Long-term follow-up results of primary and recurrent pigmented villonodular synovitis

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Abstract

Objective. Adequate documentation of the outcome of treatment of pigmented villonodular synovitis (PVNS) is sparse. Available case series show relatively short follow-up times and often combine locations or subtypes to increase patient numbers. This article describes the long-term follow-up of a single institution’s large consecutive series of PVNS.

Methods. Retrospectively, 107 PVNS patients were identified between 1985 and 2011 by searching pathology and radiology records. Treatment complications, recurrences and quality of life were evaluated. Most patients (85.2%) were primarily or secondarily treated at our institution.

Results. Both subtypes, localized PVNS [29 (27%)] and diffuse PVNS [75 (70%)] were represented. The knee was affected in 88% of patients. Treatments received were surgery, external beam radiotherapy, radiosynovectomy, targeted therapy, immunotherapy or combinations of these. Forty-nine (46%) patients had prior treatment elsewhere. The mean follow-up from diagnosis until last contact was 7.0 years (range 0.3–27.4) for localized PVNS and 14.5 years (range 1.1–48.7) for diffuse PVNS. The 1- and 5-year recurrence-free survival rates for diffuse PVNS were 69% and 32%, respectively. Quality of life, estimated by 36-item Short Form Health Survey (SF-36) scores, were not significantly different between localized and diffuse PVNS. However, both patient groups scored lower than the general population norms on the general health component (59.2 and 56.3, respectively, $P < 0.05$).

Conclusion. Recurrence rates of PVNS increase with time. Long-term follow-up shows, particularly in diffuse PVNS, it is a continually recurring problem, and over time it becomes increasingly difficult to cure. The quality of life is decreased in patients with PVNS compared with the general population.

Key words: synovitis, pigmented villonodular, therapy, treatment outcome, follow-up studies, quality of life.
modalities have been tried, such as external beam radiation therapy [12, 21, 22], radiation synovectomy [13], cryosurgery [23], total joint arthroplasty [24, 25] and immune [26] or targeted therapy [27]. Due to the small number of patients affected, no large prospective clinical trials on treatment results exist. All currently available evidence is based on retrospective case series. Outcome measures such as recurrence rates, recurrence-free survival (RFS) and joint function scores are often contaminated by combining subtypes, locations, treatments and both primary and recurrent disease to increase patient numbers, which leads to difficulties in interpretation and comparability of results [2, 10, 21, 24, 25, 28]. To the best of our knowledge, there is no information available on quality of life (QoL), an important measure in a disease as destructive as PVNS. We performed a retrospective study on a relatively large number of patients with respect to recurrence rates, RFS, complications and QoL.

**Patients and methods**

We retrospectively searched pathology and radiology patient databases on PVNS, nodular tenosynovitis, local tenosynovitis and giant cell tumour (GCT) of the tendon sheath. Between 1985 and 2011, a total of 184 patients were identified. After careful evaluation of the database records, 58% of patients were found to have PVNS. The 33% of GCT patients and 9% of patients that did not fit the histological or MRI description of PVNS were excluded. Twenty-seven per cent of PVNS patients were classified as L-PVNS, 70% as D-PVNS and 3% as unknown. The demographics of the 104 L-PVNS and D-PVNS patients included in this study are provided in Table 1. All cases were monoarticular.

Medical records were studied on clinical, pathological, radiological, treatment and follow-up information by two independent reviewers (F.G.M.V. and A.A.G.Z.). Any disagreements were resolved by consensus with a third reviewer (H.W.B.S.). QoL was evaluated by using the Dutch translation of a generic QoL instrument, the 36-item Short Form Health Survey (SF-36) [29]. The SF-36 is an instrument for measuring general health. It includes scales for physical functioning, social functioning, role physical functioning, role emotional functioning, mental health, vitality, bodily pain, general health and health change. All patients were contacted by telephone to take the SF-36 questionnaire. Sixty-two (57%) patients responded. The remaining patients could not be contacted because they had moved or changed telephone numbers. The study was approved by the institutional review board of the Radboud University Medical Center, Nijmegen (file number CMO 2012/555) and was carried out in line with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Recurrences, treatment complications and current QoL were analysed according to PVNS subtype, location and primary and recurrent disease. Since the knee was affected in 88% of patients, analyses focused on this group. Recurrences are expressed as rates. The primary patient group received all treatments at our institution, while the referred patient group had their initial treatment(s) elsewhere and was treated at our institution for recurrent disease. The length of follow-up was defined as the period between the first pathology confirmation of diagnosis and the most recent patient contact. The time to recurrence was calculated as the time from the last treatment until histologically proven recurrent disease. Statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used for demographic data and patient characteristics. Between-group differences in SF-36 scores were compared using one-way analysis of variance followed by Bonferroni post hoc comparison tests. RFS analyses were performed

| TABLE 1 Demographics | L-PVNS | D-PVNS |
|-----------------------|--------|--------|
| Patients, n (%)       | 29 (100) | 75 (100) |
| Sex                   |        |        |
| Male, n (%)           | 9 (31)  | 36 (48) |
| Age at diagnosis, mean (S.D.), years | 39.7 (13.3) | 32.1 (10.1) |
| Females, n (%)        | 20 (69) | 39 (52) |
| Age at diagnosis, mean (S.D.), years | 36.5 (14.4) | 35.7 (13.6) |
| Primary, n (%)        | 23 (79) | 33 (44) |
| Referred, n (%)       | 6 (21)  | 42 (56) |
| Location, n (%)       |        |        |
| Knee                  | 27 (93) | 64 (85) |
| Hip                   | 1 (3)   | 5 (7)  |
| Ankle                 | 0       | 6 (8)  |
| Elbow                 | 1 (3)   | 0      |
| Follow-up from diagnosis, mean (S.D.), years | 7.2 (7.0) | 13.9 (10.3) |
| Follow-up from index treatment, mean (S.D.), years | 6.6 (6.7) | 11.2 (9.8) |

Index treatment: first treatment in a tertiary centre; L-PVNS: localized pigmented villonodular synovitis; D-PVNS: diffuse pigmented villonodular synovitis.
using the Kaplan–Meier method and compared using log-rank tests. Survival estimates are presented as RFS (S.E.). Assumptions for individual tests were checked before the analyses were performed. For all data sets, differences were considered statistically significant at $P$-values $< 0.05$.

**Results**

**Localized pigmented villonodular synovitis**

The localized group contained 69% females [mean age 36.5 years (range 19.4–71.7)] and 31% males [mean age 39.7 years (range 17.1–53.3)]. The knee joint was affected in 93% of patients.

**Treatments and recurrences**

Twenty-two affected knees were primary L-PVNS patients and five patients were referred. In 83% diagnosis was confirmed by MRI. In 34% diagnosis was preoperatively determined by biopsy. All patients were treated by open or arthroscopic surgical excision. In three of these patients, PVNS was an accidental finding during prosthetic surgery. Six patients needed additional surgical treatment, five for recurrent disease, two of which were first treated at our centre, two who received initial treatment elsewhere and one who received both treatments elsewhere. One patient was operated on four times due to residual pain and hydrops; however, recurrent disease was never demonstrated. Another patient initially received yttrium radioisotopic synoviorthesis, then recurrent disease developed and surgical excision was successfully applied. One patient who developed recurrent disease after surgical intervention had a successful yttrium radioisotopic synoviorthesis.

**Follow-up**

The mean overall follow-up from diagnosis until last patient contact was 7.0 years (range 0.3–27.4). Of these knee patients, 15% of recurrences occurred within the first year and 22% within 5 years. The overall 1- and 5-year RFS was 83% and 69%, respectively (Fig. 1). For primary patients the RFS was 89% and 80%, respectively.

**Complications**

Three patients had postoperative complications after surgical excision of L-PVNS tissue—two after initial treatment, one of which had a superficial wound infection successfully treated with antibiotics. The other patient had a deep infection that was treated by two operations and one manipulation under anaesthesia because of stiffness. Another patient suffered from a femoral nerve neuropathy after a second surgical excision, but recovered spontaneously.

**Quality of life**

The SF-36 score was obtained for 70% of L-PVNS knee patients on average 6.1 years (range 1.2–19.9) after the first treatment. Table 2 shows the mean scores of all SF-36 scales. Compared with the general population [30], L-PVNS patients scored significantly lower on mental health ($P = 0.05$), vitality ($P = 0.02$) and general health ($P = 0.005$).

**Diffuse pigmented villonodular synovitis**

The D-PVNS group contained 52% females [mean age 35.7 years (range 14.4–62.2)] and 48% males [mean age 34.7 years (range 14.4–66.3)].
D-PVNS: diffuse pigmented villonodular synovitis. General population data reproduced from VanderZee KI et al. [30].

**Significant** (available at Rheumatology treatments, outlined in detail in supplementary Table S1, available at Rheumatology Online). This last group contains all recurrences, including known recurrences treated elsewhere. Their mean follow-up from diagnosis was 13.0 years (range 1.1–48.7).

Of the 37 referred patients, 26 initially received surgical excision of PVNS tissue. Six patients initially received yttrium radioisotopic synoviorthesis. In two patients, it was not possible to retrieve information on initial treatment(s). Subsequent treatments and recurrences of all D-PVNS knee patients are described in Table 3 (also see supplementary Table S1, available at Rheumatology Online).

Two patients solely treated elsewhere, one patient was advised a complete synovectomy, but it remains unclear whether it was performed because this patient was lost to follow-up. In another patient, symptoms disappeared spontaneously after two biopsies. Of the 37 referred patients, 8 patients developed one recurrence and 26 had two or more recurrences (Table 3 and see supplementary Table S1, available at Rheumatology Online). Their mean follow-up from diagnosis was 13.0 years (range 1.1–48.7).

The overall 1-, 5-, 10- and 15-year RFS for all D-PVNS knee patients was 68% (S.E. 6), 32% (S.E. 7), 25% (S.E. 7) and 16% (S.E. 7), respectively (Fig. 1). The primary group had a 1- and 5-year RFS of 92% (S.E. 5) and 65% (S.E. 10), respectively. The referred patients had a 1- and 5-year RFS of 47% (S.E. 9) and 10% (S.E. 5), respectively. The 1- and 5-year RFS for this last patient group from the first treatment at our centre until the last follow-up was 93% (S.E. 5) and 60% (S.E. 11), respectively (Fig. 2).

**Complications**

Perioperative complications after surgical excision of D-PVNS and their treatments are described in Table 4. In only four patients did the complication occur after the initial treatment (see supplementary Table S1, available at Rheumatology Online).

**Quality of life**

SF-36 scores were obtained for 53% of D-PVNS knee patients, on average 10.1 years (range 2.4–28.8) after the first treatment. Table 2 shows the mean scores of all nine SF-36 scales. Compared with the general population [30], D-PVNS patients score significantly lower on physical functioning ($P = 0.006$), mental health ($P = 0.02$), vitality ($P = 0.002$) and general health ($P < 0.001$).

**Discussion**

The limited available knowledge of the long-term outcome of PVNS treatment based on a few small studies and the lack of QoL measures motivated us to analyse our large patient group. We were able to identify 107 patients over the last 25 years. We retrospectively studied the treatment results of the knee patients by identifying recurrences, RFS, complications and QoL. These results were analysed by subgroup and primary or recurrent disease.

**Diffuse pigmented villonodular synovitis**

This study, with a long follow-up, shows an overall recurrence rate of 72% in D-PVNS of the knee. The recurrence age 32.1 years (range 16.7–52.9)]. The knee joint was most affected, in 85% of patients (Table 1). In 25% of patients the diagnosis was obtained by biopsy, while in the remaining cases diagnosis was conclusive by MRI.

## Table 2. Outcome quality of life for pigmented villonodular synovitis knee patients compared with the general population at last follow-up

|                          | L-PVNS, mean (S.D.) | D-PVNS, mean (S.D.) | General population, mean (S.D.) |
|--------------------------|---------------------|---------------------|-------------------------------|
| Physical functioning     | 72.4 (27.0)         | 68.2 (26.8)*        | 81.9 (23.2)                   |
| Social functioning       | 82.2 (27.7)         | 86.8 (25.6)         | 86.9 (20.5)                   |
| Role physical            | 68.4 (43.2)         | 69.1 (38.5)         | 79.4 (35.5)                   |
| Role emotional           | 87.7 (31.8)         | 91.2 (26.3)         | 84.1 (32.3)                   |
| Mental health            | 67.6 (18.9)*        | 70.1 (15.4)*        | 76.8 (18.4)                   |
| Vitality                 | 55.5 (19.4)*        | 55.7 (20.4)*        | 67.4 (19.9)                   |
| Bodily pain              | 68.7 (34.7)         | 74.0 (26.7)         | 79.5 (25.6)                   |
| General health           | 59.2 (18.0)*        | 56.3 (18.6)*        | 72.7 (22.7)                   |
| Health change            | 55.3 (15.8)         | 48.5 (19.4)         | 52.4 (19.4)                   |

*Significant $P$-value $< 0.05$ different compared with the general population. L-PVNS: localized pigmented villonodular synovitis; D-PVNS: diffuse pigmented villonodular synovitis. General population data reproduced from VanderZee KI et al. [30].
TABLE 3
Rates of recurrence after first diffuse pigmented villonodular synovitis treatment of the knee

| Treatment                                      | Number of patients | Number of recurrences | Average time to first recurrence, years (range) | Length of follow-up, years (range) |
|------------------------------------------------|--------------------|-----------------------|-----------------------------------------------|----------------------------------|
| Complete surgical synovectomy                  | 9                  | 2                     | 12.8 (2.8-15)                                 | 20 (1.0-27.2)                   |
| Partial surgical synovectomy                   | 3                  | 15                    | 10.7 (9.1-11.1)                               | 6 (2-15)                        |
| Surgery + EBRT                                 | 2                  | 0                     | 7.3 (5.8-10.5)                                | 6 (1.3-3.6)                     |
| Yttrium                                         | 1                  | 0                     | 19.2 (15.5)                                   | 3 (0-4)                         |
| Two stage + cryosurgery                        | 2                  | 0                     | —                                              | 6.2 (1.1-9.4)                   |
| Surgery + yttrium                              | 0                  | 1                     | 9.7 (3.2-4.6)                                 | —                                |
| Surgery + yttrium + EBRT                       | 0                  | 2                     | 4.3 (3.1-5.6)                                 | —                                |
| Unknown or lost to follow-up                   | 0                  | 4                     | —                                              | —                                |

- One patient with a total knee replacement.
- Data only available for one patient.
- EBRT: external beam radiotherapy.
- *Data incomplete.

Dino 
Blanco et al. [12] reported no recurrences in 84 primary L-PVNS patients, of whom 29 were excluded as they were incidental findings and only 26 of the remaining patients were evaluated. Our results show recurrence rates of 22% in 27 L-PVNS patients over an average 7.2 years. Two of them had already been treated elsewhere.

Both subtypes mixed

Byers et al. [7] described recurrence rates of almost 50% over 3-35 years, however, both subtypes were combined and it is unclear whether only primarily affected patients were included. As in our patient group, their patients received different treatments, including synovectomies and external beam radiotherapy.

Other relatively large case series have analysed PVNS of the knee but did not differentiate between the two subtypes [2, 11, 16, 19, 28]. Recurrence rates of between 20% and 36% were reported in 25-75 patients with a mean follow-up of 0.3-13.5 years. For these studies it is not known whether these patients were primary or recurrent cases.

Recurrence-free survival

Chiari et al. [10] reported 23 primary L-PVNS patients with a 1- and 5-year RFS of 100% and 88%, respectively, after surgical excision for all joints. For 19 primary D-PVNS patients they reported a 1- and 5-year RFS of 80% and 27%, respectively, after surgical excision. However, they combined different locations, like knees, hips and ankles, which can behave differently [28, 31]. Hips are more affected at diagnosis, caused by more joint space [28]. The mean follow-up was 80 months (range 26-294).

Our analyses focused on the knee. We found an overall 1- and 5-year RFS of 83% and 69% for L-PVNS patients, respectively. For primary L-PVNS patients, this was 89% and 80%, respectively. Similar differences were found for D-PVNS patients, with an overall 1- and 5-year RFS of 68% and 32%, respectively, and 92% and 65%, respectively, for patients first treated at our centre. These results...
Fig. 2 Kaplan-Meier curves showing recurrence-free survival for primary and referred diffuse pigmented villonodular synovitis

Uncertainty is shown by 95% CI and a number-at-risk table below the graph. The referred patients are represented in two groups. One group shows recurrence-free survival from the initial treatment, the other shows recurrence-free survival after the initial treatment in a tertiary centre. Recurrences were more frequent for referred patients initially treated elsewhere. D-PVNS: diffuse pigmented villonodular synovitis.

Table 4 Perioperative complications after surgical excision of diffuse pigmented villonodular synovitis

| Complication                  | Number of patients | Treatment of complication (number of patients)                      |
|-------------------------------|--------------------|---------------------------------------------------------------------|
| Delayed wound healing         | 2                  | Spontaneous recovery                                                |
| Local paraesthesia            | 1                  | Spontaneous recovery                                                |
| Stiffness                     | 5                  | Manipulation under anaesthesia (1); adhesiolysis (1); clinical mobilizations (2); unknown (1) |
| Superficial wound infections  | 4                  | Antibiotics                                                         |
| Neurolysis                    | 1                  | Unknown                                                             |
| Haematoma                     | 3                  | Unknown                                                             |
| Deep wound infections         | 2                  | Surgical drainage                                                   |
| Percutaneous fistula          | 1                  | Unknown                                                             |

not only confirm the importance of discerning primary from recurrent patients in analyses, but it also underlines the possibility of a biologically aggressive subgroup. However, predictive markers for biologically more aggressive behaviour have not yet been found.

Complications

The nature and number of complications agreed with the literature [7, 12, 13, 15], mostly consisting of infections and stiffness requiring manipulation. Not only the disease itself, but also its treatments, can cause loss of joint function. This is due to stiffness as a result of fibrosis, but also the development of OA. As a result, some patients even change career.

Quality of life

We found a significant impact on QoL scores compared with the general population [30]. Both subgroups, L-PVNS and D-PVNS, scored low on mental health, vitality and general health compared with the general population [30]. The D-PVNS patients also scored low on physical functioning, which might be attributed to impaired joint function due to multiple treatments with or without complications. To our knowledge, there are no QoL measurements published for PVNS patients. The SF-36 questions were asked at various times after treatment and patients received various treatments, and because of the relatively small group, all ages were analysed together. Nevertheless, there were significant differences.
Strengths and limitations

Related to the retrospective character of this study, there were missing data and some patients were lost to follow-up. However, a large number of PVNS patients were included and complete information regarding their treatments was available for all primary patients and almost complete for referred patients, including long-term follow-up.

Unfortunately, no information was available from patients who were treated first in other centres and had no recurrences. Our tertiary centre receives primary PVNS cases from other centres and our patients do not receive treatment if they are referred outside our institution. Therefore our results might be an overestimate. However, comparing our large series with published incidence numbers suggests we received most patients [2].

In addition, our results show an increase in RFS of patients first treated at our centre compared with patients first treated elsewhere. The above mentioned emphasizes the importance of centralization of care for this rare disease. Centralization may result in an increase in patient numbers treated, thereby increasing experience with specific treatments, notable effects of treatments and quality of patient registration/follow-up.

To the best of our knowledge, this is the first study that included QoL measures in PVNS patients. Measurement of QoL is increasingly important in today’s health care. Further studies should demonstrate whether or not the decreased QoL in PVNS patients in the present study is a consequence of the disease itself or of the (multiple) treatment(s) the patients received. However, it should be noted that not all patients completed the SF-36 questionnaire (70% of the L-PVNS vs 53% of the D-PVNS patients). To get an estimate of potential non-response bias, values known from all patients (age, sex, follow-up time and type of PVNS) were compared with the values that prevailed in the subgroup of those who answered. No significant difference was found between the groups, indicating that there might be no non-response bias.

Conclusions

Recurrence rates of PVNS deteriorate with time. Long follow-up rates underline that D-PVNS in particular is a continually recurring disease that over time is increasingly difficult to treat. Our findings confirm the importance of differentiating PVNS subtypes and also suggest that patients should receive treatment(s) at tertiary centres because of its rarity and destructiveness. Recurrence rates and RFS are not the only important measurements in this potentially disabling disease. The SF-36 is a useful tool, in addition to functional scores, to express treatment results. In order to design an optimal treatment, we have started a prospective study where clinical parameters, function and QoL are being studied at regular intervals pre- and postoperatively.

Rheumatology key messages

- Diffuse pigmented villonodular synovitis is a continuously recurring disease that over time, is increasingly difficult to treat.
- It is important to differentiate between subtypes, primary and recurrent pigmented villonodular synovitis.
- Quality of life seems an important additional measurement to express treatment results in pigmented villonodular synovitis.

Supplementary data

Supplementary data are available at Rheumatology Online.

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