Tenosynovial giant cell tumours

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INCIDENCE

chapter two

Higher incidence rates than previously known in Tenosynovial Giant Cell Tumours

A nationwide study in the Netherlands

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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

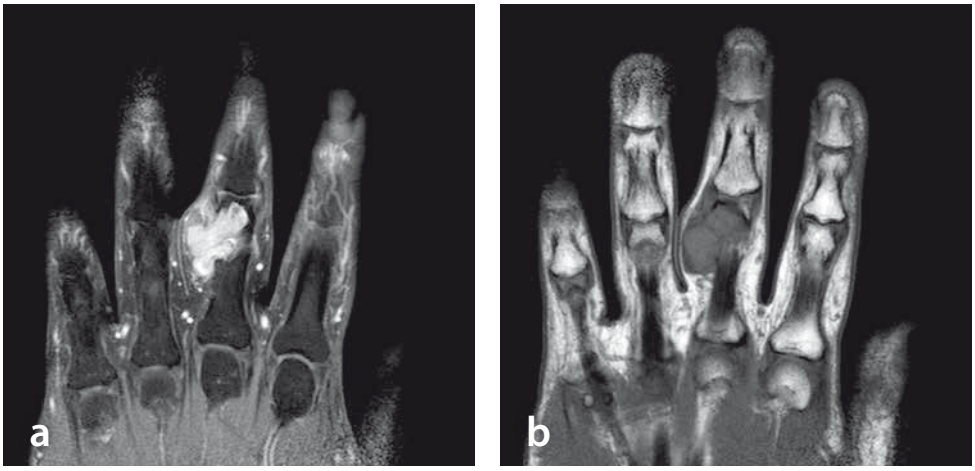

Figure 1 MRI of TGCT localized-type, affecting digits - A 43 year old male patient with a well circumscribed tumour in the proximal phalanx of the third digit of the right hand. **a.** A coronal T1-weighted MRI after intravenous contrast injection. **b.** A clear coronal T1 weighted MRI without intravenous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

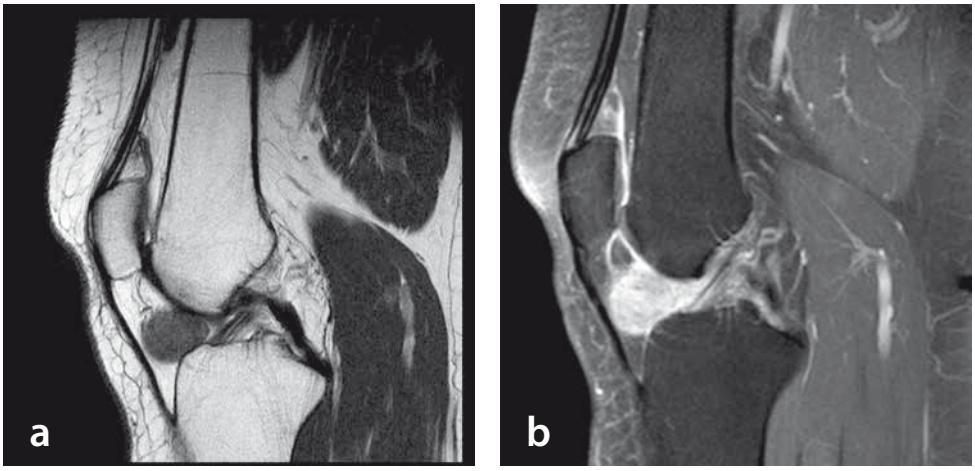

Figure 2 MRI of TGCT localized-type, extremity - Sagittal T1 weighted turbo spin echo MRI of a 47 year old female patient, affecting her right knee. A well circumscribed lesion in Hoffa's fat pad is seen. **a.** Proton density weighted MRI. **b.** Pre-saturation inversion recovery MRI.

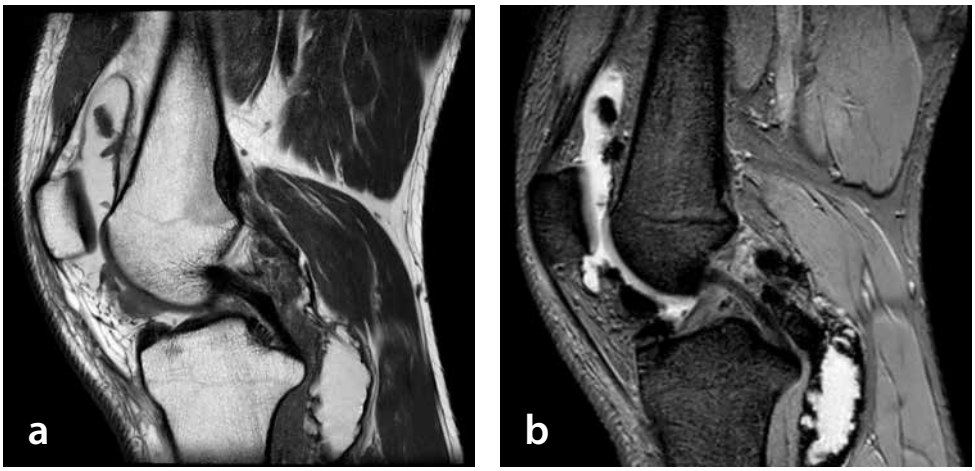

Figure 3 MRI of TGCT diffuse-type. A 23 year old male patient with an extensive proliferative synovial process around both cruciate ligaments, dominating the anterior and posterior knee compartments, intra- and extra-articular. Inside suprapatellar pouch and Baker's cyst a blooming villonodular aspect 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.

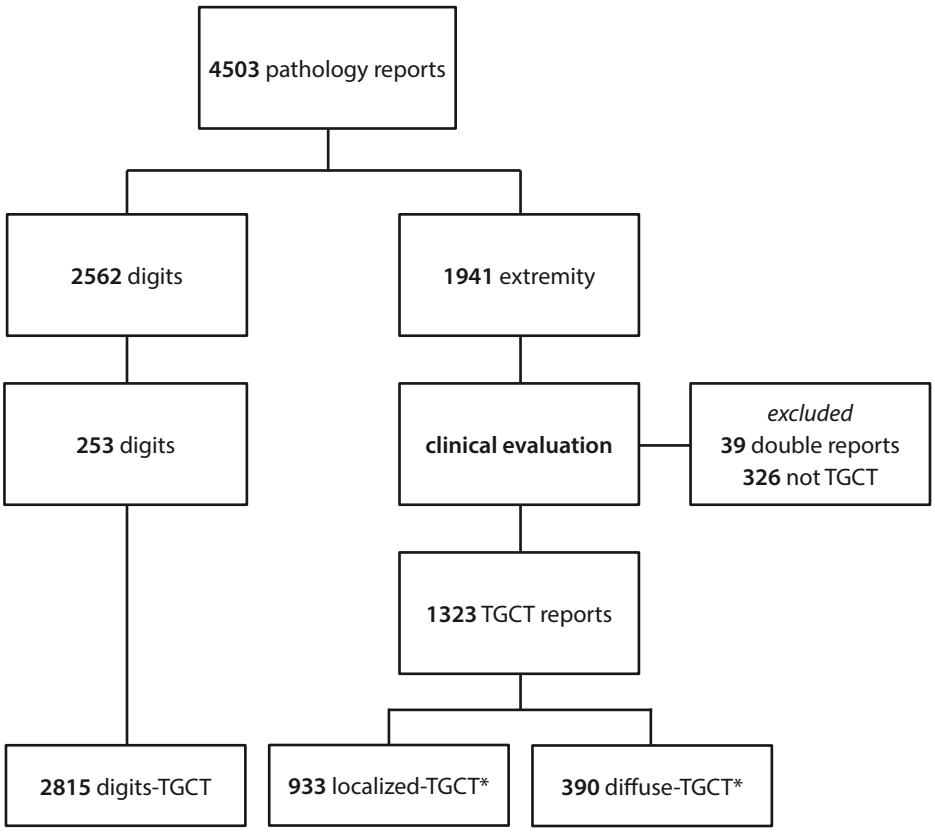

Figure 4 Inclusion flowchart

*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.

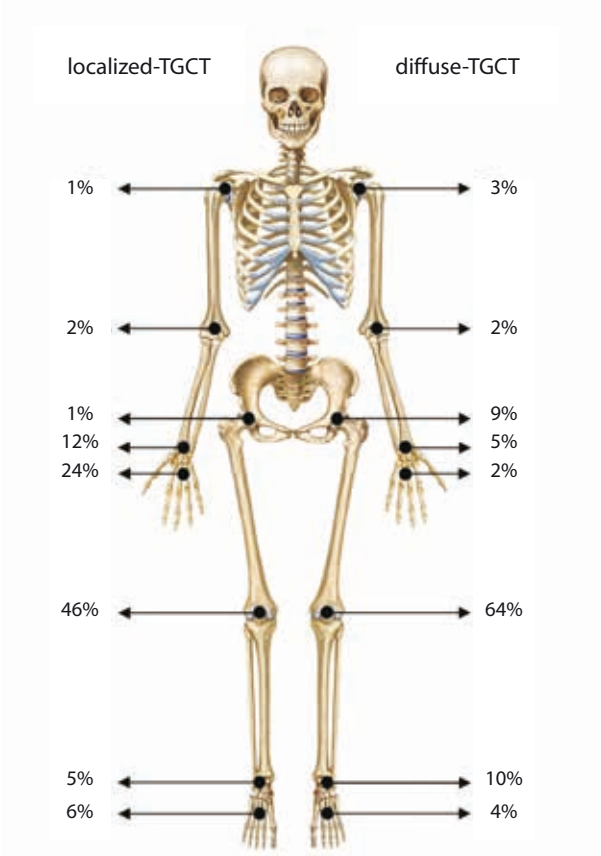

Figure 5 Skeleton, showing affected TGCT localization (fingers and toes excluded). 3% in localized-type and 1% in diffuse-type is classified as 'other'.

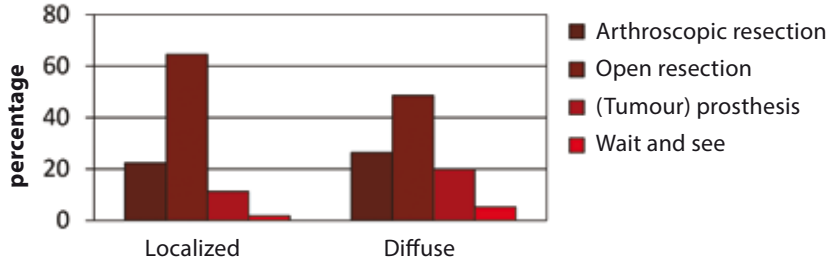

Figure 6 Bar graph initial treatment for TGCT affecting extremities in The Netherlands, excluding digits.

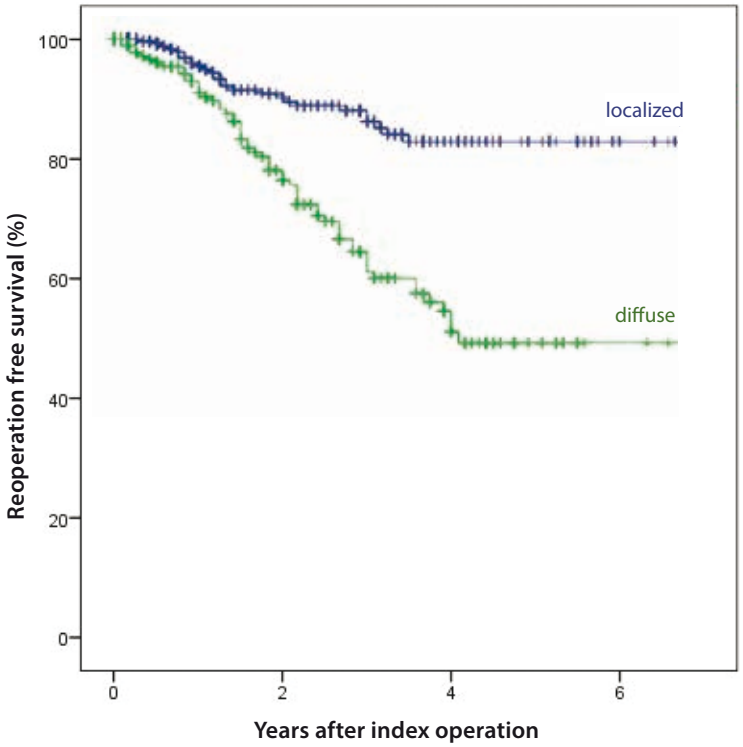

Figure 7 Reoperation due to local recurrence free survival curve in localized-extremity and diffuse-TGCT (Kaplan Meier), excluding digits. Time zero is time of primary surgery. 8 Patients died and were censored at time of death if a reoperation had not occurred.

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

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