The effect of imatinib mesylate in diffuse-type tenosynovial giant cell tumours on MR imaging and PET-CT

Mastboom, M.J.L.; Lips, W.; Langevelde, K. van; Mifsud, M.; Ng, C.; McCarthy, C.L.; ... ; Sande, M.A.J. van de

Surgical Oncology 35 (2020) 261–267

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: http://www.elsevier.com/locate/suronc

The effect of Imatinib Mesylate in diffuse-type Tenosynovial Giant Cell Tumours on MR imaging and PET-CT

M.J.L. Mastboom [a,*], W. Lips [a], K. van Langevelde [b], M. Mifsud [c], C. Ng [c], C.L. McCarthy [b], N. A. Athanasou [d], C.L.M.H. Gibbons [e,1], M.A.J. van de Sande [a,1]

[a] Orthopaedics Oncology, Leiden University Medical Centre, Leiden, the Netherlands
[b] Radiology, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, United Kingdom
[c] Orthopaedic Department, Mater Dei Hospital, Triq Dun Karm, Msida, Malta
[d] Histopathology, NDORMS, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, United Kingdom
[e] Orthopaedics Oncology, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, United Kingdom

ARTICLE INFO

Keywords:
Tenosynovial giant cell tumour
Imatinib mesylate
Radiological response

ABSTRACT

Introduction: Recurrence rates remain high after surgical treatment of diffuse-type Tenosynovial Giant Cell Tumour (TGCT). Imatinib Mesylate (IM) blocks Colony Stimulating Factor1 Receptor (CSF1R), the driver mechanism in TGCT. The aim of this study was to determine if IM reduces the tumour metabolic activity evaluated by PET-CT and to compare this response with the response seen on MR imaging.

Materials and methods: 25 Consecutive patients treated with IM (off label use) for locally advanced (N = 12) or recurrent (N = 13) diffuse-type TGCT were included, 15 male and median age at diagnosis 39 (IQR 31–47) years. The knee was most frequently affected (n = 16; 64%). The effect of IM was assessed pre- and post-IM treatment by comparing MR scans and PET-CT. MR scans were assessed by Tumour Volume Score (TVS), an estimation of the tumour volume as a percentage of the total synovial cavity. PET-CT scans were evaluated based on maximum standardized uptake value (SUV-max). Partial response was defined as more than 50% tumour reduction with TVS and a decrease of at least 30% on SUV-max.

Results: Median duration of IM treatment was 7.0 (IQR 4.2–11.5) months. Twenty patients (80%) discontinued IM treatment for poor response or intended surgery. Twenty patients experienced an adverse event grade 1–2, three patients grade 3 (creatinine increment, neutropenic sepsis, liver dysfunction). MR assessment of all joints showed 32% (6/19) partial response and 63% (12/19) stable disease, with a mean difference of 12% (P = 0.467; CI -22.4-46.0) TVS between pre- and post-IM and a significant mean difference of 23% (P = 0.021; CI 4.2–21.6) in all knee lesions. PET-CT, all joints, showed a significantly decreased mean difference of 5.3 (P = 0.004; CI 1.9–8.7) SUV-max between pre- and post-IM treatment (58% (11/19) partial response, 37% (7/19) stable disease). No correlation between MR imaging and PET-CT could be appreciated in 15 patients with complete radiological data.

Conclusion: This study confirms the moderate radiological response of IM in diffuse-type TGCT. PET-CT is a valuable additional diagnostic tool to quantify response to tyrosine kinase inhibitor treatment. Its value should be assessed further to validate its efficacy in the objective measurement of biological response in targeted systemic treatment of TGCT.

1. Introduction

Tenosynovial Giant Cell Tumour (TGCT), previously known as Pigmented Villo-Nodular Synovitis (PVNS), is a rare mono-articular tumour affecting the synovium, bursae and tendon sheath. TGCT is characterized by a chromosomal translocation (t (1; 2)), causing an

* Corresponding author.
E-mail addresses: mjlmastboom@lumc.nl (M.J.L. Mastboom), willemijn.lips@gmail.com (W. Lips), kirstenvanlangevelde@gmail.com (K. van Langevelde), maxmif@gmail.com (M. Mifsud), coljng@gmail.com (C. Ng), catherine.mccarthy@ouh.nhs.uk (C.L. McCarthy), nick.athanasou@ouh.nhs.uk (N.A. Athanasou), max.gibbons@ouh.nhs.uk (C.L.M.H. Gibbons), majvandesande@lumc.nl (M.A.J. van de Sande).
[1] Authors attributed equally.

https://doi.org/10.1016/j.suronc.2020.08.030
Received 25 April 2020; Received in revised form 19 August 2020; Accepted 23 August 2020
Available online 26 August 2020

overexpression of colony stimulating factor-1 (CSF1). This overexpression leads to recruitment of macrophages expressing the CSF1 receptor (CSF1R) that make up the majority of the tumour [1]. Histopathologically, villous thickening of the synovial membrane with infiltrates of scattered giant cells and haemosiderin containing macrophages in the subintima and extracellular haemosiderin deposition as well are seen. Occasionally, lymphocytes and plasma cells are present [2,3].

TGCT is differentiated into two types: the localized-type and the diffuse-type. Localized lesions are located in one area of the joint, sharply demarcated and show a non-aggressive behaviour. The current study focuses on diffuse-type TGCT. This subtype can affect the entire joint, extending both intra- and extra-articular, is ill-demarcated and shows a locally aggressive behaviour. It can invade surrounding structures, such as cartilage, bone, tendon or muscle [2,3]. This rare disease, with an estimated worldwide incidence rate of 4 per million person-years, most often affects the knee joint (64%) [4]. Patients present with unspecific symptoms such as joint pain, swelling, stiffness and limited range of motion. As these symptoms can cause a great quality of life burden by limitation of employment and sport-activities [5,6], treatment of this locally aggressive tumour might be required.

Diagnosing and staging the extension of TGCT is assessed on MR imaging and can be quantified by the Tumour Volume Score (TVS). PET-CT provides understanding of the metabolic activity of the lesion, expressed as maximum Standardized Uptake Values (SUV-max). So far, only little is known on the role of TVS on MR imaging and biological activity on PET-CT in the evaluation of TGCT with regards to response to treatment [7].

The current standard treatment for diffuse-type TGCT is a surgical excision, either by an arthroscopic- or open synovectomy. Recurrence rates remain high, with a recurrence free survival at 5 years of 54% after arthroscopic- and 66% after open-synovectomy in patients with therapy naïve diffuse-TGCT [8,9]. Radiotherapy is infrequently used in locally advanced or recurrent cases as an adjuvant therapy after surgical treatment. Arthroplasty may be indicated in joint destruction or due to secondary osteoarthritis of the TGCT lesion [10]. These locally aggressive treatments might induce a great quality of life burden, due to debilitating functional results. Therefore, systemic therapies are considered a valuable addition to the treatment armamentarium, typically targeting the CSF1/CSF1R axis [11].

Imatinib Mesylate (IM) blocks the driver mechanism in TGCT: the CSF1-receptor, also known as a tyrosine kinase inhibitor (TKI) [12,13]. Blay et al. presented a complete response in treatment with IM of a single case of recurrent TGCT [14]. Cassier et al. confirmed moderate activity of IM by evaluating MR images in a retrospective study of 29 TGCT patients of which 19% had a partial response and 74% a stable disease [15]. Stacchiotti et al. reported two diffuse-type TGCT patients without significant response after treatment with Nilotinib (another CSF1R inhibitor). Subsequently these patients were treated with IM and both patients had symptomatic improvement including decrease in tumour size assessed on MR imaging. One patient showed biological response on IM by PET-CT over 6 weeks [16]. Verspoor et al. evaluated 58 international patients with advanced diffuse-TGCT, of which 17 (29%) achieved complete (N = 2) or partial response (N = 15). One- and five-year progression-free survival rates were 71% and 48%, respectively [17]. Currently, in the treatment of diffuse-type TGCT, both nilotinib and imatinib are in off-label use only and no randomised phase 3 trial has been performed. On the contrary, pexidartinib, a more potent small molecule tyrosine-kinase inhibitor with strong selective activity against the CSF1 receptor, has been approved for diffuse-type TGCT by the FDA in the USA, after a placebo controlled trial [18].

This retrospective study of patients with diffuse-type TGCT aims to determine if IM reduces the tumour metabolic activity evaluated on PET-CT and to compare this response to the volumetric response measured by TVS on MR imaging.

2. Methods

Twenty-five consecutive diffuse-type TGCT patients treated with IM at the Nuffield Orthopaedic Centre in Oxford were retrospectively gathered and included. Patients were treated between June 2010 and October 2018 in an off-label setting with IM. In order to create a homogeneous patient group, the inclusion criteria were histopathologically confirmed diagnosis of diffuse-type TGCT of large joints (excluding digits) and treatment with IM. Patients without MR scans (N = 5) and PET-CT scans (N = 6) before and after IM treatment were excluded for that part.

Baseline-data were collected from medical records consisting of age at diagnosis, gender, comorbidities, tumour location, clinical status at the beginning of treatment (locally advanced tumour or recurrent disease), all tumour treatments (IM, arthroscopic- or open-synovectomy, prosthesis, radiotherapy or other systemic therapy treatments) and accompanying pathology reports. Additional data were collected regarding IM treatment: duration of treatment, dosage, reason for stopping and adverse events.

2.1. Histopathology

The pre-treatment clinical diagnosis of TGCT was confirmed by synovial biopsy histologically in all patients. Morphological features of post-treatment synovial specimens from five randomly chosen cases were analysed and compared with pre-treatment biopsies, with particular attention given to the extent of macrophage infiltration, presence of giant cells and other inflammatory elements (lymphocytes, plasma cells and lymphoid aggregates), haemosiderin deposits, fibrosis and other matrix changes in synovial tissues.

2.2. MR imaging

Pre- and post-IM treatment MR scans were reviewed by two experienced musculoskeletal radiologists (KL, CLMC). Scoring of the most senior radiologist (CLMC) was leading in non-numerical scorings. MR scans were assessed for articular, ligamentous, muscular and tendinous tissue involvement. Of note, for the knee cases, tumour within a Baker's cyst was not considered as encasement of a tendon (as there is a synovial connection between the joint space and the cyst). Based on the TGCT severity classification the tumours were categorized as either moderate or severe diffuse. The TGCT severity classification informs physicians and patients on disease extent and risk for recurrence after surgical treatment. Moderate diffuse is defined as diffuse-type with intra- and/or extraarticular disease without involvement of muscular/tendinous tissue/ligaments, with a recurrence free survival at 4 years of 59%. Severe diffuse includes intra- and extra-articular involvement and involvement of at least one of the three structures: muscular/tendinous tissue/ligaments) and a recurrence free survival at 4 years of 36% [19].

The extent of the tumour lesion was quantified by the Tumour Volume Score (TVS), an estimation of the tumour volume as a percentage of the total synovial cavity [20]. TVS of each MR scan was estimated as 10% increments of the estimated volume of the maximally distended synovial cavity involved. To illustrate, a score of 6 was defined as 60% increment of the volume of the maximally distended synovial cavity and a score of 20 described a tumour volume twice the proportion of the maximally distended synovial cavity. In this study, the average TVS scoring of both radiologists was presented. A partial response was defined as a decrease of 50% or more in TVS. An increase of 30% or more described a progressive disease. Thus, all differences between the aforementioned thresholds represented a stable disease [20].

2.3. PET-CT

The response of TGCT on IM was assessed by 18F FDG-PET-CT. The response was quantitatively evaluated by comparing the tumour

metabolic activity before and after IM treatment, measured by the maximum standardized uptake value (SUV-max) [21]. SUV-max was calculated based on the drawn region of interest in the tumour. PET-CT scan evaluations were performed by experienced nuclear medicine doctors of the Nuffield Orthopaedic Centre and collected from patient files. A decrease of SUV-max of 30% was regarded as partial PET response [22].

2.4. Statistical analysis

Analyses of all data were performed at the Leiden University Medical Centre. Descriptive data were analysed as counts and percentages for qualitative variables and medians with ranges for continuous variables. Differences between pre- and post-treatment were tested with a paired *t*-test. As the MR assessment was performed by two radiologists, the mean value of continuous variables was used for the analyses. Analyses were performed using Statistical Package for Social Statistics (SPSS) version 23.

2.5. Ethics

This study was approved by the institutional review board from the Leiden University Medical Center (medical ethical approved protocol P13.029), along with an approved addendum on October 1st, 2018.

3. Results

25 Diffuse-TGCT patients were included in this study (Table 1). Median age at diagnosis was 39.0 (IQR 31.1–47.2) years. 15 patients (60%) were male and in 16 patients (64%) TGCT was located in the knee. Nine patients suffered from comorbidities, including sarcoid, hepatitis B, tubulocystic carcinoma, hypothyroidism, paraproteinemia, polycystic kidney, renal dysfunction and migraine. Arthroscopic partial synovectomy was most often performed as treatment before start IM treatment (n = 16; 64%) and six patients did not have any previous treatments.

Table 1
Demographics.

Characteristics	N (%)	Median	IQR
Total	25 (100)		
Age at diagnosis (years)		39.0	31.1–47.2
Gender			
Male	15 (60)		
Female	10 (40)		
Comorbidities			
No comorbidities	16 (64)		
Comorbidity[a]	9 (36)		
Tumour location			
Knee	16 (64)		
Ankle	4 (16)		
Hip	3 (12)		
Wrist	1 (4)		
Elbow	1 (4)		
Clinical status tumour before IM treatment			
Locally advanced	12 (48)		
Recurrent disease	13 (52)		
Number of previous tumour treatments			
No previous treatments	6 (24)		
1	11 (44)		
2	6 (24)		
≥3	2 (8)		
Type of previous tumour treatments			
Arthroscopic synovectomy	16		
Open synovectomy	10		
(Tumour)Prosthesis	2		
Radiotherapy	1		
Other[b]	1		

[a] Two patients suffered from sarcoid. Other comorbidities were hepatitis B, tubulocystic carcinoma, hypothyroidism, paraproteinemia, polycystic kidney, renal dysfunction and migraine.
[b] Exploration of ankle, methotrexate (psoriatic arthropathy).

3.1. Treatment

The majority of patients (N = 21; 84%)) were treated with 400 mg IM daily. Median treatment duration was 7.0 months (IQR 4.2–11.5). 20 patients discontinued IM treatment of whom 16 had additional surgery (64%). Although only three patients discontinued as a result of treatment toxicity, 20 patients (80%) suffered from adverse events, mostly from grade 1 diarrhoea (N = 9; 36%) and grade 1 nausea (N = 9; 36%). 3 patients had grade 3 adverse events, consisting of creatinine increment, neutropenic sepsis and liver dysfunction (Fig. 4: patient 9, 13 and 19). 17 patients (68%) underwent subsequent treatment, of which 7 patients (28%) had multiple subsequent treatments (Table 2, Fig. 4).

3.2. Histopathology

The major difference noted between pre-treatment and post-treatment synovial specimens was a more pronounced lymphoid infiltrate in the subintima. There were scattered lymphocytes, occasional plasma cells and prominent lymphoid aggregates in most cases. Marked

Table 2
Imatinib Mesylate specifics.

Specifics	N (%)	Median	IQR
Dose (mg daily)			
400[a]	21 (84)		
200	2 (8)		
300	1 (4)		
100	1 (4)		
Duration IM treatment (months)		7.0	4.2–11.5
Reason for stopping IM treatment [b]			
Did not stop IM treatment	5 (20)		
Surgery	16 (64)		
No improvement	3 (12)		
Physicians decision	3 (12)		
Toxicity	3 (12)		
Progression of symptoms	1 (4)		
Adverse events			
No adverse events	5 (20)		
Diarrhoea	9 (36)		
Nausea	9 (36)		
Headache	5 (20)		
Fatigue	5 (20)		
Periorbital oedema	4 (16)		
Fluid retention	4 (16)		
Creatinine increment[c]	3 (12)		
Other[d,e]	7 (28)		
Number of subsequent surgeries/treatments per patient			
No subsequent surgery/treatment	8 (32)		
1	10 (40)		
2	5 (20)		
3	2 (8)		
First type of subsequent surgery/treatment			
Open synovectomy	4 (16)		
Arthroscopic synovectomy	4 (16)		
(Tumour)Prosthesis	4 (16)		
Other anti-CSF1 receptor antibody	1 (4)		
Unspecified surgical resection[f]	12 (48)		

[a] In 3 patients the dose was changed from 400 mg daily to 200 mg daily after 1 month, 6 months, and 7 years. In the table, these patients are included in 400 mg daily.
[b] 5 patients had multiple reasons for stopping treatment.
[c] 1 Patient had adverse event grade 3 creatinine increment.
[d] Other adverse event grade 1–2 were widespread depigmentation, neutropenia, mild peripheral paraesthesia in fingers and toes, and cramping in calves.
[e] 2 Patients experienced adverse event grade 3: neutropenic sepsis and liver dysfunction.
[f] Type of surgery, arthroscopic or open resection, was not specified.

degenerative change within subintimal connective tissue was noted in three cases and prominent areas of fibrosis seen in two cases; in these cases the peripheral extent of the lesion was more evident, facilitating surgical resection. There was no marked difference in the extent of the macrophage infiltrate, the number of giant cells or the extent of hemosiderin deposition pre-versus post-IM treatment.

3.3. MR imaging

20 patients were eligible for MR assessment. Four patients were excluded as no pre- or post-treatment MR scan was available and one patient was excluded because the post-treatment MR scan was not of diagnostic quality due to severe metal artefacts of a total knee replacement.

Before IM-treatment, 19 patients (95%), of which 12 knee lesions (60%), suffered from severe diffuse TGCT and 1 patient (5%) from moderate diffuse TGCT with an ankle lesion, according to the TGCT severity classification (Supplementary Material Table 1). In the knee lesions, most involved muscle, tendon and ligament were popliteus muscle (N = 10; 83%), lateral head of gastrocnemius tendon (N = 12; 100%) and PCL (N = 11; 92%). Mean time between pre- and post-treatment imaging was 431 days and median time was 287 days. 19 patients were eligible for TVS assessment, as one patient was not assessable due to only extra-articular TGCT involvement.

TVS assessment showed a mean difference between pre- and post-IM of 11.8% (P = 0.467; CI -22.4 - 46.0) for all joints and a significant mean difference of 22.9% (P = 0.021; CI 4.2–21.6) for knee lesions (Table 3, Fig. 1). 12 of 19 patients with severe diffuse-type TGCT, all joints, had stable disease (63%), 6 patients (32%) partial response and one patient (5%) progressive disease.

Regarding TGCT lesions in the knee, 10 (83%) and 8 (67%) lesions were located anterior and posterior from the posterior cruciate ligament (PCL) pre-treatment, respectively (supplementary material, Table 2). Craniocaudal direction (CC) and anteroposterior direction (AP) measurements (mm) of lesions located in the knee in the suprapatellar recess, posterior Hoffa's fat pad and posterior joint space presented mean differences between pre- and post-treatment of 11.3 (P = 0.11; CI -2.9-25.5), 6.4 (P = 0.014; CI 1.6, 11.2), and 8.5 (P < 0.001; CI 5.4, 11.6), respectively (Supplementary Material Table 3).

3.4. PET-CT

19 patients were eligible for evaluation by PET-CT. 6 patients were excluded for PET-CT evaluation, because of missing PET-scans pre- or post-IM treatment. Mean time between pre- and post-treatment imaging was 164 days and median time 124 days. A significant difference was found in all joints, (P = 0.004; CI 1.9–8.7) between mean SUV-max before IM-treatment (14.0) and mean SUV-max after treatment (8.7). 11 Patients (58%) had partial response, 7 patients (37%) had stable disease and 1 patient had progressive disease (Table 4, Fig. 2, Fig. 3, Fig. 4).

3.5. MR imaging versus PET-CT

MR scans were performed earlier on in the diagnostic process, compared to PET-CT. The mean time difference between pre-treatment MR scan and pre-treatment PET-CT was 126 days and the median time difference was 72 days. The mean time difference between post-treatment MR scan and post-treatment PET-CT was 271 days and the median time difference was 134 days. 15 Patients (nine knee lesions) had complete radiological data (4 scans in total): pre-IM and post-IM treatment MR scans and PET-CT scans. One patient showed progressive disease on both post-treatment MR imaging and PET-CT, two patients revealed stable disease on both images and four patients partial response. On the contrary, two patients were assessed with stable disease on PET-CT, but partial response on MR imaging and six patients were evaluated as stable disease on MR imaging, but partial response on PET-CT (Tables 5 and 6).

Table 3
TVS of pre- and post-IM treatment of knee lesions, other joints and all joints.

	N	Pre-treatment		Post-treatment		*p*	Df
		Mean	SD	Mean	SD		
TVS knee	12	5.9	4.5	3.6	3.4	0.021	2.3
TVS other joints	7	50.7	14.0	51.4	16.3	0.87	0.7
TVS all joints	19	22.4	23.9	21.2	25.6	0.476	1.2

Df Degrees of freedom.

4. Discussion

This is the first study to use PET-CT in the assessment of biological response in systemic therapy in diffuse-type Tenosynovial Giant Cell Tumour (TGCT). PET-CT is a reliable diagnostic tool to quantify TGCT. This retrospective cohort study confirms the efficacy of Imatinib Mesylate (IM) with a significant difference in SUV-max on PET-CT between pre- and post-IM treatment. MR assessment of TVS between pre- and post-IM also showed a significant mean difference for all knee lesions. The majority of patients discontinued treatment for intended surgery or poor response and three patients experienced grade 3 adverse events.

The moderate activity of IM, a tyrosine kinase inhibitor (TKI), in TGCT has been confirmed in the retrospective study of Cassier et al. This study, based on 29 diffuse-TGCT patients and estimated median time on IM of 4–7 months, presented 19% with a partial response and 74% with stable disease, according to Response Evaluation Criteria In Solid Tumours (RECIST) evaluated on MR imaging, after median follow-up of 11 months[15]. Subsequently, Verspoor et al. also confirmed efficacy of IM in diffuse-TGCT in 29% of 58 evaluable patients with complete or partial response, after median follow-up of 52 months. This study also showed a high percentage of discontinuation of treatment (66%) and a high grade of adverse events: 5 patients experiencing grade 3–4 toxicities [17]. The current study confirms that the use of (neo)adjuvant tyrosine kinase inhibitor may present an additional treatment option in TGCT. (Planned) surgery was performed after IM treatment due to remaining symptoms (with or without effect of IM) or extensive disease, even with a positive response to IM. Histologically, prominent degenerative change and fibrosis in the subintima was noted in several cases, facilitating surgical excision of the lesion. It is of interest that our results show that IM treatment did not appear to decrease markedly the macrophage infiltrate but did promote the lymphoid response in TGCT; IM has similarly been shown to influence the extent and nature of the T lymphocyte infiltrate in GIST [23].

The orally administered, systemic treatment with IM is not without unwanted side effects. 80% of the included patients in our study experienced one or more adverse event(s), as diarrhoea, nausea, headache, fatigue, periorbital oedema, fluid retention or creatinine increment. Three patients experienced grade 3 adverse events: creatinine increment, neutropenic sepsis and liver dysfunction. This might explain the relatively high rate of cessation of IM. The Data Monitoring Committee of the multinational, randomised, phase 3 trial (ENLIVEN), evaluating pexidartinib in patients with symptomatic TGCT, stopped patient enrolment before reaching the targeted sample size, due to the emergence of mixed and cholestatic hepatotoxicity [18]. Since TGCT is considered a benign disease, adverse events might be less accepted. In the optimisation of systemic treatment in diffuse-TGCT, understanding, monitoring and managing adverse effects is of utmost importance.

An MR scan is the current standard in diagnosing and staging diffuse-TGCT. However, the use of targeted TKI therapies is fairly new in the treatment of diffuse-TGCT. Therein, the question arises if performing an additional PET-CT scan is of additional value, especially given the young age of patients with TGCT and the associated radiation dose. MR evaluation with TVS assessment is based on estimations of the tumour

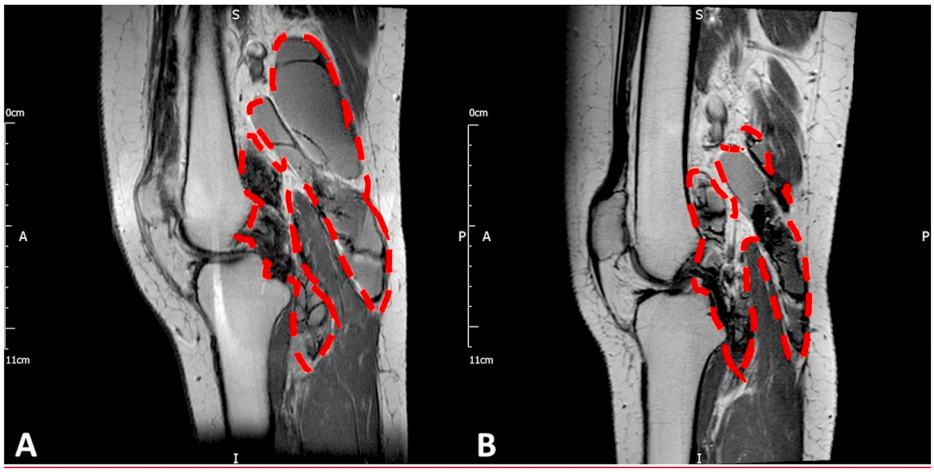

Fig. 1. Sagittal T1-weighted MR images of a patient with diffuse-TGCT of the right knee, corresponding with patient 11 in Fig. 4. The dashed red line outlines the posterior knee joint synovial cavity, only a part of this volume is tumour (the hypointense component). A) Pre-treatment MR scan showing diffuse low signal intensity tumour posterior of the posterior cruciate ligament and extending along the distal femoral metaphysis posteriorly and inside the Baker's cyst. B) MR scan after 18 months of IM-treatment with decreased tumour bulk. In addition, the amount of fluid in the popliteal cyst has decreased.
Note that the tumou
r volume score (TVS) is based on all the slices through the entire synovial cavity and not just the areas depicted in the single mid-sagittal slices [20]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
SUV-max in knee lesions, other joints and all joints of pre- and post-IM treatment.

	N	Pre-treatment		Post-treatment		*p*	Df
		Mean	SD	Mean	SD		
SUV-max knee	12	11.7	8.3	6.6	4.3	0.023	5.1
SUV-max other joints	7	17.8	3.9	12.2	8.3	0.11	5.6
SUV-max all joints	19	14.0	7.5	8.7	6.5	0.004	5.3

Df Degrees of freedom.

volume as a percentage of the total synovial cavity. Exact calculations of volume measures of the lesions are not common practice (3D volume MR scans of the whole joint are not routinely performed). In addition, if the tumour location is only extra-articular, TVS calculation is not possible. Measurements of tumour metabolic activity with SUV-max on PET-CT is a non-invasive and quantitative measure for biological activity. By keeping possible pitfalls in mind such as metastases or other hypermetabolic processes that may confound results and despite the slightly higher costs and radiation dose, assessment of PET-CT in systemic treatment of extensive diffuse-TGCT should be considered for patients receiving targeted therapy with TKI.

In the current study, no correlation between PET-CT and MR imaging could be shown. This is probably due to time difference between performing the MR imaging and PET-CT scan, incomplete radiological data and limited patient numbers. Only 15 patients (9 knee lesions) had complete pre- and post-IM treatment MR scans and PET-CT scans. In addition, all upper (n = 2) and lower limb (n = 23) joints were analysed together. The TVS method has been developed for the knee joint and specific criteria were published targeting the knee [20]. MR scan planes of the knee were fairly consistent, however standardized MR protocols for other joints were lacking. Therefore, a uniform measurement for tumour volume in non-knee joints was challenging in our preliminary study. For future studies, an evaluation of diffuse-TGCT affecting only knee lesions is preferred, since TGCT mostly affects the knee (64%) [4]. Due to the challenge of gathering an acceptable number of patients to evaluate in a rare disease like TGCT, we evaluated all joints together. In the current study, the mean difference between pre- and post IM converted to significant mean difference when TVS was assessed for the knee-subgroup.

Few limitations of this study should be considered, due to the retrospective nature. First, patients had various follow-up times and different tumour statuses at the beginning of IM treatment: some patients were already operated upon, varied IM treatment durations, diverse IM doses and dissimilar previous and subsequent treatments. Second, this study lacks information on clinical symptoms and quality of life. Also, it lacks data on the long term follow up of these patients showing the combined effect of multimodality treatment in TGCT patients. Tap et al., 2019 showed a correlation between TVS and improved patient symptoms and functional outcomes in a randomised phase 3 trial with pexidartinib, another systemic treatment in TGCT and the only available approved drug by the FDA in TGCT [18]. Lastly, to evaluate IM-treatment as a whole, histopathologic characteristics per patient pre- and post-treatment would have been helpful.

This study confirms the moderate radiological response of IM in diffuse-type TGCT. PET-CT is regarded a valuable diagnostic tool to

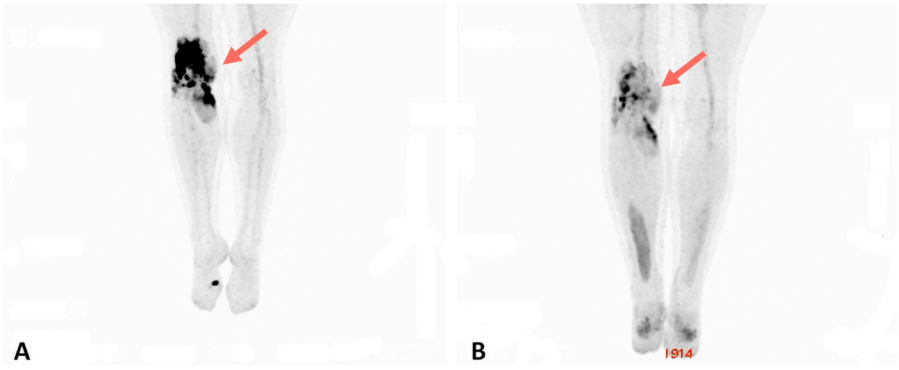

Fig. 2. PET-CT assessment of patient corresponding with the patient in Fig. 1 and patient 11 in Fig. 4. A) Baseline PET-CT scan showing marked increased FDG uptake around the right knee with a SUV-max of 27.7. B) PET-CT scan after 3.4 months of IM treatment with a significant decrease of FDG uptake with a SUV-max of 8.4 (70% reduction). Background activity is noted in the calf muscles.

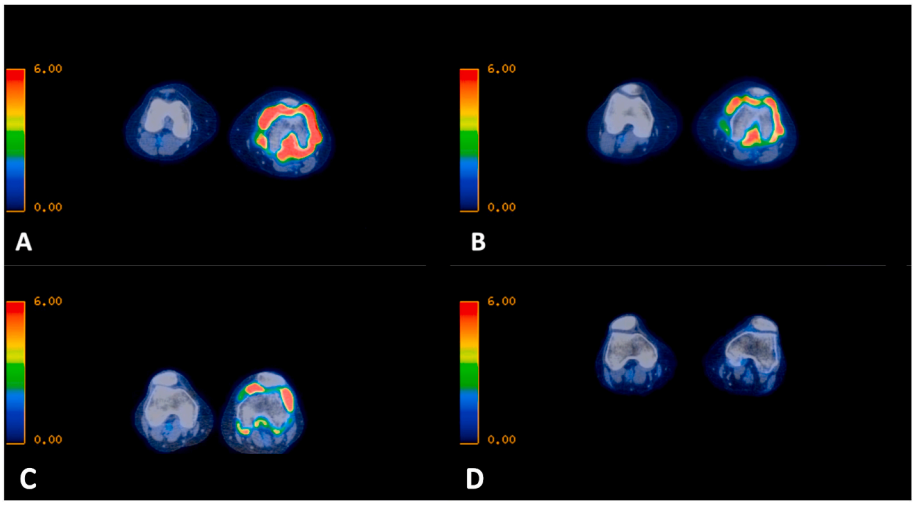

Fig. 3. A&B Short term follow-up, fused axial PET-CT images of both knees corresponding with patient 17 in Fig. 4.
C&D Long term follow-up, PET-CT assessment of patient corresponding with patient 24 in Fig. 4.
A) Baseline fused PET-CT axial slice showing high FDG uptake around the left knee with a SUV-max of 22.9.
B) PET-CT axial slice after 1.6 months of IM treatment with a marked decrease of FDG uptake with a SUV-max of 12.0 (48% reduction).
C) Baseline PET-CT transaxial slice showing abnormal high FDG uptake in the left knee with a SUV-max of 19.1.
D) PET-CT transaxial slice after 21.8 months of IM treatment with a significant decrease of FDG uptake with a SUV-max of 2.5 (87% reduction).

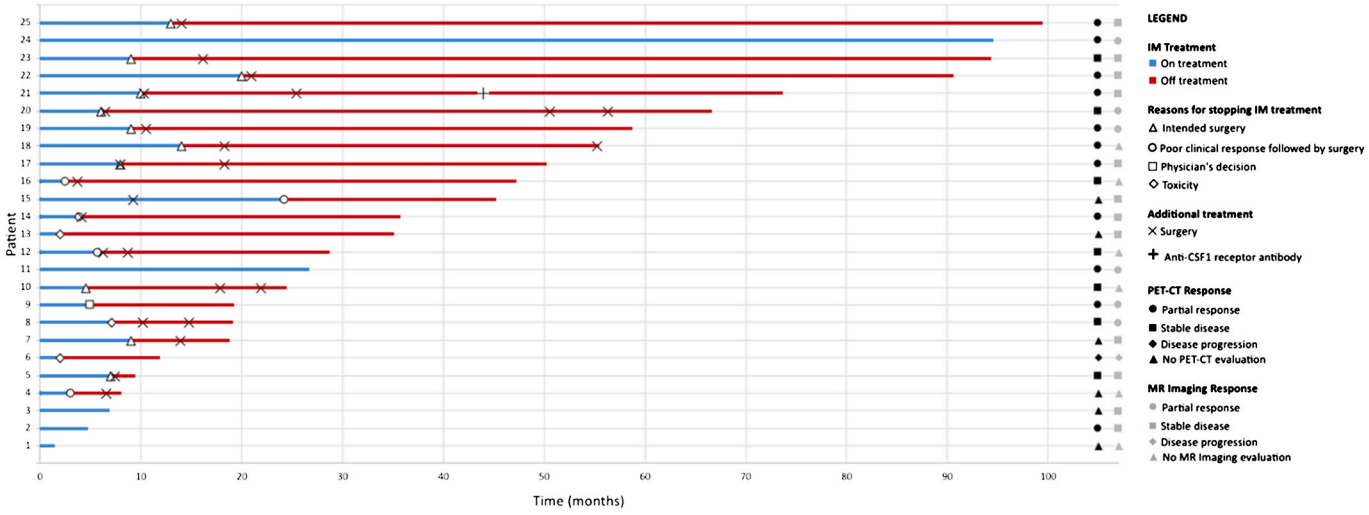

Fig. 4. Follow-up from start of IM treatment including reasons for stopping IM treatment, PET-CT response, and MR Imaging response.

Table 5
PET-CT response versus MR Imaging response.

		PET-CT response				
		Partial response	Stable disease	Progressive disease	No PET-CT evaluation	Total
MR Imaging response	Partial response	4	2	0	0	6
	Stable disease	6	2	0	4	12
	Progressive disease	0	0	1	0	1
	No MR Imaging evaluation	1	3	0	2	6
	Total	11	7	1	6	25

Table 6
PET-CT response versus MR Imaging response in knee lesions only.

		PET-CT response				
		Partial response	Stable disease	Progressive disease	No PET-CT evaluation	Total
MR Imaging responserowhead	Partial response	4	2	0	0	6
	Stable disease	2	1	0	3	6
	Progressive disease	0	0	0	0	0
	No MR Imaging evaluation	0	3	0	1	4
	Total	6	6	0	4	16

quantify the biological activity of TGCT. It can therefore be used in the assessment of the biological response in targeted systemic treatment of TGCT. There is a significant rate of grade 3 adverse events due to IM, administration should be discussed by a multidisciplinary team and administered at a medical oncology institute or tertiary cancer centre.

Declaration of competing interest

MvdS reports grants to his institution from Daiichi Sankyo, outside the submitted work.

Other authors: None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2020.08.030.

References

[1] R.B. West, B.P. Rubin, M.A. Miller, S. Subramanian, G. Kaygusuz, K. Montgomery, 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. 103 (3) (2006) 690–695.

[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. 100-101.

[3] 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. 102-103.

[4] M.J.L. Mastboom, F.G.M. Verspoor, A.J. Verschoor, D. Uittenbogaard, B. Nemeth, W.J.B. Mastboom, et al., Higher incidence rates than previously known in tenosynovial giant cell tumors, Acta Orthop. (2017) 1–7.

[5] F.G.M. Verspoor, M.J.L. Mastboom, G. Hannink, W.T.A. van der Graaf, M.A.J. van de Sande, H.W.B. Schreuder, The effect of surgery in tenosynovial giant cell tumours as measured by patient-reported outcomes on quality of life and joint function, Bone Joint Lett. J 101-B (3) (2019) 272–280.

[6] H.L. Gelhorn, S. Tong, K. McQuarrie, C. Vernon, J. Hanlon, G. Maclaine, et al., Patient-reported symptoms of tenosynovial giant cell tumors, Clin. Therapeut. 38 (4) (2016) 778–793.

[7] E. Palmerini, M. Colangeli, C. Nanni, S. Fanti, E. Marchesi, A. Paioli, et al., The role of FDG PET/CT in patients treated with neoadjuvant chemotherapy for localized bone sarcomas, Eur. J. Nucl. Med. Mol. Imag. 44 (2) (2017) 215–223.

[8] M.J.L. Mastboom, E. Palmerini, F.G.M. Verspoor, A.J. Rueten-Budde, S. Stacchiotti, E.L. Staals, et al., Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study, Lancet Oncol. 20 (6) (2019) 877–886.

[9] L. van der Heijden, C.L. Gibbons, A.B. Hassan, J.R. Kroep, H. Gelderblom, C.S. van Rijswijk, 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. 107 (4) (2013) 433–445.

[10] M.T. Houdek, M. Scorianz, C.C. Wyles, R.T. Trousdale, F.H. Sim, M.J. Taunton, Long-term outcome of knee arthroplasty in the setting of pigmented villonodular synovitis, Knee 24 (4) (2017) 851–855.

[11] M. Brahmi, A. Vinceneux, P.A. Cassier, Current systemic treatment options for tenosynovial giant cell tumor/pigmented villonodular synovitis: targeting the CSF1/CSF1R Axis, Curr. Treat. Options Oncol. 17 (2) (2016) 10.

[12] A.L. Dewar, A.C. Cambareri, A.C. Zannettino, B.L. Miller, K.V. Doherty, T. P. Hughes, et al., Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib, Blood 105 (8) (2005) 3127–3132.

[13] J.R. Taylor, N. Brownlow, J. Domin, N.J. Dibb, FMS receptor for M-CSF (CSF-1) is sensitive to the kinase inhibitor imatinib and mutation of Asp-802 to Val confers resistance, Oncogene 25 (1) (2006) 147–151.

[14] J.Y. Blay, H. El Sayadi, P. Thiesse, J. Garret, I. Ray-Coquard, Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT), Ann. Oncol. : official journal of the European Society for Medical Oncology 19 (4) (2008) 821–822.

[15] P.A. Cassier, H. Gelderblom, S. Stacchiotti, D. Thomas, R.G. Maki, J.R. Kroep, et al., Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis, Cancer 118 (6) (2012) 1649–1655.

[16] S. Stacchiotti, F. Crippa, A. Messina, S. Pilotti, A. Gronchi, J.Y. Blay, et al., Response to imatinib in villonodular pigmented synovitis (PVNS) resistant to nilotinib, Clin. Sarcoma Res. 3 (1) (2013) 8.

[17] F.G.M. Verspoor, M.J.L. Mastboom, G. Hannink, R.G. Maki, A. Wagner, E. Bompas, et al., Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumor, Sci. Rep. 9 (1) (2019) 14551.

[18] W.D. Tap, H. Gelderblom, E. Palmerini, J. Desai, S. Bauer, J.Y. Blay, et al., Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial, Lancet 394 (10197) (2019) 478–487.

[19] M.J.L. Mastboom, F.G.M. Verspoor, D.F. Hanff, M.G.J. Gademan, P.D.S. Dijkstra, H.W.B. Schreuder, et al., Severity classification of tenosynovial giant cell tumours on MR imaging, Surgical oncology 27 (3) (2018) 544–550.

[20] W.D. Tap, Z.A. Wainberg, S.P. Anthony, P.N. Ibrahim, C. Zhang, J.H. Healey, et al., Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor, N. Engl. J. Med. 373 (5) (2015) 428–437.

[21] P.E. Kinahan, J.W. Fletcher, Positron emission tomography-computed tomography standardized uptake values in clinical practice and assessing response to therapy, Semin. Ultrasound CT MR 31 (6) (2010) 496–505.

[22] J.B. Guimaraes, L. Rigo, F. Lewin, A. Emerick, The importance of PET/CT in the evaluation of patients with Ewing tumors, Radiol. Bras. 48 (3) (2015) 175–180.

[23] V.P. Balachandran, M.J. Cavnar, S. Zeng, Z.M. Bamboat, L.M. Ocuin, H. Obaid, et al., Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido, Nat. Med. 17 (9) (2011) 1094–1100.