nor tumour size (<5cm;≥5cm) yielded an association with the first local recurrence.

Conclusion

This largest international individual data study of patients with diffuse-TGCT, provides a comprehensive and up to date disease overview, evaluating the clinical profile and management of the disease. Since complete resection of diffuse-TGCT could be regarded as nearly impossible and recurrence rates are unacceptably high after both arthroscopy and open synovectomy in the knee, even in specialized centres, a multimodality approach in this disease, including adjuvant treatments, is warranted.

Introduction

In the most recent WHO classification (2013), giant cell tumour of the tendon sheath and pigmented villonodular synovitis (PVNS) were unified by one overarching term: tenosynovial giant cell tumours (TGCT). This rare, mono-articular disease arises from the synovial lining of joints, bursae or tendon sheaths in predominantly young adults[1, 2]. Excluding digits, TGCT is most commonly diagnosed around the knee and can be found in other weight bearing joints as well[1-4].

Two clinically and radiographically distinct subtypes of TGCT are defined with different natural courses of disease. The localized-type is defined as a well-circumscribed nodule. On the contrary, the diffuse-type is known as an ill-circumscribed, locally aggressive and invasive tumour (*figure 1, chapter 1, page 13*)[1, 2, 5]. Even though histopathology and genetics seem identical, the biological behaviour of both subtypes is incomparable and therefore necessitates separate evaluations, analyses and treatments. The current study focuses on diffuse-TGCT of large joints.

Macroscopically, diffuse-type TGCT involves a large part or even the complete synovial lining of a joint with either a typical villous pattern (intra-articular) or a multi-nodular appearance (extra-articular), including a diverse colour pattern, varying from white-yellow to brown-red areas. This subtype shows an infiltrative growth pattern. Definite diagnosis is established on microscopy by an admixture of mononuclear cells (histiocyte-like and larger cells) and multinucleated giant cells, lipid-laden foamy macrophages (also known as xanthoma cells), siderophages (macrophages including hemosiderin-depositions), stroma with lymphocytic infiltrate and some degree of collagenisation. Molecular analysis is generally not required to confirm the diagnosis.

Pain, (haemorrhagic) joint effusion, stiffness and limited range of motion are the main clinical complaints[6]. These non-specific symptoms frequently cause a delay in diagnosis[7]. The predominant standard of care is surgical resection of diffuse-TGCT, either arthroscopically or with an open resection or a combination of both, in order to: (1) reduce debilitating symptoms and joint destruction caused by the disease process; (2) improve limb function; and (3) minimize the risk of local recurrence. Clinical and oncological outcomes following surgery largely depend on multiple factors including preoperative diagnostic evaluation, the localization and extent of disease and possibly the choice of treatment modalities by orthopaedic surgeons[3, 5, 8-10]. Diffuse-

TGCT frequently causes significant morbidity due to the invasiveness of the surgical resection and the high rate of local recurrence (14-40% depending on surgical procedure and follow-up time), with deteriorated health-related quality of life[6, 8, 9, 11-14]. Therefore, treatment of diffuse-TGCT may include adjuvant or multimodality treatment such as external beam radiation therapy[10, 15, 16], radiation synovectomy with ^{90}Yttrium[17] or *CSF1* inhibitors, such as nilotinib, imatinib, pexidartinib, emactuzumab, cabrilazimab and MSC110[18-22]. Of note, so far none of these agents have been formally approved for use in the disease, and long-term efficacy is unknown.

The incidence of diffuse-TGCT of large joints is 4.1 per million person-years[4]. Therefore, the current literature mainly consists of relatively small, or larger but heterogeneous case-series. Risk-factors for recurrent disease in individual patients need to be identified by evaluating outcomes of different treatment strategies. Since (larger) randomized controlled trials on the role of surgery in TGCT are lacking, individual participant data meta-analysis is currently the highest achievable evidence. It offers advantages above a meta-analyses, including: (1) missing data can be accounted for at an individual patient level, (2) subgroup analyses can be performed (e.g. per affected joint) and (3) follow-up information can be updated[23]. Therefore, we aimed to collaborate with tertiary sarcoma centres across the globe to include individual patient data in this investigation.

The main aim of this international multicentre cohort study is to provide comprehensive and up to date insights on the surgical treatment and outcome for patients with diffuse-type TGCT. Oncologic results, complications and functional results are described. In addition, risk factors for local recurrence after surgical treatment are identified.

Methods

Recruitment and patient inclusion criteria

Patients of any age treated between January 1990 and December 2017 in one of 31 international sarcoma centres (supplementary material: participating international sarcoma reference centres, page 160) with histologically proven TGCT of large joints were retrospectively included. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints. Identification and collection of the patients was performed in the centres of origin and data were analysed from initial treatment at these tertiary centres. Data were encrypted and transferred to the international multicentre database at the Leiden University Medical Centre (LUMC), with patient collection ending as of May 2018.

Study parameters

Collected patient-, tumour- and treatment characteristics with corresponding definitions are shown in *appendix table 1 (chapter 7, page 158)*. The following characteristics were defined as core criteria: TGCT-type (localized-; diffuse-; unknown-type), admission status (therapy-naïve; 1st recurrence; 2nd recurrence; 3rd recurrence; etc.) date and type of initial treatment at a tertiary centre (arthroscopic synovectomy; one-staged synovectomy; two-staged synovectomy; synovectomy not specified; (tumour)prosthesis; amputation; wait and see); and first local recurrence after treatment (yes; no) in a tertiary centre. Complete data on these core criteria were necessary for reliable analyses.

Patient-, tumour- and treatment characteristics

Thirty-one specialized sarcoma centres spread throughout Europe, North America, Canada and Asia collaborated to provide a total of 1192 diffuse-TGCT cases (*table 1*). As per entry criteria, patients with localized-TGCT (N=941) and unknown type TGCT (N=36) were excluded.

Statistical analyses

The primary endpoint was local recurrence free survival (RFS) after initial treatment in a tertiary centre. Recurrent disease was defined as the presence of new disease after resection (and synovectomy) performed in a tertiary centre or progressive residual disease (as diagnosed by local investigators on repeated follow-up Magnetic Resonance (MR) imaging).

Table 1 Patient-, tumour- and treatment characteristics

Characteristics	Overall (%)
Total number	1192 (100)
Admission status (N=1192)	
Therapy naïve^	910 (76)
≥1 Surgery elsewhere^^	282 (24)
Sex (N=1192)	
Male	499 (42)
Female	693 (58)
Median age at initial treatment years (N=1122)	35
IQR	26-48
Localization (N=1192)	
Knee	758 (64)
Hip	124 (10)
Ankle	162 (14)
Foot*	63 (5)
Shoulder	15 (1)
Elbow	17 (1)
Wrist	25 (2)
Hand*	13 (1)
Other	15 (1)
Bone involvement (N=847)	
Present	259 (30)
Absent	588 (70)
Median duration of symptoms# months (N=744)	18
IQR	6-36
Type of surgical treatment at tertiary centre (N=1163)	
Arthroscopic synovectomy	159 (14)
One-staged open synovectomy	628 (54)
Two -staged open synovectomy##	187 (16)
(Tumour)prosthesis+,¥	63 (5)
Amputation¥	3 (0.3)
Wait and see$,¥	76 (7)
Synovectomy not specified	47 (4)
Median tumour size initial treatment in cm (N=701)	5.4
IQR	3.0-8.8
<5 cm	297 (42)
≥5 cm	404 (58)
Adjuvant therapy initial treatment (N=1033)	
External beam radiotherapy	58 (6)
^{90}Yttrium	60 (6)
Systemic/molecular targeted treatment	15 (1)
Other	11 (1)
None	889 (86)

IQR, Interquartile Range; ^Therapy-naïve or primary admission status at tertiary centre are considered similar; ^^≥1 Surgery elsewhere or recurrent admission status are considered similar; *Digits are excluded; #Symptoms were defined as either pain, swelling, stiffness or limited range of motion (table 7-8); ##A two-stage synovectomy is defined as two synovectomies within six months; +An arthrodesis is classified as (tumour)prosthesis; $Wait and see and conservative treatment are considered similar; ¥(Tumour)prosthesis, amputation or wait and see as initial treatment are excluded for risk and survival analyses.

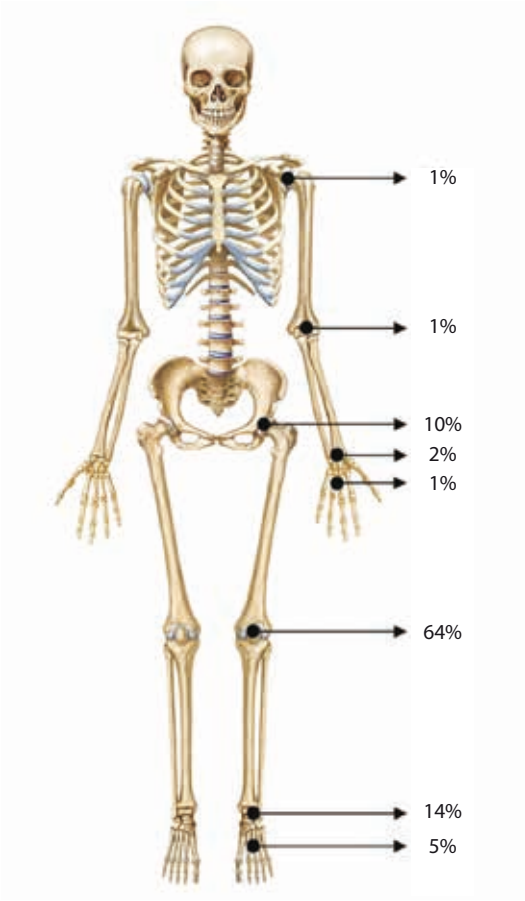


Figure 2 Skeleton showing localization of TGCT in 1192 diffuse-TGCT cases. 15 diffuse-TGCT cases were classified as 'other localization'

To investigate the effect of risk factors on the outcome, univariate analyses were performed and significant factors ($p<0.05$) were subsequently included into a multivariate analysis. Proposed risk factors were admission status (therapy-naïve versus recurrent disease), sex (male versus female), age (≤35 years versus >35 years), localization (knee versus hip versus foot/ankle versus upper extremity), bone-involvement (present versus absent), surgical technique (open versus arthroscopic) and tumour size (<5 cm versus ≥5cm). Patients with a wait and see policy or as initial treatment (tumour) prosthesis surgery or an amputation were excluded from statistical analysis (N=142).

Observed RFS probabilities at 3, 5, and 10 years were computed for all cases and subgroups based on admission status and localization.

For some patients exact survival information was not available (*appendix: proportion of data missing per variable*). In 34 out of 107 cases, we could recover the missing recurrence indicator: 9 patients had a second treatment and 25 patients had follow-up status 'alive with disease' and were classified as having recurrent disease. When the exact time of recurrence was not recorded, an approximation was applied where possible. When the date of surgery to treat a recurrence was known, this was used as the date of local recurrence instead (N=177). When this information was missing as well, the date of last recurrence was used as an upper bound (N=58). Otherwise the date of last recorded follow-up was used as an upper bound (N=69). When data on recurrence status or date of recurrence was missing and could not be recovered as described, patients were excluded for risk- and survival analyses (N=84).
Some centres did not record follow-up time for patients without recurrent disease. To prevent exclusion of these patients, we imputed their follow-up time (N=79). Multiple imputation technique was applied and 5 complete data sets were imputed using the R-package Amelia II[24]. Statistical analyses were conducted on all data sets and the results were then pooled following Rubin's rule[25].

As a consequence of the approximation of the time of recurrent disease by upper bounds in some cases, common survival methods (Kaplan-Meier estimate, logrank test) were substituted by methods that allow for interval censoring. Observed survival curves and probabilities were computed using non-parametric maximum likelihood estimates for interval censored data with the R-package interval[26]. P-values for the univariate analyses were calculated with the score test of Sun (1996)[27].
Covariates that were found to have a significant association with local recurrence free survival in the univariate analysis were included in a multivariate Cox regression analysis using the icenReg R-package, which allows for interval censored data[28].

All data were selected for completeness on core criteria (*appendix, chapter 7, page 158*). Statistical analyses were carried out using R version 3.4.1.

On purpose, an estimate of the median time to recurrence was not provided. Calculating such a median based on patients for whom a recurrence was recorded, would assume that all other patients could not experience a recurrence in the future. The extent of this so-called immortal time bias is unknown. For this reason, such an estimate will be an underestimation of the true time to recurrence.

Ethical consideration

This study is conducted according to the Declaration of Helsinki (October 2013) and approved by the institutional review board (CME) from the Leiden University Medical Center (LUMC) (May 4th, 2016; G16.015).

RESULTS

Oncologic outcome

In 966 patients with surgically treated diffuse-TGCT and complete survival data, 425 (44%) had a tumour recurrence following treatment. The recurrence free survival (RFS) continued to decrease with longer follow-up times (*table 2-3, figure 3*).

Univariate- and multivariate analyses for local recurrence

In univariate analysis of 966 patients with surgically treated diffuse-TGCT and complete core data, the risk factor admission status was found to be significantly associated with recurrence: 5-year RFS was 64% for therapy naïve patients (95% CI 60-68) compared to 25% for patients entering the tertiary hospital with recurrent disease (95% CI 19-31; p <0.001). This difference was confirmed by multivariate analysis (HR 3.5 95% CI 2.8-4.4, p<0.001).

After excluding patients admitted with recurrent disease, surgical technique was also positively associated with first local recurrence (*table 4*). This result was confirmed by cox regression analysis (HR 1.407; 95% CI 1.02-1.95, p=0.04). In a subgroup analysis of therapy naïve patients with diffuse-TGCT affecting the knee, surgical technique was not found to be associated with first local recurrence (p=0.113).

Observed recurrence free survival according to admission status and localization

Highest recurrence rates are report in TGCT affecting the knee; 43% after arthroscopic synovectomy and 37% after open synovectomy (*figure 4*). A progressively declining RFS was seen at 3, 5 and 10 years in a subgroup analysis of the knee, hip, foot/ankle and upper extremity locations in patients either admitted with therapy naïve TGCT or patients admitted with recurrent TGCT (*table 5*). After 10 years follow-up, patients with therapy naïve disease affecting the knee were found to have the lowest RFS rates of all sites (46%, 95% CI 39-54). All patients entering a tertiary hospital with recurrent disease exhibited very low RFS at 10 years (*figure 3a*).

Table 2 Oncologic outcome after surgical treatment of diffuse-TGCT of large joints of all patients primary treated at a tertiary centre

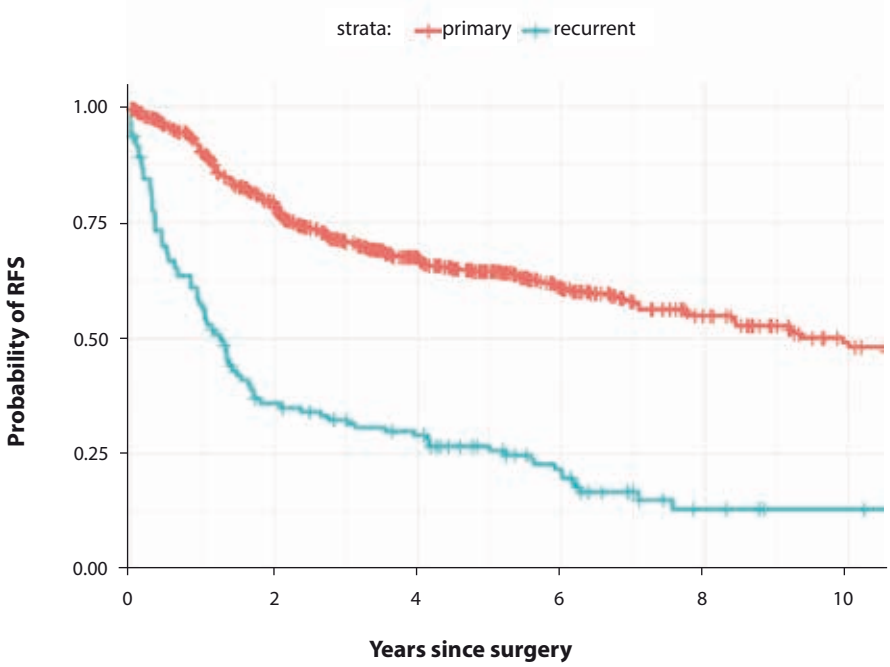
Characteristics	Overall (%)
First local recurrence after initial treatment at tertiary centre (N=966)	
Present	425 (44)
Absent	541 (56)
Total number of recurrences (N=425)	
1	267 (63)
2	85 (20)
≥3	73 (17)
Mean total number of surgeries (N=707)	2.0 (range 1-10)
Mean total number of surgeries in recurrent disease (N=425)	2.7 (1-10)
Median follow-up months (N=966)	54
95% CI	50-58
Status last follow-up (N=891)	
No evidence of disease	587 (66)
Alive with disease - wait and see	190 (21)
Alive with disease - awaiting treatment	31 (3)
Death of other disease	10 (1)
Lost to follow-up*	73 (8)

*Lost to follow-up was defined as follow-up less than 6 months or stratified during follow-up as lost to follow-up.

Table 3 Diffuse-TGCT recurrence free survival (RFS) all patients versus therapy naïve patients treated at tertiary centre

Year	N all	% RFS all (95%CI)	N therapy naïve	% RFS therapy naïve (95%CI)
3	474	62 (59-65)	372	70 (67-74)
5	297	55 (51-58)	227	64 (60-68)
10	89	40 (35-45)	70	50 (44-56)

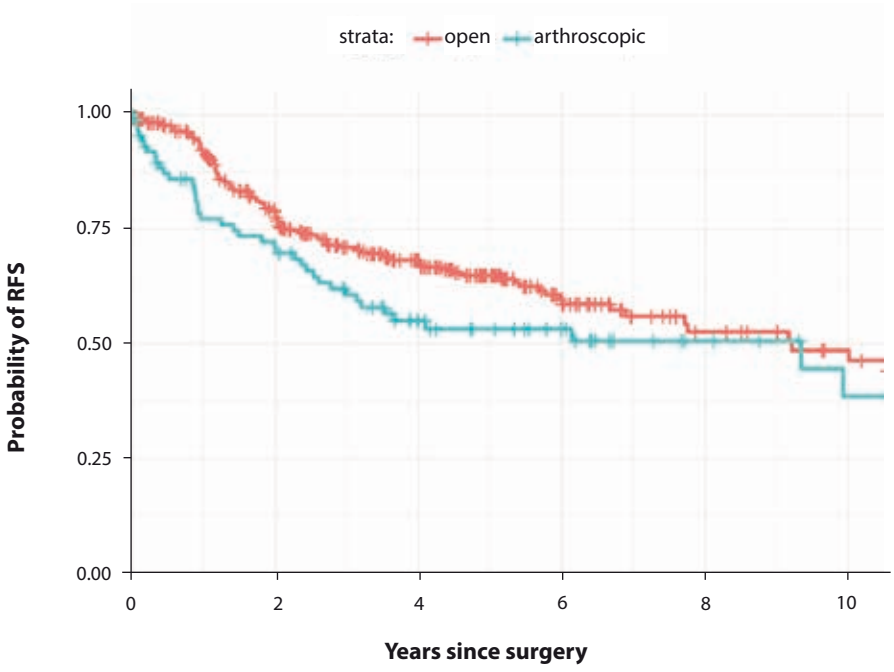
N is number of patients at risk for recurrent disease at 3, 5 and 10 years.



number at risk

primary	758	506	310	170	97	63
recurrent	208	128	88	53	30	18
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 3a Local recurrence free survival curve in diffuse-TGCT stratified for admission status (p<0.001). Time zero was date of initial resection at tertiary centre. Primary: patient with therapy-naïve disease initially treated at tertiary centre, recurrent: patient initially treated elsewhere.



number at risk

open	346	225	146	71	39	29
arthroscopic	99	65	40	25	13	8
years	*0*	*2*	*4*	*6*	*8*	*10*

Figure 3b Local recurrence free survival curve in patients with therapy naïve diffuse-TGCT affecting the knee stratified for surgical technique (p=0.11). Time zero was date of initial resection at tertiary centre. Open: open resection, arthroscopic: arthroscopic resection.

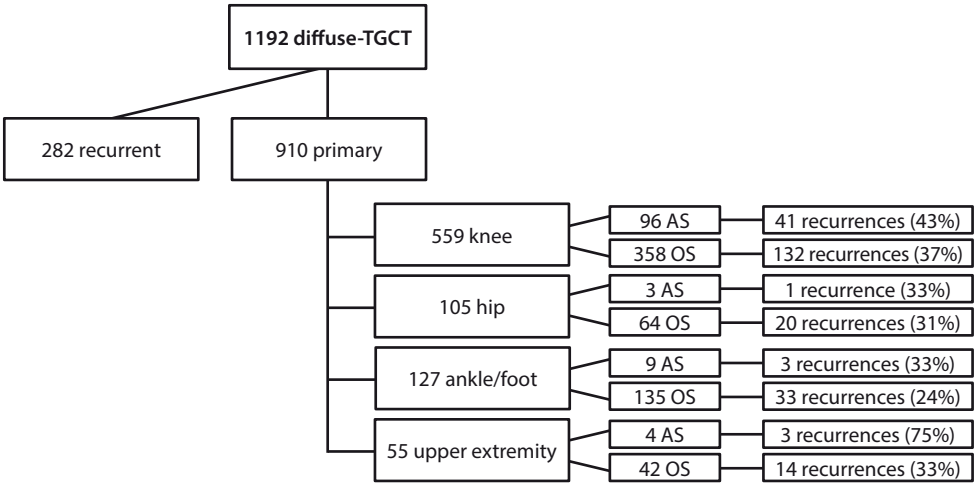


Figure 4 Flowchart of diffuse-TGCT patients with treatments and recurrences for each affected joint.
Primary: patient was first seen at tertiary centre with therapy-naïve disease, recurrent: patient initially treated elsewhere, AS: Arthroscopic synovectomy, OS: Open synovectomy. Treatments other than AS and OS were not included in this flowchart (e.g. (tumour)prosthesis, amputation, wait and see treatment).

Complications

A total of 105 (12%) complications occurred following surgical treatment of diffuse-TGCT (*table 6*). The majority of these complications developed after one- or two-staged open synovectomy (86/105; 82%). In comparison, 12 complications (11%) were reported following arthroscopic synovectomy.

Functional outcome

Prior to surgical treatment, the majority of patients had symptoms of pain (76%) and swelling (75%) (*table 7*). After surgical treatment, at final follow-up, these symptoms largely disappeared, although 37% and 24% of patients respectively were still symptomatic. Joint stiffness and limited range of motion were only present in 21% and 27% of cases, respectively, and these symptoms improved slightly after treatment (17% and 19% at final follow-up).

Table 4 Univariate analyses in 758 patients with therapy naïve diffuse-TGCT

Variable	N	%RFS at 5 years	95%CI	P value
Age				
≤35 years	391	64	59-70	0.94
>35 years	364	63	57-69	
Sex				
male	307	63	56-69	0.86
female	451	64	59-70	
Localization				
knee	471	61	56-66	0.10
hip	70	65	54-77	
foot/ankle	158	72	64-81	
upper extremity	59	59	44-74	
Size				
<5 cm	217	71	64-78	0.42
≥5 cm	295	64	58-71	
Bone involvement				
present	158	61	52-69	0.82
absent	425	64	58-69	
Surgical technique				
open	595	66	61-70	0.03
arthroscopic	120	54	44-64	

A mean of 578 (48%) patients with diffuse-TGCT had complete data on symptoms both prior to initial treatment and at final follow-up (*table 8*). The majority of patients experienced pain and swelling prior to initial treatment, of which 59% and 72% resolved after surgical treatment(s). Patients with initial complaints of stiffness and limited range of motion also improved after surgery (64% and 73%).

Table 5 Recurrence free survival probabilities at 3, 5, and 10 years for on type of TGCT, admission status and localization

Admission status	Localization	N+	% RFS at 3 years	95% CI	% RFS at 5 years	95% CI	% RFS at 10 years	95% CI
primary	knee	471	68	63-73	61	56-66	46	39-54
primary	hip	70	67	56-79	65	53-77	54	38-70
primary	foot/ankle	158	79	72-87	72	64-81	57	44-70
primary	upper extremity*	59	69	56-82	59	44-75	55	38-71
recurrent	knee	145	29	21-36	25	18-32	15	8-21
recurrent	hip	8	40	6-74	40	6-74	**	
recurrent	foot/ankle	39	43	27-59	24	10-38	18	4-33
recurrent	upper extremity*	16	25	3-47	25	3-47	15	0-33

+N: number at baseline (time point = 0), *Upper extremity including other localization, **10 years RFS and associated 95%CI of recurrent hip cases could not be estimated (due to lack of follow-up information). Primary: patient was first seen at tertiary centre with therapy-naïve disease Recurrent: patient initially treated elsewhere, 95%CI: 95% Confidence interval.

Table 6 Complications after surgical treatment at tertiary centre (N=906)

Complications after surgical treatment	N (%)
Superficial wound infection	15 (2)
Deep wound infection	10 (1)
Joint stiffness	32 (4)
Haemorrhage	7 (1)
Neurovascular damage	15 (2)
Thrombosis	1 (0.1)
Other+	25 (3)

+Other surgical complications after initial treatment included: joint luxation (hip), compartment syndrome, ligament incision during surgery, complex regional pain syndrome, tourniquet blistering, tendinitis. As osteoarthritis is either caused by extensive disease or by (multiple) treatments, it was not taken into account for complications.

Table 7 Symptoms prior to treatment and at final follow-up

Symptom	Pre-treatment	Final follow-up
Pain (PT 969, FF 630)	738 (76%)	233 (37%)
Swelling (PT 775, FF 627)	579 (75%)	149 (24%)
Joint stiffness (PT 759, FF 617)	161 (21%)	105 (17%)
Limited range of motion (PT 760, FF 624)	209 (27%)	118 (19%)
Chronic analgesic treatment* (FF 714)		92 (13%)

*Chronic analgesic treatment data was only available at final follow-up; PT, pre-treatment; FF, final follow-up

Table 8 Comparing symptoms diffuse-TGCT prior to treatment to last follow-up

	No pain last fu	Pain last fu	Total
No pain initially	118 (20%)	36 (6%)	154
Pain initially	255 (43%)	179 (31%)	434
	No swelling last fu	**Swelling last fu**	
No swelling initially	119 (20%)	13 (2%)	132
Swelling initially	328 (56%)	125 (22%)	453
	No stiffness last fu	**Stiffness last fu**	
No stiffness initially	383 (68%)	55 (10%)	438
Stiffness initially	82 (14%)	47 (8%)	129
	No limited range of motion last fu	**Limited range of motion last fu**	
No limited range of motion initially	337 (59%)	59 (10%)	396
Limited range of motion initially	128 (23%)	48 (8%)	176

Fu; follow-up

Local recurrence versus symptoms final follow-up

A higher percentage of patients with pain, swelling, stiffness and limited range of motion at final follow-up had recurrent disease (pain; 55% recurrence versus 45% no recurrence, swelling; 66% versus 34%, stiffness; 51% versus 49%, limited range of motion; 56% versus 44%).
More patients with recurrent disease 21% (64/300) used chronic analgesic treatment at last follow-up compared to patients 6% (24/388) without recurrent disease.

Surgical technique versus functional outcome at last follow-up

Surgical technique did not influence functional outcome at last follow-up (pain: 41% symptoms after AS versus 37% after OS, swelling: 29% versus 22%, stiffness: 13% versus 18%, limited range of motion: 16% versus 21%, chronic analgesic treatment: 18% versus 12%).

Chronic analgesic treatment versus complications

24% (16/67) of patients using chronic analgesic treatment had a complication, compared with 10% (50/482) of patients without a complication.

DISCUSSION

This international multicentre study offers new insights into the outcome of patients with the orphan and heterogeneous disease diffuse-type Tenosynovial Giant Cell Tumour (TGCT). The greatest strength of this dataset is that it represents the largest collection of surgically treated diffuse-TGCT patients in the scientific literature, including RFS estimates for the knee, hip, foot/ankle and upper extremity locations with long-term follow-up (>10 years). Oncologic results, complications and functional results after surgical treatment are evaluated.

Oncologic outcome diffuse-TGCT

The fundamental question of whether curative treatment is necessary, or should be attempted in non-lethal diffuse-TGCT often arises in literature. Debilitating symptoms and (progressive) joint destruction commonly result from untreated diffuse-TGCT but can also occur following treatment. At present, the choice of treatment is established by the preference of the patient, treating physician and might differ by treatment centre. Surgical treatment for the locally aggressive diffuse-TGCT is challenging, as pathologic tissue can be widely spread throughout the joint and may be technically difficult to access and remove. In extensive disease, less than radical or only partial resection could be preferred to improve symptoms with joint preservation in mind. However, higher rates of recurrence have been described after macroscopically incomplete resections[8, 29-31].

Some reports consider arthroscopic management of TGCT superior to open surgery, because of less morbidity and a shorter recovery period[32-36]. Standard arthroscopy of the knee using only anteromedial and anterolateral approaches however, does not allow surgical access to remove all areas where diseased tissue is likely to be present. Therefore Blanco et al. and Mollon et al. used multiple portals including posteromedial and posterolateral in arthroscopic synovectomy[37-39]. Chin et al. stated that knee arthroscopy alone is an inferior treatment for extra-articular TGCT[40]. Open synovectomy, either one- or two-staged, seems to be the preferred surgical approach to diffuse-TGCT in most centres, because of tumour visibility and reported lower short-term recurrence rates[11, 41, 42]. The disadvantage of a one- or two-staged open resection, could be deteriorated joint function accompanied with decreased patient health-related quality of life[13]. A systematic review showed lower recurrence rates for open synovectomy (average 14%, maximum 67%) compared to arthroscopic synovectomy (average 40%, maximum 92%) in diffuse-TGCT[11]. Patel et al. (N=214)

reported a statistically significant higher risk of recurrence in diffuse-type TGCT with arthroscopic compared to open synovectomy (83.3% vs 44.8%, RR = 1.86 95% CI 1.32–2.62, P = 0.0004)[9]. Palmerini et al. (N=206) did not find a difference in recurrence based on surgical technique for localized- and diffuse-TGCT combined[8].

A combined anterior arthroscopic- and posterior open synovectomy in the knee might be a viable option, but is only incidentally reported. Mollon et al. described the combined approach of a multiportal anterior and posterior arthroscopy and a posterior open synovectomy largely for resection of extra-articular popliteal disease, and reported two recurrences in 15 patients[38]. Colman et al. retrospectively evaluated 11 diffuse-TGCT patients treated by the combined approach and also reported relatively low short-term recurrence rates (9%)[43]. A randomized controlled trial for arthroscopic synovectomy versus open synovectomy has not been performed.

The present study calculated recurrence free survival rates for diffuse-TGTC at 3, 5 and 10 years of 62%, 55% and 40%, respectively. This clearly underlines that with longer follow-up, recurrence rates continue to increase (*table 2-3, figure 3*). The greatest risk factor for local recurrence is recurrent disease at presentation in a tertiary centre (HR 3.5 95% CI 2.8-4.4 in multivariate analyses). In therapy naïve patients with primary treatment in a tertiary centre, the largest risk factor for local recurrence was arthroscopic synovectomy. The suspicion arises that more (macroscopic) tumour tissue remains after arthroscopic synovectomy; however this largely depends on the extend of the arthroscopy performed, whether multiple and posterior portals were used to access and remove disease throughout the knee joint, and whether this approach is combined with an open approach to remove residual intra-articular disease and/or extra-articular disease extension. However, none of the assumed risk factors yielded significant differences when the analysis was performed in a subgroup of therapy naïve patients with diffuse-TGCT affecting the knee. This could be attributed to the near impossibility of achieving a complete macroscopic resection in widely spread, ill-defined diffuse-TGCT patients and the impossibility of an R0 resection: macroscopically and microscopically complete resection, neither with an arthroscopic- nor open resection.

Multimodality treatment

Within the current era of systemic targeted and multimodality therapies (some only available in trial settings) in TGCT, standalone surgical resection can no longer be regarded as the only treatment for more severe diffuse forms of the disease. Surgery has been considered the treatment of choice for decades, and the current study which included patients from 1990 onwards, consists mainly of patients treated with a surgical procedure.

High recurrence rates, as confirmed by the present study, indicate the need for adjuvant therapies to improve treatment outcomes for patients with diffuse-TGCT. Nonetheless, Gortzak et al. reported no significant differences in residual disease, complication rates and overall physical and mental health scores between patients surgically treated for TGCT of the knee with (N=34) or without (N=22) adjuvant ^{90}Yttrium, after a mean follow-up of 7.3 years[17]. Verspoor et al. evaluated 12 patients treated with surgical synovectomy and additional cryosurgery. They did not find better results compared to surgical resection alone[44]. Griffin et al. reported on 49 patients with diffuse-TGCT, most of whom had both intra- and extra-articular and recurrent disease. They reported 3 (6%) recurrences following synovectomy and radiation[10]. A meta-analysis suggested that open synovectomy (N=19 studies, N=448) or synovectomy combined with perioperative radiotherapy (11 studies, N=123) is associated with a reduced rate of recurrence[16]. Mollon et al. reserved the use of external beam radiation for patients at high risk for local recurrence, if they had the following characteristics: multiple episodes of recurrent intra-articular disease, extra-articular extension, or gross residual disease remaining following surgery[38]. Currently, sufficient data including adequate patient numbers is lacking to support the use of external beam radiation in primary cases, however the authors feel it should only be performed in specific instances such as extensive or recurrent diffuse-TGCT cases.

In patients with locally advanced TGCT or (multiple) recurrence(s), systemic therapies targeting the CSF1/CSF1R axis have been recently investigated including nilotinib, imatinib, pexidartinib (PLX3397), emactuzumab (RG7155) and cabiralizumab (FPA008). Some systemic treatments for TGCT have been proven to be effective[18, 19], and novel and potentially more potent agents are under investigation[20-22]. The disadvantages of adjuvant or targeted therapies are acute and long-term side-effects of different degrees. Therefore, additional long-term follow-up studies in this field remain indicated.

Patients with aggressive disease accompanied with a high risk of recurrence following surgery alone should be selected for (new) systemic and (neo)adjuvant treatment modalities. Diffuse-TGCT presents as a heterogeneous disease with different disease severities. Some patients present with tumours that are surgically relatively easy to access and these patients might not require (neo)adjuvant therapies. Mastboom et al. defined the most severe diffuse-TGCT subgroup on MR imaging as having diffuse-type TGCT including intra- and extra-articular disease and involvement of at least one of the following three tissues: muscle, tendon or ligament)[5]. These patients seem most eligible for multimodality or (neo)adjuvant strategies.

Complications

The literature on TGCT frequently lacks descriptions of complications after surgical treatment. This study reported a complication rate of 12% following surgical management of patients with diffuse-TGCT, predominantly after open resection (82%). The most common complication was joint stiffness after open synovectomy, which might be difficult to prevent after the surgical treatment of extensive disease. The true complication rate might be even higher, since it is suspected that not all complications are scored.

Symptoms

TGCT related symptoms are mainly pain, swelling, stiffness and limited range of motion, but these are reported with a great variability in degree and severity. Gelhorn et al. concluded that not all patients experience all symptoms to the same extent (e.g. swelling but no pain, or pain and swelling but no stiffness or limited range of motion)[6]. Symptoms prior to initial treatment at a tertiary centre were compared for each patient with symptoms at last follow-up. Initial symptoms of pain and swelling improved following treatment(s) in 43-56% of patients. This is comparable with a crowdsourcing study in 337 TGCT patients originating from 31 countries[14]. In the majority of patients, stiffness and limited range of motion did not seem to be principal symptoms either initially, or at last follow-up. These symptoms are subjective for each patient and not all patients were included with complete data. Nevertheless, pain and swelling are the main TGCT-related complaints initially and frequently improve after surgical treatment(s).

As expected, diffuse-TGCT patients with recurrent disease demonstrated higher rates of symptoms at final follow-up, including a 3.5-fold higher rate of chronic analgesic use, compared to patients without local recurrence at last follow-up. Also, patients using chronic analgesics had a higher rate of complications.

Interestingly, after arthroscopic synovectomy in diffuse-TGCT, patients exhibited more pain, swelling and a higher use of chronic analgesics, compared with open synovectomy. On the contrary, open synovectomy was associated with higher rates of stiffness and limited range of motion, which can be attributed to the larger surgical procedure resulting in additional scar tissue.

Joint specific analyses

Within this individual participant data meta-analysis, a homogeneous subgroup analysis for diffuse-TGCT affecting the knee of therapy naïve patients was performed (*figure 3b*). Despite the large number of patients in this study with diffuse-TGCT cases, the numbers in other joint locations were too small to allow analysis of those specific groups.

Limitations

The main limitation of this study is selection (referral) bias, since data on patients treated at non-specialized centres was lacking. Selection bias of affected joints seems absent when comparing percentages of affected joints (*table 1, figure 2*) with a recent incidence calculation study including nationwide coverage (in both studies 64% of diffuse-TGCT affects the knee)[4].

Even though TGCT is a benign disease, particularly diffuse-TGCT can become a chronic illness with substantial morbidity to the joint leading to functional and patient health-related quality of life impairment, caused by the course of the disease itself and multiple treatments[13]. As data were collected by local investigators or physicians according to the multicentre study design, data quality depended on data registry on site. Only data available in the source data file of the patients could be retrieved. In addition, interpretation of individual parameters could differ. No central histopathological review was performed, as it was assumed that each centre provided the correct diagnosis as set by their histopathology department. Within our study we did not collect which patient had multiportal arthroscopy or standard anterior portal arthroscopy.

Recurrence rates could either be over-estimated or under-estimated. Over-estimation could occur because the follow-up status 'alive with disease' was classified as recurrence (if recurrence data were missing). On the contrary, under-estimation could be present if patients with recurrent disease, did not return at all or did not return to their original centre. It should be noted that patients with recurrent disease had a longer follow-up compared to patients without recurrent disease. The explanation could be that patients without symptoms and (assumed) without recurrent disease were dismissed from follow-up and therefore had shorter follow-up times. In addition, if treatments were recently performed, patients also had shorter follow-up times and are still at risk of recurrence.

Conclusion

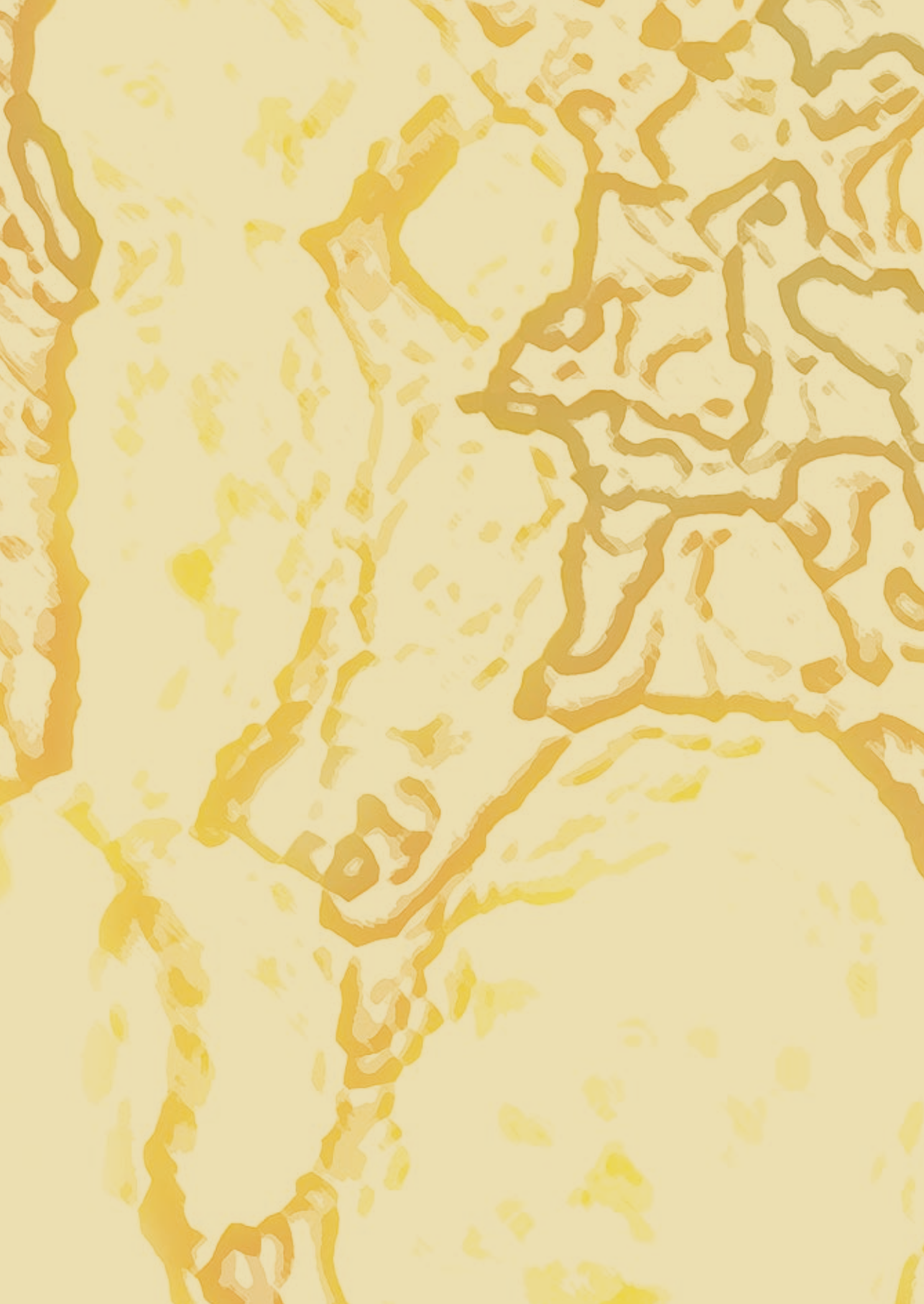
This is the largest global individual data study on patients with diffuse-type TGCT and provides a comprehensive and up to date disease overview, evaluating the clinical profile and management of TGCT. Our study demonstrated that surgery is by far the most frequently performed treatment in tertiary referral hospitals. However, even in specialised centres, local control of this heterogeneous orphan disease, remains a major issue, with overall recurrence free survival of 55% at 5 years.
Since complete resection of diffuse-TGCT is often impossible and recurrence rates are high after both arthroscopy and open synovectomy of the knee, the optimal surgical approach should be left to the discretion of an experienced surgical and multidisciplinary team. However, in the era of multimodality therapy, standalone surgical resection can no longer be regarded as the only effective treatment for patients with diffuse-TGCT and alternative or combined approaches should be considered.

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
3. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
4. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
5. Mastboom MJL, Verspoor FGM, Hanff DF, Gademan MGJ, Dijkstra PDS, Schreuder HWB, Bloem JL, van der Wal RJP, van de Sande MAJ. Severity classification of Tenosynovial Giant Cell Tumours on MR imaging. Surg Oncol. 2018;27:544-50.
6. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
7. Bhimani MA, Wenz JF, Frassica FJ. Pigmented villonodular synovitis: keys to early diagnosis. Clin Orthop Relat Res. 2001(386):197-202.
8. 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(2):210-7.
9. 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(4):808-15.
10. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
11. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
12. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
13. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
14. Mastboom MJ, Planje R, van de Sande MA. The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life. Interactive journal of medical research. 2018;7(1):e4.
15. Heyd R, Seegenschmiedt MH, Micke O. [The role of external beam radiation therapy in the adjuvant treatment of pigmented villonodular synovitis]. Zeitschrift fur Orthopadie und Unfallchirurgie. 2011;149(6):677-82.
16. Mollon B, Lee A, Busse JW, Griffin AM, Ferguson PC, Wunder JS, 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(4):550-7.
17. Gortzak Y, Vitenberg M, Frenkel Rutenberg T, Kollender Y, Dadia S, Sternheim A, 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(7):984-8.

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. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
20. 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(8):949-56.
21. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). ASCO conference 2017. 35 (15 Supplement 1).
22. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference. 2018.
23. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. Bmj. 2010;340:c221.
24. Honaker J, King G, Blackwell M. Amelia II: a program for missing data. J Stat Softw. 2011;45:1-54.
25. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc. 1996;91:473-89.
26. Fay MP, Shaw PA. Exact and Asymptotic Weighted Logrank Tests for Interval Censored Data: The interval R package. Journal of statistical software. 2010;36(2).
27. Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. Statistics in medicine. 1996;15(13):1387-95.
28. Anderson-Bergman C. icenReg: Regression Models for Interval Censored Data in R. J Stat Softw. 2017;81(12):1-23.
29. Schwartz HS, Unni KK, Pritchard DJ. Pigmented villonodular synovitis. A retrospective review of affected large joints. Clin Orthop Relat Res. 1989(247):243-55.
30. Ogilvie-Harris DJ, McLean J, Zarnett ME. Pigmented villonodular synovitis of the knee. The results of total arthroscopic synovectomy, partial, arthroscopic synovectomy, and arthroscopic local excision. J Bone Joint Surg Am. 1992;74(1):119-23.
31. Chin KR, Barr SJ, Winalski C, Zurakowski D, Brick GW. Treatment of advanced primary and recurrent diffuse pigmented villonodular synovitis of the knee. J Bone Joint Surg Am. 2002;84-A(12):2192-202.
32. de Carvalho LH, Jr., Soares LF, Goncalves MB, Temponi EF, de Melo Silva O, Jr. Long-term success in the treatment of diffuse pigmented villonodular synovitis of the knee with subtotal synovectomy and radiotherapy. Arthroscopy. 2012;28(9):1271-4.
33. Kubat O, Mahnik A, Smoljanovic T, Bojanic I. Arthroscopic treatment of localized and diffuse pigmented villonodular synovitis of the knee. Collegium antropologicum. 2010;34(4):1467-72.
34. Loriaut P, Djian P, Boyer T, Bonvarlet JP, Delin C, Makridis KG. Arthroscopic treatment of localized pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20(8):1550-3.
35. Rhee PC, Sassoon AA, Sayeed SA, Stuart MS, Dahm DL. Arthroscopic treatment of localized pigmented villonodular synovitis: long-term functional results. American journal of orthopedics. 2010;39(9):E90-4.

36. Noailles T, Brulefert K, Briand S, Longis PM, Andrieu K, Chalopin A, et al. Giant cell tumor of tendon sheath: Open surgery or arthroscopic synovectomy? A systematic review of the literature. Orthop Traumatol Surg Res. 2017;103(5):809-14.
37. Blanco CE, Leon HO, Guthrie TB. Combined partial arthroscopic synovectomy and radiation therapy for diffuse pigmented villonodular synovitis of the knee. Arthroscopy. 2001;17(5):527-31.
38. 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(1):260-6.
39. Chang JS, Higgins JP, Kosy JD, Theodoropoulos J. Systematic Arthroscopic Treatment of Diffuse Pigmented Villonodular Synovitis in the Knee. Arthroscopy techniques. 2017;6(5):e1547-e51.
40. Chin KR, Brick GW. Extraarticular pigmented villonodular synovitis: a cause for failed knee arthroscopy. Clin Orthop Relat Res. 2002(404):330-8.
41. Flandry FC, Hughston JC, Jacobson KE, Barrack RL, McCann SB, Kurtz DM. Surgical treatment of diffuse pigmented villonodular synovitis of the knee. Clin Orthop Relat Res. 1994(300):183-92.
42. Sharma V, Cheng EY. Outcomes after excision of pigmented villonodular synovitis of the knee. Clin Orthop Relat Res. 2009;467(11):2852-8.
43. 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(3):883-90.
44. Verspoor FG, Scholte A, van der Geest IC, Hannink G, Schreuder HW. Cryosurgery as Additional Treatment in Tenosynovial Giant Cell Tumors. Sarcoma. 2016;2016:3072135.



TREATMENT

chapter nine

Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumour

international, multicentre study

M.J.L. Mastboom*[1], F.G.M. Verspoor*[2], G. Hannink[2], R.G. Maki[3], A. Wagner[4], E. Bompas[5], J. Desai[6], A. Italiano[7], B.M. Seddon[8], W.T.A. van der Graaf[9], J.-Y. Blay[10], M. Brahmi[10], L. Eberst[10], S. Stacchiotti[11], O. Mir[12], M.A.J. van de Sande[1], H. Gelderblom[13], P. A. Cassier[10]

Submitted.

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Medical Oncology, Monter Cancer Centre & Cold Spring Harbor Laboratory, Long Island, NY, USA

[4] Medical Oncology, Dana Farber Cancer Institute, Boston, USA

[5] Medical Oncology, Institut de Cancérologie de l'Ouest, Nantes, France

[6] Medical Oncology, Peter Mac Callum Cancer Centre, Melbourne, Australia

[7] Medical Oncology, Institut Bergonié, Bordeaux, France

[8] Medical Oncology, University College Hospital, London, United Kingdom

[9] Medical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands

[10] Medical Oncology, Centre Léon Bérard, Lyon, France

[11] Medical Oncology, Istituto Nazionale Tumori, Milano, Italy

[12] Medical Oncology, Gustave Roussy Institute, Villejuif, France

[13] Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

*Authors contributed equally to this work.

Abstract

Background

Tenosynovial Giant Cell Tumours (TGCT), are rare colony stimulating factor-1(CSF-1)-driven proliferative disorders affecting joints. Diffuse-type TGCT often causes significant morbidity due to local recurrences necessitating multiple surgeries. Imatinib mesylate (IM) blocks CSF-1 receptor. This study investigated the long term effects of IM in TGCT.

Methods

We conducted an international multi-institutional retrospective study to assess the activity of IM: data was collected anonymously from individual patients with locally advanced, recurrent or metastatic TGCT.

Results

Sixty-two patients from 12 institutions across Europe, Australia and the United States were identified. Thirty-nine patients were female (63%), median age at treatment start was 45 (range 20-80) years, with a median time from diagnose to treatment of 3.5 (range 0-38,2) years. Median follow-up after treatment start was 52 (IQR 18-83) months. Four patients with metastatic TGCT progressed rapidly on IM and were excluded for further analyses. Seventeen of 58 evaluable patients achieved CR or PR. One- and five-year progression-free survival rates were 71% and 48%, respectively. Thirty-eight (66%) patients discontinued IM after a median of 7 (range 1-80) months. Reported adverse events in 45 (78%) patients were among other edema (48%) and fatigue (50%), mostly grade 1-2 (89%). Five patients experienced grade 3-4 toxicities.

Conclusion

This study confirms, with additional follow-up, the efficacy of IM in TGCT. In responding cases we confirmed prolonged IM activity on TGCT symptoms even after discontinuation, but with high rates of treatment interruption and additional treatments.

Introduction

Tenosynovial giant-cell tumour (TGCT), historically known as pigmented villonodular synovitis (PVNS), is a rare, at times locally aggressive neoplasm affecting the joints or tendon sheaths in young adults. It is most common around large joints such as the knees, ankles and hips[1, 2]. Known subtypes are localized and diffuse TGCT. The localized subtype comprises a single nodule and has a favourable course while the diffuse subtype involves the synovial lining as well as surrounding structures and is associated with a significant risk of recurrence (>50% depending on follow up times), despite being a benign neoplasm[2-4]. Metastatic forms have been described, but seem to occur very rarely[5, 6].

Surgical resection is the primary treatment for both subtypes. However, diffuse TGCT is difficult to remove completely and often requires a total synovectomy, or at time a joint replacement, or rarely even amputation[1, 2, 7]. In patients with extensive and/or recurrent TGCT, other available treatment modalities include radiation synovectomy[8], external beam radiation therapy[9], and cryosurgery[10]. Their therapeutic value has only been assessed in retrospective, in most cases single centre series and their long term side effects and complications are poorly described[11].
Recurrent TGCT is rarely lethal, but frequently becomes a debilitating chronic illness with substantial morbidity to the joints and quality of life impairment, caused by the disease itself and the multiple treatments[2, 12].

In TGCT, a neoplastic clone constitutes a subpopulation (2-16%)[13] of cells that overexpress colony-stimulating factor-1 (CSF-1). A t(1;2) translocation that links the *CSF1* gene on chromosome 1p13 to the *COL6A3* gene on chromosome 2q35 has been described and is believed to be responsible for the overproduction of CSF1 by neoplastic cells[13, 14]. Inhibition of CSF1/CSF-1 receptor (CSF-1R) signaling has shown efficacy in the treatment of locally advanced and recurrent diffuse TGCT[15-17].
Imatinib mesylate (IM) inhibits the CSF-1R kinase among other kinases[17]. We have previously reported on the efficacy of IM in TGCT. In the present study we provide long term follow-up on these initial patients and data on 33 additional consecutive patients.

Methods

This retrospective study was conducted at 12 referral centres across Europe (9 institutions), the United States of America (2 institutions), and Australia (1 institution). The file of all patients with locally advanced, recurrent or metastatic TGCT, treated with IM were reviewed. Patients information were extracted from individual patients' files at each institution by the local investigators and was provided in an anonymous form for final analyses. Histopathologic examination was performed at centre of origin by pathologists with extensive experience in mesenchymal tumours. Response was measured using version 1.0 of Response Evaluation Criteria in Solid Tumours (RECIST). Data were described using percentages for qualitative variables and medians with ranges for continuous variables. Patients were not treated on a research protocol. They provided informed consent to treatment with a 'off-label' medical treatment, and treatment decision was left to the treating physician. This retrospective analysis was approved by the Ethics Committee in Lyon (Committee for the Protection of Individuals, Sud-Est IV, Lyon, France – L10-153 dated 9 December 2010).

Survival was plotted using the Kaplan-Meier method. Progression-free survival (PFS) was calculated from the date IM was started to the date of disease progression or death. The time to treatment failure (TTF) was calculated from the date IM was started to the date it was stopped because of toxicity, disease progression, or death, whichever occurred first. For patients with a surgical resection or other additional therapy after treatment with IM, PFS and TTF were censored at the time of surgery. Disease specific survival was calculated from the date IM was started to the date of death due to TGCT. Symptomatic response was defined as improvement of pain and/or joint function in patients who had symptoms at baseline. All statistical analyses were performed using R version 3.4.0 (R Foundation, Vienna, Austria).

Results

Patients

A total of 62 patients with histopathologically proven TGCT treated with imatinib were identified, their main characteristics are described in *Table 1*. Briefly, median age at diagnosis was 39 (IQR 31-53) years and 45 (IQR 36-56) years at start of treatment with IM, the majority of patients were female (N=39, 63%), and the knee (N=35, 56%) was the most commonly affected joint (*Table 1*). At

start of IM treatment, three (5%) patients had biopsy proven metastatic disease, 15 (24%) locally advanced disease and 44 (71%) locally recurrent disease. Among patients with prior operations for TGCT (n=47), the median number of prior operations was 2 (range 1-9), and the time since the last operation was 23 (range 1-192) months. Median follow up of all patients was 52 (IQR 18-83) months.

Treatment efficacy

Sixty-one patients received 400 mg and one patient received 600 mg IM daily. The 3 patients with metastatic disease at treatment start progressed rapidly on IM and were excluded from further analysis. One other patient with metastatic disease after multiple surgical treatments and IM, was excluded for further analyses too, leaving 58 patients for the rest of the analysis.

Median duration of IM treatment was 9 (IQR 5-27) months. At last follow-up, the majority of patients (n=38; 66%) had discontinued treatment. Seventy-seven percent (95% CI 67-89), 41% (95% CI 29-57) and 36% (95% CI 25-52) of patients were still on IM after 6-, 12- and 24-months, respectively (*figure 1*). The treatment failure-rate was 82% (95% CI 71-95) after 12 months.

Response could not be assessed in 3 patients, two of which were lost to follow-up and one who discontinued early due to febrile neutropenia, leaving 55 patients with locally advanced or locally recurrent TGCT assessable for response. Seventeen patients (31%; 95% CI 19-43) had a RECIST-defined response, including 2 (4%) patients with a complete response. The median time to best response was 6 (range 1-23) months.

Forty of 51 patients (78%) reported symptom improvement (*table 2*), including 14 of 15 patients with radiological response (CR or PR). Among patients with radiological SD, 22 of 30 patients (73%), for whom data was available, had symptom improvement.

The 1-, 2- and 5-years overall PFS, metastatic patients (N=4) excluded, was 71% (95% CI 60-85), 60% (95% CI 48-75) and 48% (95% CI 36-65) respectively, (*figure 2*)**.**

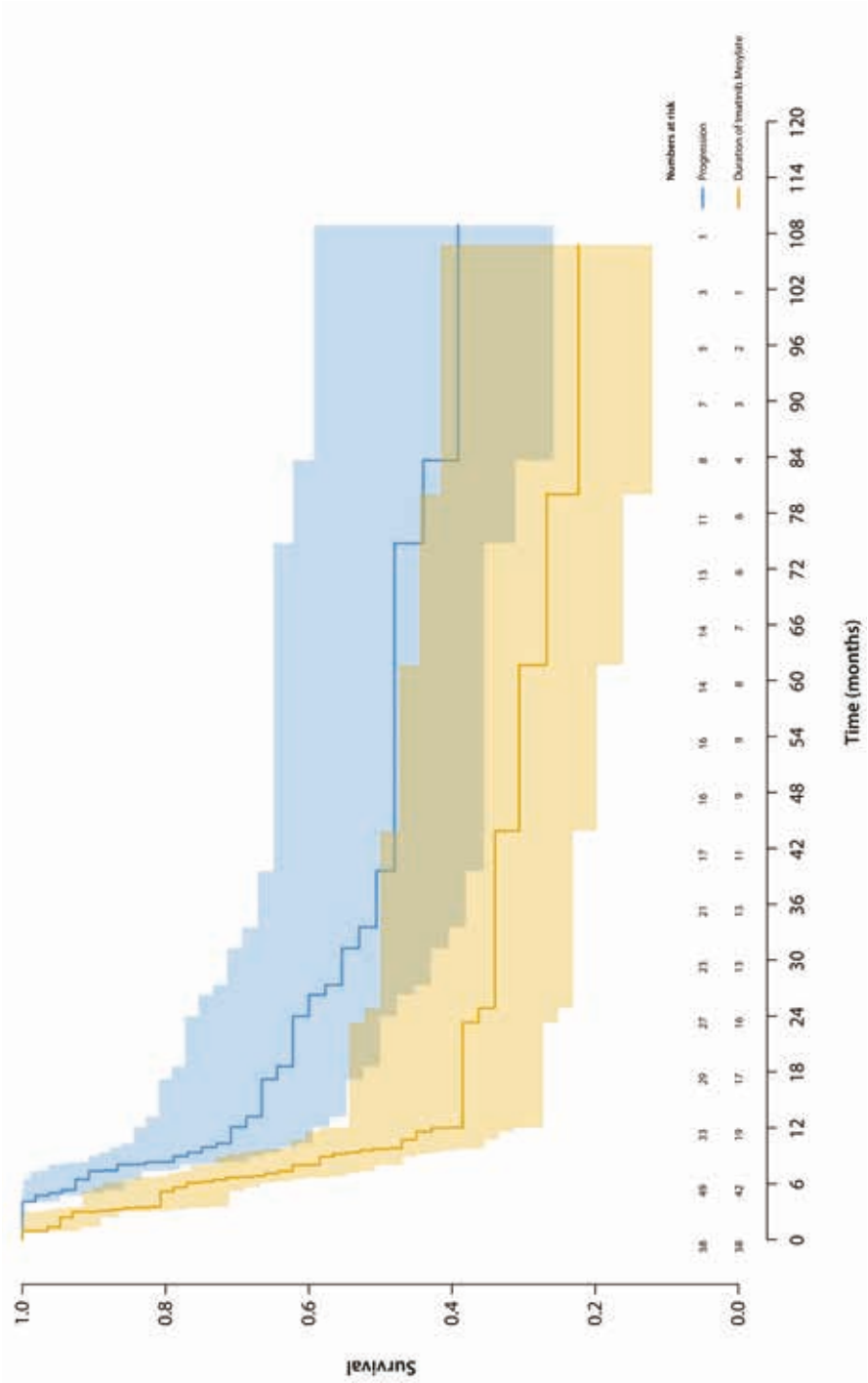


Figure 1 Duration of imatinib mesylate treatment and progression free survival of this treatment in patients with locally advanced or recurrent diffuse-type TGCT.

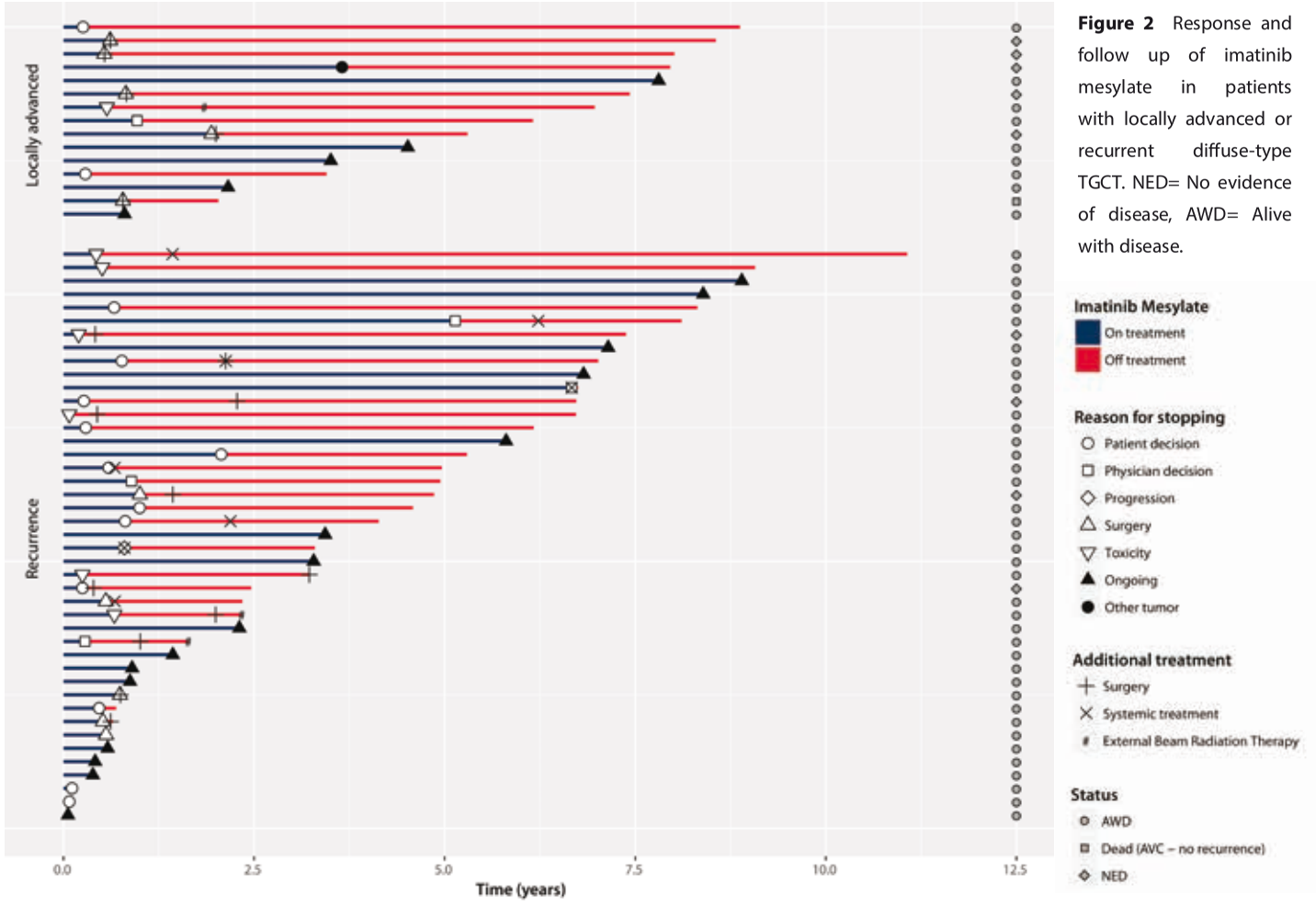


Figure 2 Response and follow up of imatinib mesylate in patients with locally advanced or recurrent diffuse-type TGCT. NED= No evidence of disease, AWD= Alive with disease.

Table 1 Descriptive of diffuse-type TGCT patients receiving imatinib mesylate treatment

	Patients N (%)
Total	62 (100)
Median age at diagnosis (IQR), yrs	39 (31-53)
Median time from diagnosis to start IM (IQR), yrs	3.5 (1-8)
Sex	
Male	23 (37)
Female	39 (63)
Tumour location	
Knee	35 (56)
Ankle	11 (18)
Hip	6 (10)
Foot	4 (6)
Shoulder	1 (2)
Elbow	1 (2)
Head and Neck	2 (3)
Wrist	2 (3)
Surgery before start IM	
None	15 (24)
1-2	24 (39)
3-4	13 (21)
>4	10 (16)
Median N of surgeries (range)	2 (1-9)
Median time since last surgery (range), mo	23 (1-192)
Disease status	
Locally advanced	20 (32)
Recurrence after surgery	39 (63)*
Metastatic disease	3 (5)

Abbreviations: TGCT= Tenosynovial Giant Cell tumour, IM= imatinib mesylate, N= Number of patients, mo=months, yrs= years. *One of the locally recurrent patients progressed to metastatic disease.

Table 2 Summary of imatinib mesylate efficacy in patients with locally advanced or recurrent diffuse-type TGCT

Parameter	Patients N (%)
RECIST best response*	
Complete remission	2 (4)
Partial response	15 (27)
Stable disease	36 (65)
Progressive disease	2 (4)
Overall response rate	17 (31)
Rate of disease control	53 (96)
Symptomatic response	40 (78)**
Median IM treatment duration (IQR), mo	9.3 (5-26)
Median PFS (IQR), mo	18 (8-55)

Abbreviations: TGCT= Tenosynovial Giant Cell tumour, IM= imatinib mesylate, N= Number of patients, mo=months, yrs= years, IQR= inter quartile range. Overall response rate includes complete remission and partial response; Rate of disease control includes complete remission, partial response and stable disease; Symptomatic response was indicated as present or not (40/51=78%). Metastatic patients (n=4) were excluded. *N=3 RECIST best response not available; **N=9 symptomatic response not available.

Follow-up

Overall 38/58 patients (66%), metastatic patients (N=4) excluded, eventually discontinued IM after a median of 7.0 (range 1-80 months). the most common reason for treatment discontinuation was patient decision to stop (n=14, which possibly reflect low grade chronic toxicity), followed by planned surgery (n=10), toxicity (n=7), physician's decision (n=5) and progression (n=1). One patient discontinued IM because of the diagnosis of another tumour requiring therapy. Among the 27 patients who discontinued treatment for reasons other than surgery or progression, progression (either radiological progression or requirement for another line of therapy – i.e. surgery, other medical therapy or radiotherapy) eventually occurred 17 patients after a median of 12 (range 4-84) months, while 10 patients never progressed (nor required additional therapy) after a median follow-up to 78 (range 1-109) months, suggesting that IM was able to provide prolonged symptomatic relief at least in a proportion of patients.

Safety

Forty-five of 58 patients (78%), metastatic patients (N=4) excluded, reported at least one adverse event with IM. The most common adverse events were edema (N=28, 48%), fatigue (N=29, 50%), nausea (N=21, 34%) and skin rash/dermatitis (N=7, 12%), mostly grade 1-2 (89%). Additional grade 1-2 complaints were diarrhea, reflux, auditory hallucinations, conjunctivitis, sexual impairment, asthenia, alopecia, cramps and dyspnea. Five (11%) patients had grade 3-4 toxicities, including neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue (*table 3*).

Table 3 Main toxicities associated with imatinib mesylate and reasons for discontinuation, metastatic patients excluded

	Patients N (%)	
Variable	**All grades**	**Grade 3-4**
Edema/ fluid retention	28 (48)	1 (2)
Fatigue	29 (50)	1 (2)
Nausea	20 (34)	
Skin rash/ dermatitis	7 (12)	2 (3)
Other*	15 (26)	3 (5)
Treatment status		
Continued on IM	20 (34)	
Stopped IM	38 (66)	
Reason for stopping		
Progression	1 (2)	
Toxicity	7 (12)	
Surgery	10 (17)	
Patient choice	14 (24)	
Physician decision	5 (9)	
Other tumour	1 (2)	

IM= imatinib mesylate, N= Number of patients. Forty-five (78%) patients reported at least one adverse event with IM. *Other grade 1-2 complaints were diarrhea, reflux, auditory hallucinations, conjunctivitis, sexual impairment, asthenia, alopecia, cramps and dyspnea. Five (11%) patients had grade 3-4 toxicities, including neutropenia, acute hepatitis, auditory hallucinations.

Discussion

To our knowledge, this retrospective study provides the largest case series, with long follow-up, of patients with locally advanced, recurrent or metastatic diffuse-type TGCT treated with IM. We confirmed that IM has activity in TGCT with an overall response rate of 31% in patients with locally advanced/recurrent TGCT. Interestingly all patients with metastatic TGCT progressed on IM, suggesting that metastatic TGCT is either a different disease or loses its dependency on the CSF1/CSF1R axis during malignant transformation. The main issue, is the drop-off rate, with more than half of the patients discontinuing therapy within a year of therapy (59%; 95% CI 29-57), in most cases for unclear reasons (patients decision, physician's decision) suggesting an unfavourable efficacy/toxicity balance. Eleven percent of patients reported grade 3-4 toxicities, which is consistent with the rates reported with IM for adjuvant gastrointestinal stromal tumours (GIST) or chronic myeloid leukaemia (CML)[18-21].

To date, surgical resection remains the treatment of choice for diffuse-type TGCT, but is associated with high recurrence rates and multiple additional surgeries[11]. It is challenging to balance between increased morbidity of multiples or invasive surgeries[12, 22], alternative therapeutic options, and daily symptoms of the tumour. A more aggressive resection or other multimodality treatments, such as external beam radiation therapy, radiosynovectomy and cryosurgery, may adversely affect joint function, quality of life and development of osteoarthrosis, which, given the young age group, are relevant factors[2, 23]. This would justify a less invasive approach, using systemic therapy, provided those are associated with tumour shrinkage and, most importantly, symptomatic improvements[24]. In the present study, age, localization and gender distribution were consistent with the literature[10, 23, 25]. The extent of disease in our patient group is emphasized by an disease specific survival of 90% including four metastatic patients and 49% of patients had three or more surgeries before start IM. Similar to previous case-series, we calculated a 1- and 5-years PFS of 71% and 48%, metastatic patients excluded, respectively[10, 23, 25]. Because of heterogeneity of patients and a variety of treatments, it is debatable to compare these numbers.

The overall response rate appears higher compared to nilotinib (6% (95% CI unknown), a different tyrosine kinase inhibitor, with similar potency against CSF1R[26]. Our overall response rate (31% (95% CI 19-43, metastatic patients (N=4) excluded) was consistent with our previous report on the

short term results of IM (19% (95% CI 4-34) with similar disease control rate (96% versus 93%)[17]. In the present study, 38 (66%) patients discontinued IM; 14 (37%) without subsequent treatment, of which ten patients had stable disease at final follow up. Thirteen (62%) patients eventually progressed, after discontinuing IM for toxicity or non-specific medical reason (N=21, 55%). Both stable and progressive patients can be a result of discontinuing IM treatment or the natural course of disease.

Newer, more specific inhibitors of CSF1R, currently only available in trial-setting such as emactuzumab (RG7155)[27], pexidartinib (PLX3397)[15], and cabiralizumab[28] (FPA008, Five-Prime), have shown promising clinical activity on similar groups of diffuse TGCT patients in prospective clinical studies with more formal criteria and timelines for response assessment than this retrospective series. Emactuzumab (N=29)[16] had an overall response rate of 86% (two patients with a complete response) and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months). Pexidartinib showed (N=23)[15] an overall response rate of 52% (all patients had a partial response) and a rate of disease control of 83%. Responses were associated with an improved joint function (median duration of response exceeded eight months). The preliminary results with cabiralizumab (N=22) are consistent, with radiographic response and improvement in pain and function in five out of 11 patients[28]. However, long term efficacy data have not yet been reported with these newer agents.

Virtually all patients treated with IM for either CML or GISTs, experience[29] at least one mild or moderate adverse effect (grade 1-2). Toxicities of IM are determined by the disease stage and the doses used, advanced disease and higher doses result in more frequent and severe toxicities. Most side effects occur early in the course of treatment and tend to decrease in frequency and intensity in time[29]. We consider a 10-15% rate of grade 3-4 toxicities in a generally benign but locally aggressive disease, such as diffuse TGCT, too high. Only 22% of patients did not experience any side effects.

Although target anti-cancer therapies are described as 'well tolerated', the perception of tolerability may vary in the context of a, most often, benign condition. Understanding, monitoring and managing the side effects will be important to optimize systemic therapy for patients with TGCT.

Discontinuation of treatment due to toxicities was seen for IM (this series), emactuzumab[15] and pexidartinib[16] in 12%, 20% and 9% patients, respectively. TGCT patients might be less willing to cope with adverse event-related and study-related procedures. Here, we report prolonged clinical benefit and symptomatic relief, even after discontinuation of treatment. A similarly persistent effect was observed was also observed with monoclonal antibodies and more specific CSF1R tyrosine kinase inhibitors this[24]. This suggest that intermittent treatment administration may be an option to improve long term tolerability.

The place of systemic treatment in a benign, locally aggressive disease, such as TGCT, and how to optimally deliver this treatment, remains unclear. More specifically, the role of CSF1R inhibitors in the peri-operative setting still needs to be explored: the number of patients who underwent operation after IM in our series is too low to draw any conclusions. Despite limitations related to its retrospective nature, this study adds to the knowledge of targeting the CSF-1/CSF-1R pathway in patients with TGCT. An optimal treatment strategy should be developed for the patient group that benefits most from systemic therapy. The combination of a short period of treatment and the durable effect after discontinuation, should be pursued. It is challenging to maintain compliance for years, especially with, even "minor", toxicities, in the context of a non-life-threatening disease.

A limitation of all, including this, clinical TGCT studies is the lack of a control group and the absence of specific and validated patient-reported outcome measures to document treatment-induced symptomatic, functional and economic (back to work) improvement[16]. Quality of life and functional forms should be implemented. These measures are critical endpoints in demonstrating clinical relevance and impact of treatments for benign diseases in which death is not a relevant outcome variable[30]. Clinical benefit necessitates objective measures to correlate with tumour reduction.

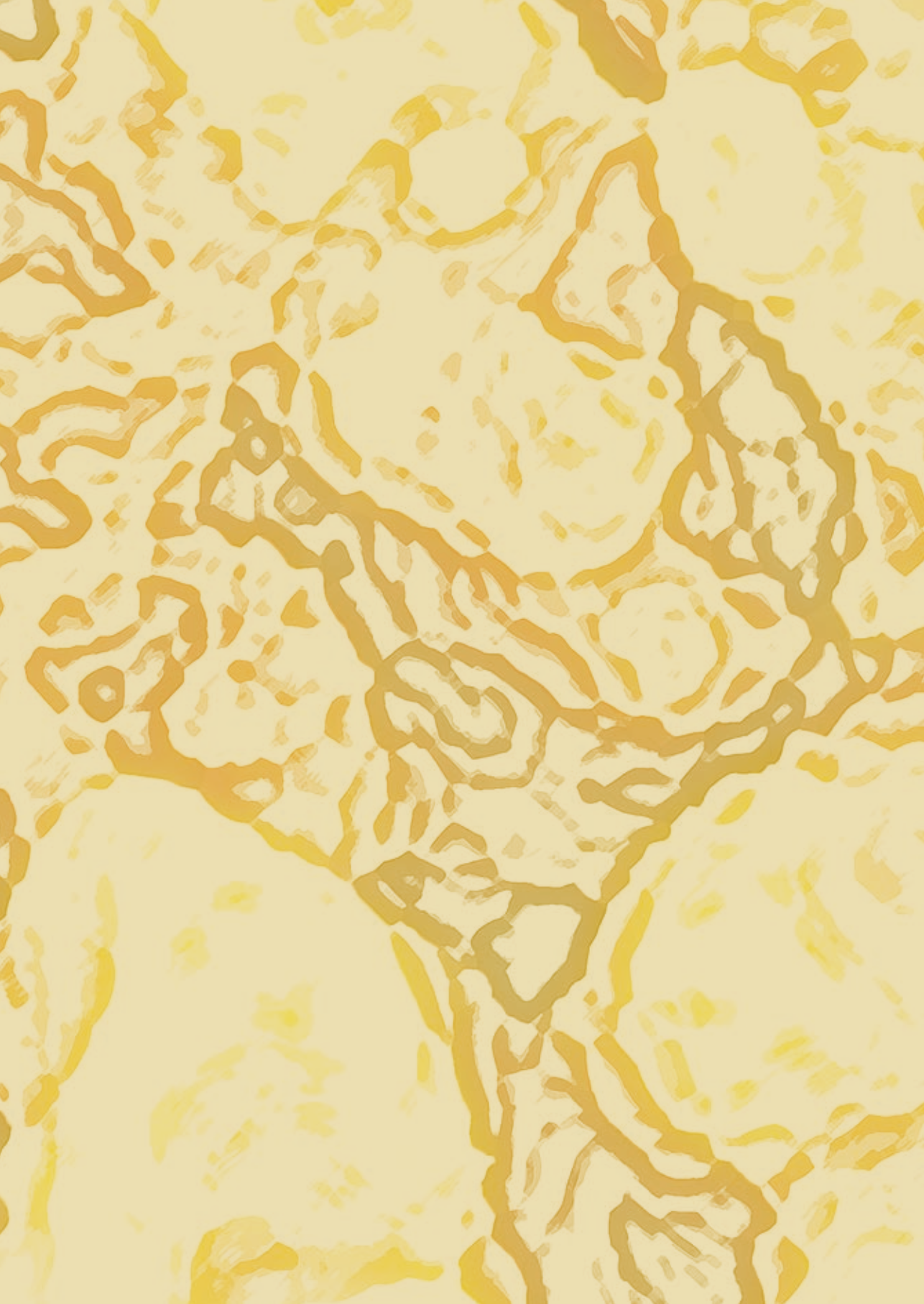
Conclusion

Identification of a biologic aggressive subgroup of diffuse TGCT, at risk of increased surgical morbidity or recurrent disease, should aid to decide which patients benefit most of systemic treatments. With the advent of more potent CSF-1R inhibitors, such as emactuzumab, pexidartinib and cabiralizumab, the role of IM in extensive TGCT might weaken, but may be balanced by the favourable safety profile of IM. Availability of these new compounds, both in terms of registration and reimbursement, will ultimately define the prescribed drug in daily practice.

References

1. Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented Villonodular Synovitis: A Retrospective Single-Centre Study of 122 Cases and Review of the Literature. Seminars in Arthritis and Rheumatism. 2011;40 (6):539-46.
2. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
3. Ravi V, Wang WL, Lewis VO. Treatment of tenosynovial giant cell tumor and pigmented villonodular synovitis. Curr Opin Oncol. 2011.
4. de saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, diffuse/localized type. In: Fletcher CD, Bridge JA, Hogedoorn PC, Mertens F, eds. WHO classification of tumours of Soft Tissue and Bone. 2013;5(4th ed. Lyon: IARC Press).
5. Yoon HJ, Cho YA, Lee JI, Hong SP, Hong SD. Malignant pigmented villonodular synovitis of the temporomandibular joint with lung metastasis: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(5):e30-6.
6. Righi A, Gambarotti M, Sbaraglia M, Frisoni T, Donati D, Vanel D, et al. Metastasizing tenosynovial giant cell tumour, diffuse type/pigmented villonodular synovitis. Clin Sarcoma Res. 2015;5:15.
7. Mastboom MJL, Verspoor FGM, Gelderblom H, van de Sande MAJ. Limb Amputation after Multiple Treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch Cases. Case reports in orthopedics. 2017;2017:7402570.
8. Shabat S, Kollender Y, Merimsky O, Isakov J, Flusser G, Nyska M, et al. The use of surgery and yttrium 90 in the management of extensive and diffuse pigmented villonodular synovitis of large joints. Rheumatology. 2002;41 (10):1113-8.
9. Heyd R, Seegenschmiedt MH, Micke O. [The Role of External Beam Radiation Therapy in the Adjuvant Treatment of Pigmented Villonodular Synovitis.]. Z Orthop Unfall. 2011.
10. Verspoor FG, Scholte A, van der Geest IC, Hannink G, Schreuder HW. Cryosurgery as Additional Treatment in Tenosynovial Giant Cell Tumors. Sarcoma. 2016;2016:3072135.
11. Verspoor FG, van der Geest IC, Vegt E, Veth RP, van der Graaf WT, Schreuder HW. Pigmented villonodular synovitis: current concepts about diagnosis and management. Future Oncol. 2013;9(10):1515-31.
12. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
13. 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. Proceedings of the National Academy of Sciences of the United States of America. 2006;103 (3):690-5.
14. 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. American Journal of Surgical Pathology. 2007;31 (6):970-6.
15. 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. The New England journal of medicine. 2015;373(5):428-37.
16. 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(8):949-56.

17. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649-55.
18. Casali PG, Le Cesne A, Poveda Velasco A, Kotasek D, Rutkowski P, Hohenberger P, et al. Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol. 2015;33(36):4276-83.
19. Essat M, Cooper K. Imatinib as adjuvant therapy for gastrointestinal stromal tumors: a systematic review. Int J Cancer. 2011;128(9):2202-14.
20. Joensuu H, Trent JC, Reichardt P. Practical management of tyrosine kinase inhibitor-associated side effects in GIST. Cancer Treat Rev. 2011;37(1):75-88.
21. Kalmanti L, Saussele S, Lauseker M, Muller MC, Dietz CT, Heinrich L, et al. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. Leukemia. 2015;29(5):1123-32.
22. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
23. 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(2):210-7.
24. Brahmi M, Vinceneux A, Cassier PA. Current Systemic Treatment Options for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis: Targeting the CSF1/CSF1R Axis. Current treatment options in oncology. 2016;17(2):10.
25. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
26. Gelderblom H, Pérol D, Chevreau C, Tattersall MNH, Stacchiotti S, Casali PG. An open-label international multicentric phase II study of nilotinib in progressive pigmented villo-nodular synovitis (PVNS) not amenable to a conservative surgical treatment. Proc Am Soc Clin Oncol. 2013;31 (suppl)(abstr 10516).
27. Ries CH, Cannarile MA, Hoves S, Benz J, Wartha K, Runza V, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer cell. 2014;25(6):846-59.
28. Sankhala KK, Blay J-Y, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). . American Society of Clinical Oncology. 2017;Conference: 2017 Annual Meeting ASCO. United States. 35 (15 Supplement 1).
29. Thanopoulou E, Judson I. The safety profile of imatinib in CML and GIST: long-term considerations. Arch Toxicol. 2012;86(1):1-12.
30. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.



The effect of surgery in Tenosynovial Giant Cell Tumours as measured by patient reported outcomes on quality of life and joint function

M.J.L. Mastboom*[1], F.G.M. Verspoor*[2], G. Hannink[2], W.T.A. van der Graaf[3] , M.A.J. van de Sande[1], H.W.B Schreuder[2]

Accepted in Bone Joint J.

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Medical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands

*Authors contributed equally to this work.

Abstract

Aim

To evaluate health-related quality of life (HRQoL) and joint function in TGCT patients before and after surgical treatment.

Patients and methods

This prospective cohort study run in two Dutch referral centres, assessed patient-reported outcome measures (SF-36, VAS and WOMAC) in 359 consecutive patients with localized- and diffuse-type TGCT of large joints. Patients with recurrent disease (N=121) and a wait-and-see policy (N=32) were excluded. Collected data were analysed at specified time intervals pre-(baseline) and/or postoperatively up to 5 years.

Results

In total 206, 108 localized- and 98 diffuse-type, TGCT patients were analysed. Median age at diagnosis of localized- and diffuse-type was 41 (IQR 29-49) and 37 (IQR 27-47) years, respectively. SF-36 analyses showed statistically significant and clinically relevant deteriorated preoperative- and direct postoperative scores compared with general population means, depending on subscale and TGCT subtype. After 6 months of follow up, these scores improved to general population means and continued to be fairly stable the following years. VAS scores, for both-subtypes, showed no clinically relevant differences pre- or postoperatively. Pain experience varied hugely between patients and also over time. WOMAC scores, for both TGCT subtypes, showed no clinically relevant differences pre- versus postoperatively. However, in diffuse-type patients WOMAC pain and physical function scores showed a trend towards improvement postoperatively.

Conclusion

Patients report a significant better HRQoL after surgery in TGCT whereas joint function showed a trend towards improvement. Pain scores –which vary hugely between patients and in patients over time- did not improve. A disease specific patient-reported outcome measure would help to decipher impact of TGCT on patients' daily life and functioning in more detail.

Introduction

Tenosynovial giant cell tumours (TGCT) of large joints, historically known as pigmented villonodular synovitis (PVNS), are rare colony stimulating factor-1 (CSF-1)-driven proliferative, mono-articular disorders. They affect the joints or tendon sheaths at all ages, however mostly at young adulthood. It most commonly affects large, weight bearing joints such as knees, ankles and hips[1, 2]. The incidence rate of localized-extremity (excluding digits) and diffuse-type TGCT is 10 and 4 per million person years, respectively[3]. Localized-type comprises a single nodule and has a favourable course after surgical treatment. Diffuse-type involves the synovial lining as well as surrounding structures. It can behave locally aggressive and is challenging to remove completely. There is a significant risk of recurrence after surgical treatment (>50% depending on follow up times)[2, 4, 5].

Diffuse-type TGCT often requires one or multiple synovectomies, or at times a joint replacement, and rarely even amputation[1, 2, 6]. In patients with extensive and/or recurrent TGCT, other available treatment modalities include radiation synovectomy[7], external beam radiation therapy[8], and cryosurgery[9] of which the effects are controversial[10]. More recently, systemic therapy has been introduced, targeting the CSF-1 receptor. At first treatment with the multi targeting tyrosine kinase inhibitor imatinib started, very recently more promising data of a CSF-1 specific targeting agent were presented[11-13]. Systemic treatment may need to be given for one to several years, but the optimal treatment duration has still to be determined. Despite the variety of treatments, it is unclear which one is the most effective with the least impact on quality of life.

A limitation of most clinical TGCT studies is the absence of disease specific and validated patient-reported outcome measures (PROMs) to document disease and treatment related functioning and symptomatology. Overall survival is the primary endpoint in oncologic clinical trials, however this is not appropriate for TGCT, which is rarely lethal[14]. Alternate treatment endpoints in TGCT include response rates, progression free survival, and avoidance of morbid therapies. As indicated, quality of life (QoL) and functional scores are of utmost importance, but they are mostly not reported or only described for small, heterogeneous patient groups[2, 15]. The impact of therapies and the relevance of treatment outcomes to patients' quality of life is therefore essential especially in a benign but locally aggressive disease[16,17].

The aim of our study is to investigate HRQoL, pain and joint function in surgically treated non-recurrent TGCT patients, pre- and/ or postoperatively over time.

Methods

This prospective cohort study was conducted at two Dutch referral centres; Radboud University Medical Centre (RadboudUMC) and Leiden University Medical Centre (LUMC)**.** Between 2011 until 2018 patients diagnosed with primary therapy-naïve or recurrent TGCT (magnetic resonance imaging (MRI) and histological confirmed) of large joints, were asked to participate. Large joints were defined as all joints except the digits. Three hundred and fifty-nine consecutive patients were identified; 136 (38%) with localized TGCT, 223 (62%) with diffuse TGCT. During regular outpatient clinic visits, patients who consented were requested to complete PROMs questionnaires. To further reduce heterogeneity of the group, patients with recurrent disease at presentation, treated conservatively (wait-and-see policy) and patients in absence of QoL and function scores after primary surgery, were excluded from this analysis (*figure 1*). Also, if patients developed relapse after surgical treatment, they were excluded from this time on. Hundred-and-eight localized- and 98 diffuse-type therapy-naïve patients were used for final analyses (*figure 1*).

The study protocol (RadboudUMC (file number CMO 2012/555) and LUMC (file number CMO P13.029)) was approved by the local institutional ethical review boards and was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent. Patients provided written informed consent when they completed questionnaires (SF 36, VAS and WOMAC).

The used PROMs included the Dutch translation of a generic HRQoL instrument, the 36-item Short Form Health Survey (SF-36)[18], a Visual Analog Scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). SF-36 is an instrument for measuring general health, including eight subscales: Physical functioning (PF), Social functioning (SF), Role limitations due to physical problems (RP), Role limitations due to emotional problems (RE), General mental health (MH), Vitality (VT), Bodily pain (BP) and General health (GH). SF-36 scores were computed by summing the item scores and transforming the scores onto a 100-point scale (0= "worst health" and 100= "best health"). VAS for worst pain was used to estimate patients pain

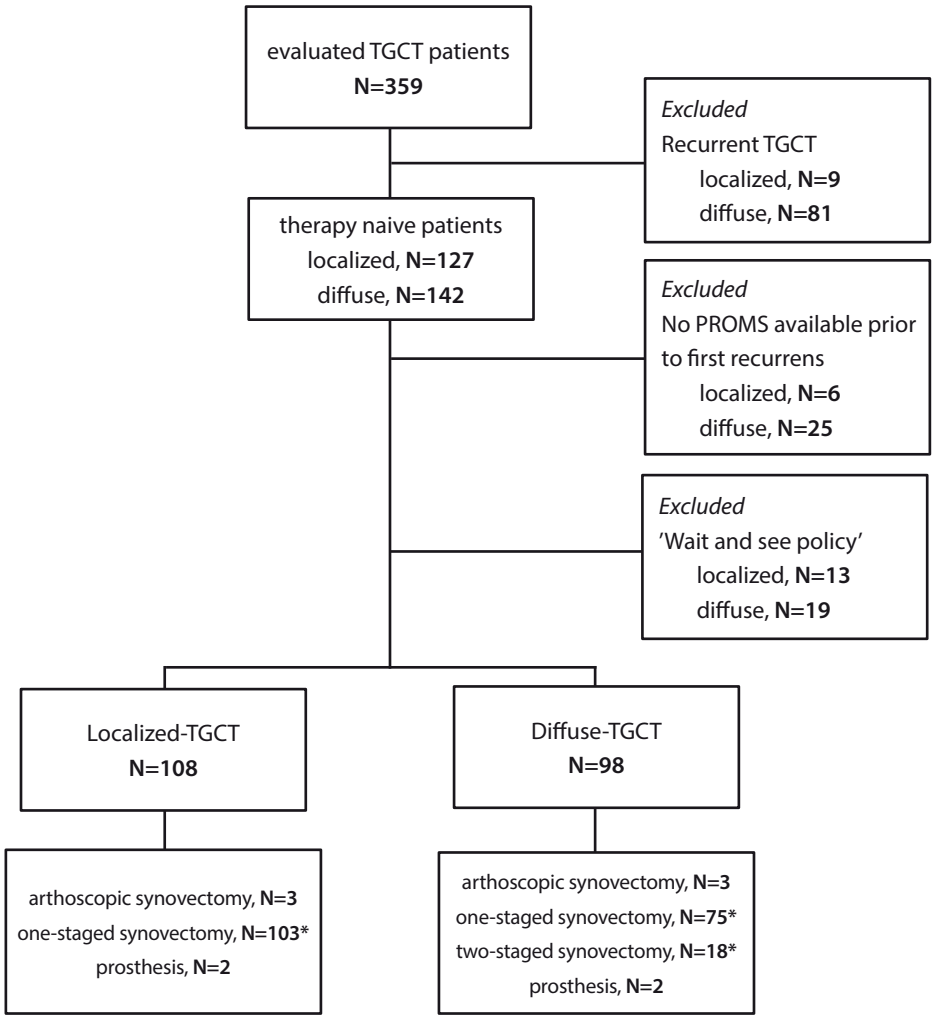


Figure 1 Flowchart of consecutive patients with TGCT, included for quality of life analyses.
*Additional cryosurgery in two localized- and five diffuse-type TGCT patients

intensity of the affected joint for the past 24 hours, using a series of 0- to 10-point (0= "no pain" and 10= "pain as bad as you can imagine")[19]. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate affected joint function[20]. The WOMAC is a 24-item instrument assessing pain, stiffness and difficulty performing daily activities originally designed for osteoarthritis. All items are measured on a 5 point scale; ranging from "no" up to "worst imaginable". The WOMAC data were standardized to a range of values from 0-100, for which lower values indicate more pain, more stiffness, or worse physical functioning. Gelhorn et al. [16] used a modified version of WOMAC for TGCT patients.

Patient demographics and clinical, histological, radiological, treatment and follow-up data were extracted from individual patients' files at each institution by the local investigator (FGMV or MJLM) and were provided in an anonymous form for analyses. Definitive histological diagnosis was performed at the centre of origin by dedicated pathologists with extensive experience in mesenchymal tumours. Recurrences and PROMs were analysed according to TGCT subtype. Data were described using percentages for qualitative variables and medians with interquartile ranges (IQR) for continuous variables.

As patient questionnaires were completed at different points in time they were categorized in the following time intervals: pre-surgery (=0 or baseline), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months. At final analyses we did not have questionnaires in all time intervals for each individual patient, some had solely pre- or post-operative scores. In case of recurrent disease after primary treatment in a therapy-naïve patient, QoL and functions scores were used up to recurrence development, confirmed on MR imaging. Follow-up time was defined as the period between first TGCT confirmation (MR imaging and histologic) and most recent patient contact. Time to recurrence was calculated as time from first treatment until proven (MR imaging and histologic) first recurrent disease. Differences between QoL scores (SF-36, VAS, WOMAC) were tested using t-tests. SF-36 scores were compared with Dutch general population scores[18], and WOMAC and VAS baseline (preoperative) scores were compared with postoperative scores.

To estimate the clinical relevance, the mean differences were compared with the minimal clinically important difference (MCID). MCID is a QoL measure that represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered clinically relevant by the value patients place on change[21]. The MCID for SF-36 has been estimated

at to be 10 points by Escobar et al.[22] in patients undergoing total knee replacement. For VAS pain a MCID of 2 was used[23]. The MCID for standardized WOMAC values has been estimated at around 15-20 points[22], with relative improvements of 21-41% for its subscales[23-25]. We used a MCID for WOMAC of 20 points based on consensus in the project team and the study of van der Wees et al.[26] All statistical analyses were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered statistically significant.

Results

Patients

After exclusion of patients with recurrent disease (N=121) and patients with a wait-and-see policy (N=32), 206 patients remained for further analyses (*figure 1*). Median age at diagnosis of localized- (N=108) and diffuse-type (N=98) TGCT was 41 (IQR 29-49) and 37(IQR 27-47) years, respectively. The majority of patients were female (localized N=62 (57%)), had diffuse-type TGCT N=64 (65%)), and had the knee as the most common affected joint in both subtypes (localized N=84 (78%)) and diffuse N=72 (74%)). Pain (localized N=61 (57%) and diffuse N=58 (60%)) and swelling (localized N=66 (61%) and diffuse N=65 (67%)) were the most prevalent clinical symptoms at diagnosis for both subtypes (*table 1*).

Treatments

As primary treatment, three (3%) localized-type patients were treated with arthroscopic synovectomy, 103 (95%) with one-staged synovectomy and two (2%) with (endo-)prosthesis. Seven patients (6%) had a first recurrence after median 2.9 (2.1-5.6) years. Overall median follow up of localized therapy-naïve patients was 2.0 (IQR 0.7-4.6) years. At final follow up, 104 (96%) patients had no evidence of disease, 4 (4%) patients were alive with disease, without planned treatment.

Diffuse-type patients were treated with arthroscopic (N=3 (3%)), one-staged (N=75 (76%)) or two-staged (N=18 (19%)) synovectomy. Two patients received an (endo-) prosthesis. Twenty-seven patients (28%) had a first recurrence after median 1.3 (1-3) years, thereafter they were excluded from further analyses. Overall median follow up of diffuse-type patients was 2.7 (IQR 1.4-4.9) years. At final follow up, 70 (71%) patients had no evidence of disease, 27 (28%) patients were alive with disease and one patient died of another disease.

Table 1 Characteristics of therapy-naïve TGCT patients

	Localized N (%)	Diffuse N (%)
Total	108	98
Median age at diagnosis (IQR), yrs.	41 (29-49)	37 (28-47)
Sex		
Male	46 (43)	34 (35)
Female	62 (57)	64 (65)
Tumour localization		
Knee	84 (78)	72 (74)
Ankle	10 (9)	10 (10)
Hip	1 (1)	7 (7)
Other	13 (12)	9 (9)
Pre-surgery symptoms		
Pain	61(57)	58 (60)
Swelling	66 (61)	65 (67)
Loss of function	8 (7)	20 (21)
Stiffness	5 (5)	14 (14)
Recurrent disease		
No	101 (94)	71 (72)
Yes	7 (6)	27 (28)
Median time to first recurrence (IQR)	2.9 (2.1-5.6)	1.3 (1-3)
Complications		
None	106 (98)	91 (93)
Deep wound infection	-	2 (2)
Superficial wound infection	1 (1)	2 (2)
Hemorrhage	-	1 (1)
Joint stiffness	1 (1)	1 (1)
Neurovascular damage	-	1 (1)
Median follow up time (IQR), yrs	2.0 (0.7-4.6)	2.7 (1.4-4.9)

Abbreviations: TGCT= Tenosynovial Giant Cell Tumours, N= Number of patients, mo=months, yrs= years, IQR= inter quartile range, other= Foot, shoulder, elbow, wrist or temporomandibular joint, AWD= alive with disease.

HR Quality of life

Compared to Dutch general population means18, localized-type patients preoperatively scored significantly lower on PF(13.2(95%CI 6.0-20.5)), SF(18.7(95%CI 10.3-27.2)), RP(25.8(95%CI 11.9-39.8)), RE(20.6(95%CI 7.3-34.0)) and BP(21.2(95%CI 12.7-29.8)). These differences were also clinically relevant (mean difference> MCID 10). This effect lasted up to 3 months postoperatively on RP(40.1(95%CI 16.7-63.5)) and BP(17.2(95%CI 2.2-32.1)). Thereafter, these means improved to general population means and continued fairly stable during the following years (*figure 2a, table 2b*).

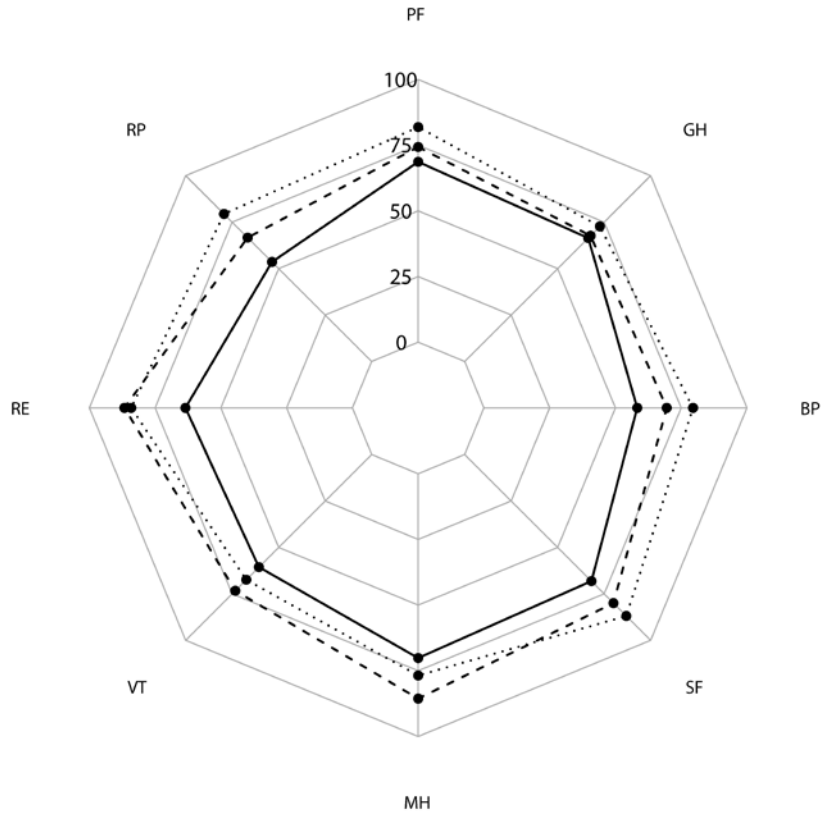


Figure 2a SF-36 scores of localized-type, therapy-naïve, TGCT patients.
Spider plot showing SF-36 scores preoperative (baseline), 6-12 months postoperatively and of Dutch general population means[18]: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), general mental health (MH), vitality (VT), bodily pain (BP) and general health (GH).

Diffuse-type patients preoperatively scored statistically significant and clinically relevant (mean difference> MCID 10) lower on PF(23.7 (95% CI 16.7-30.8)), SF (15.6 (95% CI 8.8-22.5)), RP (37.4 (95% CI 25.3-49.5)), VT (10.0 (95% CI 3.5-16.4)) and BP (21.6 (95% CI 14.7-28.5)) compared to general population means. This difference with the general population remained significant for up to 3 months postoperatively on PF (21.9 (95% CI 5.0-38.8)), SF (19.9 (95% CI 3.0-36.9)), RP (40.1 (95% CI 16.2-64.1)), VT (13.0 (95% CI 1.5-24.5)) and BP (22.4 (95% CI 5.3-39.4)) and up to 6 months

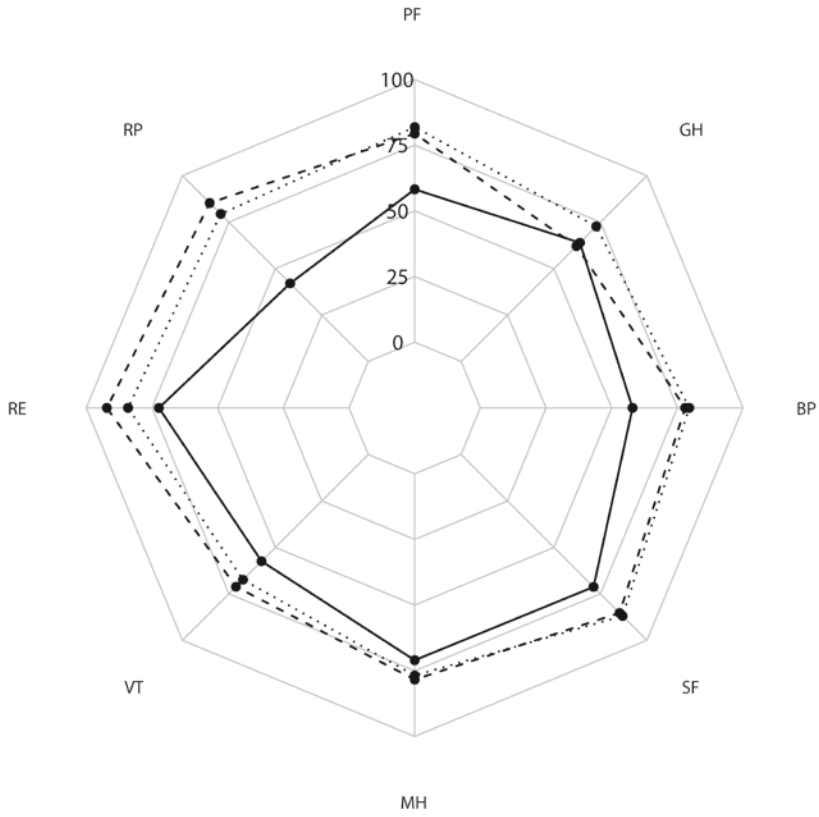


Figure 2b SF-36 scores of diffuse-type, therapy-naïve, TGCT patients.
Spider plot showing SF-36 scores preoperative (baseline), 6-12 months postoperatively and of Dutch general population means[18]: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), general mental health (MH), vitality (VT), bodily pain (BP) and general health (GH).

Table 2a SF-36 scores of localized-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up compared with general population means.

SF-36 subscales	General population (mean (SD))	Time intervals in months							
		0 N=42	**0-3 N=14**	**3-6 N=11**	**6-12 N=15**	**12-24 N=16**	**24-36 N=15**	**36-48 N=10**	**48-60 N=8**
Physical functioning (PF)	81.9 (23.2)	68.7* (23.0)	67.1 (23.8)	69.1 (22.6)	74.3 (16.7)	78.8 (19.9)	77.0 (17.9)	73.0 (33.0)	75.6 (23.7)
Social functioning (SF)	86.9 (20.5)	68.2* (26.9)	81.3 (22.3)	87.5 (17.7)	80.0 (22.1)	85.9 (19.3)	83.3 (21.5)	71.3 (27.7)	76.6 (29.5)
Role physical (RP)	79.4 (35.5)	53.6* (44.7)	39.3* (43.5)	56.8 (40.5)	66.7 (38.6)	78.1 (36.4)	71.7 (32.6)	72.5 (41.6)	71.9 (38.8)
Role emotional (RE)	84.1 (32.3)	63.5* (42.8)	88.1 (28.1)	81.8 (40.5)	86.7 (27.6)	77.1 (35.9)	88.9 (24.1)	90.0 (31.6)	83.3 (35.6)
Mental health (MH)	76.8 (18.4)	70.1 (18.9)	79.4 (17.5)	83.3 (14.3)	85.6 (15.3)	74.8 (17.3)	81.1 (11.3)	83.2 (11.9)	80.5 (19.4)
Vitality (VT)	67.4 (19.9)	60.6 (20.9)	66.2 (20.4)	67.3 (23.4)	73.3 (18.4)	60.9 (14.2)	69.0 (16.9)	61.5 (24.7)	63.8 (25.0)
Bodily pain (BP)	79.5 (25.6)	58.3* (27.3)	62.3* (27.8)	71.1 (25.8)	69.5 (18.9)	74.7 (25.3)	71.7 (24.1)	72.8 (33.0)	71.3 (33.4)
General health (GH)	72.7 (22.7)	66.4 (18.3)	65.0 (14.1)	73.2 (15.2)	67.7 (16.4)	64.4* (15.4)	70.0 (17.7)	63.5 (22.1)	65.0 (15.1)

N= number of questionnaires. *=statistically significant, underlined scores are clinically relevant (mean difference > MCID 10). SF-36 questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

Table 2b SF-36 scores of diffuse-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up compared with general population means.

SF-36 subscales	General population (mean (SD))	Time intervals in months							
		0 N=47	**0-3 N=14**	**3-6 N=17**	**6-12 N=17**	**12-24 N=17**	**24-36 N=15**	**36-48 N=15**	**48-60 N=13**
Physical functioning (PF)	81.9 (23.2)	58.2* (23.7)	60.0* (31.6)	67.1* (23.6)	79.4 (12.0)	71.8 (22.2)	72.3 (18.9)	73.3 (25.0)	79.6 (17.1)
Social functioning (SF)	86.9 (20.5)	71.3* (23.2)	67.0* (31.6)	75.0 (25.8)	85.3 (14.8)	88.2 (16.8)	85.8 (16.3)	82.5 (27.9)	86.5 (15.7)
Role physical (RP)	79.4 (35.5)	42.0* (40.7)	39.3* (44.6)	60.3 (44.2)	85.3 (28.0)	75.0 (36.4)	70.0 (40.3)	78.3 (37.6)	90.4 (16.3)
Role emotional (RE)	84.1 (32.3)	72.3 (40.1)	78.6 (38.4)	86.3 (29.0)	92.2 (18.7)	82.4 (35.6)	93.3 (18.7)	84.4 (35.3)	92.3 (20.0)
Mental health (MH)	76.8 (18.4)	71.0 (18.4)	74.3 (15.6)	78.4 (14.0)	78.4 (16.3)	75.8 (20.1)	78.4 (14.9)	74.9 (22.0)	77.8 (18.6)
Vitality (VT)	67.4 (19.9)	57.4* (21.8)	54.4* (21.4)	62.4 (21.1)	71.2 (19.9)	61.2 (23.0)	63.7 (18.8)	66.3 (28.4)	65.4 (23.5)
Bodily pain (BP)	79.5 (25.6)	57.9* (23.1)	57.1* (31.7)	70.0 (22.3)	77.9 (17.0)	77.2 (23.0)	70.0* (16.9)	76.0 (22.5)	79.4 (22.1)
General health (GH)	72.7 (22.7)	63.9* (13.6)	63.6 (19.1)	62.9* (13.6)	62.1* (16.9)	62.4* (19.9)	62.0* (11.6)	65.7 (17.3)	66.9 (15.2)

N= number of questionnaires. *=statistically significant, underlined scores are clinically relevant (mean difference > MCID 10). SF-36 questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

postoperatively on PF (14.8 (95% CI 3.3-26.4)). Thereafter, the mean SF-36 scores of diffuse-type patients improved to Dutch general population means and continued fairly stable the following years. Compared to general population means diffuse-type patients scored statistically significant and clinically relevant lower on GH 3-6 months (10.6 (95% CI 9.8-23.2)), 6-12 months (10.3 (95% CI 2.3-18.9)) and 24-36 months (10.7 (95% CI 4.5-16.9)) postoperatively (*figure 2b, table 2b*).

Visual analog scale for pain

No statistical significant nor clinical relevant difference in pain scores were found in localized-type patients preoperatively (median VAS score 4, IQR 1-6) versus 3 months postoperatively (median VAS score 3.5, IQR 1-5), which in fact remained the same up to five years follow up**.** Median VAS scores in diffuse-type patients showed no clinical relevant difference preoperatively (median VAS score 4, IQR 2-6) versus 3 months postoperatively (median VAS score 2, IQR 1-4), and also here the scores remained the same up to five years follow up. Pain experience in both subtypes TGCT varied widely between and within patients over time (range 0-7 years follow up).

Joint function

Mean WOMAC scores on pain, stiffness and physical functioning for both localized- and diffuse-type patients showed no significant differences pre-(baseline) versus postoperatively. Patients of both subtypes scored significantly better at some postoperative time intervals compared to baseline scores, however mostly clinically irrelevant (mean difference< 20) (*table 3a and b*).

In diffuse-type patients (*table 3b*) WOMAC pain and physical function scores showed a trend towards improvement in scores from preoperatively (baseline) to postoperative up to 5 years follow-up.

Table 3a WOMAC scores of localized-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up

WOMAC scores (mean (SD))	Time intervals in months							
	0 N=35	**0-3 N=12**	**3-6 N=9**	**6-12 N=14**	**12-24 N=9**	**24-36 N=8**	**36-48 N=5**	**48-60 N=5**
Pain	73.1 (20.9)	74.2 (17.4)	86.7* (13.7)	83.9 (16.5)	70.0 (22.4)	85.0* (11.0)	81.0 (29.2)	95.0* (5.0)
Stiffness	73.5 (25.1)	59.4 (19.3)	77.8 (21.4)	79.5 (25.8)	59.7 (32.3)	67.2 (25.8)	85.0 (22.4)	80.0 (11.2)
Physical	75.0 (21.4)	76.5 (19.4)	88.1* (13.1)	89.8* (11.8)	74.7 (20.6)	86.0 (11.6)	82.1 (33.9)	92.6* (7.1)
Total	74.7 (20.1)	74.6 (17.8)	87.4* (13.5)	87.7* (13.0)	72.5 (21.3)	84.2 (10.6)	82.1 (31.8)	92.1* (6.6)

WOMAC= standardized Western Ontario and McMaster Universities Osteoarthritis Index. In the standardized WOMAC (0-100) sum scores, higher values indicate less pain, stiffness or better physical functioning. N= number of questionnaires.*=statistically significant, underlined scores are clinically relevant (mean difference > MCID 20). WOMAC questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

Table 3b WOMAC scores of diffuse-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up

WOMAC scores (mean (SD))	Time intervals in months							
	0 N=31	**0-3 N=11**	**3-6 N=10**	**6-12 N=9**	**12-24 N=12**	**24-36 N=11**	**36-48 N=10**	**48-60 N=9**
Pain	59.8 (20.9)	68.2 (23.5)	73.5 (17.2)	75.6 (21.0)	79.6* (22.7)	77.7* (20.8)	77.5* (22.8)	85.0* (21.2)
Stiffness	60.9 (24.1)	62.5 (17.7)	76.3 (24.6)	69.4 (19.9)	68.8 (22.3)	69.3 (18.8)	72.5 (21.1)	75.0 (25.8)
Physical	63.9 (18.8)	68.3 (18.7)	73.7 (22.2)	82.7* (15.7)	81.0* (23.1)	76.7 (21.5)	82.1* (18.2)	84.2* (19.5)
Total	62.8 (18.7)	67.8 (18.4)	73.9 (20.3)	80.1* (16.1)	79.7* (22.4)	76.3 (20.2)	80.3* (18.0)	83.6* (19.4)

WOMAC= standardized Western Ontario and McMaster Universities Osteoarthritis Index. In the standardized WOMAC (0-100) sum scores, higher values indicate less pain, stiffness or better physical functioning. N= number of questionnaires.*=statistically significant, underlined scores are clinically relevant (mean difference > MCID 20). WOMAC questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

Discussion

To our knowledge, this study provides the largest prospective cohort, including longest follow up time, to report on PROMs in therapy-naïve patients with localized- and diffuse-type TGCT of large joints followed up until relapse of disease or end of study. In both TGCT subtypes HRQoL (SF-36) was statistically significant and clinically relevant decreased before surgical treatment on the main physical domains (RP, PF, BP) and some mental domains (SF, RE, VT) compared to general population means. These low scores lasted for up to 6 months postoperatively depending on TGCT subtype and SF-36 subscale. Thereafter, all SF-36 subscales improved to general population means and continued fairly stable the following years. Pain experience (VAS) in both subtypes varied widely between and within patients over time. Mean function (WOMAC) scores on pain, stiffness and physical functioning for both subtypes TGCT showed no clinically relevant difference pre-(baseline) versus postoperatively. However, in diffuse-type patients WOMAC pain and physical function scores showed a trend towards improvement in scores from preoperatively(baseline) to postoperatively up to five years follow-up.

TGCT can behave locally aggressive causing joint destruction and provoke significant pain, swelling, decrease in range of motion, and stiffness[11]. This morbidity can lead to impairment of HRQoL and function because of pain, medication use, disability, the knowledge of having a tumour (despite its benign character), and loss of working hours[16]. To improve these consequences, treatments are performed, which –unfortunately- might contribute to further joint destruction[10]. The prolonged course of the disease and the need for multiple surgeries has been reported to result in a worse joint function for many patients[27]. In addition to the physical and financial burden for the patient, TGCT also involves high healthcare burden[28]. Finding an efficient treatment is important.

This study reported on the loss of HRQoL in patients with TGCT compared to general population means. The improvements in HRQoL after surgical resections were present 3-6 months after surgery. This could be explained by the morbidity of an operation and the associated recovery time.

We did not find statistically significant and clinically relevant differences in pain experience. This might be explained by a variability in symptom experience as described by Gelhorn et al.[16] They found that not all patients experience all symptoms and there was variability in how patients experienced symptoms within and among days.

The statistically significant but lack of clinically relevant improvement in joint function (WOMAC) could be explained by the destruction the disease already caused, or by the small number of questionnaires left after exclusion of many patients to optimize the homogeneity of the patient group. The lack of disease specific instruments to evaluate adequate PROMs for TGCT, may have led to underreporting disease specific issues.

SF-36 was developed to get more general insight into patients' health and as a means of making comparisons across conditions[29]. VAS was developed as a pain assessment tool used for cancer patients[19]. The WOMAC was originally developed to evaluate the outcome of a total knee replacement in patients with osteoarthritis.[20] SF-36, VAS and WOMAC are a good start in assessing the patients perspective in TGCT, since they are validated, easy to apply and globally known. These measures are frequently used for other diseases, allowing to compare TGCT patients with other patient groups, for example patients with joint replacements for osteoarthrosis[30,22,31]. Gelhorn et al. investigated 'patient-reported symptoms of TGCT'. They concluded that pain (VAS), swelling, stiffness and impaired joint function (WOMAC) are important PROMs.

Van der Heijden et al. [15] evaluated 30 patients with therapy-naïve and recurrent diffuse-type TGCT at a mean of 8 (range 2-32) years after diagnosis. HRQoL impairment (SF-36) was seen in all patients initially treated with arthroscopic synovectomy (62 range 26-94) and an open synovectomy (80 range 63-98), compared to healthy controls[15]. The patient population was small and heterogeneous, in which outcome measures were assessed at different time points after treatment. In the study of Verspoor at al.[2], which experienced similar limitations, HRQoL (SF-36) scores were not significantly different between localized- and diffuse-type TGCT. However, both patient groups had impaired HRQoL compared to general population means one the general health subscale. Diffuse patients also scored significantly lower on other subscales (PF, MH and VT). The current study, with a more homogenous, larger patient cohort and measurements at categorized time intervals, showed a similar impairment in therapy-naïve patients on PF preoperatively for both subtypes and up to 6 months postoperatively in diffuse-type patients who generally need more extensive surgery compared to localized-type TGCT.

Case series reporting on joint function before treatment often included both subtypes, various localizations, a mixture of therapy-naïve and recurrent TGCT including multiple treatments[15, 27, 32-34]. Therefore, it is extremely challenging to perform a meta-analysis to prove treatment effect(s) in the rare disease TGCT. Through the emergence of systemic treatments for TGCT, attention for additional outcome measures besides recurrences has been raised, such as HRQoL and joint function. International cooperation has been initiated, resulting in large registries including QoL and joint function[35]. In the recent years targeted therapy has been added to the armamentarium. At ASCO 2018 results of pexidartinib (PLX3397)[12], a selective inhibitor of CSF-1 receptor, KIT, and FLT3-ITD, were promising in a randomized, placebo controlled, phase 3 study. Pexidartinib compared to placebo resulted in an significantly improved overall response rate (39.3% vs 0%) and PROMIS physical function (4.06 vs 0.89), after a median 6 months follow up[12]. In this study range of motion, PROMIS physical function, worst stiffness and pain response were secondary endpoints[12]. The joint localization of TGCT might influence physical function[36, 37]. Therefore, a sensitivity analysis was performed on our patients with TGCT affecting the knee, which showed similar results to our primary analysis. In a univariate analyses on TGCT locations with recurrent disease as outcome, Palmerini et al.[38] did not find a difference between knees, hips and ankles.

Two crowdsourcing studies[39, 40], using an online patient support-group, reported on physical function and HRQoL in TGCT patients. In patients with diffuse-type TGCT, recurrences requiring repeated surgery and joint replacement were reported to have a lower HRQoL and functional outcome[39, 40]. Because of selection bias, it is possible that severe cases including (additional) recurrences were more likely to be online to complete the e-survey. However, all studies, including the current one suggest an impaired effect on HRQoL and function in patients with TGCT. The challenge remains to find the exact quantification method.

This study has some limitations that need to be discussed. Because of the rarity of TGCT, it is challenging to perform a prospective study with adequate patient numbers. To reduce heterogeneity of the patient group, we chose to exclude recurrent patients, at the expense of decreasing patient numbers. Still, heterogeneity in severity and duration of illness remained.

Selection bias should be taken into account, because this study only contains patients from two tertiary Dutch referral centres. Overrepresentation of extensive disease, could have resulted in an overestimation of the impact on HRQoL and joint function. Also, patients with complaints more often visit the outpatient clinic completing questionnaires. These patients might have more extended, metastatic, disease. By excluding patients with recurrent TGCT, this possible bias was reduced. On the contrary, patients who do well, like localized-type TGCT patients, were discharged early reducing their follow up time and number of questionnaires.

It should be noticed that HRQoL and function scores were taken at variable points after treatment for individual patients, which reduced numbers at some specific time points. Not all patients had preoperatively and postoperative available measures, causing an increase in the range of these outcome measures. Furthermore, it is preferred to adjust SF-36 measures for age, because of physiologically declined HRQoL and joint function decrease in ageing[18, 41]. In the current study correction for age could not be achieved by differences in ages per time interval and the age distribution within time intervals.

Patients with localized-type TGCT generally do not have a high burden of their disease. The question is whether PROMs are essential in patients with localized disease, who can generally be treated curatively with a radical excision and are not eligible for systemic therapy. To date, surgical resection remains the treatment of choice for TGCT, but is associated with high recurrence rates and multiple additional surgeries in diffuse-type disease.[10] The balance between increased morbidity of multiple or invasive surgeries[15, 42], alternative therapeutic options, and daily symptoms of the tumour is challenging. A more aggressive resection or other multimodality treatments, such as external beam radiation therapy, may adversely affect QoL, joint function and the development of osteoarthrosis, which are, given the young adult age group, factors of major importance[2, 38]. Use of a control group and of specific and validated PROMs will better document treatment-induced symptomatic, functional and economic (back to work) consequences of these treatments[16].

When systemic treatments show tumour growth arrest and symptomatic improvements, a less invasive approach would be justified[11]. The recent studies on targeted therapy used a control group and as secondary outcome measure PROMIS physical function[12].

These measures are critical endpoints in demonstrating clinical relevance and impact of treatments for benign diseases in which death is no outcome variable.[16] Clinical benefit necessitates objective measures to correlate with tumour reduction. When significant changes in TGCT specific developed outcome measures are found, one should try to specify if this is the consequence of the disease itself, of the 'multiple' treatment(s) received, or of other factors, such as comorbidities, the knowledge of having a tumour or issues not related to disease.

Conclusion

Patients report a significant better HRQoL after surgery in TGCT whereas joint function showed a trend towards improvement. Pain scores –which vary hugely between patients and in patients over time- did not improve. A disease specific patient-reported outcome measure would help to decipher impact of TGCT on patients' daily life and functioning in more detail.

References

1. Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented Villonodular Synovitis: A Retrospective Single-Centre Study of 122 Cases and Review of the Literature. Seminars in Arthritis and Rheumatism. 2011;40 (6):539-46.
2. Verspoor FGM, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
3. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
4. Ravi V, Wang WL, Lewis VO. Treatment of tenosynovial giant cell tumor and pigmented villonodular synovitis. Curr Opin Oncol. 2011.
5. de saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, diffuse/localized type. In: Fletcher CD, Bridge JA, Hogedoorn PC, Mertens F, eds. WHO classification of tumours of Soft Tissue and Bone. 2013;5(4th ed. Lyon: IARC Press).
6. Mastboom MJL, Verspoor FGM, Gelderblom H, van de Sande MAJ. Limb Amputation after Multiple Treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch Cases. Case reports in orthopedics. 2017;2017:7402570.
7. Shabat S, Kollender Y, Merimsky O, Isakov J, Flusser G, Nyska M, et al. The use of surgery and yttrium 90 in the management of extensive and diffuse pigmented villonodular synovitis of large joints. Rheumatology. 2002;41 (10):1113-8.
8. Heyd R, Seegenschmiedt MH, Micke O. [The Role of External Beam Radiation Therapy in the Adjuvant Treatment of Pigmented Villonodular Synovitis.]. Z Orthop Unfall. 2011.
9. Verspoor FG, Scholte A, van der Geest IC, Hannink G, Schreuder HW. Cryosurgery as Additional Treatment in Tenosynovial Giant Cell Tumors. Sarcoma. 2016;2016:3072135.
10. Verspoor FG, van der Geest IC, Vegt E, Veth RP, van der Graaf WT, Schreuder HW. Pigmented villonodular synovitis: current concepts about diagnosis and management. Future Oncol. 2013;9(10):1515-31.
11. Brahmi M, Vinceneux A, Cassier PA. Current Systemic Treatment Options for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis: Targeting the CSF1/CSF1R Axis. Current treatment options in oncology. 2016;17(2):10.
12. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO Annual Meeting. 2018.
13. Giustini N, Bernthal NM, Bukata SV, Singh AS. Tenosynovial giant cell tumor: case report of a patient effectively treated with pexidartinib (PLX3397) and review of the literature. Clin Sarcoma Res. 2018;8:14.
14. Gounder MM, Thomas DM, Tap WD. Locally Aggressive Connective Tissue Tumors. J Clin Oncol. 2018;36(2):202-9.
15. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
16. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
17. 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. The New England journal of medicine. 2015;373(5):428-37.
18. VanderZee KI, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med. 1996;3(2):104-22.
19. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129-38.
20. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40.
21. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.
22. Escobar A, Quintana JM, Bilbao A, Arostegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important

differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage. 2007;15(3):273-80.
23. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis. 2005;64(1):29-33.
24. Angst F, Ewert T, Lehmann S, Aeschlimann A, Stucki G. The factor subdimensions of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) help to specify hip and knee osteoarthritis. a prospective evaluation and validation study. J Rheumatol. 2005;32(7):1324-30.
25. White DK, Keysor JJ, Lavalley MP, Lewis CE, Torner JC, Nevitt MC, et al. Clinically important improvement in function is common in people with or at high risk of knee OA: the MOST study. J Rheumatol. 2010;37(6):1244-51.
26. van der Wees PJ, Wammes JJ, Akkermans RP, Koetsenruijter J, Westert GP, van Kampen A, et al. Patient-reported health outcomes after total hip and knee surgery in a Dutch University Hospital Setting: results of twenty years clinical registry. BMC Musculoskelet Disord. 2017;18(1):97.
27. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
28. Burton TM, Ye X, Parker ED, Bancroft T, Healey J. Burden of Illness Associated with Tenosynovial Giant Cell Tumors. Clin Ther. 2018;40(4):593-602 e1.
29. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. Rheumatology (Oxford). 1999;38(9):870-7.
30. Verspoor FG, Hannink G, Scholte A, Van Der Geest IC, Schreuder HW. Arthroplasty for tenosynovial giant cell tumors. Acta orthopaedica. 2016;87(5):497-503.
31. Veenhof C, Bijlsma JW, van den Ende CH, van Dijk GM, Pisters MF, Dekker J. Psychometric evaluation of osteoarthritis questionnaires: a systematic review of the literature. Arthritis Rheum. 2006;55(3):480-92.
32. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
33. Ozturk H, Bulut O, Oztemur Z, Bulut S. Pigmented villonodular synovitis managed by Yttrium 90 after debulking surgery. Saudi Medical Journal. 2008;29 (8):1197-200.
34. Wu CC, Pritsch T, Bickels J, Wienberg T, Malawer MM. Two incision synovectomy and radiation treatment for diffuse pigmented villonodular synovitis of the knee with extra-articular component. Knee. 2007;14 (2):99-106.
35. Mastboom M, Verspoor F, Rüeten-budde A, Gelderblom H, Stacchiotti S, Daolio P, et al. Risk factors in Tenosynovial Giant Cell Tumours, evaluated in 17 international sarcoma centres. 2018(99).
36. Della Valle AG, Piccaluga F, Potter HG, Salvati EA, Pusso R. Pigmented villonodular synovitis of the hip: 2- to 23-year followup study. Clinical Orthopaedics and Related Research. 2001;(388):187-99.
37. Schwartz GB, Coleman DA. Pigmented villonodular synovitis of the wrist and adjacent bones. Orthopaedic Review. 1986;15 (8):526-30.
38. 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(2):210-7.
39. van der Heijden L, Piner SR, van de Sande MA. Pigmented villonodular synovitis: a crowdsourcing study of two hundred and seventy two patients. Int Orthop. 2016;40(12):2459-68.
40. Mastboom MJ, Planje R, van de Sande MA. The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life. Interact J Med Res. 2018;7(1):e4.
41. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055-68.
42. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).

chapter eleven

DAILY LIVING

The patient perspective on the impact of Tenosynovial Giant Cell Tumours on daily living

crowdsourcing study on physical function and quality of life

M.J.L. Mastboom[1], R. Planje[1], M.A.J. van de Sande[1]

Interact J Med Res. 2018 Feb 23;7(1):e4.

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

Abstract

Background

Tenosynovial Giant Cell Tumour (TGCT) is a rare, benign lesion affecting the synovial lining of joints, bursae, and tendon sheaths. It is generally characterized as a locally aggressive and often recurring tumour. A distinction is made between localized- and diffuse-type. The impact of TGCT on daily living is currently ill-described.

Objective

The aim of this crowdsourcing study was to evaluate the impact of TGCT on physical function, daily activities, societal participation (work, sports, and hobbies), and overall quality of life from a patient perspective. The secondary aim was to define risk factors for deteriorated outcome in TGCT.

Methods

Members of the largest known TGCT Facebook community, PVNS is Pants!!, were invited to an e-survey, partially consisting of validated questionnaires, for 6 months. To confirm disease presence and TGCT-type, patients were requested to share histological or radiological proof of TGCT. Unpaired t tests and chi-square tests were used to compare groups with and without proof and to define risk factors for deteriorated outcome.

Results

Three hundred thirty-seven questionnaires, originating from 30 countries, were completed. Median age at diagnosis was 33 (interquartile range [IQR]=25-42) years, majority was female (79.8% [269/337]), diffuse TGCT (70.3% [237/337]), and affected lower extremities (knee 70.9% [239/337] and hip 9.5% [32/337]). In 299 lower-extremity TGCT patients (32.4% [97/299]) with disease confirmation, recurrence rate was 36% and 69.5% in localized and diffuse type, respectively. For both types, pain and swelling decreased after treatment; in contrast, stiffness and range of motion worsened. Patients were limited in their employment (localized 13% [8/61]; diffuse 11.0% [21/191]) and sport-activities (localized 58% [40/69]; diffuse 63.9% [147/230]). Compared with general US population, all patients showed lower Patient-Reported Outcomes Measurements Information System-Physical Function (PROMIS-PF), Short Form-12 (SF-12), and EuroQoL 5 Dimensions 5

Levels (EQ5D-5L) scores, considered clinically relevant, according to estimated minimal important difference (MID). Diffuse versus localized type scored almost 0.5 standard deviation lower for PROMIS-PF (P<.001) and demonstrated a utility score of 5% lower for EQ-5D-5L (P=.03). In localized TGCT, recurrent disease and ≥2 surgeries negatively influenced scores of Visual Analog Scale (VAS)-pain/stiffness, SF-12, and EQ-5D-5L (P<.05). In diffuse type, recurrence resulted in lower score for VAS, PROMIS-PF, SF-12, and EQ-5D-5L (P<.05). In both types, patients with treatment ≤1year had significantly lower SF-12.

Conclusions

TGCT has a major impact on daily living in a relatively young and working population. Patients with diffuse type, recurrent disease, and ≥2 surgeries represent lowest functional and quality of life outcomes. Physicians should be aware that TGCT patients frequently continue to experience declined health-related quality of life and physical function and often remain limited in daily life, even after treatment(s).

Introduction

Tenosynovial Giant Cell Tumour (TGCT), previously pigmented villonodular synovitis (PVNS), is a rare, proliferative neoplasm affecting the synovial lining of joints, bursae, and tendons sheaths. According to growth pattern, a radiological distinction is made between a well-circumscribed lesion (localized type) and a locally more aggressive lesion (diffuse type)[1, 2]. The incidence rate reveals its rarity: for localized type (excluding digits), 10.2 per million person-years and for diffuse type, 4.1 per million person-years. TGCT is a monoarticular disease, concerning large joints, typically about the knee: 46% in localized-type and 64% to 75% in diffuse-type. Male-female ratio is about 1:1.5 for both types, with a median age at the time of TGCT diagnosis of 30 to 50 years[1-3]. Most common initial symptoms are pain, stiffness, and swelling. Additional symptoms might be limited range of motion, instability, giving way, and locking complaints[4]. Due to these unspecific signs and the rarity of the disease, patients frequently experience a delay of years in diagnosis[3, 5, 6]. To treat these symptoms, current treatment of choice is surgical excision, either by arthroscopic or open synovectomy[7]. After surgical resection, high recurrence rates are known, with the localized type up to 50% and the diffuse type up to 92%[6].

Once TGCT is diagnosed, a high health care burden is identified with a significant increase in health care costs, ambulatory expenses, and physical therapy[8]. In describing treatment benefits and standard oncologic end points, patient-reported outcome instruments are increasingly used. Visual Analog Scale (VAS) for worst pain-stiffness and Patient-Reported Outcomes Measurement Information System- Physical Function (PROMIS-PF) questionnaires were identified as most valuable measures for TGCT symptoms in a relatively small TGCT patient cohort (n=22)[4].

The impact of TGCT symptoms following surgery(s) and recurrences on daily living, sports, and work activities is currently ill-described. Although TGCT is not considered lethal, this tumour is hypothesized to have major impact on daily living. Especially diffuse disease is notorious for its negative influence on both local recurrence risk and functional outcome[9].

Use of an e-survey is a unique possibility to reach a large elusive TGCT population and to globally evaluate impact of TGCT on patients' daily life. This crowdsourcing study evaluates effect of TGCT on physical function, daily activities, societal participation (work, sports, and hobbies), and overall quality of life from a patient perspective. Secondary aim is to define risk factors for deteriorated outcome in TGCT.

Methods

Study design

This cross-sectional crowdsourcing study was performed at Leiden University Medical Centre, Leiden, The Netherlands, in accordance with good clinical practice [the Declaration of Helsinki (2000)]. This study was conducted from December 2016 until end of May 2017 (6 months), using the largest known online TGCT community on Facebook, PVNS is Pants!!, to gather participants for the Web-based questionnaire. The study was conducted conforming to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES), the checklist focusing on Web-based surveys[10] (*Appendix 1*). NetQuestionnaire (NetQ) was used to complete the TGCT questionnaire. NetQ is a professional Web-survey software, approved for (bio)medical research and supported by the Leiden University Medical Centre (LUMC). Respondents were able to review and change their answers before submitting.

Patients and Recruitment

Members of PVNS is Pants!! were requested to participate in our international crowdsourcing study "Evaluation of Tenosynovial Giant Cell Tumour on daily living" (*Appendix 2*). At the time of writing (December, 2016), this closed Facebook community contained 2179 members. A patient-friendly TGCT-research-related message was posted in the Facebook community every 4 weeks to encourage TGCT patients to complete the questionnaire. Additional study updates and easily understandable information on TGCT were posted on the page of a newly designed TGCT study Facebook account[11].

All members of the Facebook community had access to the questionnaire. Solely patients with TGCT diagnosis were requested to participate in this study. To achieve a higher level of evidence, confirmation of TGCT (histological or radiological) was requested after completing the questionnaire. Sending (anonymized) medical reports to our protected email account was highly desirable but left to the discretion of the participant.

Members of Facebook community PVNS is Pants!! have been notified that (research-minded) doctors are members of this closed Facebook community for several years. Participation in this study was voluntary, and no incentives were offered. Informed consent was given by completing the survey. This study was approved by the Institutional Review Board (CME) from our institution (registration number P16.232, December 5, 2016).

Unique site visitors were determined by Internet protocol (IP) addresses. When duplicate entries were detected, the most recent one was included in the analyses. All password-protected documents were only accessible to TGCT researchers and saved on the secured departmental drive of our hospital. Data of participants were anonymized when medical proof was received or when the participant did not respond to our third request for medical confirmation. To ascertain TGCT diagnosis and TGCT type, all medical reports were verified by 2 TGCT researchers (MJLM, RP). When in disagreement, medical reports were checked by the senior orthopaedic surgeon (MAJS) for final conclusion.

Questionnaire

On the very active Facebook community PVNS is Pants!!, several patient-initiated questionnaires and polls were performed, for instance, about treatments, coping strategies, daily limitations, and emotional struggles. Members expressed their desire for studies regarding these topics, since the majority of TGCT studies concern physical function and recurrent disease as outcome parameters. Therefore, a Web-based questionnaire, using mostly validated questionnaires, was composed to describe impact of TGCT on health-related outcome and daily living from a patient perspective. A prerequisite was that the questionnaire would be relevant for the heterogeneous TGCT population: for different large joints, different ages, males or females, localized or diffuse type, and for patients at different treatment stages.

To assess relevance and completeness of our questionnaire, a pilot test with the composed questionnaire was performed. One dedicated orthopaedic oncologic surgeon (MAJS), 2 medical doctors (MJLM, RP), and 5 TGCT patients in our outpatient clinic, all fluent in written and spoken English language, tested the e-survey. Validated questionnaires were used as published by the owners. After the pilot test, a few nonvalidated questions were added or rephrased (*Appendix 3*).

Nonvalidated questions concerned patient and tumour characteristics, medical history, TGCT symptoms, performed treatments, recurrences, employment status, sports, and number of visits to general practitioner and orthopaedic surgeon. The majority of questions had a multiple-choice character, including a not applicable or other answer option. The exact number of nonvalidated questions depended on given answers. For instance, patients with an extensive TGCT-related history were asked additional questions on their history, in contrast to the patients awaiting their initial treatment.

Validated questionnaires on physical function and quality of life included: VAS for worst pain and stiffness in the last 24 hours, PROMIS-PF items, Short Form-12 Health Survey (SF-12), and EuroQoL EQ-5D-5L (EQ-5D-5L Descriptive System and EQ-5D-5L VAS). A total of 32 validated questions were included. VAS for pain and stiffness was used to estimate patient's pain and stiffness intensity for the past 24 hours: no pain/stiffness at all (0) and worst pain/stiffness imaginable (10).

PROMIS-PF instruments were used to measure self-reported capability of physical activities. In this study, short forms of physical functioning for lower and upper extremity were used with 5 response options: without any difficulty (5), with a little difficulty (4), with some difficulty (3), with much difficulty (2), and unable to do (1). Raw score was calculated by summing up the values of the response to each question and was converted into a T score by the Assessment Centre from PROMIS-PF. A mean of a standardized T score of 50 with a standard deviation of 10 reflects the general US population[12].

The SF-12, a generic measure of health status, functioned as a shorter alternative for the SF-36. Number of answer options differed per question. Physical component summary (PCS) score and mental component summary (MCS) score were calculated. Similar to PROMIS-PF, the general US population had a mean of 50 with a standard deviation of 10[13].

The EQ-5D-5L is one of the most commonly used generic health status measures in the world. Its descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, with the following 5 levels of problems per dimension: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5)[14]. For each participant, answers per dimension were combined into an EQ-5D-5L health state. This health state was converted into a single index value (so-called utility score) for quality of life, by using the Crosswalk Index Value Calculator version 1.0 from the EuroQoL Group[15]. Utility scores were measured on an ordinal scale of 0 to 1, with 0 indicating death and 1 indicating full health[16]. Crosswalk valuation set for US population was used for all participants, since majority of the patients originated from the United States (42.7% [144/377]). A specific analysis, called sensitivity analysis, was performed using the valuation set for UK population, the second largest patient population (20.2% [68/337]) in this study. Scores calculated with US valuation set were compared with scores obtained by using UK valuation set to assess representativeness of the scores from validated questionnaires[14] (*Appendix 4*).

Statistical Analysis

NetQ automatically captured questionnaire answers into an SPSS 23 file. Evaluation of TGCT on daily living was mainly descriptive.

Chi-square tests were used to compare patient groups with and without medical proof regarding gender (male vs female), TGCT localization (knee vs other large lower extremity joints [hip, ankle, and foot]), initial surgery (arthroscopy vs [one- or two-staged] open synovectomy), recurrence (yes vs no), total number of surgeries (1 surgery vs ≥2 surgeries), and time since last treatment for TGCT (≤1 year ago vs >1 year ago) (*Appendix 5*).

Independent t tests were used to compare the mean age at the time of diagnosis and continuous scores of validated questionnaires. All reported P values were two-tailed. Statistical significance level was defined at P<.05.

Effect size, as a quantitative measure of the strength of a phenomenon, was calculated for both PROMIS-PF and SF-12 scores in localized- and diffuse-type patients, compared with general US population score. Effect size, or Cohen d, is the ratio of difference between two means divided by the standard deviation, expressed in standard deviation units. An effect size between 0.2 and 0.5 is considered small, 0.5 and 0.8 medium, and above 0.8 large[17].

The minimal important difference (MID), a quality of life measure, represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered clinically relevant by the value patients place on change. MID for EQ-5D-5L Index Scores is estimated between .037 and .069, based on the simulation-based instrument-defined MID estimates[18]. MID for PROMIS-PF was determined by Yost et al. in advanced-stage cancer patients[19]. Differences in T scores between 4.0 and 6.0 were considered clinical relevant. MID for SF-12 PCS and MCS scores were calculated by Díaz-Arribas et al. in >450 patients with low back pain and were stated at >3.29 for PCS and >3.77 for MCS[20].

Results

The TGCT questionnaire was initiated by 445 participants within a time frame of 6 months. For the present analysis, only fully completed, unique questionnaires (337) were included (*Figure 1*). The majority of incomplete questionnaires were early dropouts with a great lack of information and therefore unsuitable for analysis.

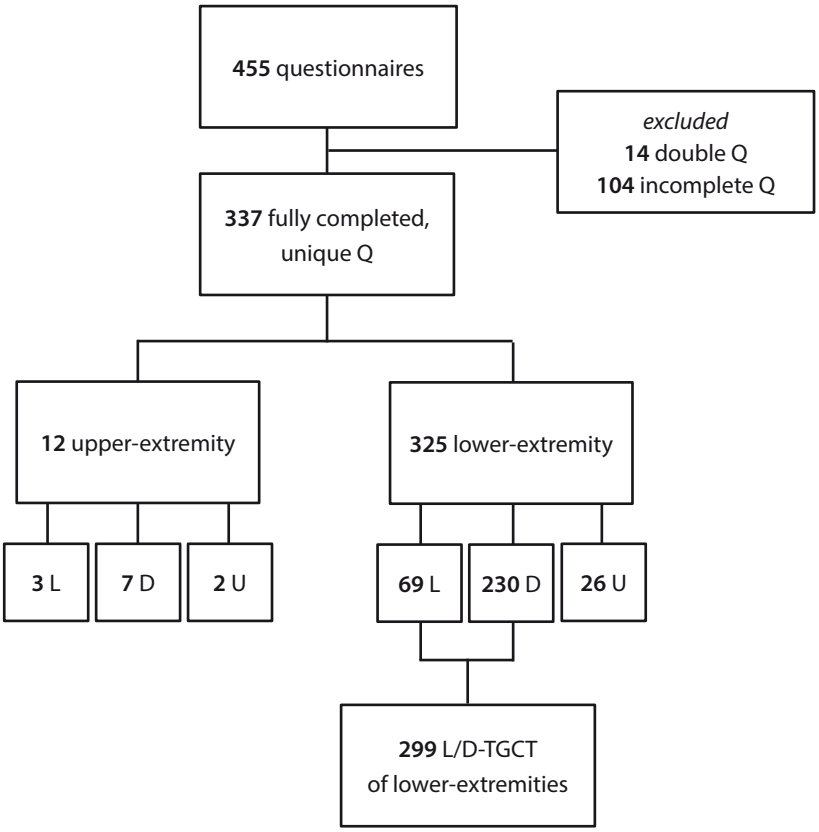


Figure 1 Flowchart Tenosynovial Giant Cell Tumour (TGCT) questionnaire.
Q: Questionnaires; L: Localized-TGCT; D: Diffuse-TGCT; U: Unknown-type TGCT

Most patients were female (79.8% [269/337]) and median age at diagnosis was 33 (interquartile range [IQR]=25-42) years. Patients originated from 30 different countries (United States: 42.7% [144/337]; United Kingdom: 20.2% [68/337]; and the Netherlands: 12.8% [43/337]). TGCT was typically located in lower extremities: knee (70.9% [239/337]), hip (9.5% [32/337]), ankle (11.0% [37/337]), and foot (3.0% [10/337]). Diffuse TGCT was diagnosed in 237 of 337 (70.3%) patients (*Table 1*). According to few TGCT patients with TGCT located in the upper extremity, 12 out of 337 patients (3.6%) were excluded for further analyses. Additionally, 26 out of 337 lower-extremity

Table 1 Patient and tumour characteristics (N=337)

Characteristics	Value
Age at time of questionnaire (years), median (IQR[a])	41 (32-50)
Age at time of TGCT diagnosis (years), median (IQR)	33 (25-42)
Total, N (%)	337 (100)
Gender, n (%)	
Male	68 (20.2)
Female	269 (79.8)
Country of residence, n (%)	
United States of America	144 (42.7)
United Kingdom	68 (20.2)
The Netherlands	43 (12.8)
Australia	22 (6.5)
Canada	14 (4.2)
Other	46 (13.6)
TGCT[b] localization, n (%)	
Knee	239 (70.9)
Hip	32 (9.5)
Ankle	37 (11.0)
Foot	10 (3.0)
Shoulder	4 (1.2)
Elbow	6 (1.8)
Wrist	2 (0.6)
Other[c]	7 (2.1)
TGCT type, n (%)	
Localized	72 (21.4)
Diffuse	237 (70.3)
Unknown	28 (8.3)

[a]IQR: interquartile range (25-75%)

[b]TGCT: tenosynovial giant cell tumour

[c]Other included multiple TGCT locations (all in lower extremity)

patients (7.7%) with unknown TGCT type were also excluded (*Figure 1*). Questionnaires of 299 lower-extremity patients with localized or diffuse TGCT were analysed.

Disease Confirmation

Confirmation of TGCT was sent by 32.4% (97/299) of lower-extremity participants. In 81% (78/97) TGCT type was in concordance with questionnaire answer, in 16/97 (16%) medical reports TGCT type did not match the answer and was therefore adjusted according to the report and 3/97 (3%) patients answered TGCT type unknown and TGCT type was added in consistence with the report. No important differences between patients with and without medical proof were detected (*Appendix 5*), neither for localized or diffuse type separately. Therefore, patients with medical proof were considered representative for the entire study population and additional analyses were performed for the entire patient group.

Medical History and Tenosynovial Giant Cell Tumour Symptoms

5/69 (7%) and 29/230 (12.6%) in localized- and diffuse-type patients, respectively, had an autoimmune disease, mostly diabetes mellitus type I, Hashimoto, psoriasis, and thyroid disease. In all, 22/69 (32%) of localized-type and 70/230 (30.4%) of diffuse-type patients experienced a

Table 2 Initial and current symptoms for localized and diffuse Tenosynovial Giant Cell Tumour (TGCT) (n=337)

TGCT[a]-related symptom	Localized TGCT (n=69)		Diffuse TGCT (n=230)	
	Initial, n (%)	Current, n (%)	Initial, n (%)	Current, n (%)
Pain	57 (83)	47 (68)	186 (80.9)	170 (73.9)
Swelling	53 (77)	29 (42)	190 (82.6)	139 (60.4)
Stiffness	38 (55)	41 (59)	128 (55.7)	148 (64.3)
Limited range of motion	38 (55)	29 (42)	140 (60.9)	149 (64.8)

[a]TGCT: tenosynovial giant cell tumour

trauma at TGCT-affected joint, before diagnosis; sports injuries or fall incidents leading to a sprain or rupture. In all, 5/69 (7%) and 12/230 (5.2%) of patients in localized and diffuse TGCT had surgery of the affected joint before TGCT diagnosis, respectively, for example, meniscus or anterior cruciate ligament (ACL) reconstructions. In all, 6/230 (2.6%) of diffuse-type participants experienced both trauma and surgery before TGCT diagnosis.

Majority of patients (92.6% [277/299]) were treated for TGCT. For both types, pain and swelling improved compared with initial situation. After treatment, more patients reported stiffness and

Table 3 Treatment characteristics of 277 treated tenosynovial giant cell tumour (TGCT) patients

Treatment	Localized TGCT[a] (n=67)	Diffuse TGCT (n=210)
Initial surgery, n (%)		
Arthroscopic synovectomy	38 (57)	113 (53.8)
Open synovectomy (one- or two-staged)	26 (39)	90 (42.9)
Combined arthroscopic/open synovectomy	3 (4)	0 (0.0)
Total joint replacement/(tumour) prosthesis	0 (0)	5 (2.4)
Amputation	0 (0)	2 (1.0)
Adjuvant therapy, n (%)	5 (7)	53 (25.2)
Radiotherapy	4 (6)	18 (8.6)
90-Yttrium	1 (1)	14 (6.7)
Systemic	0 (0)	15 (7.1)
Other[b]	0 (0)	6 (2.9)
Recurrent disease, n (%)	24 (36)	146 (69.5)
Additional surgery, n (%)	23 (34)	125 (59.5)
Arthroscopic synovectomy	7 (10)	32 (15.2)
Open synovectomy (one- or two-staged)	10 (15)	74 (35.2)
Combined arthroscopic/open synovectomy	1 (1)	4 (1.9)
Total joint replacement/(tumour) prosthesis	2 (3)	12 (5.7)
Amputation	3 (4)	3 (1.4)

[a]TGCT: tenosynovial giant cell tumour
[b]Other adjuvant therapies were cryosurgery, burning tools, steroid injections, or combination of multiple adjuvant therapies

limited range of motion (*Table 2*). A minority of the patients (<6%) currently experienced additional symptoms, including instability, buckling, hyperextension and/or hypermobility, clicking or locking or popping of joint, numbness, electric shocks, tingling, dull ache, heat of the affected joint, or hematoma.

Treatment(s)

Most performed initial surgery was arthroscopic synovectomy (57% [38/67] localized, 53.8% [113/210] diffuse) and open synovectomy, one- or two-staged (39% [26/67] localized, 42.9% [90/210] diffuse). In all, 5/67 (7%) localized-type and 53/210 (25.2%) diffuse-type patients had adjuvant therapies after initial surgery, mainly radiotherapy and 90-Yttrium. In all, 24/67 (36%) of localized type had recurrent disease after 1.5 (range 1-6) years, in contrast to 146/210 (69.5%) of diffuse type after 2.2 (range 1-23) years (*table 3*). Additional surgery was performed in 23/67 (34%) of localized type and 125/210 (59.5%) of diffuse type, predominantly open synovectomy (one- or two-staged).

Impact of Tenosynovial Giant Cell Tumour on Daily Life

Due to TGCT, 8/61 (13%) and 21/191 (11.0%) of working population in localized and diffuse TGCT, respectively, was currently not able to (fully) perform their employment. Of these patients, 4/8 (50%) localized patients and 17/21 (81%) diffuse patients had recurrent disease. Majority of patients, 40/69 (58%) of localized and 147/230 (63.9%) of diffuse type, were unable to perform sport activities. In these patients, recurrent disease presented in 15/40 (38%) of localized type and 94/147 (63.9%) of diffuse type. Disease burden was estimated by mean number of visits to general practitioner (5.6 [range 1-50] visits for localized type, 7.1 [range 1-60] visits for diffuse type), and orthopaedic surgeon (8.3 [range 1-97] visits for localized type, 11.9 [range 1-100] visits for diffuse type). Results of validated questionnaires are shown in *Table 4* (localized vs diffuse type), *Table 5* (localized type), and *Table 6* (diffuse type). Results with positive association are described in the text.

Worst Pain and Stiffness in Last 24 Hours: Visual Analog Scale Score

For localized type, best VAS pain score was 2.76 and VAS stiffness score was 2.80. In diffuse type, best scores for pain and stiffness were 3.04 and 3.08, respectively. Patients with recurrence of TGCT had deteriorated VAS score for pain and stiffness (P=.01 localized type and P<.001 diffuse type). In localized type, patients with ≥2 surgeries had higher VAS score for pain (P=.02) and stiffness (P=.01).

Table 4 Risk factor comparison of 69 localized versus 230 diffuse tenosynovial giant cell tumour (TGCT) of lower extremities

TGCT[a]-type	Worst pain VAS[b] score, 0 best score and 10 worst score		Worst stiffness VAS score, 0 best score and 10 worst score		PROMIS-PF[c] T score, mean 50 (SD 10), MID[d] 4.0–6.0			SF-12[e], PCS[f] score, mean 50 (SD 10), MID >3.29			SF-12, MCS[g] score, mean 50 (SD 10), MID >3.77			EQ-5D-5L DS[h] utility score, 0 death and 1 full health, MID .037–.069	
	Mean	*P*[i]	*Mean*	*P*[i]	*Mean*	*d*[j]	*P*[i]	*Mean*	*d*[j]	*P*[i]	*Mean*	*d*[j]	*P*[i]	*Mean*	*P*[i]
Localized	3.36	.24	3.46	.14	44.5	0.55	*<.001*	40.5	0.95	.08	47.5	0.25	.40	0.76	*.03*
Diffuse	3.79		4.01		41.3	0.87		38.1	1.19		46.3	0.38		0.72	

[a]TGCT: tenosynovial giant cell tumour
[b]VAS: Visual Analogue Scale
[c]PROMIS-PF: Patient-Reported Outcomes Measurement Information System-Physical Functioning
[d]MID: minimal important difference represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered important by the value patients place on change[18-20]
[e]SF: Short-Form
[f]PCS: physical component summary
[g]MCS: mental component summary
[h]DS: descriptive system
[i]*P*: *P* value
[j]*d*: Cohen *d* or effect size, ratio of difference between 2 means divided by the standard deviation

Table 5

Risk factor comparison of 69 localized tenosynovial giant cell tumour (TGCT) of lower extremities.

Risk-factors	Worst pain VAS[a] score, 0 best score and 10 worst score		Worst stiffness VAS score, 0 best score and 10 worst score		PROMIS-PF[b] T score, mean 50 (SD 10), MID[c] 4.0-6.0		SF-12[d], PCS[e] score, mean 50 (SD 10), MID >3.29		SF-12, MCS[f] score, mean 50 (SD 10), MID >3.77		EQ-5D-5L DS[g] utility score, 0 death and 1 full health, MID .037-.069	
	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]
Gender												
Male (n=14)	2.93	.53	3.29	.79	48.5	*.04*	43.3	.23	49.4	.42	.81	.18
Female (n=55)	3.47		3.51		43.5		39.8		47.0		.75	
Age of diagnosis												
<35 years (n=36)	3.36	.997	3.39	.82	44.1	.63	40.1	.74	45.4	.07	.76	.95
≥35 years (n=33)	3.36		3.55		45.0		40.9		49.8		.77	
TGCT localization												
Knee (n=53)	3.04	.08	3.13	.07	44.2	.57	41.0	.43	47.2	.63	.77	.41
Hip, ankle, foot, other (n=16)	4.44		4.56		45.5		38.8		48.6		.74	
Initial surgery												
Arthroscopy (n=38)	3.45	.58	3.26	.63	44.2	.52	40.7	.96	47.2	.73	.76	.92
Open surgery[h] (n=26)	3.04		3.62		45.6		40.8		48.0		.77	
Recurrence												
Yes (n=24)	4.50	*.01*	4.71	*.01*	42.8	.20	38.3	.17	45.7	.27	.70	*.01*
No (n=45)	2.76		2.80		45.4		41.7		48.5		.80	
Total no. of surgeries												
1 surgery (n=44)	2.77	*.02*	2.86	*.01*	45.4	.20	42.2	*.03*	48.4	.19	.79	*.02*
≥2 surgeries (n=23)	4.48		4.65		42.6		36.7		45.0		.71	
Last treatment for TGCT												
≤1 year ago (n=31)	3.77	.26	3.81	.38	42.4	.06	37.6	*.04*	46.0	.34	.74	.29
>1 year ago (n=36)	3.00		3.19		46.1		42.6		48.3		.78	

[a]VAS: Visual Analogue Scale. [b]PROMIS-PF: Patient-Reported Outcomes Measurement Information System-Physical Functioning. [c]MID: minimal important difference represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered important by the value patients place on change[18-20]. [d]SF: Short-Form. [e]PCS: physical component summary. [f]MCS: mental component summary. [g]DS: descriptive system. [h]One- or two staged open synovectomy. [i]*P*: *P* value

Table 6

Risk factor comparison of 230 diffuse tenosynovial giant cell tumour (TGCT) of lower extremities.

Risk-factors	Worst pain VAS[a] score, 0 best score and 10 worst score		Worst stiffness VAS score, 0 best score and 10 worst score		PROMIS-PF[b] T score, mean 50 (SD 10), MID[c] 4.0-6.0		SF-12[d], PCS[e] score, mean 50 (SD 10), MID >3.29		SF-12, MCS[f] score, mean 50 (SD 10), MID >3.77		EQ-5D-5L DS[g] utility score, 0 death and 1 full health, MID .037-.069	
	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]	score	*P*[i]
Gender												
Male (n=51)	3.63	.70	4.13	.71	42.2	.23	39.9	.11	49.0	*.04*	.75	.17
Female (n=179)	3.84		3.98		41.0		37.5		45.6		.71	
Age of diagnosis												
<35 years (n=119)	3.70	.58	3.74	.09	42.1	.07	39.2	.07	46.9	.38	.73	.22
≥35 years (n=109)	3.89		4.32		40.4		36.8		45.6		.71	
TGCT localization												
Knee (n=170)	3.78	.93	3.92	.07	41.6	.29	38.1	.99	46.3	.98	.73	.40
Hip, ankle, foot, other (n=60)	3.82		4.55		40.5		38.1		46.3		.71	
Initial surgery												
Arthroscopy (n=113)	3.93	.82	4.19	.64	41.6	.66	38.3	.86	45.6	.64	.73	.25
Open surgery[h] (n=190)	3.84		4.01		41.2		38.0		46.4		.70	
Recurrence												
Yes (n=146)	4.23	*<.001*	4.55	*<.001*	40.5	*.02*	37.7	.49	45.1	*.04*	.70	*.02*
No (n=84)	3.04		3.08		42.7		38.7		48.2		.75	
Total no. of surgeries												
1 surgery (n=86)	3.79	.69	3.74	.09	42.0	.20	38.7	.48	46.1	.89	.73	.44
≥2 surgeries (n=124)	3.94		4.38		40.8		37.7		46.3		.71	
Last treatment for TGCT												
≤1 year ago (n=72)	4.10	.37	4.35	.37	40.4	.17	35.4	*.01*	45.6	.59	.70	.17
>1 year ago (n=138)	3.76		4.00		41.8		39.5		46.5		.73	

[a]VAS: Visual Analogue Scale. [b]PROMIS-PF: Patient-Reported Outcomes Measurement Information System-Physical Functioning. [c]MID: minimal important difference represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered important by the value patients place on change[18-20]. [d]SF: Short-Form. [e]PCS: physical component summary. [f]MCS: mental component summary. [g]DS: descriptive system. [h]One- or two staged open synovectomy. [i]*P*: *P* value

Patient-Reported Outcomes Measurements Information System-Physical Function: T Score

All TGCT patients had clinically relevant impaired T scores (44.5 and 41.3 for localized and diffuse type, respectively) compared with the general US population (T score of 50). Corresponding effect size was medium for localized type (d=0.55) and large for diffuse type (d=0.87). When comparing both types, diffuse-type patients scored lower (P<.001). In localized type, female patients scored lower (P=.04). Diffuse-type recurrent patients had decreased scores (P=.02).

Short Form-12 Health Survey: Physical and Mental Component Summary Score

In comparison with general US population (score of 50), both types had impaired PCS (40.5 localized and 38.1 diffuse type) and MSC scores (47.5 localized and 46.3 diffuse type). In all patients in all compared groups, PCS score was clinically relevant declined, in contrast to MCS score which did not transcend the MID threshold in majority of patient groups. A large effect size was calculated for mean PCS scores (0.95 and 1.19 for localized and diffuse type, respectively) and a medium effect size (0.25 and 0.38 for localized and diffuse type, respectively) for MCS scores. In localized type, higher number of surgeries (≥2) affected PCS score negatively (P=.03). Localized- and diffuse-type patients who underwent treatment for TGCT ≤1 year ago, showed lower PCS score (P=.04 localized, P=.01 diffuse). In diffuse type, female patients demonstrated a decreased MCS score (P=.04), as well as patients with recurrence of TGCT (P=.04).

EuroQoL 5 Dimensions 5 Levels Health Questionnaire: Index Value

All patients, in all groups (Tables 4-6), presented declined EQ5D-5L utility scores compared with full health (1), and all scores transcended MID threshold. Overall, utility score was lower in diffuse patients compared with localized patients (P=.03). In localized type, participants with recurrence of TGCT and ≥2 surgeries scored lower (P=.01 and P=.02, respectively). Similarly, diffuse patients with recurrence had decreased scores (P=.02). Median health question VAS score was 75 (IQR 65-85) for localized and 75 (IQR 56.5-85) for diffuse type. No differences between scores calculated with US and UK valuation sets were detected in sensitivity analysis (*Appendix 4*).

Discussion

Principal Findings

The name of the largest online community of patients with TGCT, PVNS is pants!!, suggests impact on quality of life. One of the community members motivated the name: "Pants is British slang for crap or garbage." To date, it is unknown what the effect of TGCT on daily living is. A questionnaire was composed in consultation with TGCT patients to determine functional, socioeconomic, and health burden for TGCT patients. We intended to evaluate TGCT in the real world and concluded that TGCTs have a large impact on daily living, with declined health-related quality of life and limitations in daily activities, sports, work, and hobbies: especially the diffuse type of lower extremities and recurrent disease including multiple surgeries.

Limitations

The most important limitation to this study is selection bias. By using crowdsourcing to gather data, it is likely to have a higher number of patients with severe or recurrent diseases[21]. Consequently, when extrapolating these results to generally described populations of TGCT patients in literature, care should be taken not to overestimate the decreased physical function and additional socioeconomic limitations. TGCT usually affects young adults. Since younger patients are more likely to be on the World Wide Web, and our included patient population had a median age of 33 (25-42) years at time of diagnosis, also in concordance with the WHO classification[1, 2] and Mastboom et al.[3], we considered our participants representative for the heterogeneous disease TGCT. Additionally, the CHERRIES was completed. This checklist provides an understanding of the sample (self-)selection and its possible differences from a representative sample[10] (*Appendix 1*). An additional limitation to this study is that patients in different stages of different treatments were included. To assess comparability within study population, we compared patients who had treatment less than a year ago with performed treatment over a year ago. No positive associations were discovered, except for the SF-12 PCS score in both types. This underlines the postoperative limitations during the first year of follow-up after treatment. As we set out to evaluate impact of TGCT on daily living in the real world heterogeneous TGCT population, the inclusion of patients in different treatment stages matched intention of our study. Furthermore, a known disadvantage of quality of life questionnaires (eg, SF-12) is the generalizability of the questions. Impaired overall quality of life could be attributed to TGCT but also to additional physical abnormalities or

psychological problems. Also questionnaires may be completed by patients that have been ill-informed on their disease. In all, 28 patients filled out unknown type of TGCT, and 16% of patients who confirmed TGCT with medical proof filled out localized TGCT instead of diffuse TGCT or vice versa. Undeniably, differentiating in localized and diffuse TGCT is challenging even for (un) specialized physicians. The relatively high recurrence rate in this study could also be reflected by unawareness of disease specifics. Recurrence rates in our study were 36% and 70% for localized and diffuse type, compared with on average 4% to 6% (up to a maximum of 50%) and 14% to 40% (up to a maximum of 92%) according to van der Heijden et al.[6], respectively. It is conceivable that residual disease or clinical symptoms were filled out as recurrent disease.

The use of self-reported questionnaires harbours the risk of incorrectly answered questions. One could argue that all patients should have been analysed together, not subdividing into localized and diffuse type. However, differences between two types are major, and therefore separate analyses were necessary for a realistic view of impact of TGCT on daily living.

Crowdsourcing

The presumed definition of crowdsourcing is the practice of obtaining services, ideas, or content by collecting contributions from a comprehensive group from an online community rather than from traditional data suppliers[9]. However, the exact definition for crowdsourcing remains controversial, as 40 definitions originating from 32 unique articles, published between 2006 and 2011, were described by Estellés-Arolas[22]. It is therefore challenging to well define crowdsourcing coherently. After analyses of the 40 (sometimes contrasting) definitions, 8 characteristics common to any given crowdsourcing initiative were found: the crowd, the task at hand, the recompense obtained, the crowdsourcer or initiator of the crowdsourcing activity, what is obtained by them following the crowdsourcing process, the type of process, the call to participate, and the medium. First, in our study, the crowd is presented by patients with TGCT (preferably confirmed by medical reports). Second, the task at hand is completing a questionnaire about the effect of TGCT on daily living. Third, participating in this study was voluntary, therefore no recompenses were offered. Fourth, the initiators of this study are members of the Facebook group PVNS is Pants!! accompanied with the executors, known as the authors of this paper. Fifth, the researchers and subsequently the participants and TGCT patients gain more knowledge on the impact of TGCT on

daily living. Sixth, the type of process is an evaluation process, aiming to evaluate effect of TGCT on daily living. Seventh, all patients with TGCT, fluent in English language, were invited to complete the questionnaire. Lastly, the medium Facebook was used to broadcast the questionnaire.

Facebook is the best applicable social network site for survey research, because it is continuously growing, internationally known and exceeds 2 billion users globally (June 2017). The Facebook community PVNS is Pants!!, created in 2009, is the largest TGCT online support group and mainly consists citizens of the United States. On this very active, closed Facebook community, patients are daily updating experiences on their disease, ask for advice from fellow TGCT patients, and comment on other posts to provide their knowledge or sympathy. By actively posting and commenting on research proposals, patients expressed their willingness to participate in research on TGCT. From these posts, we learned that adequate patient information on TGCT is lacking. Our crowdsourcing study stimulated patients' involvement in research and was an opportunity to align research questions with the public's interest[23, 24]. TGCT is a rare disease and time to definitive diagnosis is prolonged due to unspecific symptoms and unfamiliarity of the disease[5]. A challenge in studying a rare disease is the lack of big data. Crowdsourcing is an effective and low-cost alternative to traditional methods of participant recruitment due to the possibility to reach large groups of individuals in a relatively short time frame[25]. Van der Heijden et al.[9] concluded that crowdsourcing is a promising way for evaluation of rare diseases. Czajka et al.[21] used crowdsourcing to efficiently recruit a global cohort and is the largest study on patients with multiple hereditary exostoses. Crosier et al.[26] used Facebook to recruit patients with auditory hallucinations; within 6 weeks, over 250 patients had completed this survey. Pohlig et al.[27] concluded that enrollment of patients in prospective studies is time-consuming and could be facilitated by use of crowdsourcing.

To obtain a higher level of scientific value, patients were requested for medical proof to ascertain TGCT diagnosis. To our knowledge, no other crowdsourcing studies considered disease confirmation. Patient data and outcome for validated questionnaires were comparable for patients with and without medical proof. Patients were not uniformly diagnosed and treated as they originated from 30 different countries globally. Neither was distinguished between treatment in peripheral or tertiary referral centres. Nevertheless, we consider our study group a reflection of the current worldwide situation and believe that declined impact on daily living is clinically

relevant for all patients. In contrast to malignant diseases, survival rates are not of interest for TGCT with its benign character. According to high recurrence rates, quality of life (prior and after treatment) is essential to evaluate.

Patient-Reported Outcome Measures

Patient reported outcome measures (PROMs) are increasingly used in health policy, patient-centred care, and shared clinical decision making[28]. In the era of personalized medicine, patient involvement is increasing in shared decision making for different treatment strategies with functional outcome and quality of life. In our study, members of the largest online TGCT community were involved in establishing the questionnaire Evaluation of TGCT on daily living.

Functional outcome and health-related quality of life are only spars reported for TGCT. Four studies have reported on standardized PROMS[4, 9, 29, 30]. Currently, validated PROMS for TGCT patients do not exist. In accordance with Gelhorn et al.[4], VAS for worst pain and stiffness and PROMIS-PF questionnaires were used. Conform van der Heijden et al.[9, 29] and Verspoor et al.[30], the SF-12, a quality of life questionnaire, was included, known as the shorter version of the SF-36. One study identified a high health care burden with a significant increase in health care costs, ambulatory costs, and physical therapy in 9328 TGCT patients[8].

In benign diseases, including TGCT, death is not an outcome variable. Besides tumour reduction, critical endpoint measures are clinical relevance and impact of treatment. Currently, clinical TGCT studies lack specific and validated PROMs to document treatment-induced symptomatic, functional, and economic (back to work) improvement[31]. To obtain an impression of physical function and quality of life in TGCT patients, participants in our study were requested to complete different validated questionnaires. In our experience, PROMIS-PF was most useful in determining these functional factors. To minimize the multitude of questions and include the most important components for clinical TGCT studies, we would propose a combination of PROMIS-PF and a short quality of life questionnaire, for instance EQ5D5L, in clinical practice.

Risk Factors for Deteriorated Outcome

Risk factors for deteriorated outcome in our study were diffuse-type TGCT, recurrent disease, and ≥2 surgeries performed. This is in concordance with current literature on risk factors for a high recurrence rate. According to the necessity of mutilating surgeries to treat recurrences, we considered risk factors for recurrent disease comparable to risk factors for deteriorated outcome. Higher recurrence rate in diffuse TGCT compared with localized TGCT is exuberant described[1, 5-7, 30, 32-34]. Bruns et al.[34] described 173 patients treated in 10 orthopaedic departments in Germany and Austria and reported higher recurrence rates in institutions treating less than 20 cases for TGCT, in diffuse disease, in the hip joint and after arthroscopy. Schwartz et al.[35] described 99 patients with TGCT in the knee, hip, elbow, or shoulder. They concluded that localization in the knee, previous surgical procedures, and incomplete synovectomy were related significantly to higher number of subsequent recurrences. On the basis of current literature and to investigate possible risk factors for recurrent disease thoroughly, gender, age at time of diagnosis, TGCT localization, initial surgery, presence of recurrence, total number of surgeries, and time since last treatment for TGCT, were compared.

Conclusions

TGCTs have major impact on daily living in a relatively young, working population (median age at diagnosis, 33 years). Majority of symptoms improve after treatment, however, symptoms remain in about half of the TGCT patients; especially in patients with diffuse type, recurrent disease, and ≥2 surgeries. The high recurrence rate in diffuse TGCT results in clinically important deteriorated outcome in physical function and health-related quality of life. In preventing recurrent disease, and its deteriorated outcome, an extensive mutilating surgery might be necessary. Physicians should be aware that TGCT patients frequently experience symptoms and limitations in daily life and societal participation (work, sports, and hobbies), even after treatment(s). We deem it important for future research to evaluate treatment, including its effectiveness on improving quality of daily living. With this study, we hope to increase knowledge on TGCT among treating physicians, highlight the importance of quality of life, and to offer research-based information to patients.

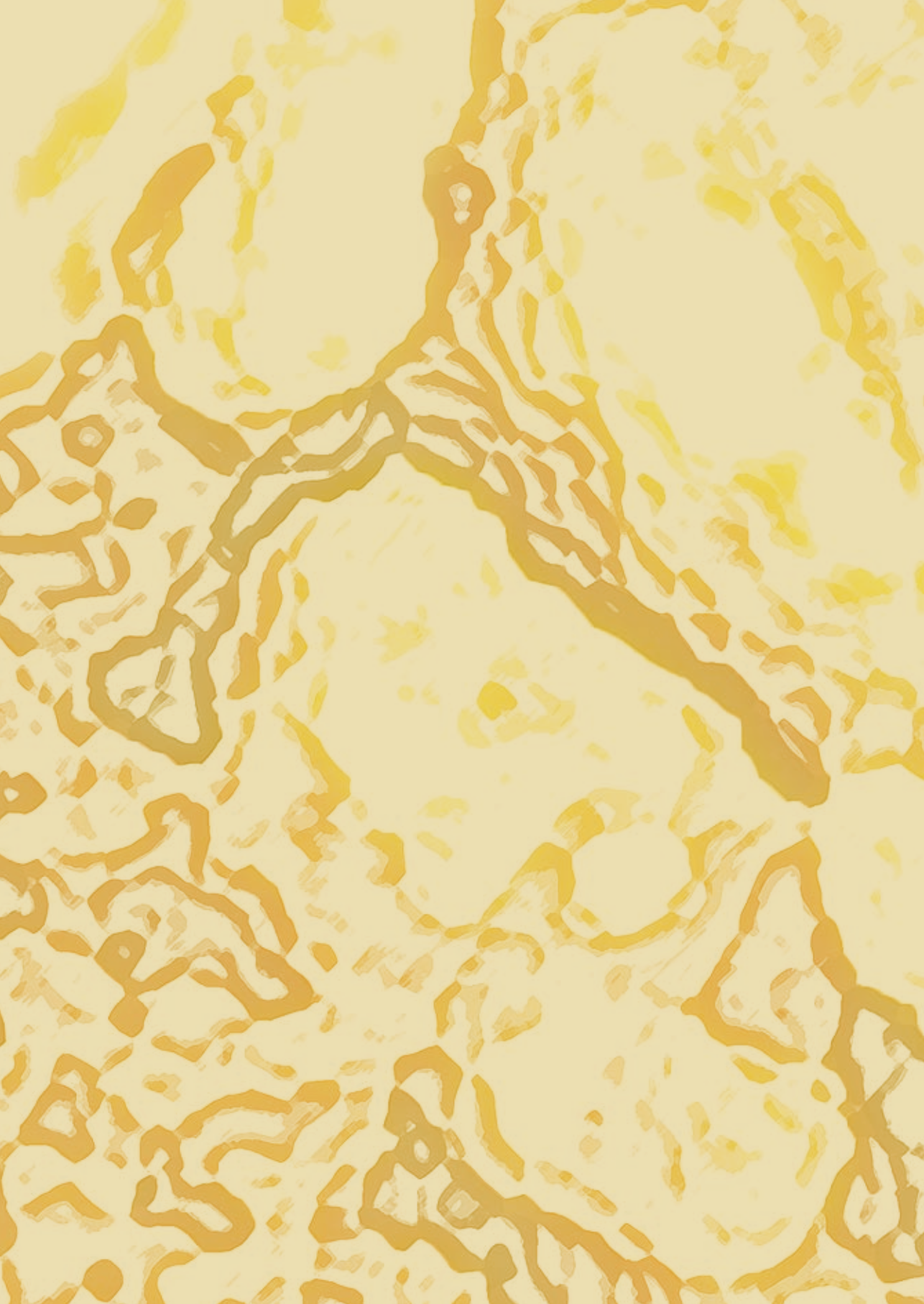
Supplementary data

Supplementary data are available in the online version of this article: http://www.i-jmr.org/2018/1/e4

References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
3. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. Acta orthopaedica. 2017:1-7.
4. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
5. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
6. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
7. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res. 2017;103(1S):S91-S7.
8. Burton T, Ye X, Parker E, Bancroft T, Healey JH. Burden of Illness in Patients With Tenosynovial Giant Cell Tumors. ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 22nd Annual International Meeting; Boston, MA, USA2017.
9. van der Heijden L, Piner SR, van de Sande MA. Pigmented villonodular synovitis: a crowdsourcing study of two hundred and seventy two patients. Int Orthop. 2016;40(12):2459-68.
10. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004;6(3):e34.
11. Study T. TGCT Study Facebook Webpage https://www.facebook.com/profile.php?id=1000132659555822016.
12. HealthMeasures. PROMIS (Patient-Reported Outcomes Measurement Information System) Physical Function Scoring Manual [Manual]. www.healthmeasures.net2017.
13. Ware JE, Kosinski M, Keller SD. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 1995.
14. van Reenen M, Janssen B. EQ-5D-5L User Guide. In: Group E, editor. Basic information on how to use the EQ-5D-5L instrument. Version 2.1 ed2015.
15. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
16. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5-21.
17. Sawilowsky SS. New Effect Size Rules of Thumb. Journal of Modern Applied Statistical Methods. 2009;8(2):597-9.
18. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores. Value Health. 2017;20(4):644-50.
19. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. J Clin Epidemiol. 2011;64(5):507-16.
20. Diaz-Arribas MJ, Fernandez-Serrano M, Royuela A, Kovacs FM, Gallego-Izquierdo T, Ramos-Sanchez M, et al. Minimal Clinically Important Difference in Quality of Life for Patients with Low Back Pain. Spine (Phila Pa 1976). 2017.

21. Czajka CM, DiCaprio MR. What is the Proportion of Patients With Multiple Hereditary Exostoses Who Undergo Malignant Degeneration? Clin Orthop Relat Res. 2015;473(7):2355-61.
22. Estellés-Arolas E, González-Ladrón-de-Guevara F. Towards an integrated crowdsourcing definition. J Inf Sci. 2012;38(2):189-200.
23. Truitt AR, Monsell SE, Avins AL, Nerenz DR, Lawrence SO, Bauer Z, et al. Prioritizing research topics: a comparison of crowdsourcing and patient registry. Quality of life Research. 2017.
24. Bartek MA, Truitt AR, Widmer-Rodriguez S, Tuia J, Bauer ZA, Comstock BA, et al. The Promise and Pitfalls of Using Crowdsourcing in Research Prioritization for Back Pain: Cross-Sectional Surveys. J Med Internet Res. 2017;19(10):e341.
25. Kuang J, Argo L, Stoddard G, Bray BE, Zeng-Treitler Q. Assessing Pictograph Recognition: A Comparison of Crowdsourcing and Traditional Survey Approaches. J Med Internet Res. 2015;17(12):e281.
26. Crosier BS, Brian RM, Ben-Zeev D. Using Facebook to Reach People Who Experience Auditory Hallucinations. J Med Internet Res. 2016;18(6):e160.
27. Pohlig F, Lenze U, Muhlhofer HML, Lenze FW, Schauwecker J, Knebel C, et al. IT-based Psychosocial Distress Screening in Patients with Sarcoma and Parental Caregivers via Disease-specific Online Social Media Communities. In Vivo. 2017;31(3):443-50.
28. Gagnier JJ. Patient reported outcomes in orthopaedics. J Orthop Res. 2017;35(10):2098-108.
29. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
30. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
31. 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(8):949-56.
32. Chiari C, Pirich C, Brannath W, Kotz R, Trieb K. What affects the recurrence and clinical outcome of pigmented villonodular synovitis? Clin Orthop Relat Res. 2006;450:172-8.
33. Ehrenstein V, Andersen SL, Qazi I, Sankar N, Pedersen AB, Sikorski R, et al. Tenosynovial Giant Cell Tumor: Incidence, Prevalence, Patient Characteristics, and Recurrence. A Registry-based Cohort Study in Denmark. The Journal of rheumatology. 2017;44(10):1476-83.
34. Bruns J, Ewerbeck V, Dominkus M, Windhager R, Hassenpflug J, Windhagen H, et al. Pigmented villo-nodular synovitis and giant-cell tumor of tendon sheaths: a binational retrospective study. Arch Orthop Trauma Surg. 2013;133(8):1047-53.
35. Schwartz HS, Unni KK, Pritchard DJ. Pigmented villonodular synovitis. A retrospective review of affected large joints. Clin Orthop Relat Res. 1989(247):243-55.



AMPUTATION

chapter twelve

Limb amputation after multiple treatments of Tenosynovial Giant Cell Tumour

Series of 4 Dutch cases

M.J.L. Mastboom[1], F.G.M. Verspoor[2], H. Gelderblom[3], M.A.J. van de Sande[1]

Case Rep Orthop. 2017;7402570.

[1] Orthopaedic Surgery, Leiden University Medical Centre, Leiden, the Netherlands

[2] Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

Summary

In Tenosynovial Giant Cell Tumours (TGCT), previously named Pigmented Villonodular Synovitis (PVNS), a distinction is made between a single nodule (localized-type) and multiple nodules (diffuse-type). Diffuse-type is considered locally aggressive. Onset and extermination of this orphan disease remain unclear. Surgical resection is the most commonly performed treatment. Unfortunately, recurrences often occur (up to 92%), necessitating reoperations and adjuvant treatments. Once all treatments fail or if severe complications occur; limb-amputation may become unavoidable. We describe four cases of above knee amputation after TGCT diagnosis.

Background

Tenosynovial Giant Cell Tumour (TGCT) is considered an orphan, mono-articular, locally aggressive neoplasm[1]. TGCT patients complain of continued pain, swelling and a decreased range of motion of the affected joint[2]. Typically, younger patients (below the age of 40 years) are affected. Time to definitive diagnosis usually takes several years[1]. TGCT develops along the synovial lining of joints, tendon sheaths and bursae[1, 3]. Two extremes along a continuum of one disease process are described: a single nodule (localized-type) and multiple nodules (diffuse-type)[1, 2, 4]. These two subtypes differ in their clinical and radiological presentation, response to treatment and prognosis. Histologically, no differences are detected[1, 5]. Exact onset remains unclear. Current findings are pleading for both a reactive inflammatory disorder and a clonal neoplastic proliferation, provoking a CSF1 overexpression; suggesting the tumour-landscaping effect[6]. The localized-type (Giant Cell Tumour of Tendon Sheath) is defined as a demarcated benign mass, most commonly occurring in fingers (85%). Lesions are small (between 0.5 and 4 cm), typically lobulated and white to grey along with yellow and brown areas[1, 2, 4]. Reported recurrences ensuing surgical treatment are relatively low: 0-6%[4]. On the contrary, the diffuse-type (Diffuse-type Giant Cell Tumour (Dt-GCT), previously named Pigmented VilloNodular Synovitis (PVNS)), shows extensive involvement of the entire synovial membrane and tends to have the capability to grow infiltrative through adjacent structures[2, 4]. Dt-GCT affects mostly weight-bearing joints: predominantly the knee-joint (75%), followed by the hip-joint (15%). At present, surgery remains the gold standard, while systemic targeted treatments are only available in trial-settings[7]. Recurrence rates for Dt-GCT is 14% (up-to 67) after open synovectomy and 40% (up-to 92) after arthroscopic synovectomy[4]. Recurrent or

resistant disease, frequently necessitate multiple mutilating surgeries, end occasionally inevitably in total joint arthroplasties[8]. Once all treatments fail or severe complications occur: limb-amputation may become unavoidable. To our knowledge, current literature lacks reports of limb-amputation in TGCT patients, but patient groups often discuss the possibility on online fora ("PVNS is pants" closed Facebook community; https://www.facebook.com/groups/91851410592/?ref=ts&fref=ts)[9]. To underline potentially aggressiveness of TGCT, four patient history scenarios are described.

Case presentation

Case 1

A female, aged 46, was diagnosed with TGCT. Initial TGCT treatment consisted of three arthroscopic synovectomies. First synovectomy was supplemented with low-dose radiation, consecutive two synovectomies with intra-articular 90Yttrium. Fourteen years later, an Magnetic Resonance Imaging (MRI) scan revealed recurrent TGCT, including bone-involvement. A total knee replacement (TKR) was performed. Four years later, her knee started to hurt and swell again. Infection parameters were elevated, MRI showed extensive synovitis and a PET-CT showed enhancement around her TKR, suspect for recurrent TGCT. Her range of motion was impaired, with a flexion-extension of 50-20-0. Twenty-three years after initial diagnosis, she was referred to our tertiary orthopaedic oncologic centre. TGCT re-excision was not an option, as a result of extensive tumour growth (*Figure 1a*, *Figure 1b*). Imatinib (a tyrosine kinase inhibitor with activity against CSF1R) was started for four months. Besides the tumour growing outwards from her operation-scar, a nearby fistula revealed and started leaking. She was admitted with malaise, fever, elevated infection parameters, a red swollen right leg and not able to mobilize. During four weeks of admission she was treated with several blood transfusions attributed to persistent anaemia, intravenous antibiotics and analgesics. After an investigational tyrosine-kinase-inhibitor (TKI) in compassionate use was started, she was discharged. After a fall, a few days after she was discharged, her condition worsened. She was readmitted and treated with intravenous antibiotics for an acute Staphylococcus aureus infection, provoked by TGCT growing outside the operation scar composing a direct connection to the TKR. To avoid septic shock: an urgent above knee amputation seemed a live-saving procedure. Within one month, signs of osteomyelitis revealed. Treatment with debridement, antibiotics and irrigation stabilized the patient. At one year follow-up, there were no signs of local recurrence or infection and her phantom pain was decreasing.

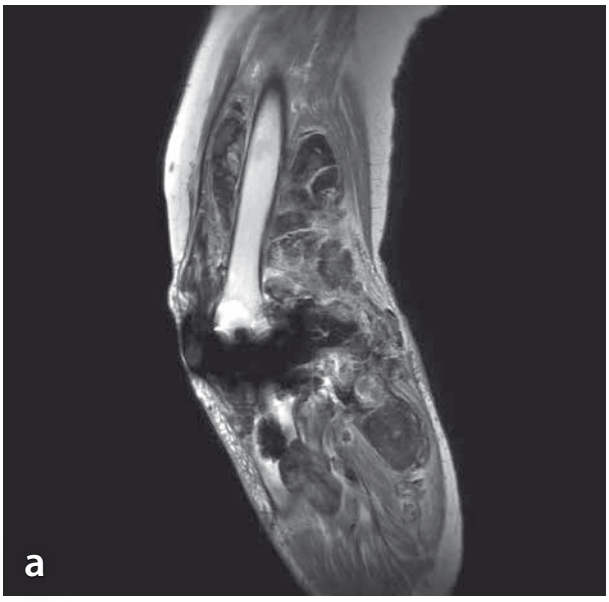


Figure 1a Sagittal T1-weighted MR image, turbo spin echo, after intravenous contrast injection in a 69 year old female patient with recurrent, end stage TGCT on the right side. Extensive tumour growth around her total knee replacement (TKR), involving the entire knee-joint: anterior and posterior, ranging from high up supra-patellar pouch to below tibia-fibular joint, including bone-involvement.

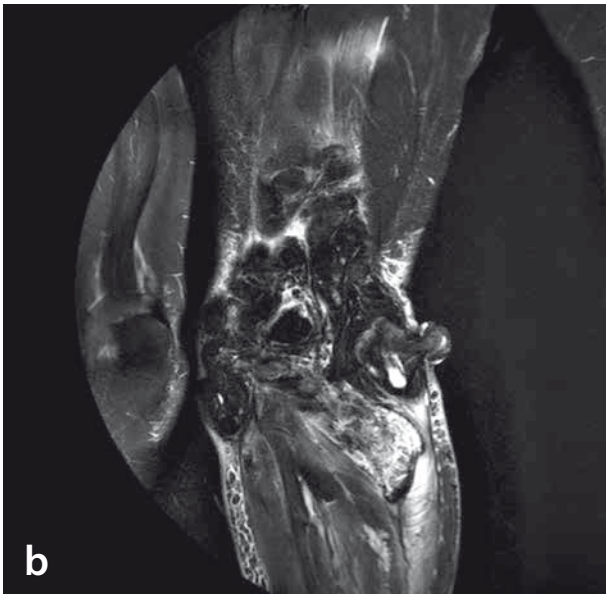


Figure 1b Sagittal Short-TI Inversion Recovery metal clear MR image of the posterior part of the right knee, revealing extensive tumour growth, also growing outside the body. Characteristic TGCT blooming effect is seen attributed to scattered areas of low signal intensity, typical for iron deposition.

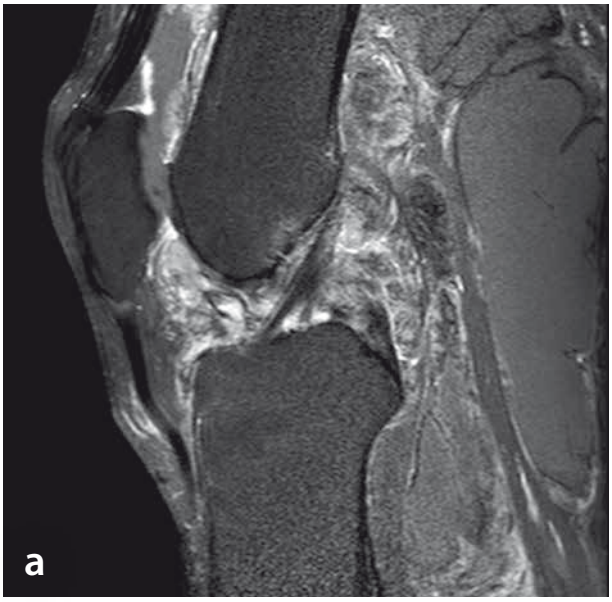


Figure 2a Left knee sagittal T1-weighted MR image after intravenous contrast injection with fat suppression in a 61-year old male patient with extensive recurrent Dt-GCT, showing characteristic blooming effect.

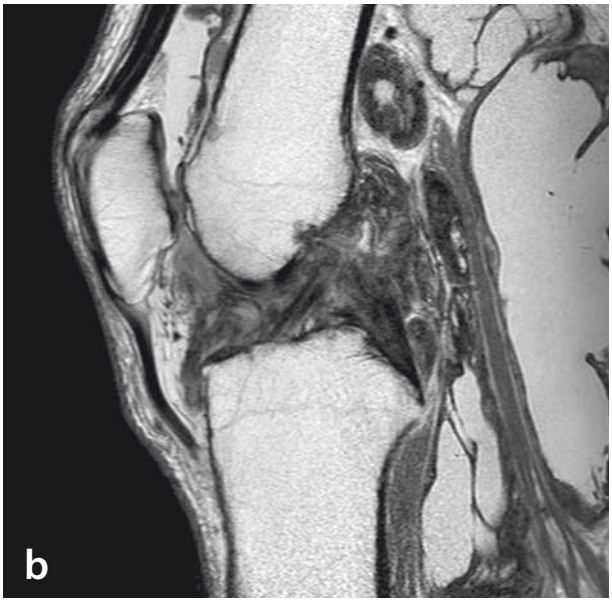


Figure 2b Sagittal turbo-spin echo proton density-weighted MR image presents Dt-GCT located intra- and extra-articular, posterior a large Baker's cyst including tumour involvement.

Case 2

A 63-year old male was referred to our tertiary hospital with recurrent Dt-GCT of his left knee. Two years prior to referral, Dt-GCT was diagnosed and (partial) arthroscopically removed elsewhere. MRI showed a diffuse TGCT growth-pattern involving all compartments of the entire knee-joint, including a Bakers cyst (*Figure 2a, Figure 2b*). Consequently, a two-staged anterior and posterior synovectomy in two tempi was performed; macroscopically all pathological tissue was removed. There was chondromalacia grade 3-4. A few months later, the patient suffered progressive knee pain again. Recurrent Dt-GCT lesions, including bone-involvement and progressive osteoarthritis were seen on X-ray and MRI. A transarticular distal femoral resection and resection of all Dt-GCT tissue was performed. The knee joint was reconstructed using an EndoProsthetic-Reconstruction (EPR). Thereafter patient's knee function seemed to improve. However, several months later, swelling and increasing knee pain developed. C-reactive protein (CRP) and erythrocyte sedimentation rate were elevated, nevertheless cultures of aspirated knee fluid were negative. Along with general deterioration of the patient, wound debridement, antibiotics, irrigation, and retention (DAIR) was performed. Two out of six cultures, showed coagulase negative staphylococci without a sign of recurrent TGCT. Despite the DAIR procedure, his EPR had to be replaced with a gentamicin loaded spacer. Because of the difficulty to treat the low-grade infection, his spacer was replaced with a gentamicin and vancomycin loaded spacer. Thereafter, patient's condition improved, his infection parameters declined and cultures of an open biopsy were negative. The EPR was re-implanted. Unfortunately the low grade infection recurred again. After two additional DAIR procedures the patient preferred an above-knee amputation over another DAIR procedure, life-long antibiotics or a third 2-stage revision. At present he is pain-free and ambulatory with an above knee prosthetic leg.

Case 3

A 67 year old male had a TKR after years of indistinct progressive knee-pain. Peroperatively a benign tumour with few giant cells was diagnosed as a coincidental finding. A few months later a supra-patellar biopsy showed a mixed malignant appearance, including TGCT components. Unexpectedly, lymphadenopathy on his groin, did not show malignant cells, but reactive cells. The patient suffered of systemic symptoms: night sweats, weight loss and infection like symptoms (not specified). Both for the lymphadenopathy and his painful right knee he received radiotherapy (70 Gy on both locations, treatment for uncontrollable pain). Histopathologic revision, by a tertiary specialized pathologist in a reference centre, showed a Dt-GCT. Aggressive tumour progression, including bone-involvement provoked TKR failure (*Figure 3, Figure 4a, Figure 4b*). Within one year, several histologically proven Dt-GCT lung metastases were discovered. Molecular research revealed a t(1;6)(p13;q27) translocation (*Supplementary materials*), this is not the typical t(1;2)(p13,q33) translocation, however literature shows different variants on this translocation. Final diagnosis through FISH technique confirmed Dt-GCT. Discomforting pulmonal symptoms expressed multiple lung, pleural and costal metastases. Inside the thorax, numerous suspected lymph nodes were seen. When he developed pulmonary symptoms; an investigational TKI was started, which had an effect on his lung-metastases, but not on his irradiated painful lymphademic leg (*Figure 5a, Figure 5b*). Complaints of tiredness, disguise, a very oedematous right leg with a leaking protuberance and persisting anaemia provided discomfort. Attributed to the TKI, pulmonary symptoms disappeared and his lung metastases stabilized. However, a hospital admission due to pneumonia on both sides and pulmonary embolisms caused a repercussion. As a last resort, the primary-tumour was resected by amputation, complicated with 4 Litres blood loss and desaturation (until 90%), necessitating admission to the intensive care unit. Histopathology confirmed Dt-GCT without malignant cells, however margins were not disease free. Residual and recurrent disease was seen on MRI three months post-operatively and clinically observed. After six months, a debulking procedure was performed on his amputated stump. The TKI did not show effect on the metastases anymore and was discontinued after one year of compassionate use. Currently, his phantom pain is acceptable.

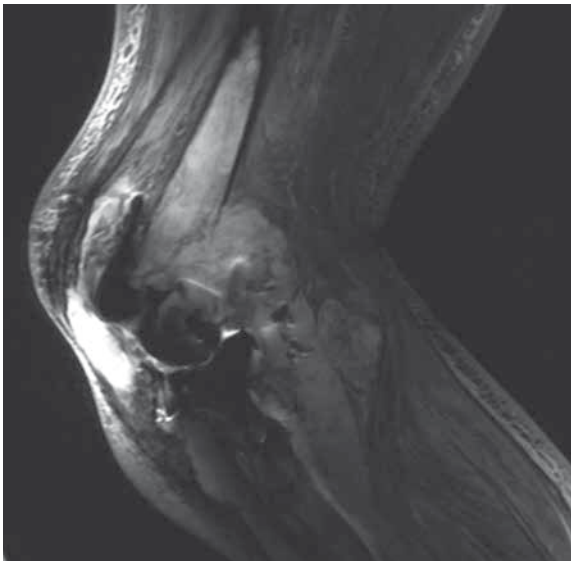


Figure 3 Metal artefact reducing sequelae sagittal T2 weighted turbo inversion recovery MR image of the right knee of a 67 year old male patient, with a TKR in situ. Extensive tumour progression around TKR and bone invasion is shown.

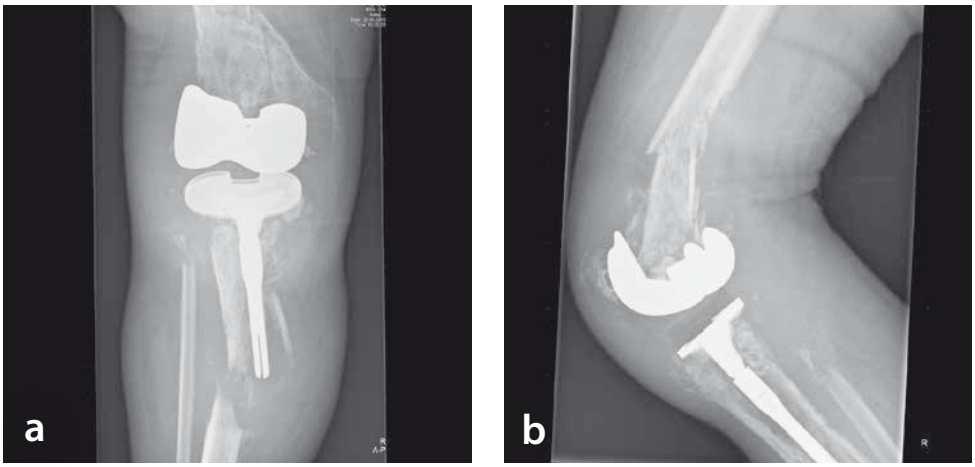


Figure 4 a & b X-rays (anterior-posterior and sagittal) of failing total knee replacement, attributed to aggressive TGCT progression including bone-involvement, after radiotherapy treatment.

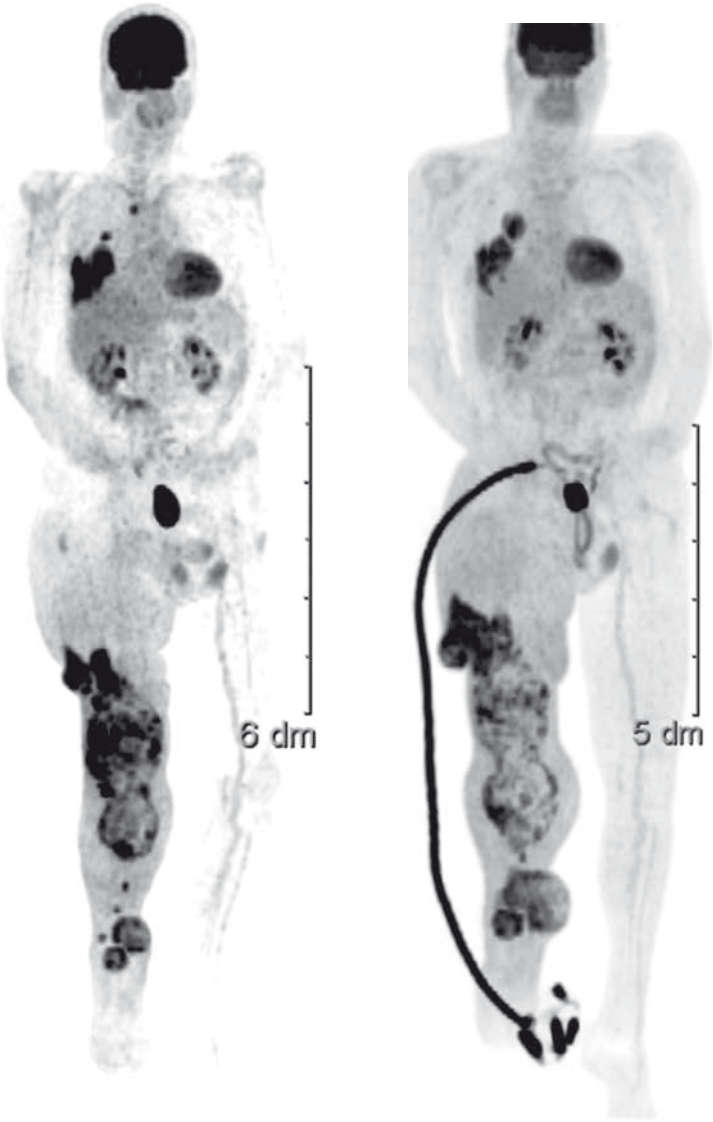


Figure 5 a&b PET CT-scan showing extensive TGCT around the right knee-joint and multiple lung, pleural and costal metastases. When pulmonary symptoms developed; an investigational tyrosine-kinase-inhibitor (TKI) was started (**a.** prior to treatment, **b.** after treatment), which had an effect on his pulmonary-metastases, but not on his irradiated painful lymphademic leg.

Case 4

After years of indistinct knee-complaints, a biopsy proved Dt-GCT in a 17 year old male. Intra-articular 90Yttrium was not effective. After a partial open synovectomy, Dt-GCT recurred. A two-staged anterior and posterior synovectomy in two tempi (complicated by haemorrhage) was performed at a tertiary oncology centre. During the following 13 years, the patient underwent a total of seven surgeries in an effort to treat Dt-GCT, including a knee-arthrodesis using a compression plate and screws (*Figure 6*). Osteosynthesis was removed several years later because of a low grade osteomyelitis and persisting anaemia. Subsequently, a two-staged anterior and posterior debulking synovectomy was performed (*Figure 7* shows MRI prior to debulking). After another debulking procedure, local tumour control did not seem feasible. An above knee amputation was performed at the age of 30. Histopathological revision proved Dt-GCT, without malignant cells. After several years of painless walking with an external prosthesis, pulmonary symptoms occurred. Imatinib, an investigational TKI, chemotherapy and radiotherapy had no effect on pulmonary and lymph node metastases. Despite all efforts, deterioration of the patient seemed irreversible. The patient deceased at the age of 35 years.

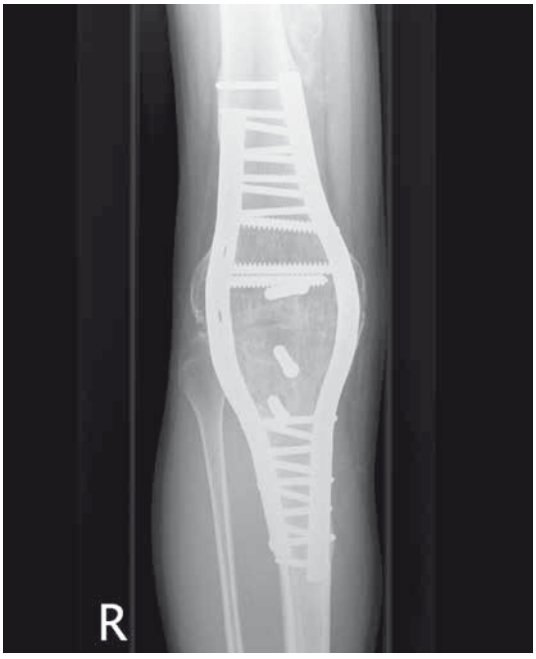


Figure 6 Knee-arthrodesis after multiple Dt-GCT surgeries in a 26 year old man, using a compression plate and screws.

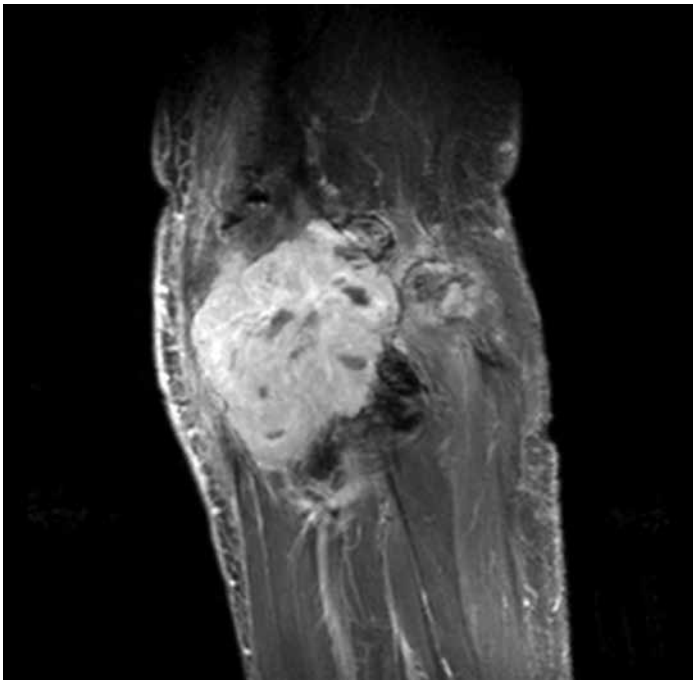


Figure 7 Sagittal T1 weighted Spectral Presaturation with Inversion Recovery MR image after intravenious contrast, of a 28 year old male patient revealing a large, extra-articular TGCT tumour mass. Patients history describes multiple surgical treatments, including removal of osteosynthesis material for a knee arthrodsesis.

Discussion

TGCT onset is typically slow and patients present with unspecified complaints[1]. Pain, swelling and stiffness in the involved joint might be misinterpreted as osteoarthritis, rheumatoid arthritis, a meniscal tear or other ligamentous injury[2]. Because of the rarity of the disease, definitive diagnosis may take several years and patients present with extensive disease. Frequently, patients are referred to a tertiary hospital, after several arthroscopic or open synovectomies and even radiotherapy (case number 1)[10, 11]. Besides declined functional outcome and quality of life[10], these patients are at risk of repeated recurrences and extensive resistant disease[7]. Multiple surgeries increase the risk of infection. Continued inflammation, joint usuration and bone involvement may lead to articular destruction that might worsen (pre-existing) osteoarthritis[2]. A total joint replacement or even an endoprosthetic-reconstruction may become inevitable[8, 12]. Occasionally, total joint arthroplasty is the primary procedure performed in TGCT[8]. Only seldom, an above-knee amputation as a last resort in treatment of TGCT is mentioned[13-16].

Is an above knee amputation justified in an essentially benign, but locally aggressive disease? After (major) complications, for example periprosthetic infections, in primary total knee arthroplasties, above knee amputations are performed[17, 18]. Our amputation cases also attributed to severe prosthetic infections (case 1 and 2). Radiotherapy, applied in case 1 (in a non-specialized hospital) and 3 (in order to decrease severe pain-complaints), increases risk of prosthetic failure, infection and wound healing. The overall prevalence of above-the-knee amputation after TKA is estimated at 0.36%[17]. When severe pain, a swollen joint, limited range of motion and stiffness impair range of motion: an above-knee amputation might increase patients mobility[17, 19]. Therefore, we feel amputation is justified in extreme TGCT cases.

TGCT is a heterogeneous disease. Some cases are instantly diffusely spread intra- and extra-articular or even show malignant characteristics. Metastases in histologically benign TGCT are extremely rare, called an implantation phenomenon and conservatively treatment is suggested[14]. Symptomatic free metastases in case 3 were conservatively treated. Physicians should be aware of the potentially aggressive course of TGCT. Multiple mutilating surgeries decline functional outcome and quality of life[10]. Expert centres need to cooperate on these rare cases to understand the biology underlying these different clinical behaviours.

West et al. discovered a central role for CSF1 in the pathogenesis of TGCT[6]. Multiple trials with systemic therapies targeting CSF-1 receptor, show promising results as novel treatment method for diffuse-TGCT[7]. Emactuzumab (RG7155) (a monoclonal antibody against CSF1R) showed an objective response in 26 of 28 (86 %) TGCT patients[20]. Prolonged tumour regression is described in patients, treated with tyrosine kinase inhibitor PLX3397[21]. (Serious) adverse events in emactuzumab and PLX3397 are investigated. Currently, two studies are recruiting patients with recurrent or unresectable TGCT diffuse-type: MCS110 (a CSF1-directed monoclonal antibody, NCT01643850) and FPA008 (an anti-CSF1R monoclonal antibody, NCT02471716). In the near future, if these systemic treatments are approved, multiple surgeries and final limb amputation, hopefully, will become obsolete.

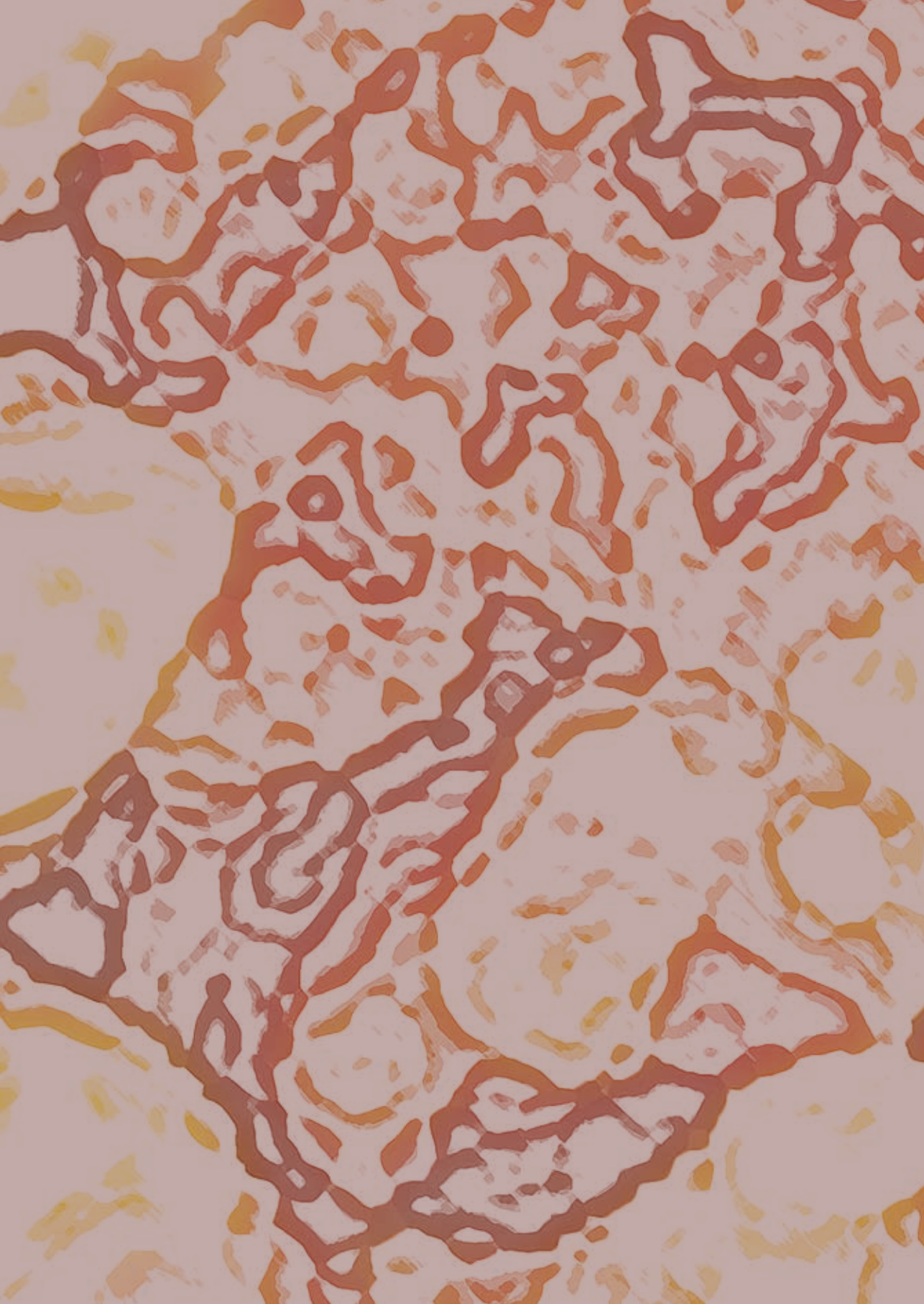
To our knowledge, this is the first case-series focussing on limb-amputation after multiple treatments of TGCT. In order to prevent extensive final treatments, like amputations, further investigation of TGCT risk factors for recurrences is essential in proper primary-treatment planning. In the orphan TGCT, knowledge of disease impact can be improved. Patients suffering extensive disease including patients after multiple mutilating surgeries, might experience higher quality of life once they feel in control of their own life again. Performing an above-knee amputation may therefore be considered in extreme and extensive TGCT cases.

Conclusion

Frequently, TGCT is successfully treated with radical surgical excision. In a substantial percentage of cases, it presents as an aggressive and extensive disease that requires complex treatments, and, in extreme cases, can even lead to limb-sacrificing surgery. Quick diagnosis and adequate treatment of this rare condition are important factors for outcome. Therefore, it is essential that these patients get referred to specialized centres at an early stage. We described four extensive Dt-GCT cases, treated with an above-knee amputation as final treatment.

References

1. de St. Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, localized type/diffuse type. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4th ed. Lyon: IARC Press; 2013. p. 100-3.
2. Tyler WK, Vidal AF, Williams RJ, Healey JH. Pigmented villonodular synovitis. The Journal of the American Academy of Orthopaedic Surgeons. 2006;14(6):376-85.
3. Mankin H, Trahan C, Hornicek F. Pigmented villonodular synovitis of joints. Journal of surgical oncology. 2011;103(5):386-9.
4. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
5. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
6. 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(3):690-5.
7. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
8. Verspoor FG, Hannink G, Scholte A, Van Der Geest IC, Schreuder HW. Arthroplasty for tenosynovial giant cell tumors. Acta orthopaedica. 2016:1-7.
9. van der Heijden L, Piner SR, van de Sande MA. Pigmented villonodular synovitis: a crowdsourcing study of two hundred and seventy two patients. Int Orthop. 2016;40(12):2459-68.
10. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
11. Flandry F, Hughston JC, McCann SB, Kurtz DM. Diagnostic features of diffuse pigmented villonodular synovitis of the knee. Clinical orthopaedics and related research. 1994(298):212-20.
12. Gonzalez Della Valle A, Piccaluga F, Potter HG, Salvati EA, Pusso R. Pigmented villonodular synovitis of the hip: 2- to 23-year followup study. Clin Orthop Relat Res. 2001(388):187-99.
13. Layfield LJ, Meloni-Ehrig A, Liu K, Shepard R, Harrelson JM. Malignant giant cell tumor of synovium (malignant pigmented villonodular synovitis). Archives of pathology & laboratory medicine. 2000;124(11):1636-41.
14. Asano N, Yoshida A, Kobayashi E, Yamaguchi T, Kawai A. Multiple metastases from histologically benign intraarticular diffuse-type tenosynovial giant cell tumor: a case report. Human pathology. 2014;45(11):2355-8.
15. Hamlin BR, Duffy GP, Trousdale RT, Morrey BF. Total knee arthroplasty in patients who have pigmented villonodular synovitis. The Journal of bone and joint surgery American volume. 1998;80(1):76-82.
16. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
17. Sierra RJ, Trousdale RT, Pagnano MW. Above-the-knee amputation after a total knee replacement: prevalence, etiology, and functional outcome. The Journal of bone and joint surgery American volume. 2003;85-a(6):1000-4.
18. Khanna V, Tushinski DM, Soever LJ, Vincent AD, Backstein DJ. Above knee amputation following total knee arthroplasty: when enough is enough. The Journal of arthroplasty. 2015;30(4):658-62.
19. Fedorka CJ, Chen AF, McGarry WM, Parvizi J, Klatt BA. Functional ability after above-the-knee amputation for infected total knee arthroplasty. Clinical orthopaedics and related research. 2011;469(4):1024-32.
20. Cassier PA, Italiano A, Gomez-Roca CA et al., CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: A doseescalation and dose-expansion phase 1 study, The Lancet Oncology, vol. 16, no. 8, pp. 949–956, 2015.
21. Tap WD, Wainberg ZA, Anthony SP et al., "Structureguided blockade of CSF1R kinase in tenosynovial giant-cell tumor," New England Journal of Medicine, vol. 373, no. 5, pp. 428–437, 2015.



SUMMARY

chapter thirteen

Summary of this thesis

Summary of thesis

Both localized- and diffuse-type tenosynovial giant cell tumours (TGCT) are defined a benign disease as metastases or lethal outcome very rarely occur. Diffuse-type TGCTs are regarded more challenging to treat because they have an infiltrating growth pattern and lack anatomical boundaries which make complete resection difficult and at times technically impossible or undesirable with joint function preservation and health-related quality of life in mind. Within this present era of systemic targeted and multimodality therapies (available in trial settings), standalone surgical resection cannot be regarded as the gold standard anymore for all cases. This thesis aims to unravel the heterogeneity of TGCT, to improve oncologic results and maintain joint functionality and health-related quality of life, by addressing several disease aspects. Patient selection for different treatment options is improved by translational research, risk factor identification, treatment outcome evaluation and disease severity stratification.

Up to date incidence calculations are necessary for diagnostic purposes. Therefore, **chapter 2** determined worldwide incidence rates in TGCT affecting digits, TGCT localized-extremity and TGCT diffuse-type. Previous incidence rate calculations originated from 1980, in which a US county study calculated an incidence rate of 9 and 2 per million person-year in localized- (including digits) and diffuse-TGCT, respectively (Myers 1980). By use of PALGA, the non-profit nationwide network and registry of histo- and cytopathology in The Netherlands, a search was performed for TGCT in a 5-year time frame. Subsequently these data were clinically verified in the corresponding Dutch hospitals. Dutch TGCT incidence calculations were converted to world population incidence rates. Finally, incidence rates of TGCT affecting digits was 29, localized-type extremity TGCT 10 and diffuse-type TGCT 4 per million person-years. All three groups showed a female predilection and highest number of new cases in age-category 40 to 59 years. The knee was most often affected: localized-extremity (46%) and diffuse-type (64%), mostly treated with open-resection: localized (65%) and diffuse (49%). Reoperation rate due to local recurrence for localized-extremity was 9%, diffuse-TGCT 23%. Compared to the initial US-county study, our study showed a 5-fold higher incidence rate in localized-type (combining localized-digits and localized-extremity), and a more than 2.6 fold higher incidence rate in diffuse-type. This difference could be attributed to our nationwide coverage and because of increased awareness about the disease.

The controversy that localized- and diffuse-type TGCT are clinically and radiologically two different types, while histopathologically they seem indistinguishable is evaluated in **chapter 3**. Abundant expression of Colony Stimulating Factor1 (*CSF1*), due to genomic rearrangements, is believed to be the driver mechanism in tumour formation. This study aimed to correlate *CSF1*-expression and *CSF1*-rearrangement with the biological behaviour of different TGCT-types and with clinical outcome (recurrence). Along a continuum of extremes, therapy naïve knee TGCT patients with >3-year follow-up, mean age 43 (range 6-71) years, 56% female were selected. Nine localized- (two recurrences), 16 diffuse-type (nine recurrences) and four synovitis as control were included. The use of *CSF1* split-apart FISH, consecutive to mRNA ISH, showed to be an auxiliary diagnostic tool, with 76% of TGCT harbouring *CSF1*-gene rearrangement. A clear association was not revealed between *CSF1* over-expression or *CSF1* rearrangement and the biological behaviour of different TGCT-characteristics (e.g. localized-/diffuse-type and clinical outcome (recurrence)) of the knee. Since localized- and diffuse-TGCT differ clinically, **chapter 4** established a severity classification to stratify different disease severity stages. This classification may aid to identify eligible patients for systemic targeted therapy or trials for novel agents. Parameters were defined by field-experts to assess disease extension on MR images. Type of TGCT, articular involvement, involvement of muscular/tendinous tissue and ligaments showed good inter- and intra-rater agreement (Kappa ≥0.66), had adequate number of presence (minimum of 20%) and yielded positive association on first recurrence. Ranging from highest to lowest hazard ratios these four MR parameters constructed the TGCT severity classification for all large joints, including four distinct severity-stages. Recurrence free survival at 4 years (log rank $p<0.0001$) was 94% in mild localized, 88% in severe localized, 59% in moderate diffuse and 36% in severe diffuse. The TGCT severity classification informs physicians and patients on disease extent and risk for first local recurrence after surgical treatment.

As the clinical behaviour of TGCT is very heterogeneous and probably multifactorial, **chapter 5** evaluated the unexplored influence of female sex hormones on symptoms in TGCT. Female sex hormones (oestrogen and progesterone) elevate during pregnancy. Since an increase in TGCT-related symptoms during pregnancy is observed in the outpatient clinic and on online TGCT

patient fora, we hypothesized that these increased symptoms were influenced by female sex hormones. Fifty-six percent of pregnant patients reported an increase in TGCT-related symptoms, predominantly swelling of the affected joint. Influences of sex specific hormones and female fertile life phase specific hormones were determined by comparing recurrence free survival rates between the sexes and pre- versus post-menopausal women. No differences were found in recurrence free survival rates, between both sexes, (localized- (p=0.206 ≤50 years, p=0.935 >50 years); diffuse-type (p=0.664 ≤50 years, p=0.140 >50 years)), neither in pre- versus post-menopausal women (localized- (p=0.106); diffuse-type (p=0.666)). This makes a causal relation with female sex hormones unlikely. Finally, presence of female sex hormonal receptor-status in available tumour tissue was assessed. In all examined localized- and diffuse-TGCT tissue-samples, oestrogen or progesterone hormone-receptor staining was negative and could therewith not be linked to the increased TGCT-related symptoms.

Many case-series in adults are described, whereas only 76 pediatric patients with TGCT were reported, according to our systematic review, presented in **chapter 6.** This study compared TGCT in children with TGCT in adults, calculated incidence rate and evaluated clinical behavior of TGCT in children. The standardized pediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively. In 57 children diagnosed and treated between 1995 and 2015, in one of the four tertiary sarcoma centers in The Netherlands, symptoms were swelling, pain, and limited range of motion with a median time before diagnosis of 12 (range 1-72) months. With the numbers available, differences in presentation between children and adults were not observed in terms of sex, symptoms before diagnosis, first treatment, recurrent disease, follow-up status, or median time to follow-up. The 2.5-year recurrence-free TGCT survival rate after open resection was similar between children and adults: 85% (95%CI 67%-100%) versus 89% (95%CI 83%-96%) in localized, respectively (p=0.527) and 53% (95%CI 35%-79%) versus 56% (95%CI 49%-64%) in diffuse type, respectively (p=0.691). Although the incidence of pediatric TGCT is low, it should be considered in the differential diagnosis in children with chronic mono-articular joint effusions. Recurrent disease after surgical treatment of this orphan disease was comparable between children and adults.

In the literature, **chapter 7** and **chapter 8** presented the largest series of both localized- and diffuse-type TGCT. Two-thousand one-hundred and sixty-nine (941 localized-, 1192 diffuse-, 36 unknown-type) histologically proven TGCT cases of large joints were included, treated between 1990-2017 in one of 31 collaborating sarcoma centers globally.

In localized-TGCT (**chapter 7**), 62% was female with median age at first treatment of 39 years and median follow-up of 37 months. 67% affected the knee and primary treatment at tertiary center was one-staged open resection in 71%. Total number of recurrent disease was 13% with local recurrence free survival at 3, 5 and 10 years of 88%, 83% and 79% respectively. The largest risk factor for recurrent disease was prior recurrence ($p<0.001$). Complications were noted in 4% after surgical treatment of localized-TGCT. Initial symptoms of pain and swelling improved after surgical treatment(s) in 71% and 85%. Only including therapy naïve cases, tumour size ≥5 cm versus <5cm HR 2.50(95%CI 1.32-4.74;$p=0.005$) and initial treatment with arthroscopy versus open HR 2.18(95%CI0.98-4.84;$p=0.056$) yielded positive association with local recurrence in both univariate and multivariate analyses. Relatively low complication rates and good functional outcome warrant an open approach with complete resection in localized-TGCT, to reduce recurrence rates in high risk patients.

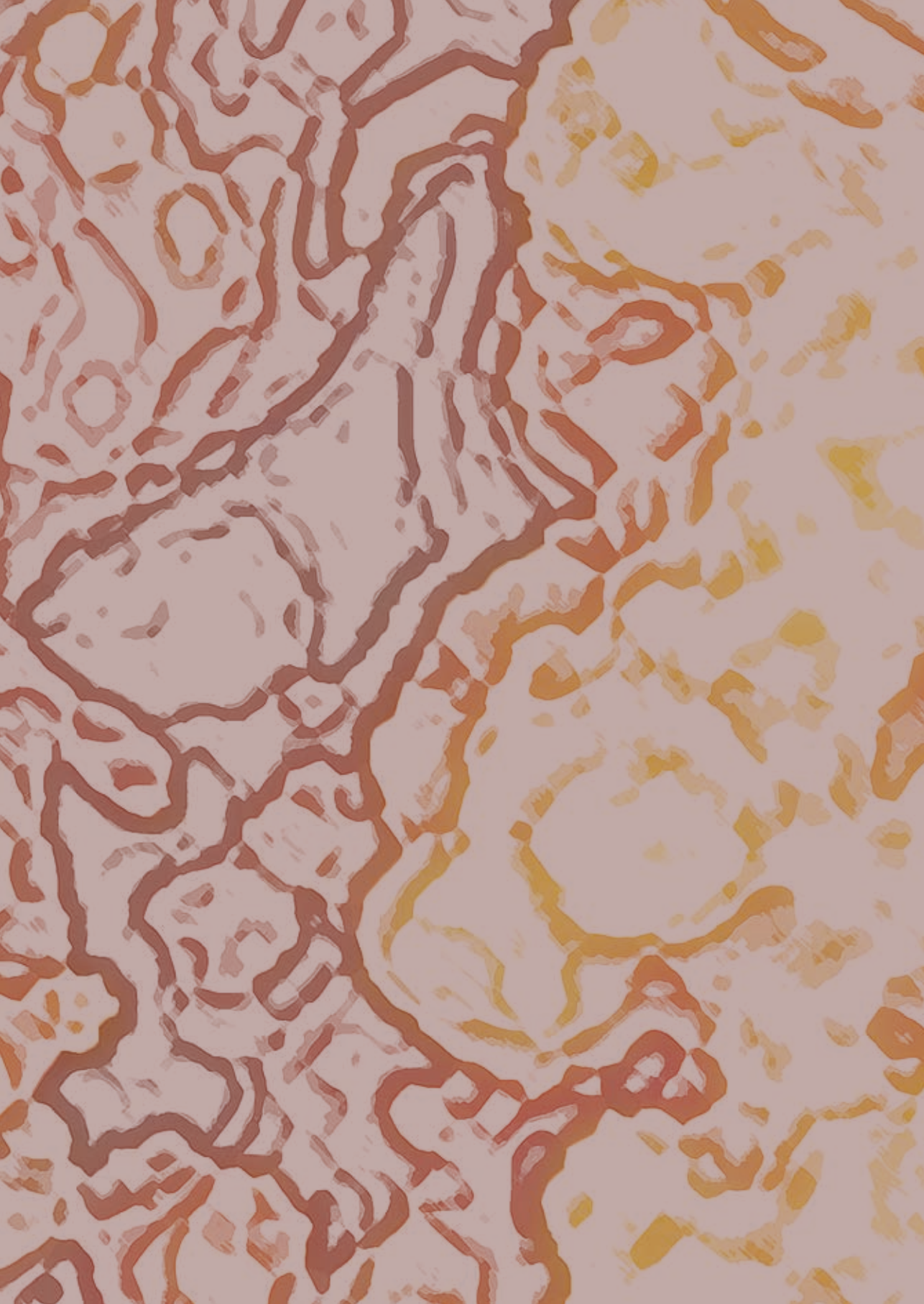
In diffuse-TGCT (**chapter 8**), 58% was female, median age 35 years and median follow-up 54 months. 64% affected the knee and in 53% primary treatment was one-staged open synovectomy. 45% had first local recurrence, accompanied with local recurrence free survival at 3, 5 and 10 years of 62%, 55% and 40%, respectively. Largest risk factor for recurrent disease was prior recurrence (HR 3.5 95%CI 2.8-4.4, $p<0.001$) with a 5 years RFS in therapy naïve patients compared with patients treated elsewhere of 64% and 25%, respectively. Complications were noted in 12%. Initial symptoms of pain and swelling improved after surgical treatment(s) in 59% and 72% of patients respectively. In a subgroup analyses including therapy naïve cases affecting the knee, neither sex (male;female), age (≤35years;>35years), bone-involvement (present;absent), surgical technique (open;arthroscopic) nor tumour size (<5cm;≥5cm) yielded an association with first local recurrence. Since complete resection of diffuse-TGCT could be regarded as nearly impossible and recurrence rates are unacceptably high after both arthroscopy and open synovectomy in the knee, even in specialized centres, standalone surgical resection cannot be regarded the gold standard anymore in the era of multimodality therapies.

Chapter 9 described long term effects of imatinib mesylate, a non-selective *CSF1* inhibitor, in TGCT. Sixty-two patients from 12 institutions across Europe, Australia and the United States used imatinib as treatment. Thirty-nine patients were female (63%), median age at treatment start was 45 years, with a median time from diagnose to treatment of 3.5 years. Median follow-up after treatment start was 52 months. Four patients with metastatic TGCT progressed rapidly on imatinib mesylate and were excluded for further analyses. Seventeen (29%) of 58 evaluable patients achieved complete or partial response. One- and five-year progression-free survival rates were 71% and 48%, respectively. Thirty-eight (66%) patients discontinued imatinib after a median of 7 months. Reported adverse events in 45 (78%) patients were mostly grade 1-2 (89%) (e.g. edema (48%) and fatigue (50%)). Five patients experienced grade 3-4 toxicities, including neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue. This study confirmed the known efficacy of imatinib in TGCT. In responding cases, prolonged activity of imatinib on TGCT symptoms was confirmed, even after discontinuation, but with high rates of treatment interruption and additional treatments. Limitations of this study are related to the retrospective study design, the lack of a control group and the absence of patient reported outcome measures. To evaluate patients reported outcome measures, **chapter 10** focused on joint function and health-related quality of life outcome after surgical treatment in a prospective cohort study. Patient-reported outcome measures (Short Form (SF)-36, Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) were assessed in a homogeneous group of 206 consecutive patients with localized- (N=108) and diffuse-type (N=98) TGCT of large joints, initially treated with (arthroscopic/open) synovectomy at either Leiden University Medical Center or Radboud University Medical Center. In particular, the physical component of SF-36 subscales showed significant and clinically relevant deteriorated scores preoperative- and direct postoperative compared with general population means, in both localized- and diffuse-TGCT. Six months after surgery, SF-36 scores improved to general population means and continued fairly stable the following years. Median pain (VAS) scores, for both-subtypes, showed no clinically relevant difference pre- or postoperatively. Pain experience differed tremendously between patients and over time. Mean function (WOMAC) scores, for both TGCT subtypes, showed no clinically relevant differences (effect size < MCID 20) pre- versus postoperatively. However, in diffuse-type patients WOMAC pain and physical function scores showed a trend toward improved preoperative versus postoperative scores. To conclude, patients report a significant better health-related quality

of life after surgery in TGCT whereas joint function showed a trend towards improvement. To evaluate patient reported outcomes in an even larger group of patients, **chapter 11** conducted a crowdsourcing study in the largest TGCT patient support group. To evaluate the impact of TGCT on daily living; physical function, daily activities, societal participation (work, sports and hobbies) and overall health-related quality of life was assessed. Secondary aim was to define risk factors for deteriorated outcome in TGCT with the use of validated questionnaires (VAS for worst pain and stiffness, Patient Reported Outcomes Measurement Information System-physical functioning (PROMIS-PF), SF-12 and EuroQoL (EQ-5D-5L)). In a timeframe of six months, TGCT patients were invited to complete the online questionnaire. To confirm disease presence and TGCT-type, patients were requested to share histological- or radiological-proof of TGCT. Three-hundred thirty-seven questionnaires (32% with disease confirmation), originating from 30 countries, were completed. Median age at diagnosis was 33 (IQR 25-42) years, majority was female (80%), diffuse-TGCT (70%) and affected lower extremities: knee (71%) and hip (10%). In 299 lower extremity TGCT-patients, recurrence-rate was 36% and 70% in localized- and diffuse-type, respectively. Due to TGCT, 13% of localized- and 11% of diffuse-type was unable to (fully) perform their employment and 58% of localized- and 64% of diffuse-type was unable to practice sport-activities. For both types, pain and swelling decreased after treatment, but stiffness worsened and range of motion decreased. This could be attributed to (multiple) surgical treatments, inducing scar tissue, cartilage wear and adhesions. Compared with general United States population, all patients showed declined, clinically relevant, PROMIS-PF scores, SF-12 physical and mental scores and EQ-5D-5L utility-score. When comparing localized- and diffuse-TGCT, diffuse-type scored almost 0.5 standard-deviation lower for PROMIS-PF ($p<0.001$) and 5% lower for EQ-5D-5L ($p=0.03$). In localized-TGCT, recurrent disease and ≥2 surgeries negatively influenced scores of VAS-pain/stiffness, SF-12 physical and EQ-5D-5L ($p<0.05$). In diffuse-type, recurrence resulted in lower score for VAS-pain/stiffness, PROMIS-PF, SF-12 mental and EQ-5D-5L ($p<0.05$). In both types, patients with treatment ≤1 year ago scored significantly lower on SF-12 physical. This study demonstrated that TGCT has major impact on daily living in a relatively young and working population. Physicians and other relevant health care providers (e.g. physiotherapists) should be aware that TGCT patients frequently continue to experience declined health-related quality of life and physical function and often remain limited in daily activities, employment and sports, even after treatment(s).

Extreme final treatment measures in TGCT, an above knee amputation, are presented in **chapter 12.** High recurrence rates are known in diffuse-TGCT (up to 92%), necessitating reoperations and adjuvant treatments. Once all treatments fail or if severe complications occur, limb amputation may become unavoidable. Four cases treated with this last resort treatment for TGCT, an above-knee amputation, were described.

Conclusions, clinical implications and future perspectives for the subject of this thesis are discussed in **chapter 14**.



chapter fourteen

DISCUSSION

General discussion & Future perspectives

General discussion

In the 2013 WHO classification of tumours of soft tissue and bone, giant cell tumour of the tendon sheath and pigmented villonodular synovitis (PVNS) were unified in one overarching name: tenosynovial giant cell tumours (TGCT)[1, 2]. To date, among most treating physicians, the disease still remains best known with the term PVNS[3]. With this thesis, we want to create disease awareness and update knowledge on disease and treatment outcome.

TGCT is a rare heterogeneous disease (**chapter 2**) with a wide clinical spectrum; patients of all ages are affected (**chapter 5** and **6**), including different joints (both small and large), various disease stages and severities. This heterogeneity challenges research initiatives, as current literature mainly consists of relatively small single centre observational case-series that often compare apples to oranges. Frequently, series have a retrospective design and level of evidence is not exceeding level III-IV. To achieve solutions on unmet medical needs, we need to set up research projects that reach higher levels of evidence through thorough (inter)national, multicentre collaborative studies.

1. Translational research

The translocation (1;2)(p13;q35) that is responsible for overexpression of Colony Stimulating Factor 1 (CSF1), is thought to be the driver mechanism of this disease[4, 5]. It remains unclear when and why this translocation forms, but it remains a 'local problem' as TGCT is a mono-articular disease. An unravelled clinical question is how to differentiate the biological behaviour of different TGCT-types with clinical outcome (recurrence). All TGCT cases show CSF1 over-expression. By the use of correlative microscopy for CSF1 mRNA ISH and consecutive CSF1 split-apart FISH, we were able to detect CSF1-gene rearrangement in 76% of the TGCT cases; 77% for localized-TGCT and 75% for diffuse-TGCT. The relatively high percentage of rearrangement in our study could be attributed to our scoring on preselected areas, based on high CSF1 expression. In addition, our DNA FISH analysis, using bacterial artificial chromosome (BAC) clones (RP11-354C7 and RP11-96F24) bracketing CSF1 locus, identified not only a translocation, but also an inversion for CSF1 rearrangements. In diagnosing TGCT, CSF1 mRNA-ISH in combination with CSF1 split-apart FISH; using digital correlative microscopy, is an auxiliary diagnostic tool to identify rarely occurring neoplastic cells. Although this helps the diagnostic process, in **chapter 3** we were unable to use this technique and differentiate for biological behaviour of TGCT by evaluating CSF1 over-expression or rearrangement.

2. Individually tailored treatment

Physical joint examination is generally nonspecific in the clinical diagnosis of TGCT. A specialized musculoskeletal radiologist can however diagnose TGCT on magnetic resonance (MR) imaging, which is the most distinctive imaging technique[6-10]. MR imaging can also be a differentiating tool to determine tumour severity staging and for evaluation of disease extent during follow-up. The TGCT severity classification in **chapter 4** defines TGCT extension on MR imaging to classify disease severity. This classification, including four distinct severity-stages, could attribute to a treatment strategy flowchart and improve the homogeneity in clinical studies. Definitive diagnosis however is established by histopathology, either by biopsy or surgical resection.

The fundamental question whether curation is necessary in a locally aggressive disease often arises in literature. Debilitating symptoms and (progressive) joint destruction commonly result in treatment of the diseased tissue. At present, the choice of treatment is established by preference of the patient, treating physician and might differ per centre. Most common performed treatment is surgical excision, aiming for local tumour control. Localized-TGCT presents as a well circumscribed lesion and recurrence rates after arthroscopic and open synovectomy are reported similar (6% after arthroscopic and 4% after open synovectomy)[11]. Surgical treatment for the locally aggressive diffuse-TGCT is more challenging, as pathologic tissue can be widely spread and technically difficult to reach. In extensive disease (**chapter 4**, severe diffuse stage), irradical resection could be preferred with joint preservation in mind. However, higher rates of recurrences are described after macroscopically incomplete resections[12-15]. As primary treatment for diffuse-TGCT, either an arthroscopic- or (one- or two staged) open synovectomy or a combination of these two treatments is performed. Physicians in favour of arthroscopic resection claim fast recovery, a lower complication rate and less joint morbidity[13, 16-22]. However, frequently at the cost of inadequate excision, high recurrence rates (on average 40% in diffuse-TGCT) and a theoretical risk of joint seeding and portal contamination[11, 23]. A complete synovectomy is generally impossible with traditional arthroscopy, therefore Blanco et al. and Mollon et al. used multiple portals in arthroscopic synovectomy[24, 25]. Chin et al. stated that knee arthroscopy is an inferior treatment for extra-articular TGCT[26]. Nowadays, open synovectomy, either one- or two-staged, is the preferred surgical therapy in most centres, because of clear tumour visibility and lower short term recurrence rates (on average 14% in diffuse-TGCT)[11, 27, 28]. The disadvantage of a one- or two-staged

open resection, could be deteriorated joint function accompanied with decreased health-related quality of life (**chapter 9**)[29]. A combined anterior arthroscopic- and posterior open synovectomy in the knee is only incidentally reported. Mollon et al. described the combined approach of an anterior arthroscopy and posterior open synovectomy (N=15 patients), with low recurrence rates[25]. Colman et al. retrospectively subdivided 48 diffuse-TGCT patients in three groups; either treatment with an arthroscopy, the combined approach or an open approach. They concluded that the combined approach is a feasible option because of relatively low short term recurrence rates (9%)[30]. **Chapter 7** revealed that the longer the follow-up, the higher the recurrence rates. Localized-TGCT had a recurrence rate of 21% and diffuse-TGCT 69% after initial surgical resection at a tertiary oncology centre with a follow-up of more than 10 years. The suspicion arouses that most patients will develop a recurrence when you wait long enough. The main question remains: is the recurrent disease accompanied by debilitating symptoms or joint destruction?
In general, all surgical treatments harbour the risk of complications. Literature frequently lacks descriptions of complications. **Chapter 7** reports a complication rate of 4% in localized-TGCT and 12% in diffuse-TGCT after initial surgical treatment at a tertiary centre. Most common complication in diffuse-TGCT was joint stiffness, which might be difficult to prevent in surgical treatment of extensive disease.

In extensive diffuse disease, radical excision is next to impossible as residual tumour cells (micro- R1 or macroscopically R2) may persist. In diffuse-TGCT, joint destruction and secondary osteoarthritis is frequently present. When chronic symptoms persist, joint arthroplasty might become inevitable, especially in large joints with tight capsules including a higher risk of bone involvement, such as the hip and ankle[29, 31, 32].

A combination of surgery and external beam radiation is considered in extensive or recurrent diffuse-TGCT. Radiotherapy may kill residual tumour cells, but possibly at the cost of increased (delayed) complications, especially in re-operation, and impaired functional outcome[15, 33-35]. Blanco et al. reported that partial arthroscopic synovectomy of the knee combined with external beam radiation might reduce the risk of recurrence (N=22 patients)[24]. A meta-analysis suggested that open synovectomy (N=19 studies) or synovectomy combined with perioperative radiotherapy (N=11 studies) is associated with a reduced rate of recurrence[34]. Mollon et al. reserved additional

external beam radiation for patients at high risk for local recurrence, if they had the following characteristics: multiple recurrent intra-articular disease, extra-articular extension, or gross residual disease remaining following surgery[25]. Currently, sufficient data including adequate patient numbers is lacking to support the additional value of external beam radiation in primary cases and should only be performed in specific extensive or recurrent diffuse-TGCT cases.

Additional reported treatment modalities include radiation synovectomy with 90yttrium[36] and cryosurgery[37, 38], for which the therapeutic value is inconclusive and their long-term side effects and complications are unknown. Bickels et al. treated seven patients with diffuse-TGCT of the ankle with subtotal synovectomy and intra-articular ^{90}yttrium and warned not to use ^{90}yttrium as additional treatment because of unacceptable high rate of serious complications[39]. Gortzak et al. reported no significant differences in residual disease, complication rate and overall physical and mental health scores between patients surgically treated for TGCT of the knee with (N=34) or without (N=22) adjuvant 90Yttrium, after a mean follow-up of 7.3 years[36]. Chin et al. subdivided patients, after surgical resection without disease eradication, into three groups: group I combined arthroscopic and open synovectomy (five patients), group II combined synovectomy in combination with intra-articular radiation synovectomy (dysprosium-165) (30 patients), and group III combined resection and three months postoperatively external beam radiation (five patients). They concluded that group I and Group II showed similar increases in postoperative flexion compared with group III[15]. Verspoor et al. evaluated 12 patients treated with surgical synovectomy and additional cryosurgery. They did not find better results compared to surgical resection alone[37].

Diffuse-TGCT grows locally aggressive. Therefore, systemic therapy, with possible (severe) side effects, seems justified in this benign but debilitating disease. Colony Stimulating Factor1 (CSF1), due to genomic rearrangements, is believed to be the driver mechanism in tumour formation. By a paracrine loop, the CSF1 excreting tumour cells, attract non-neoplastic cells, carrying the CSF1 receptor. Interruption of this pathway is the aim of systemic targeted therapies. Targeted therapy might be used as treatment independently or to primarily down-stage the disease and facilitate consecutive surgical resection. Non-selective CSF1 inhibitor therapies with nilotinib[40] or imatinib (**chapter 8**) and newer, more potent selective CSF1 inhibitors such as pexidartinib[41], emactuzumab[42], cabiralizumab[43]; or a monoclonal antibody such as MSC110 (clinicaltrial.gov) seem promising.

Results are usually tumour-centric presented, using Response Evaluation Criteria in Solid Tumors (RECIST); complete response, partial response, stable disease and progressive disease; and patient centric, using symptom improvement evaluation. In a randomized, placebo-controlled phase 3 study, pexidartinib showed an improved overall response rate (complete response and partial response merged) of 39% in the pexidartinib-group (N=61) and 0% of placebo-group (N=59), after median six months follow-up. PROMIS physical function, worst stiffness and pain response was significantly better in patients treated with pexidartinib[41]. Emactuzumab (N=29) had an overall response rate of 86% and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months)[42]. Preliminary results of cabiralizumab showed partial response in 5 out of 11 patients and positive functional status improvements by Ogilvie-Harris score (from 2 to 7)[43]. Ogilvie-Harris score combines pain, synovitis, range of motion and functional capacity on a scale of 0 to 12.
Complete response was reported in a total of four patients; two patients treated with emactuzumab[42] and two patients treated with imatinib, presented in **chapter 8**.
Reported mild side effects include edema, change of hair colour, fatigue, nausea and skin rash/ dermatitis, but also moderate to severe side effects such as neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue. Despite these side effects, in selected patients with extensive and recurrent diffuse-TGCT, CSF1 inhibitors might offer a solution. Treatment optimization is yet to be established; optimal agent, therapy duration, timing of surgery, toxicity profile and mechanism of resistance.

A challenging rare subgroup of soft tissue sarcoma patients, comprises multifocal, malignant or metastatic disease resembling TGCT (four patients with metastatic TGCT in **chapter 8** and two patients in **chapter 11**). These patients are incidentally reported in case-series[44]. The largest series of Li et al. included seven patients with malignant TGCT and concluded that these tumours should be regarded as a distinct sarcoma with considerable morphologic variability, metastatic propensity, and lethality[45]. As specialized centres see these patients extremely rare, upcoming research should reveal whether TGCT is capable of malignant transformation or whether this malignant tumour should be regarded a different (malignant) entity.

To summarize, several treatment modalities in the heterogeneous disease TGCT are available. Current literature fails to specify patient characteristics per treatment modality and lacks randomized controlled trials, impeding definitive treatment of choice for each individual, based on efficacy and safety. A solution for the difficulty of performing a randomized controlled trial might be the so called stepped wedge cluster design. This is a special form of a randomised study in which an intervention at group level is implemented in stages[46]. To contribute to personalized treatment, careful evaluation of health-related quality of life and functional outcome (**chapter 9** and **10**), not just local recurrence and complications, should be included in patient follow-up. In addition, large scaled studies based on individual participant data meta-analysis provide a higher form of evidence in comparison with small heterogeneous case series. Advantages include that missing data can be accounted for at the individual level, subgroup analyses can be performed (e.g. per affected joint) and up to date disease status or follow-up information can be updated continuously (**chapter 7**)[47].

3. Centralized treatment in a multidisciplinary team

TGCT onset is typically slow and patients present with unspecified symptoms[1, 2, 48, 49]. Pain, swelling, and stiffness of the involved joint might be misinterpreted as osteoarthritis, rheumatoid arthritis, a meniscal tear, or other ligamentous injury[50]. Because of the rarity of the disease, definitive diagnosis may take several years and patients present with extensive disease[11, 51, 52]. After several (arthroscopic or open) synovectomies and even radiotherapy, patients are still referred to a tertiary hospital. Besides declined functional outcome and health-related quality of life, these patients are at risk of repeated recurrences, therapy resistant disease and higher risk of complications[29]. Continued inflammation, joint usuration and bone involvement may lead to articular destruction that might worsen (pre-existing) osteoarthritis[50]. By creating more public awareness, involving relevant dedicated health care providers (e.g. rheumatologists, general practitioners, physiotherapists), delay of diagnosis should be reduced by referring patients to specialized centres at an early stage to provide optimal treatment(s)[53]. Specialized centres treat multiple patients with TGCT and this rare disease is considered daily practice. Therefore, all members of the multidisciplinary team are highly trained to recognize disease specifics. Members of the multidisciplinary TGCT team include dedicated physicians with experience in musculoskeletal oncology in the field of pathology, radiology, orthopaedic oncology, arthroscopic orthopaedics, radiotherapy, medical

oncology and if necessary paediatric orthopaedics. To prevent end stage treatment options, such as limb amputation (**chapter 11**), centralization of treatment should become state of the art. Two examples of advantages of centralization of treatment are provided by the tertiary oncology centre in Leiden (LUMC). Every half year a patient centred newsletter is send to all patients with TGCT. This newsletter includes information on recent literature and (new) studies at patient level. In addition, the TGCT-team of the LUMC is active on Facebook, with their own up to date Facebook page ('TGCT study') and within the closed Facebook-group 'PVNS is pants' (**chapter 10**).

4. Patient-centred outcome measures

Outcome of TGCT treatments should be measured on how the patient is feeling. The mantra for patient-centred treatment is: don't make the treatment worse than the problem. Perhaps a debilitating operation costs more than the disease itself in the view of health-related quality of life and joint function preservation. Taking the factor time into account is necessary, as short term satisfying results could emerge into deteriorated outcome in the long run. Defining specific treatment options for each individual patient is of utmost importance. Would this individual patient benefit more from conservative treatment or side effects of targeted therapy? Mild side effects might be considered acceptable, however moderate to severe side effects seem less justifiable in a non-lethal disease.

Assessment of health-related quality of life and functional outcome in TGCT is necessary. However, specific patient reported outcome instruments have yet to be defined. A few studies, including **chapter 9** and **10**, have reported disease outcome from a patient perspective[15, 25, 29, 36, 48, 54, 55]. Used validated questionnaires included worst pain and worst stiffness numeric rating scale (NRS), short form (SF) health survey-12 and SF-36, Euroqol 5 (EQ5D5L), knee-injury osteoarthritis outcome score (KOOS), hip disability osteoarthritis outcome score (HOOS), Toronto extremity salvage score (TESS), musculoskeletal tumour society (MSTS) score, patient reported outcomes measurement information system physical function (PROMIS-PF) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). None of these patient reported outcome instruments are specifically designed for rarely lethal, but morbid musculoskeletal tumours. Gelhorn et al. performed research interviews regarding symptom experience to test the relevance and content validity of several existing patient reported outcome instruments. They recommended PROMIS-PF as most suitable questionnaire[48]. PROMIS-PF is subdivided in an upper- (11 questions) and lower-extremity part (13

questions). Since TGCT affects all joints, measurements eligible for all these locations would be the aim. In addition, general health-related quality of life measures are important to compare TGCT with other musculoskeletal disorders.

A major disadvantage of standardized questionnaires is that they include questions not applicable for each individual participant. Therefore, the item response theory (IRT) and Computer Adaptive Testing (CAT) are developed. IRT examines the response characteristics of individual items and the relationship between responses to individual items and the responses to each other item in a domain. By using IRT, CAT is a method that selects subsequent questions (from the item bank) based on the responses until predetermined termination criteria are met. Hereby only relevant questions are asked and the amount of questions is greatly reduced. This ensures a higher amount of patients willing to complete the questionnaire[56]. Relevant questions could be extracted from the PROMIS databank, including over 300 measures of physical, mental, and social health for use with the general population and with individuals living with chronic conditions (http://www.healthmeasures.net). For future self-reported outcome evaluations in TGCT, we would propose the CAT method by use of the PROMIS item bank.

Besides well-defined subjective outcome measures, objective outcome measures also need to be determined to structure clinical evaluation. The timed up and go test provides information on physical strength by measuring the time (seconds) to rise from and return to a chair with three meters walking in between[57]. Another functional measure is the six-minute walk test, not just determining joint range of motion, but looking at performance of the individual[58].

5. Limitations

This thesis consists of multiple cohort studies. At times, patients are present in several cohorts. Patients treated in the RadboudUMC or LUMC, were also present in the PALGA search to calculate the incidence (**chapter 2**). In the evaluation of impact on daily living (**chapter 11**), a Facebook cohort is used in which Dutch patients were present, which were also registered with the PALGA search. This overlap of patients in the cohort studies could have influenced the results. However, since each study had a unique research question to evaluate different aspects of the disease, this influence is considered minimal.

To conclude, TGCT is a chronic debilitating illness with large impact on daily living. It is a challenge for physicians to provide optimal personalized treatment, since TGCT patients present as a heterogeneous group, trials with targeted therapies are ongoing and a standardized treatment algorithm is lacking. Based on our experience, literature and the TGCT severity classification on MR imaging* (**chapter 4**), we propose a treatment algorithm for TGCT of all large joints as a foundation to build upon and to evolve (*figure 1 and figure 2*). In addition to the physical and financial burden for the patient, TGCT also involves a high healthcare burden with rising costs after diagnosis[59]. Current developments are promising: increasing disease awareness, centralization of care, several targeted therapy trials, evaluation of personalized follow-up questionnaires and ongoing prospective international collaboration studies. These initiatives should be expanded to achieve new insights in TGCT.

*The TGCT severity classification on MR imaging contains four distinct severity stages:

1. **Mild localized** contains localized-type, either intra- or extra-articular involvement without involvement of muscular/tendinous tissue/ligaments.
2. **Severe localized** includes localized-type, either intra- or extra-articular lesions and either or both involvement of muscular/tendinous tissue/ligaments.
3. **Moderate diffuse** comprises diffuse-type with intra- and/or extra-articular disease without involvement of muscular/tendinous tissue/ligaments.
4. **Severe diffuse** is diffuse-type including intra- and extra-articular involvement and involvement of at least one of the three structures (muscular/tendinous tissue/ligaments)

Future perspectives

1. Translational research

The driver mechanism in TGCT tumour formation seems to be over-expression of CSF1. Only a minority (2-16%) of cells in the tumorous tissue harbour the CSF1 rearrangement[4, 5]. Despite the few tumour cells, they disrupt the entire surrounding area in different degrees of extent. We expect the neoplastic cell to be a synovial like mononuclear cell, as was proposed by West et al.[4] They reported that CSF1 expressing cells also express CD68, without CD163 co-expression, and therefore expect CSF1 expressing neoplastic cells to be derived from synovial-lining cells. Identification of this neoplastic cell could attribute in investigations of new treatment modalities.

Dynamic contrast-enhanced MR imaging and histopathology research revealed high vascularization in both localized- and diffuse-TGCT, showing marked enhancement on T1-weighted images with a delayed wash-out[60, 61]. Angiogenesis is induced by CSF1 through vascular endothelial growth factor (VEGF)[62]. Formation of blood vessels is fundamental for tumour development. A possible therapeutic target would be to control this increased vascularity by inhibiting VEGF, for example with Bevacizumab (Avastin)[63].

2. Individually tailored treatment

It is unclear whether curation of diffuse-TGCT is possible at present, since residual tumour cells (micro- R1 or macroscopically R2) remain after surgical resection, optimal targeted therapy is under investigation and treatment with other therapies is inconclusive. A common question arises: is wait and see or conservative treatment justified in the locally aggressive diffuse-TGCT? Forthcoming research should provide answers on degree of joint destruction and (impaired) health-related quality of life in a wait and see or conservative treatment course.

Currently, data on tumour progression after quitting targeted therapy treatment is lacking. Future investigations should focus hereon. Also, several experimental studies with targeted therapy can be thought of, for example investigation of intermittent use (drug holidays), the possibility of intra-articular injection and the option of isolated limb perfusion with CSF1 blockers/inhibitors.

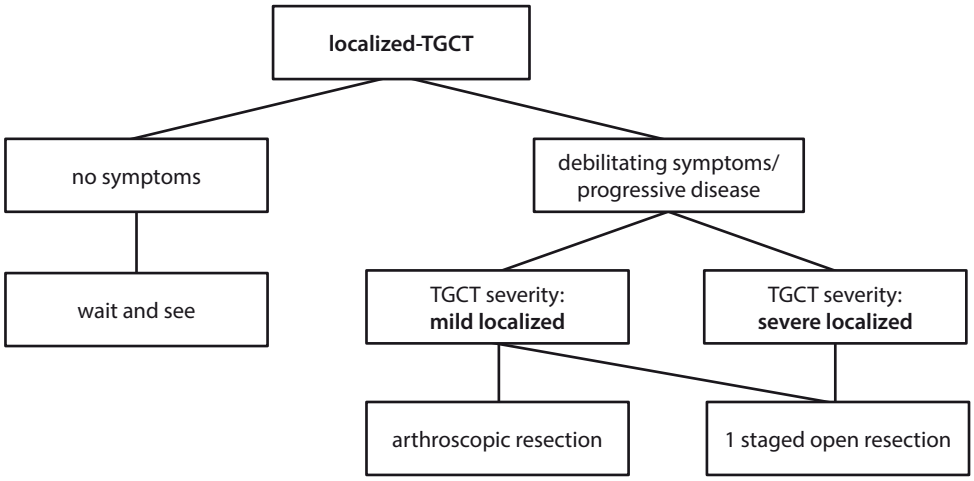
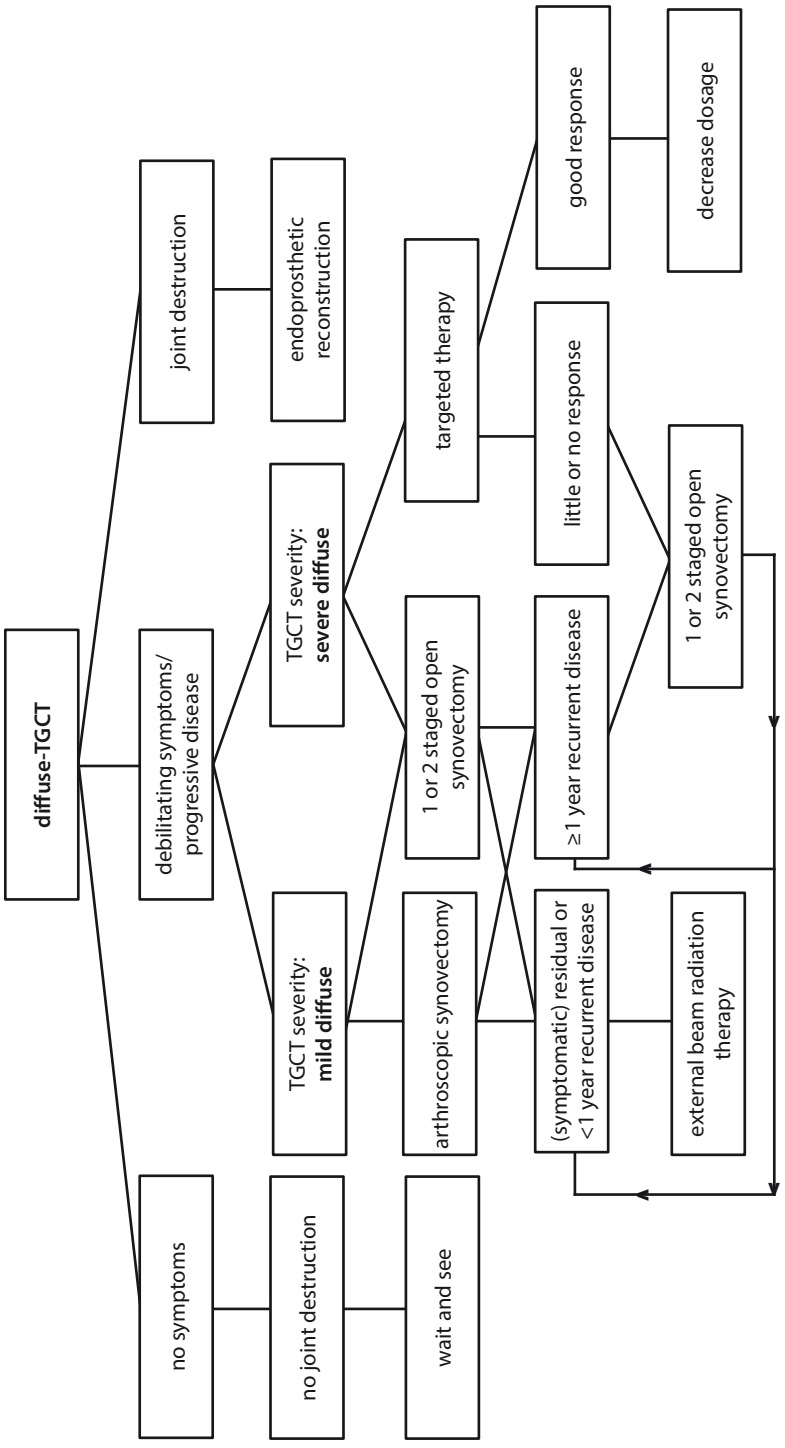


Figure 1 Proposed treatment algorithm for localized-TGCT of large joints. Balance between disease severity and potential treatment morbidity should be individually tailored for each patient. Wait and see and conservative treatment are considered similar. Open resection could be preferred above an arthroscopic resection to potentially reduce the risk of recurrence, but arthroscopic resection should not be excluded as a potentially curative surgical technique in selected cases.

Figure 2 ***(right page)*** Proposed treatment algorithm for diffuse-TGCT of large joints to be discussed in a multidisciplinary soft tissue tumours team. Treatment proposal should balance between disease severity and potential treatment morbidity and should be individually tailored for each patient. Wait and see and conservative treatment are considered similar, but should include a (2-)yearly MR imaging for follow-up to evaluate possible progressive disease (T1- and T2-weighted fast spin echo, possibly other fluid sensitive sequences, and preferably a scan after administration of contrast). Excision for functional improvement and joint preservation should be proposed in symptomatic patients. An open synovectomy could be preferred above an arthroscopic synovectomy in extra-articular disease (**chapter 7**), to reduce the risk of recurrence. External beam radiation therapy can only be advised in recurrent or severe diffuse cases and might be succeeded by targeted therapy in the near future. If arthroplasty is anticipated, radiotherapy should not be considered lightly. As the preferred dosage of radiotherapy is unknown, a moderate dose is recommended. Since targeted therapy trials are ongoing, no specific targeted therapy is advised. The timing and duration of (neo)adjuvant targeted therapy around surgery should be subject of future research.


diffuse-TGCT
no symptoms
debilitating symptoms/ progressive disease
joint destruction
no joint destruction
endoprosthetic reconstruction
TGCT severity: mild diffuse
TGCT severity: severe diffuse
wait and see
arthroscopic synovectomy
1 or 2 staged open synovectomy
targeted therapy
(symptomatic) residual or <1 year recurrent disease
≥1 year recurrent disease
little or no response
good response
external beam radiation therapy
1 or 2 staged open synovectomy
decrease dosage

Future treatment studies should combine current knowledge into new studies to improve treatment modalities. Recurrent disease, (short- and long-term) complications, health-related quality of life and joint function should be evaluated as outcome. Patients could be stratified by the TGCT severity classification (**chapter 4**), that may be improved by using biological differentiation using next generation sequencing or new MR imaging techniques. In a prospective cohort study, several different treatment groups could be evaluated and compared:

- Wait and see/conservative treatment in case of mild symptoms
- Surgical treatment (open versus arthroscopic resection, one versus two-staged synovectomy)
- Neoadjuvant targeted therapy + surgical treatment
- Surgical treatment + adjuvant targeted therapy
- Neoadjuvant external beam radiation + surgical treatment
- Surgical treatment + adjuvant external beam radiation

The intervention at group level could be implemented in stages, by use of the stepped wedge cluster design[46]. Best modality to monitor response of tumour activity is yet to be established. There might also be a role for dynamic contrast-enhanced MR imaging or fluorodeoxyglucose-positron emission tomography (FDG-PET), as TGCT shows high FDG update[64].

Evaluation of different treatment modalities, patient characteristics, disease severity and biological behaviour could result in a prediction model. This prediction model should predict individual risk profiles, that can then be linked to recommended treatment strategies and should take patient characteristics, affected joint, volume of disease, disease extent, performed treatment(s) and possibly histopathologic or genetic features into account.

3. Centralized treatment in a multidisciplinary team

The current trend in rare diseases is centralization of treatment that necessitates (highly) specialized expertise. Diffuse-TGCT treatment should sail along this trend. In addition, centralization of diffuse-TGCT treatment could be realized by creating more public awareness and easy available reliable information.

4. Patient-centred outcome measures

For future self-reported outcome evaluations in TGCT, the CAT method by use of the PROMIS item bank could be used. Preferably in the form of an easy accessible application on a mobile device. A new feature could be to not only link the application to the electronic patient dossier, but to also provide feedback to each individual patient personally, on how they are performing in the field of physical, mental and social health compared with themselves at specified time periods previously. As TGCT is known with recurrent disease developing years after initial surgical treatment, patients are more likely to continue completing questionnaires if they are short and simple.

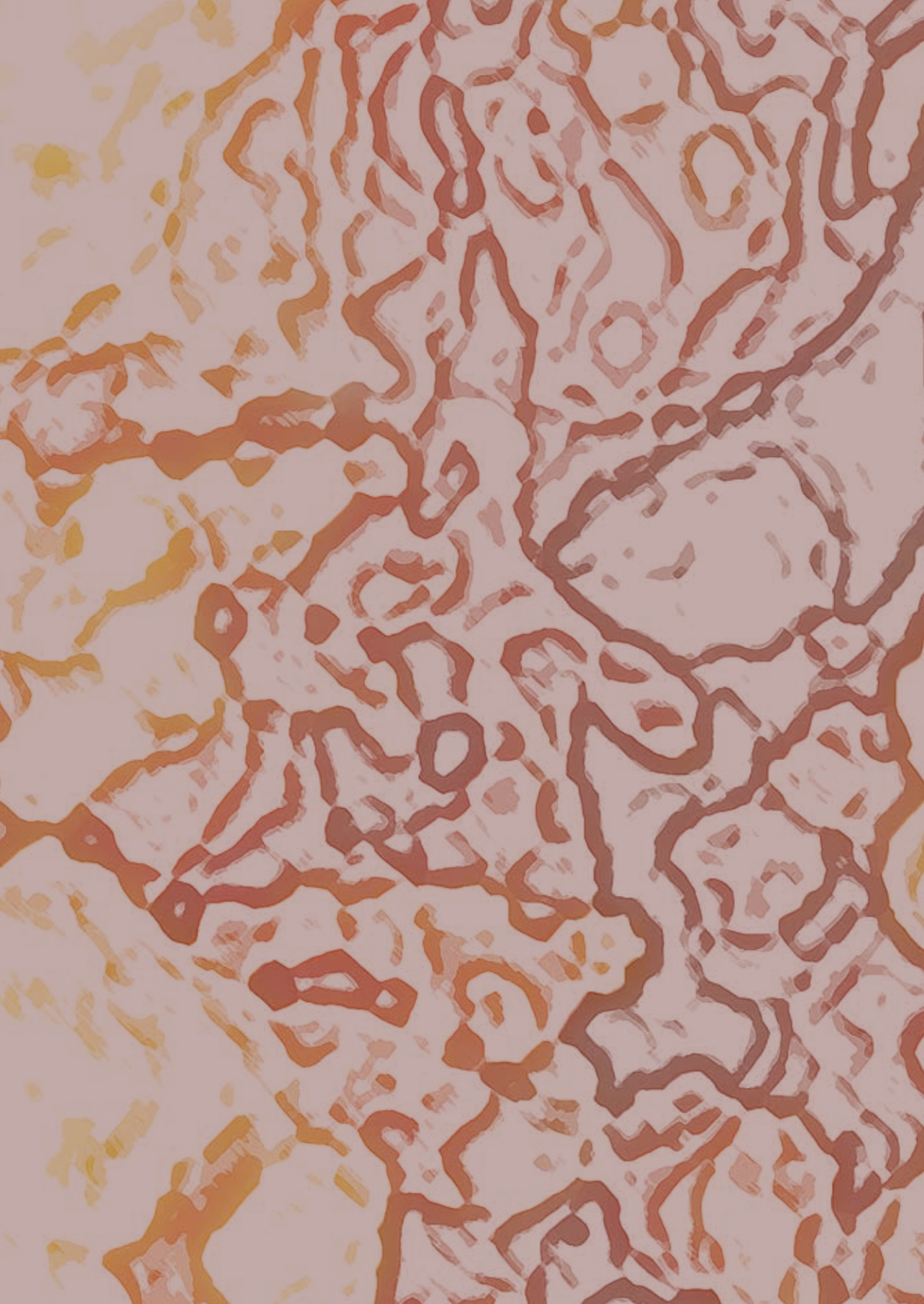
References

1. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 52013. p. 102-3.
2. de St. Aubain S, van de Rijn M. Tenosynovial giant cell tumour, localized type. In: Fletcher CDM BJ, Hogendoorn PCW, Mertens F, editor. WHO Classification of Tumours of Soft Tissue and Bone. 5. 4 ed2013. p. 100-1.
3. 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(4):808-15.
4. 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(3):690-5.
5. 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. The American journal of surgical pathology. 2007;31(6):970-6.
6. Poletti SC, Gates HS, 3rd, Martinez SM, Richardson WJ. The use of magnetic resonance imaging in the diagnosis of pigmented villonodular synovitis. Orthopedics. 1990;13(2):185-90.
7. Hughes TH, Sartoris DJ, Schweitzer ME, Resnick DL. Pigmented villonodular synovitis: MRI characteristics. Skeletal radiology. 1995;24(1):7-12.
8. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. Radiographics. 2008;28(5):1493-518.
9. Nordemar D, Oberg J, Brosjo O, Skorpil M. Intra-Articular Synovial Sarcomas: Incidence and Differentiating Features from Localized Pigmented Villonodular Synovitis. Sarcoma. 2015;2015:903873.
10. Wang C, Song RR, Kuang PD, Wang LH, Zhang MM. Giant cell tumor of the tendon sheath: Magnetic resonance imaging findings in 38 patients. Oncology letters. 2017;13(6):4459-62.
11. van der Heijden L, Gibbons CL, Hassan AB, Kroep JR, Gelderblom H, van Rijswijk CS, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium--a critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433-45.
12. Schwartz HS, Unni KK, Pritchard DJ. Pigmented villonodular synovitis. A retrospective review of affected large joints. Clin Orthop Relat Res. 1989(247):243-55.
13. Ogilvie-Harris DJ, McLean J, Zarnett ME. Pigmented villonodular synovitis of the knee. The results of total arthroscopic synovectomy, partial, arthroscopic synovectomy, and arthroscopic local excision. J Bone Joint Surg Am. 1992;74(1):119-23.
14. 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(2):210-7.
15. Chin KR, Barr SJ, Winalski C, Zurakowski D, Brick GW. Treatment of advanced primary and recurrent diffuse pigmented villonodular synovitis of the knee. J Bone Joint Surg Am. 2002;84-A(12):2192-202.
16. De Ponti A, Sansone V, Malchere M. Result of arthroscopic treatment of pigmented villonodular synovitis of the knee. Arthroscopy. 2003;19(6):602-7.
17. Jain JK, Vidyasagar JV, Sagar R, Patel H, Chetan ML, Bajaj A. Arthroscopic synovectomy in pigmented villonodular synovitis of the knee: clinical series and outcome. Int Orthop. 2013;37(12):2363-9.
18. de Carvalho LH, Jr., Soares LF, Goncalves MB, Temponi EF, de Melo Silva O, Jr. Long-term success in the treatment of diffuse pigmented villonodular synovitis of the knee with subtotal synovectomy and radiotherapy. Arthroscopy. 2012;28(9):1271-4.

19. Kubat O, Mahnik A, Smoljanovic T, Bojanic I. Arthroscopic treatment of localized and diffuse pigmented villonodular synovitis of the knee. Collegium antropologicum. 2010;34(4):1467-72.
20. Loriaut P, Djian P, Boyer T, Bonvarlet JP, Delin C, Makridis KG. Arthroscopic treatment of localized pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20(8):1550-3.
21. Rhee PC, Sassoon AA, Sayeed SA, Stuart MS, Dahm DL. Arthroscopic treatment of localized pigmented villonodular synovitis: long-term functional results. American journal of orthopedics. 2010;39(9):E90-4.
22. Noailles T, Brulefert K, Briand S, Longis PM, Andrieu K, Chalopin A, et al. Giant cell tumor of tendon sheath: Open surgery or arthroscopic synovectomy? A systematic review of the literature. Orthop Traumatol Surg Res. 2017;103(5):809-14.
23. Verspoor FG, van der Geest IC, Vegt E, Veth RP, van der Graaf WT, Schreuder HW. Pigmented villonodular synovitis: current concepts about diagnosis and management. Future oncology. 2013;9(10):1515-31.
24. Blanco CE, Leon HO, Guthrie TB. Combined partial arthroscopic synovectomy and radiation therapy for diffuse pigmented villonodular synovitis of the knee. Arthroscopy. 2001;17(5):527-31.
25. 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(1):260-6.
26. Chin KR, Brick GW. Extraarticular pigmented villonodular synovitis: a cause for failed knee arthroscopy. Clin Orthop Relat Res. 2002(404):330-8.
27. Flandry FC, Hughston JC, Jacobson KE, Barrack RL, McCann SB, Kurtz DM. Surgical treatment of diffuse pigmented villonodular synovitis of the knee. Clin Orthop Relat Res. 1994(300):183-92.
28. Sharma V, Cheng EY. Outcomes after excision of pigmented villonodular synovitis of the knee. Clin Orthop Relat Res. 2009;467(11):2852-8.
29. van der Heijden L, Mastboom MJ, Dijkstra PD, van de Sande MA. Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients. Bone Joint J. 2014;96-B(8):1111-8.
30. 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(3):883-90.
31. Verspoor FG, Hannink G, Scholte A, Van Der Geest IC, Schreuder HW. Arthroplasty for tenosynovial giant cell tumors. Acta orthopaedica. 2016;87(5):497-503.
32. Hamlin BR, Duffy GP, Trousdale RT, Morrey BF. Total knee arthroplasty in patients who have pigmented villonodular synovitis. J Bone Joint Surg Am. 1998;80(1):76-82.
33. Heyd R, Seegenschmiedt MH, Micke O. The role of external beam radiation therapy in the adjuvant treatment of pigmented villonodular synovitis. Zeitschrift fur Orthopadie und Unfallchirurgie. 2011;149(6):677-82.
34. Mollon B, Lee A, Busse JW, Griffin AM, Ferguson PC, Wunder JS, 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(4):550-7.
35. Griffin AM, Ferguson PC, Catton CN, Chung PW, White LM, Wunder JS, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer. 2012;118(19):4901-9.
36. Gortzak Y, Vitenberg M, Frenkel Rutenberg T, Kollender Y, Dadia S, Sternheim A, 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(7):984-8.

37. Verspoor FG, Scholte A, van der Geest IC, Hannink G, Schreuder HW. Cryosurgery as Additional Treatment in Tenosynovial Giant Cell Tumors. Sarcoma. 2016;2016:3072135.
38. Mohler DG, Kessler BD. Open synovectomy with cryosurgical adjuvant for treatment of diffuse pigmented villonodular synovitis of the knee. Bulletin. 2000;59(2):99-105.
39. Bickels J, Isaakov J, Kollender Y, Meller I. Unacceptable complications following intra-articular injection of yttrium 90 in the ankle joint for diffuse pigmented villonodular synovitis. J Bone Joint Surg Am. 2008;90(2):326-8.
40. 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.
41. Tap WD, Gelderblom H, Stacchiotti S, Palmerini E, Ferrari S, Desai J, et al. Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). ASCO conference 2018.
42. 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(8):949-56.
43. Sankhala KK, Blay JY, Ganjoo KN, Italiano A, Hassan AB, Kim TM, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). ASCO conference 2017. 35 (15 Supplement 1).
44. Sistla R, J VSV, Afroz T. Malignant Pigmented Villonodular Synovitis-A Rare Entity. Journal of orthopaedic case reports. 2014;4(4):9-11.
45. Li CF, Wang JW, Huang WW, Hou CC, Chou SC, Eng HL, et al. Malignant diffuse-type tenosynovial giant cell tumors: a series of 7 cases comparing with 24 benign lesions with review of the literature. The American journal of surgical pathology. 2008;32(4):587-99.
46. Dekkers OM. The stepped wedge design. Nederlands tijdschrift voor geneeskunde. 2012;156(9):A4069.
47. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. Bmj. 2010;340:c221.
48. Gelhorn HL, Tong S, McQuarrie K, Vernon C, Hanlon J, Maclaine G, et al. Patient-reported Symptoms of Tenosynovial Giant Cell Tumors. Clin Ther. 2016;38(4):778-93.
49. Stephan SR, Shallop B, Lackman R, Kim TW, Mulcahey MK. Pigmented Villonodular Synovitis: A Comprehensive Review and Proposed Treatment Algorithm. JBJS Rev. 2016;4(7).
50. Tyler WK, Vidal AF, Williams RJ, Healey JH. Pigmented villonodular synovitis. The Journal of the American Academy of Orthopaedic Surgeons. 2006;14(6):376-85.
51. Hufeland M, Gesslein M, Perka C, Schroder JH. Long-term outcome of pigmented villonodular synovitis of the hip after joint preserving therapy. Arch Orthop Trauma Surg. 2017.
52. Gonzalez Della Valle A, Piccaluga F, Potter HG, Salvati EA, Pusso R. Pigmented villonodular synovitis of the hip: 2- to 23-year followup study. Clin Orthop Relat Res. 2001(388):187-99.
53. Ogura K, Yasunaga H, Horiguchi H, Ohe K, Shinoda Y, Tanaka S, et al. Impact of hospital volume on postoperative complications and in-hospital mortality after musculoskeletal tumor surgery: analysis of a national administrative database. J Bone Joint Surg Am. 2013;95(18):1684-91.
54. van der Heijden L, Piner SR, van de Sande MA. Pigmented villonodular synovitis: a crowdsourcing study of two hundred and seventy two patients. Int Orthop. 2016;40(12):2459-68.

55. Verspoor FG, Zee AA, Hannink G, van der Geest IC, Veth RP, Schreuder HW. Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. Rheumatology (Oxford). 2014;53(11):2063-70.
56. Hung M, Stuart AR, Higgins TF, Saltzman CL, Kubiak EN. Computerized Adaptive Testing Using the PROMIS Physical Function Item Bank Reduces Test Burden With Less Ceiling Effects Compared With the Short Musculoskeletal Function Assessment in Orthopaedic Trauma Patients. Journal of orthopaedic trauma. 2014;28(8):439-43.
57. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal of the American Geriatrics Society. 1991;39(2):142-8.
58. Demers C, McKelvie RS, Negassa A, Yusuf S, Investigators RPS. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. American heart journal. 2001;142(4):698-703.
59. Burton T, Ye X, Parker E, Bancroft T, Healey JH. Burden of Illness in Patients With Tenosynovial Giant Cell Tumors. ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 22nd Annual International Meeting; Boston, MA, USA2017.
60. Dale K, Smith HJ, Paus AC, Refsum SB. Dynamic MR-imaging in the diagnosis of pigmented villonodular synovitis of the knee. Scandinavian journal of rheumatology. 2000;29(5):336-9.
61. Barile A, Sabatini M, Iannessi F, Di Cesare E, Splendiani A, Calvisi V, et al. Pigmented villonodular synovitis (PVNS) of the knee joint: magnetic resonance imaging (MRI) using standard and dynamic paramagnetic contrast media. Report of 52 cases surgically and histologically controlled. La Radiologia medica. 2004;107(4):356-66.
62. Curry JM, Eubank TD, Roberts RD, Wang Y, Pore N, Maity A, et al. M-CSF signals through the MAPK/ERK pathway via Sp1 to induce VEGF production and induces angiogenesis in vivo. PloS one. 2008;3(10):e3405.
63. Nissen MJ, Boucher A, Brulhart L, Menetrey J, Gabay C. Efficacy of intra-articular bevacizumab for relapsing diffuse-type giant cell tumour. Ann Rheum Dis. 2014;73(5):947-8.
64. Amber IB, Clark BJ, Greene GS. Pigmented villonodular synovitis: dedicated PET imaging findings. BMJ case reports. 2013;2013.



chapter fifteen

SAMENVATTING

Summary in Dutch

(Nederlandse samenvatting)

Nederlandse samenvatting

Tenosynoviale reusceltumoren (*tenosynovial giant cell tumours,* TGCT) zijn zeldzame goedaardige tumoren. Deze aandoening werd voorheen *pigmented villonodular synovitis* (PVNS) genoemd. De tumoren ontstaan vanuit het synoviale membraan van een gewricht – het membraan dat de gewrichtsvloeistof aanmaakt, vanuit de peesschede of de slijmbeurs. Een TGCT kan gewrichtsklachten geven als pijn, zwelling, stijfheid of bewegingsbeperking in verschillende mate van ernst. Hierdoor kan de tumor een hoge morbiditeit veroorzaken in een relatief jonge, werkende populatie. Op grond van klinische en radiologische kenmerken worden twee typen onderscheiden: het gelokaliseerde type dat zich uit als een goed afgrensbare nodus, en het diffuse type dat lokaal invasief is. TGCT kan behandeld worden met een operatie, een medicijn in onderzoeksverband en eventueel aanvullend radiotherapie. Het is nog niet bekend welke behandeling het meest effectief is. Het vaststellen van de meest geschikte behandeling is uitdagend doordat de tumor zo zeldzaam is, patiënten erg van elkaar verschillen en elke behandeling andere nadelen (bijwerkingen, recidieven, complicaties) kent.

Het doel van dit proefschrift was de kennis te verbeteren van de pathofysiologie en het biologisch gedrag van TGCT, van het diagnostisch proces bij deze aandoening en van de kwaliteit van leven bij TGCT-patiënten, om betere behandelmethoden te vinden. Door bewustzijn te creëren en publiciteit te genereren, wordt bijgedragen aan de verbetering van de medische behandeling van TGCT. In dit proefschrift worden verscheidene kennishiaten gedicht op het gebied van de incidentie, histopathologische en hormonale karakteristieken, stratificatie van ziekte-ernst en ziektelast bij kinderen. Daarnaast zijn de langetermijneffecten van systemische doelgerichte therapie en de kwaliteit van leven na chirurgische behandeling onderzocht. Tenslotte wordt in dit proefschrift de grootst bekende, wereldwijde studie gepresenteerd met individuele data van patiënten met gelokaliseerde of diffuse TGCT.

Actuele incidentieberekeningen zijn noodzakelijk voor het diagnostisch proces. In **hoofdstuk 2** is het wereldwijde incidentiecijfer berekend voor TGCT in vingers en/of tenen, gelokaliseerde TGCT van de grote gewrichten, en voor diffuse TGCT. De tot nu toe gehanteerde TGCT-incidentie, gebaseerd op een provinciale Amerikaanse studie uit 1980, is 9,2 voor het gelokaliseerde type (inclusief vingers en tenen), en 1,8 per miljoen persoonsjaren voor het diffuse type (Myers 1980).

Door middel van het Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA) werden alle mogelijke TGCT-patiënten in Nederland geïdentificeerd, die in een periode van vijf jaar waren gediagnosticeerd. De diagnose werd geverifieerd op basis van de klinische data in de lokale ziekenhuizen. De Nederlandse incidentiecijfers zijn op basis van leeftijdsopbouw omgezet naar wereldwijde incidentiecijfers. De hiermee berekende incidentie is voor TGCT van vingers en tenen 29, voor het gelokaliseerde type van grote gewrichten 10, en voor het diffuse type 4 per miljoen persoonsjaren. In alle drie de groepen waren vrouwen oververtegenwoordigd en was de incidentie het hoogst in de leeftijdscategorie 40 tot 59 jaar. De knie was het vaakst aangedaan: bij 65% van de patiënten met gelokaliseerd type TGCT en bij 49% van de patiënten met diffuus type. Het aantal heroperaties vanwege een lokaal recidief was 9% bij gelokaliseerde en 23% bij diffuse TGCT. Vergeleken met de oorspronkelijke incidentiestudie uit Amerika, toont deze studie een 5 keer verhoogde incidentie voor gelokaliseerde type (vingers, tenen en grote gewrichten gecombineerd) en een 2,6 keer zo hoge incidentie voor diffuus type TGCT. Deze hogere incidentie zou verklaard kunnen worden door onze landelijke dekking en vanwege groeiende bekendheid met de ziekte.

Het onderzoek beschreven in **hoofdstuk 3** is gericht op de tegenstrijdigheid dat gelokaliseerd en diffuus type TGCT klinisch en radiologisch verschillend zijn, maar histopathologisch niet te onderscheiden zouden zijn. De belangrijkste stimulans voor tumorformatie in TGCT is een overvloedige expressie van de *Colony Stimulating Factor 1* (CSF1), veroorzaakt door een genetische translocatie. Deze studie onderzocht of er een correlatie bestond tussen de expressie en genetische herstructurering van CSF-1, en het biologisch gedrag en klinische uitkomst van beide TGCT-subtypes – waarbij klinische uitkomst werd gedefinieerd als lokaal recidief. Langs een continuüm van uitersten werden patiënten geselecteerd die niet eerder behandeld waren voor TGCT van hun knie en een follow-up van minstens 3 jaar hadden. Negen patiënten met gelokaliseerde (2 recidieven), 15 met diffuse TGCT (9 recidieven) en 4 patiënten met synovitis (als controle) werden geïncludeerd. De gemiddelde leeftijd was 43 (spreiding 6-71) jaar en 56% was vrouw. De combinatie van de technieken *CSF1*-split apart-FISH (*fluorescence in situ hybridization*) na mRNA-*in situ hybridization* bleek een diagnostisch hulpmiddel. Hiermee werd in 76% van de tumoren genetische herstructurering van CSF-1 gedetecteerd. Concluderend, er werd geen duidelijk verband gevonden tussen CSF1-expressie en CSF1-herstructurering met biologisch gedrag en klinische uitkomst.

Binnen het gelokaliseerde en diffuse type TGCT bestaat een grote verscheidenheid in ziekte-ernst. Daarom is in **hoofdstuk 4** een classificatie ontwikkeld gebaseerd op ziekte-uitgebreidheid, om te kunnen stratificeren tussen verschillende ziektestadia. Als eerste hebben experts parameters gedefinieerd om de uitgebreidheid van ziekte te beschrijven op basis van een MRI scan. Vier parameters kwamen vaker dan 20% voor op MRI, toonden goede overeenkomst binnen en tussen beoordelaars (kappa ≥0.66) en toonden een positieve correlatie met een lokaal recidief: 1. het TGCT-type, 2. betrokkenheid van het gewricht, 3. betrokkenheid van spier- of pees-weefsel; en 4. betrokkenheid van ligament(en). Vervolgens werd de *TGCT severity classificatie* voor grote gewrichten geconstrueerd. Op basis van hazard ratio's van de vier genoemde parameters, aflopend van hoog naar laag, werd een classificatie met vier onderscheidende ziektestadia gemaakt. De recidiefvrije overleving na 4 jaar (log rank p<0.0001) was 94% voor het *mild localized*-stadium, 88% voor *severe localized,* 59% voor *moderate diffuse* en 36% voor het *severe diffuse*-stadium. Met deze *TGCT severity classificatie* wordt zowel de arts als de patiënt geïnformeerd over ziekte-uitgebreidheid en het risico op een eerste, lokaal recidief na chirurgische behandeling. Deze classificatie kan bijdragen aan de identificatie van geschikte patiënten voor systemische doelgerichte therapie of voor trials met nieuwe medicijnen. Daarnaast kan het toepassen van deze classificatie, door de data meer objectiveerbaar te maken, de uitkomsten van wetenschappelijk onderzoek naar TGCT vergelijkbaarder maken.

Patiënten rapporteren een toename van TGCT-gerelateerde klachten tijdens zwangerschap, zowel bij polikliniekbezoeken als op online TGCT-patiëntenfora. Onze hypothese was dat dit veroorzaakt wordt door veranderingen in vrouwelijke geslachtshormonen. Geslachtshormonen (oestrogeen en progesteron) stijgen tijdens de zwangerschap. **Hoofdstuk 5** beschrijft het eerste onderzoek naar de invloed van vrouwelijke geslachtshormonen op symptomen van TGCT. Vijfenzestig procent van de onderzochte zwangeren rapporteerden middels een vragenlijst een toename van TGCT-gerelateerde symptomen, voornamelijk zwelling van het aangedane gewricht. De invloed van geslachtspecifieke hormonen en van de vrouwelijke vruchtbare leeftijdsfasen werden beoordeeld door het vergelijken van de recidiefvrije overleving tussen mannen en vrouwen, en tussen pre- en postmenopauzale vrouwen. Er werd geen verschil gevonden in recidiefvrije overleving voor geslacht (gelokaliseerd type TGCT (p=0.206 ≤50 jaar, p=0.935 >50 jaar; diffuse type (p=0.664 ≤50 jaar, p=0.140 >50 jaar)) en ook niet tussen pre- versus postmenopauzale vrouwen (gelokaliseerde

type (p=0.106); diffuse type (p=0.666)). Dit resultaat maakt een causale relatie tussen vrouwelijke geslachtshormonen en lokaal recidief erg onwaarschijnlijk. Daarnaast werd de oestrogeen- en progesteronreceptor status onderzocht in TGCT-weefsel van zowel het diffuse als gelokaliseerde type. Deze receptoren bleken afwezig. Dus ook op histopathologisch niveau werd geen verband gevonden tussen toename van vrouwelijke hormonen en de toename van de TGCT-gerelateerde klachten tijdens zwangerschap.

Medische publicaties over TGCT bij kinderen zijn zeldzaam: na onze systematische review blijkt slechts over 76 kinderen met TGCT gepubliceerd te zijn. In **hoofdstuk 6** worden de klinische kenmerken en beloop van TGCT bij kinderen vergeleken met die bij volwassenen. Daarnaast wordt de incidentie op de kinderleeftijd berekend. De gestandaardiseerde pediatrische TGCT-incidentie van grote gewrichten was 2,42 en 1,09 per miljoen persoonsjaren in respectievelijk gelokaliseerde en diffuse TGCT. In vier tertiaire sarcoom-centra in Nederland zijn 57 kinderen gediagnosticeerd en behandeld tussen 1995 en 2001. Gerapporteerde symptomen waren pijn, zwelling en beperkte bewegingsuitslag met een mediane duur van symptomen van 12 (range 1-72) maanden. Er was geen verschil tussen kinderen en volwassenen ten aanzien van geslacht, symptomen voor diagnose, gelokaliseerde of diffuse type, eerste behandeling, percentage lokaal recidief, follow-upstatus of follow-upduur. De 2.5 jaar recidiefvrije overleving na open resectie was vergelijkbaar tussen kinderen en volwassenen: respectievelijk 85% (95%CI 67%-100%) versus 89% (95%CI 83%-96%) bij het gelokaliseerde type (p=0.527) en respectievelijk 53% (95%CI 35%-79%) versus 56% (95%CI 49%-64%) bij het diffuse type (p=0.691). Ondanks de lage pediatrische incidentie zou TGCT in de differentiaaldiagnose moeten staan bij kinderen met langdurige zwelling van één gewricht. De kans op recidief-ziekte na chirurgische behandeling van deze aandoening is vergelijkbaar voor kinderen en volwassenen.

In **hoofdstuk 7** en **hoofdstuk 8** wordt de tot nu toe grootste serie patiënten beschreven met gelokaliseerd of diffuus type TGCT. Er werden 2169 patiënten geïncludeerd (941 gelokaliseerd, 1192 diffuus en 36 onbekend type) met histologisch bewezen TGCT van grote gewrichten, behandeld tussen 1990 en 2017 in één van de 31 deelnemende internationale sarcoomcentra.
Van de patiënten met gelokaliseerd type TGCT (**hoofdstuk 7**) was 62% vrouw, met een mediane leeftijd tijdens eerste behandeling van 39 jaar, en een mediane follow-up van 37 maanden. De

knie was aangedaan in 67% en de initiële behandeling in een tertiair centrum was open resectie in 71% van de patiënten. In totaal kreeg 13% van de patiënten een recidief, met een recidiefvrije overleving op 3, 5 en 10 jaar van respectievelijk 88%, 83% en 79%. De grootste risicofactor voor een lokaal recidief was het hebben van een eerder recidief (p<0.001). In 4% van alle chirurgisch behandelde patiënten met gelokaliseerde TGCT werd een complicatie geregistreerd. Initiële symptomen van pijn en zwelling verbeterden na chirurgische behandeling bij respectievelijk 71% en 85% van de patiënten. Wanneer alleen niet eerder behandelde patiënten werden geïncludeerd, werd een positieve associatie gevonden met een lokaal recidief bij een tumor grootte ≥5 cm (versus <5cm [HR 2.50(95%CI 1.32-4.74;p=0.005)]) en na behandeling met arthroscopie (versus open [HR 2.18(95%CI0.98-4.84;p=0.056)]). Deze associatie bleek zowel uit univariate als multivariate analyses. Het relatief lage complicatierisico en de goede functionele uitkomsten ondersteunen de keuze voor een open, complete resectie bij patiënten met een gelokaliseerde TGCT en een hoog risico op recidieven, met als doel recidiefpercentages verder te verlagen.

Van de patiënten met een diffuus type TGCT (**hoofdstuk 8**) was 58% vrouw, met een mediane leeftijd van 35 jaar en een mediane follow-up van 54 maanden. Het kniegewricht was aangedaan in 64%; en 53% van de patiënten onderging als initiële behandeling een *one-staged* open synovectomie in een tertiair centrum. In totaal kreeg 45% van de patiënten een lokaal recidief, met een recidiefvrije overleving op 3, 5 en 10 jaar van respectievelijk 62%, 55% en 40%. Het eerder hebben gehad van een recidief bleek de grootste risicofactor voor recidief van de ziekte (HR 3.5 95%CI 2.8-4.4, p<0.001), met een 5 jaar recidiefvrije overleving van 64% in niet eerder behandelde patiënten, vergeleken met 25% bij patiënten die elders behandeld waren en met een recidief naar een tertiair centrum werden verwezen. 12% van de patiënten had een complicatie als gevolg van de chirurgische behandeling. Initiële symptomen van pijn en zwelling verbeterden na operatie bij respectievelijk 59% en 72% van de patiënten. In een subgroepanalyse van niet eerder behandelde patiënten met TGCT in de knie, behandeld in een tertiair centrum, werd geen verband gevonden tussen het optreden van een lokaal recidief en de volgende factoren: geslacht, leeftijd (jonger dan 35 jaar of 35 en ouder) bot-betrokkenheid (wel of niet), chirurgische techniek (open of arthroscopisch) en tumor grootte (kleiner dan 5cm of 5cm en groter). Onze conclusie is dat een op zichzelf staande chirurgische behandeling niet langer de gouden standaard moet zijn, gezien het relatief hoge complicatierisico en het zeer hoge recidiefrisico, zeker in dit tijdperk

van multimodale therapieën. De onmogelijkheid van het uitvoeren van een radicale resectie van diffuse TGCT, verklaart waarschijnlijk het onacceptabel hoge recidief percentage na zowel open als arthroscopische resectie, zelfs in gespecialiseerde centra.

Hoofdstuk 9 beschrijft de lange termijneffecten van het gebruik van imatinib mesylaat, een niet-selectieve CSF1-remmer, bij patiënten met diffuus type TGCT. In totaal 62 patiënten uit 12 centra in Europa, Australië en de Verenigde Staten van Amerika gebruikten imatinib als behandeling. In deze groep waren 39 patiënten vrouw (63%), met een mediane leeftijd van 45 jaar ten tijde van de start van de behandeling en een mediane duur vanaf diagnose tot start van de behandeling van 3,5 jaar. De mediane follow-up vanaf start van de behandeling was 52 maanden. Vier patiënten met metastasen van TGCT werden geëxcludeerd uit de analyses wegens ernstige ziekteprogressie, ondanks behandeling met imatinib. Van de overgebleven 58 patiënten bereikten 17 gehele of gedeeltelijke respons (29%). De progressievrije overleving van de gehele groep na 1 en 5 jaar waren respectievelijk 71% en 48%. 38 patiënten stopten met gebruik van imatinib na 7 maanden (66%). Gerapporteerde bijwerkingen in 45 (78%) patiënten waren voornamelijk graad 1-2 (89%) (zoals oedeem (48%) en moeheid (50%)). Vijf patiënten ervaarden graad 3-4 toxiciteit, inclusief neutropenie, acute hepatitis, gezichtsoedeem, huidtoxiciteit en moeheid.
Deze studie bevestigt de werkzaamheid van een tyrosinekinaseremmer zoals imatinib in TGCT. Zelfs na staking van de behandeling werd effect gezien, echter met hoge percentages behandelonderbrekingen en additionele behandelingen (zoals operaties). Deze resultaten geven richting aan het effect van imatinib, met als beperking het retrospectieve studie karakter, het ontbreken van een controlegroep en het ontbreken van patiëntgerapporteerde uitkomstmaten.

Hoofdstuk 10 beschrijft een prospectieve cohortstudie naar gewrichtsfunctie en gezondheidgerelateerde kwaliteit van leven-uitkomsten na chirurgische behandeling, om de patiëntgerapporteerde uitkomstmaten te evalueren. In totaal 206 opeenvolgende patiënten met gelokaliseerd (N=108) en diffuus type (N=98) TGCT van grote gewrichten, behandeld met arthroscopische of open synovectomie in het Leids Universitair Medisch Centrum of Radboud Universitair Medisch Centrum, werden geïncludeerd. Patiënten rapporteerden middels het Short Form 36 (SF-36), de Visual Analogue Scale (VAS) en de Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Bij zowel gelokaliseerde als diffuse TGCT scoorden

de patiënten vooral op de fysieke component van de SF-36-subschalen significant en klinisch relevant slechter pre-operatief en direct postoperatief vergeleken met de algemene bevolking. Zes maanden na chirurgische behandeling verbeterden de SF-36 scores naar de gemiddelden van de algemene populatie; deze bleven de volgende jaren tamelijk stabiel. Mediane pijnscores, gemeten middels de VAS, vertoonden geen klinisch relevant verschil pre- of postoperatief, in geen van beide subtypes. Pijnbeleving verschilde enorm tussen patiënten en in de tijd. Gemiddelde functiescores (WOMAC) vertoonden in beide subtypes geen klinisch relevant verschil (effect size < MCID 20) pre- versus postoperatief. Echter, bij diffuse TGCT-patiënten toonden pijnscores en fysieke functiescores uit de WOMAC een trend richting verbetering pre- versus postoperatieve scores. Op alle drie de onderzochte schalen rapporteerden patiënten een significant betere gezondheidgerelateerde kwaliteit van leven na chirurgie voor hun TGCT, en een trend richting verbetering van gewrichtsfunctie.

In de grootst bekende TGCT-patiënten groep werd in **hoofdstuk 11** de impact van TGCT op het dagelijks leven onderzocht. De volgende aspecten werden geëvalueerd: fysieke functie, dagelijkse activiteiten, sociale participatie (werk, sport en hobby's) en gezondheidgerelateerde kwaliteit van leven. Een tweede doel was het definiëren van risicofactoren voor verslechterde uitkomsten bij TGCT, door middel van vier gevalideerde vragenlijsten: VAS worst pain and stiffness; Patient Reported Outcomes Measurement Information System for Physical Function (PROMIS-PF); SF-12 en EuroQoL (EQ-5D-5L). Gedurende zes maanden werden TGCT-patiënten uitgenodigd om de online vragenlijsten in te vullen. Patiënten werden verzocht om histologisch of radiologisch bewijs van TGCT te delen om ziekteaanwezigheid en TGCT-subtype te bevestigen. In totaal werden 337 vragenlijsten volledig ingevuld (32% met ziektebevestiging), door patiënten afkomstig uit 30 landen. De mediane leeftijd tijdens de diagnose was 33 (IQR 25-42) jaar, en de meerderheid was vrouw (80%) en had een tumor van het diffuse type (70%) in een van de onderste ledematen: knie (71%) en heup (10%). Het recidiefpercentage was 36% bij gelokaliseerde en 70% bij diffuse TGCT, van in totaal 299 patiënten met TGCT in een onderste extremiteit. Ruim 1 op de 10 patiënten was door de TGCT niet in staat om zijn of haar werk (volledig) uit te voeren (gelokaliseerde 13%, diffuse type 11%). Meer dan de helft van de patiënten was niet in staat om sportactiviteiten te beoefenen (gelokaliseerde type 58%; diffuse type 64%). In beide subtypes verminderden pijn en zwelling na een chirurgische behandeling, maar stijfheid en bewegingsbeperking namen toe. Littekenweefsel,

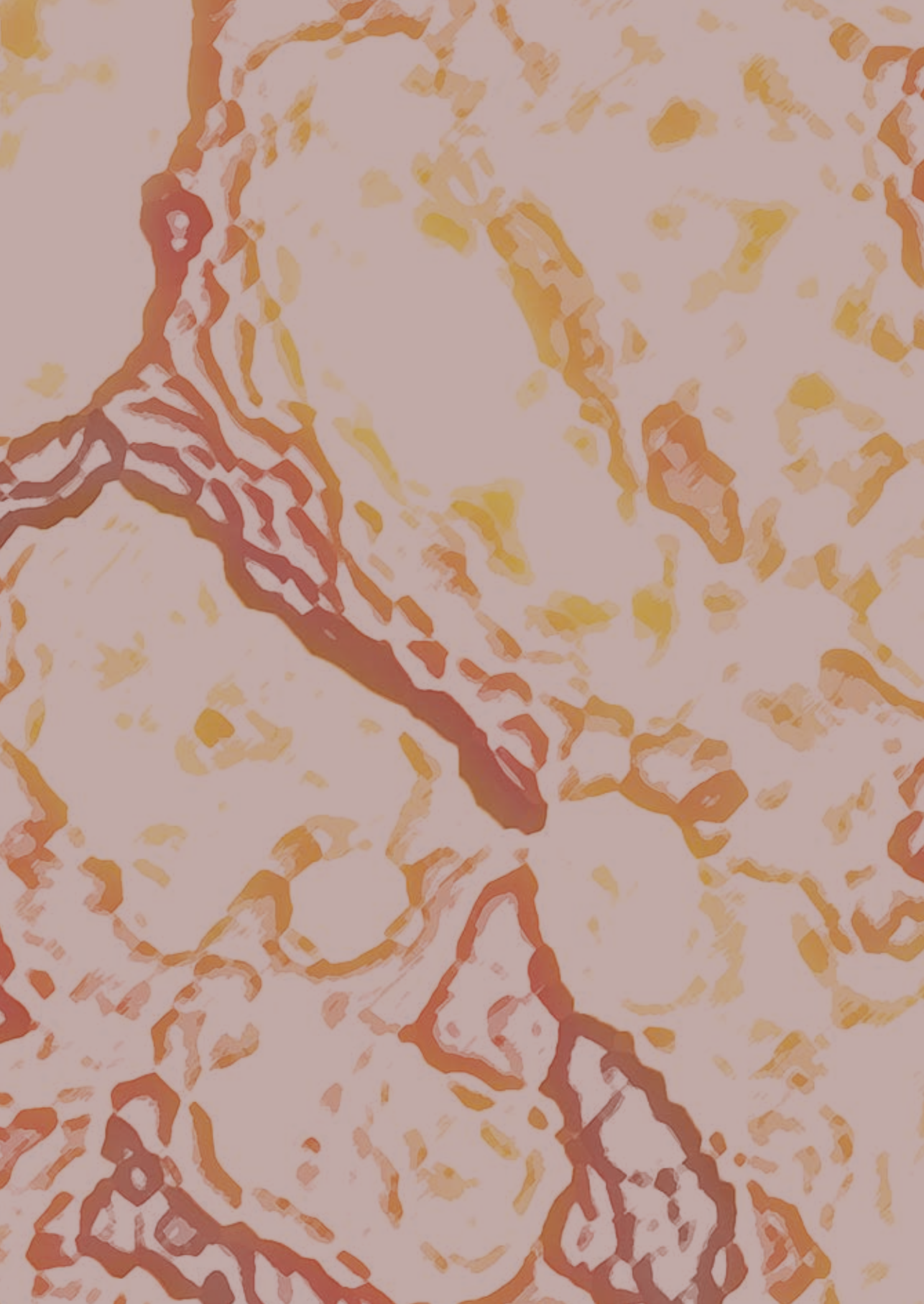
kraakbeenslijtage en verklevingen, veroorzaakt door (meerdere) chirurgische behandelingen, kunnen de toegenomen stijfheid en bewegingsbeperking verklaren. Vergeleken met de algemene Amerikaanse bevolking toonden alle patiënten een klinisch relevant lagere PROMIS-PF-scores, fysieke en mentale scores op de SF-12 en EQ-5D-5L-utiliteitscores. Wanneer het gelokaliseerde en het diffuse type met elkaar vergeleken worden, scoorden patiënten met het diffuse type bijna 0,5 standaarddeviatie lager op de PROMIS-PF ($p<0,001$), en 5% lager op de EQ-5D-5L ($p=0,03$). Bij patiënten met het gelokaliseerde type had de aanwezigheid van een recidief en 2 of meer operaties een negatieve invloed op de pijn- en stijfheidscores op de VAS, fysieke scores op SF-12 en EQ-5D-5L-scores ($p<0,05$). In diffuse-type resulteerde recidief ziekte in lagere VAS-pijn/stijfheid, PROMIS-PF, SF12 mentaal en EQ-5D-5L scores ($p<0,05$). In beide types scoorden patiënten met behandeling korter dan 1 jaar geleden significant lager op de fysieke component van de SF-12. Deze studie toont aan dat TGCT een grote impact heeft op het dagelijks leven in een relatief jonge werkende patiëntenpopulatie. Artsen en andere betrokken zorgverleners, bijvoorbeeld fysiotherapeuten, dienen zich ervan bewust te zijn dat TGCT-patiënten frequent een verminderde kwaliteit van leven en beperkingen in hun fysiek functioneren ervaren en dat ze gehinderd blijven in dagelijkse activiteiten zoals werk en sportactiviteiten, zelfs na behandeling(en).

Hoofdstuk 12 beschrijft een extreme, definitieve behandelingsmaatregel bij TGCT: een bovenbeenamputatie. Bij diffuse TGCT is er zeer vaak sprake van recidieven (tot wel 92% beschreven), die heroperaties en aanvullende behandelingen noodzakelijk maken. Als alle behandelingen falen of ernstige complicaties optreden, kan amputatie onvermijdelijk zijn. Dit hoofdstuk beschrijft vier ziektegeschiedenissen waarin een amputatie van het bovenbeen het laatste redmiddel bleek.

Concluderend, TGCT is een chronische ziekte met een grote impact op het dagelijks leven. Voor artsen is het uitdagend om de optimale gepersonaliseerde behandeling te bewerkstelligen, omdat TGCT patiënten erg van elkaar verschillen, trials met doelgerichte therapie nog gaande zijn en er geen gestandaardiseerd behandel algoritme bestaat. Als fundament en om verder te ontwikkelen wordt een behandel algoritme voorgesteld voor TGCT van alle grote gewrichten in **hoofdstuk 14**. Dit algoritme is gebaseerd op onze ervaring, de literatuur en *de TGCT severity classificatie* op MRI scans (**hoofdstuk 4**). Naast de fysieke en financiële last voor de patiënt zorgt TGCT ook voor

stijgende medische kosten na diagnose. Huidige ontwikkelingen zijn veelbelovend: groeiend bewustzijn, centralisatie van zorg, verscheidene doelgerichte therapie trials, evaluatie van gepersonaliseerde follow-up vragenlijsten en lopende prospectieve internationale samenwerking studies. Deze initiatieven moeten uitgebreid worden om nieuwe inzichten te krijgen in TGCT.

De discussie, klinische implicaties en toekomstperspectieven over het onderwerp van dit proefschrift worden besproken in **hoofdstuk 14**.



APPENDICES

chapter sixteen

list of publications

Scientific articles

Outcome of surgical treatment for patients with diffuse-type Tenosynovial Giant Cell Tumours
M.J.L. Mastboom, E. Palmerini, F.G.M. Verspoor, A.J. Rueten-Budde, S. Stacchiotti, E. Staals, G. Schaap, P.C. Jutte, W. Aston, H. Gelderblom, A. Leithner, D. Dammerer, A. Takeuchi, Q. Thio, X. Niu, J.S. Wunder, TGCT study group & M.A.J. van de Sande
Submitted

Surgical treatment of localized-type Tenosynovial Giant Cell tumours of large joints
M.J.L. Mastboom, E. Staals, F.G.M. Verspoor, A.J. Rueten-Budde, S. Stacchiotti, E. Palmerini, G. Schaap, P.C. Jutte, W. Aston, A. Leithner, D. Dammerer, A. Takeuchi, Q. Thio, X. Niu, J.S. Wunder, TGCT study group & M.A.J. van de Sande
Submitted

Can increased symptoms of Tenosynovial Giant Cell Tumours during pregnancy be explained by a change in female sex hormones?
M.J.L. Mastboom, F.G.M. Verspoor, R. Planje, H.W.B. Schreuder, M.A.J. van de Sande
Submitted

Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumour
M.J.L. Mastboom*, F.G.M. Verspoor*, G. Hannink, R.G. Maki, A. Wagner, E. Bompas, J. Desai, A. Italiano, B.M. Seddon, W.T.A. van der Graaf, J.Y. Blay, M. Brahmi, L. Eberst, S. Stacchiotti, O. Mir, M.A.J. van de Sande, H. Gelderblom, P.A. Cassier (*Shared first authorship)
Submitted

Outcome after 52 Salto Ankle prostheses implanted by a single surgeon
F.W.M. Faber, **M.J.L. Mastboom**, S.T. van Vliet-Koppert, I.C.E. Bouman, P.M. van Kampen
Adv Orthopedics. 2018 Aug;2735634 doi: 10.1155/2018/2735634

The effect of surgery in Tenosynovial Giant Cell Tumours as measured by patient reported outcomes on quality of life and joint function
M.J.L. Mastboom*, F.G.M. Verspoor*, G. Hannink, W.T.A. van der Graaf, M.A.J. van de Sande, H.W.B. Schreuder (*Shared first authorship)
Accepted in Bone Joint J

Does CSF1 over-expression or rearrangement influence biological behaviour in tenosynovial giant cell tumours of the knee?
M.J.L. Mastboom, D.M. Hoek, J.V.M.G. Bovée, M.A.J. van de Sande, K. Szuhai
Histopathology. 2018 Aug; doi: 10.1111/his.13744

Severity classification of Tenosynovial Giant Cell Tumours on MR imaging
M.J.L. Mastboom*, F.G.M. Verspoor*, D.F. Hanff, M.G.J. Gademan, P.D.S. Dijkstra, H.W.B. Schreuder, J.L. Bloem, R.J.P. van der Wal, M.A.J. van de Sande (*Shared first authorship)
Surg Oncol. 2018 Sept;27(3):544-550. doi.org/10.1016/j.suronc.2018.07.002

Incidence and Demographics of Giant Cell Tumor of Bone in The Netherlands: First Nationwide Pathology Registry Study
A.J. Verschoor, J.V.M.G. Bovée, **M.J.L. Mastboom**, P.D.S. Dijkstra, M.A.J. van de Sande, H. Gelderblom
Acta Orthop. 2018 Jul 10:1-5. doi: 10.1080/17453674.2018.1490987

Tenosynovial Giant Cell Tumors in Children: A Similar Entity Compared With Adults
M.J.L. Mastboom, F.G.M. Verspoor, D. Uittenbogaard, G.R. Schaap, P.C. Jutte, H.W.B. Schreuder, M.A.J. van de Sande
Clin Orthop Relat Res. 2018 Sept;476(9):1803-1812

The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life.
M.J.L. Mastboom, R. Planje, M.A.J. van de Sande
Interact J Med Res. 2018 Feb 23. doi: 10.2196/ijmr.9325

Treatments of Tenosynovial Giant Cell Tumors of the Temperomandibular joint -Report of three cases and a review of literature
F.G.M. Verspoor, **M.J.L. Mastboom**, W.L.J. Weijs, A.C. Koetsveld, H.W.B. Schreuder, U. Flucke
Int J of Oral Maxillofac Surg. 2018 april doi.org/10.1016/j.ijom.2018.04.001

Higher incidence rates than previously known in tenosynovial giant cell tumors.
Mastboom M.J.L., Verspoor, F.G.M., Verschoor A.J., Uittenbogaard D., Nemeth B., Mastboom W.J.B., Bovée J.V.M.G., Dijkstra P.D.S., Schreuder H.W.B., Gelderblom H., Sande van de M.A.J., TGCT study group.
Acta Orthop. 2017 Aug 8:1-8. doi: 10.1080/17453674.2017.1361126

Limb Amputation after Multiple Treatments of Tenosynovial Giant Cell Tumour: Series of 4 Dutch Cases.
Mastboom M.J.L., Verspoor F.G.M., Gelderblom H., van de Sande M.A.J.
Case Rep Orthop 2017 Jun 28. doi: 10.1155/2017/7402570

Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumour around the knee: a retrospective analysis of 30 patients.
van der Heijden L., **Mastboom M.J.L.**, Dijkstra P.D.S., van de Sande M.A.J.
Bone Joint J 2014 Aug;96-B(8):1111-8. doi: 10.1302/0301-620X.96B8.33608

Oral presentations

Tenosynovial Giant Cell Tumours: surgery or targeted therapy?
EMSOS 2018 Amsterdam, The Netherlands

Riskfactors in Tenosynovial Giant Cell Tumours
EMSOS 2018 Amsterdam, The Netherlands; BOOS 2018 Edinburgh, Scotland; MSTS 2018 NYC, USA; CTOS 2018 Rome, Italy

Role of CSF1 in Tenosynovial Giant Cell Tumours
EMSOS 2018 Amsterdam, The Netherlands; BOOS 2018 Edinburgh, Schotland

The patient perspective on the impact of Tenosynovial Giant Cell Tumors on daily living
EMSOS 2018 Amsterdam, The Netherlands

Severity classification of Tenosynovial Giant Cell Tumours on MR imaging
BOOS 2018 Edinburgh, Scotland; EMSOS 2017 Budapest, Hungary; CTOS 2017 Hawaii, USA

Tenosynovial Giant Cell Tumours affecting large joints in Children
ISOLS 2017 Kanazawa, Japan; EPOS 2018 Oslo, Norway

A nationwide study on Tenosynovial Giant Cell Tumours in the Netherlands
ISOLS 2017 Kanazawa, Japan; EMSOS 2017 Budapest, Hungary; NOV 2017 Den Bosch, The Netherlands

Preliminary results on the international multicenter retrospective Tenosynovial Giant Cell Tumour Study
EMSOS 2016 La Baule, France; MSTS 2016 Detroit, USA; CTOS 2016 Lisbon, Portugal

Tenosynovial Giant Cell Tumours Observational Platform Project (TOPP)
ESMO 2016 Copenhagen, Denmark

Heeft pre-operatief een 3T-MRI nut bij chronische polsklachten?
NOV 2015 Den Bosch, The Netherlands; scientific meeting LUMC, Leiden, The Netherlands

Functional outcome and quality of life after the surgical treatment for diffuse-type giant-cell tumours
ISOLS 2013, Bologna, Italy; ISCOMS 2013, Groningen, The Netherlands

Poster presentations

Prospective multicenter study in diffuse-type Tenosynovial Giant Cell Tumours
EMSOS 2018 Amsterdam, The Netherlands; ASCO 2018 Chicago, USA

Severity classification of Tenosynovial Giant Cell Tumours on MR imaging
MSTS 2018 NYS, USA

CSF1 over-expression and CSF1 split do not predict clinical outcome in Tenosynovial giant cell tumours
CTOS 2017 Hawaii, USA; MSTS 2018 NYC, USA; CTOS 2018 Rome, Italy

The effect of Tenosynovial Giant Cell Tumours on daily living; an online cross-sectional analysis of functionality and quality of life in 337 patients
CTOS 2017 Hawaii, USA

First results of the international multicenter retrospective Tenosynovial Giant Cell Tumour Study
ISOLS 2017 Kanazawa, Japan

Consider Tenosynovial Giant Cell Tumours in chronic mono-arthritis in children
EMSOS 2017 Budapest, Hungary

Limb amputation as a result of Tenosynovial Giant Cell Tumour
EMSOS 2016 La Baule, France

What is the use of 3T-MRI in chronic wrist complaints?
Haga scientific day and nurse evening 2015, The Hague + SEOHS 2015, Leiden, The Netherlands

Functional results and quality of life after open synovectomy for giant cell tumors of synovium in the knee
CTOS 2013 New York City, USA + EMSOS 2013 Gothenburg, Sweden

Awards and honors

Best Oral Talk award. *BOOS Edinburgh, Schotland, 2018*

Young Investigator award. *CTOS Hawaii, USA, 2017*

Nomination Best Paper award. *ISOLS Kanazawa, Japan, 2017*

Young Investigator award. *MSTS Detroit, USA, 2016*

acknowledgements

Met behulp van dit proefschrift hebben we een bijdrage kunnen leveren aan het verder ontrafelen van de mysteriën omtrent een ongelooflijk interessant ziektebeeld: tenosynoviale reusceltumoren. Veel dank aan alle nationale en internationale TGCT-patiënten die bereid zijn geweest hun persoonlijke ervaringen te delen, zowel op de poli, als op Facebook, als via hun artsen.

Dankzij de hulp, de adviezen en het geduld van velen, is dit proefschrift tot stand gekomen. Hiervoor wil ik onderstaande personen heel hartelijk bedanken:

Dr. M.A.J. van de Sande, ik voel me zeer vereerd om een van jouw eerste promovenda te mogen zijn. Jouw enthousiasme werkt zo aanstekelijk dat ik in een mum van tijd een recordaantal projecten was gestart, in samenwerking met verschillende afdelingen en ziekenhuizen. Gelukkig heb ik het merendeel, mede dankzij jouw volhardendheid, weten af te ronden. Jouw talent voor multi-tasken is bewonderenswaardig. Ik heb altijd kunnen rekenen op 100% toewijding en zeer snelle feedback. Dankzij jou heb ik het belang van (internationale) samenwerking ingezien en écht onderzoek leren doen. Bedankt voor de sturing en het vertrouwen en alle kansen in zowel binnen- en buitenland.

Prof. Dr. P.D.S. Dijkstra, inspirerend hoe jij kliniek en wetenschap weet te combineren en hoe de patiënt daarin altijd centraal staat. Bedankt voor je inzet en enthousiasme, de begeleiding van mijn wetenschappelijke carrière, de kritische noot zo nodig, het mentorschap en de deur die altijd openstaat.

Prof. Dr. H. Gelderblom, bedankt voor de introductie in de medische oncologie. Door de vrijheid en ruimte die ik kreeg, waarbij ik altijd binnen kon lopen voor een discussie, heb ik me verder kunnen ontplooien.

Prof. Dr. R.G.H.H. Nelissen en stafleden orthopaedie, bedankt voor alle mogelijkheden en kansen die ik heb gekregen op de afdeling orthopaedie, welke ik altijd graag met beide handen aangreep.

Prof. Dr. H.W.B. Schreuder, zonder de intensieve samenwerking met Nijmegen was dit boek niet half zo mooi geworden. Door onze samenwerking kwamen er veel gedegen studie-initiatieven, werden alle data verdubbeld, kritisch geëvalueerd en uiteindelijk afgerond middels een presentatie en publicatie. Bedankt voor deze solide basis.

Dr. F.G.M. Verspoor, dankzij onze power-samenwerking, duidelijke afspraken, heftige discussies en zorgvuldige werken zijn onze beider proefschriften naar een hoger niveau gebracht. Tijdens onze (langdurige) telefoongesprekken ontstonden altijd weer nieuwe initiatieven en ideeën of juist oplossingen voor bestaande problemen. Samen hebben wij bijgedragen aan het verder ontrafelen van deze interessante, soms ongrijpbare ziekte. Ik ben erg trots dat we dit samen hebben gedaan!

Alle collaborating centers, co-auteurs in binnen- en buitenland: veel dank. Door gedegen samenwerking wordt er steeds meer bekend over deze eerder zo ongrijpbare ziekte. Breaking borders! **Dear co-authors from all over the world**, thank you for your collaboration in our national and international studies: I greatly appreciate it.

Collegae van de C3 en later C2, zonder jullie relativeringsvermogen en humor was dit traject niet zo bruisend geweest!

Medische studenten Daniël, Rosa, Willemijn, Femke en Marijn, jullie enthousiasme en frisse blik hebben enorm bijgedragen aan dit proefschrift.

Secretaresses van de orthopaedie, Anika, Saskia en Marisa, altijd erg fijn dat jullie snel en adequaat regelen wat er geregeld moest worden.

Maartje en Britta, mijn keuze voor jullie als mijn paranimfen was snel gemaakt. Sinds de middelbare school zijn we een onafscheidelijk drietal, ook al zijn we soms duizenden kilometers van elkaar verwijderd. Ik hou niet van verrassingen, alleen van die van jullie!

Masque en QQ, vooral ProzaQQ, bedankt voor de betrokkenheid en zeer welkome afleiding.

Lieve Gerritje en Marieke: de leuksten, dat blijven we!

Marja en Romy, erg fijn om tegelijkertijd in 'hetzelfde schuitje' te zitten.

Lisanne, bedankt voor je niet aflatende interesse in mijn onderzoek en je inspirerende design skills: ik ben heel trots op de omslag en lay-out van dit proefschrift. Voor ons is geen berg te hoog ;)

Hardloopbuddy's, LUHV Currimus vooral Dave, Jan G, Jan vR, Bart en Chris, jullie geven me altijd veel energie.

Mam, bedankt voor je geduld en dat je altijd naar mijn nog-net-niet-affe presentaties wilde luisteren. **Pap**, bedankt voor je inhoudelijke discussies als ik vastgelopen was. **Elvire, Bas, Daphne en Joost**, verstand op nul is het allerleukst met jullie.

Liefste Leander, mijn altijd aanwezige steun en toeverlaat, naar jou gaat de meeste dank uit. Jouw robuuste vertrouwen in mij, geeft mij kracht en energie om hoge(re) doelen te bereiken. Jouw relativeringsvermogen heeft sterk bijgedragen aan de afronding van dit proefschrift en het feestelijke etentje bij iedere publicatie houden we erin. Wij samen zijn een super-team!

Alle anderen die op enigerlei wijze hebben bijgedragen aan de totstandkoming van dit proefschrift wil ik hiervoor hartelijk danken.

curriculum vitae

Monique Josephine Leonie Mastboom was born in Nijmegen on October 19th 1988 and grew up in a family of six in Enschede, The Netherlands. In 2004-2005 she spent a year as exchange student in Bloomfield Hills, Michigan, USA, where she played ice-hockey and ran cross-country in the varsity team. Two years after high school graduation in the USA, she also graduated from VWO profile nature & health at Bonhoeffer college, Enschede. In that same year she started medical school in the LUMC, Leiden. In 2008 she founded the Leids Universitaire Hardloopvereniging (LUHV) Currimus, with which she organized and attended multiple relay races and cross-country tournaments. Between 2009 and 2010 joined the board of the Enige Leidse Commissie Introductie Dagen (EL CID), to organize the introduction week for new students. While joining several medical missions in the Amazon jungle of Peru in 2011, she assisted during large traumatic, orthopaedic and reconstructive surgeries and her interest in the functioning of the musculoskeletal system was enlarged.

After graduating from Medical School, she started working as ANIOS Orthopaedics in the Haga Hospital, The Hague. In 2016 her research internship on Tenosynovial Giant Cell Tumours at the department of Orthopaedic Surgery at the LUMC, Leiden was started. During this internship she visited 95 hospitals in The Netherlands for an incidence calculation study, collaborated with the other three Dutch orthopaedic oncologic centres (Prof. Dr. H.W.B. Schreuder, Drs. F.G.M. Verspoor, Dr. G.R. Schaap, Dr. P.C. Jutte), collaborated with 30 international sarcoma centres and worked together with seven different departments in the LUMC. This research resulted in a series of translational, clinical and multicentre studies that formed the base of this PhD-thesis (Prof. Dr. P.D.S. Dijkstra, Prof. Dr. A.J. Gelderblom, Dr. M.A.J. van de Sande). Most studies were presented at international scientific meetings, awarded at the annual MSTS conference in Detroit 2016 with the young investigator award, at the bi-annual ISOLS conference in Kanazawa 2017 with a nomination for the best paper award, at the annual CTOS conference in Hawaii 2017 with the young investigator award and at the annual BOOS conference in Edinburgh 2018 with the best oral talk award. Monique will continue her orthopaedic career in Regionale Opleiding Groep Orthopaedie Oost.

During her medical training and research internship she ran four marathons (New York 2013, Tokyo 2015, Valencia 2015, Amsterdam 2017) and three running climbs during the Alpe d'HuZes (2017). Monique lives together with Leander Lignac in Amsterdam. They are expecting their first child in February 2019.

Although it's rare, it still needs care !