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Higher incidence rates than previously known in tenosynovial giant cell tumors
A nationwide study in The Netherlands

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Background and purpose — Tenosynovial giant cell tumors (TGCT) are rare, benign tumors, 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-years in localized (including digits) and diffuse TGCT, respectively. We aim to determine nationwide and worldwide incidence rates (IR) in TGCT affecting digits, localized-extremity TGCT and diffuse-type TGCT.

Material and methods — Over a 5-year period, the Dutch Pathology Registry (PALGA) identified 4,503 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 — 2,815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. Dutch IR in digits, localized-extremity, and diffuse-type TGCT was 34, 11 and 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. The knee joint was most often affected: localized-extremity (46%) and diffuse-type (64%) TGCT, mostly to grey, yellow and brown mottled areas (de St. Aubain Somerhausen and van de Rijn 2013). Based on anatomical site of the localized-type tumor, differentiation is made into a group affecting digits and a group occurring in and around larger joints (Ushijima et al. 1986, Chiari et al. 2006). TGCT affecting digits is defined as a localization distal to metacarpal or metatarsal bones; localized-extremity TGCT is defined as

Tenosynovial giant cell tumors (TGCT) are a rare entity, affecting generally young patients (below the age of 40 years), with an equal sex distribution. The World Health Organization (WHO) classification of Tumors of Soft Tissue and Bone (2013) distinguishes 2 TGCT types: localized and diffuse lesions (de St. Aubain Somerhausen and van de Rijn 2013). Microscopically the 2 types show no clear difference. However, on magnetic resonance imaging (MRI) discrimination between these types is made (Murphey et al. 2008). The localized type was previously described as giant cell tumor of tendon sheath, nodular synovitis or localized pigmented villonodular synovitis (PVNS). The typical macroscopic aspect is a well circumscribed, small (about 0.5 to 4 centimeters) usually lobulated lesion, with white to grey, yellow and brown mottled areas (de St. Aubain Somerhausen and van de Rijn 2013). Based on anatomical site of the localized-type tumor, differentiation is made into a group affecting digits and a group occurring in and around larger joints (Ushijima et al. 1986, Chiari et al. 2006). TGCT affecting digits is defined as a localization distal to metacarpal or metatarsal bones; localized-extremity TGCT is defined as

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all sites near joints proximal and including metacarpal and metatarsal joints.

In localized TGCT, most lesions are found in the digits of hands 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 (Verspoor et al. 2013, Stephan et al. 2016). A systematic review showed a recurrence rate of 15%, after an average follow-up of 37 to 79 months (Fotiadis et al. 2011).

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 an open approach (Verspoor et al. 2013, Stephan et al. 2016). A systematic review reported an average recurrence rate of 6% after arthroscopic resection and 4% after open resection (with variable follow-up) (van der Heijden et al. 2013).

The diffuse-type TGCT, previously called diffuse pigmented villonodular synovitis (PVNS) or synovitis (villo)nodularis pigmentosa (SVP), is a more destructive and locally aggressive tumor (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, multicolored appearance, including white, yellow and rust-colored areas (de St. Aubain Somerhausen and van de Rijn 2013). 75% are located around the knee joint (van der Heijden et al. 2013). Current treatment is surgical excision (Gonzalez Della Valle et al. 2001, Verspoor et al. 2013, Stephan et al. 2016). 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 (van der Heijden et al. 2013). In extensive disease, perioperative radiotherapy might reduce recurrence rate (Griffin et al. 2012, Mollon et al. 2015). Patients with (multiple) recurrences experience impaired quality of life (van der Heijden et al. 2014).
According to the WHO classification of 2002 and 2013, the incidence rate (IR) in TGCT is not exactly known (de St. Aubain Somerhausen and Dal Cin 2002, de St. Aubain Somerhausen and van de Rijn 2013). Current TGCT IRs are based on 1 single US-county study completed in 1980, with an IR of 9 and 2 per million person-years in localized (including digits) and diffuse TGCT, respectively (Myers and Masi 1980). Verschoor and coworkers (personal communication 2015) performed the initial nationwide registry based study on giant cell containing tumors 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 behavior, however, demands 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 recurrence rate at individual patient level through extensive additional data collection at participating hospitals.

Material and methods

Data collection was performed by collaboration of physicians from the TGCT study group, and in special collaboration with Radboud University Medical Center and Medical Spectrum Twente, data collection was performed. Data capturing and analyses were performed in the Leiden University Medical Center.

A search in PALGA, the non-profit nationwide network and registry of histo- and cytopathology in The Netherlands, was performed (Casparie et al. 2007). To find all patients with TGCT, between January 2009 and January 2014, the search terms ‘Tenosynovial Giant Cell Tumor’, ‘Pigmented Villonodular Synovitis’ and a variety of synonyms were used, with TGCT, between January 2009 and January 2014, the search terms ‘Tenosynovial Giant Cell Tumor’, ‘Pigmented Villonodular Synovitis’ and a variety of synonyms were used, either as a code or as free text (Verschoor 2015, personal communication) (Appendix, 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, but 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 1,941 pathology reports to 95 Dutch hospitals of origin. Departments of pathology received a request to collaborate in this nationwide study. After approval, personal hospital identifiers were obtained and the departments concerned (mostly orthopedics 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 anonymous. 75 of 95 attributed hospitals collaborated, including all specialized and academic centers.

Clinical evaluation started with 1,941 eligible TGCT cases. In 1,576 (81%) cases, diagnosis was confirmed. 253 reports were determined to be in digits and amended in digits group. For included extremity TGCT cases (n = 1,323), 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, and results were pooled according to standard Rubin’s rules (Rubin 1996). All imputed data were checked for errors.

Finally, 1,323 patients with histologically proven TGCT were included (Figure 4).

In addition to the 2,562 patients with TGCT affecting digits that were already identified based on the pathology reports, 253 additional patients with TGCT affecting digits were discovered during clinical data evaluation. 2,815 patients with TGCT affecting digits were identified (2,649 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 (IBM Corp, Armonk, NY, USA) was used for analyses. The IR was separately estimated for localized TGCT, either digits or extremity, and diffuse-type TGCT per year, by using the number of histologically proven cases of 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-year 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 years.

Ethics, funding, and potential conflicts of interest

Research was 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. The study was approved by the Institutional Review Board (CME) from our institution (registration number G16.024, 22 April 2016). No funding or benefits were received by any of the authors. There is no conflict of interest involving any of the authors.

Results

During a 5-year period, 2,815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. TGCT affected digits 3 and 7 times more often compared with localized-extremity and diffuse TGCT, respectively. Dutch TGCT IRs were 34 (CI 33–35) in TGCT affecting digits, 11 (CI 11–12) in localized-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 TGCT 45 (IQR 34–56) years, and diffuse TGCT 47 (IQR 32–61) years. Male:female ratio was about 1:1.5 for any type.

The Table shows IRs per million person-years for calendar years 2009 up to and including 2013, sex, and age categories of the 3 different TGCT groups. In these 3 groups: IRs over disaggregated years were quite similar, female IRs were slightly higher compared with 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, the following results were based on localized-extremity and diffuse-type TGCT. 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.
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 Basis Administratie (GBA)) for all patients, 8 patients (7 localized and 1 diffuse TGCT) were 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 the localized-extremity type, reoperation-free survival at 2 and at 5 years was 90% and 83%, respectively. In the 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 center: 9% of localized type (excluding digits) and 18% of diffuse type.

**Discussion**

Microscopically, localized-extremity and diffuse TGCT are identical (de St. Aubain Somerhausen and van de Rijn 2013). A distinction is made between localized-digits and localized-extremity TGCT, based on anatomical location and histological differences (Ushijima et al. 1986, Chiari et al. 2006). TGCT lesions affecting digits are characterized as multiple, small (average 1 centimeter) 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, rarely showing inflammatory cells. Conversely, localized-extremity TGCT are typically single, relatively large (average 2 centimeters) 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 (Ushijima et al. 1986).

Because of the rarity of the disease, the current TGCT literature contains predominantly retrospective, relatively small cohort studies, including heterogeneous data (Chiari et al. 2006). 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...
Monaghan 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 with the initial US-county study (Myers and Masi 1980), our study showed a 5-fold higher IR in localized TGCT (combining localized-digits and localized-extremity), and a more than 2.6-fold higher IR in diffuse-type TGCT. 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 also represented in our search. In addition, PALGA data are based on input of physicians and sometimes lack specificity. For instance, affected joint: “upper extremity”, “hand”, or “wrist” could all turn out, after clinical evaluation, to be affected digits.

In our search, 1,941 patients were clinically evaluated and 1,323 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, the date when the 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 with the literature, we found comparable average recurrence rates for localized-extremity TGCT (9%) and for diffuse-type TGCT (23%) (van der Heijden et al. 2013). As local recurrence might develop years after initial surgery (Verspoor et al. 2014), and PALGA provided pathology reports with a maximum time 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 (Casperie et al. 2007). TGCT patients without a biopsy or treatment are not represented in this pathology-based cohort.

Second, our IR in localized-extremity and diffuse-type TGCT could be marginally over- or underestimated, because 21% of eligible TGCT patients were not clinically evaluated and were therefore imputed. Analyses with and without imputed data were comparable. PALGA identified 1,941 eligible TGCT patients, scattered over 95 Dutch hospitals. Regarding different hospital boards, the different departments concerned (pathology, orthopedics, general surgery), and different local legislation, it was challenging to evaluate all eligible TGCT patients.

Third, a clinical distinction between localized-extremity and diffuse-type TGCT is difficult, especially for clinicians not familiar with this rare disease (Flandry et al. 1994).

Subsequently, an overestimation of IR in localized-digits TGCT might be present. IR of digits is based solely on PALGA registry numbers, in contrast to localized-extremity and diffuse TGCT IRs, which were clinically evaluated.

Global IR 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 are important. The majority of our investigated patients lacked 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 not to resolve and not to be cured.

In The Netherlands, traditionally, larger orthopedic clinics have been treating TGCT or have diagnosed TGCT as an incidental finding during arthroscopy or endoprosthetic replacement. When (severe) complaints occur, patients are commonly referred to specialized tertiary sarcoma centers. 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 center. Remarkably, only 18% of diffuse TGCT was primarily treated in tertiary oncology centers.

In summary, this study is the first nationwide study and the first to offer detailed analyses of IRs in TGCT. IRs for TGCT of digits, localized-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, a slight predisposition in female patients, median age around 47 years at first treatment, and are primarily treated with an open resection. The recurrence rate in the diffuse type is 2.6 times higher compared with the localized-extremity type. TGCT is still considered a rare disease, though is 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

The pathology reports were provided by PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands. We thank Reinier de Graaf Gasthuis, orthopedic department, Delft, The Netherlands for their collaboration.

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