Long-term functional outcomes of diffuse pigmented villonodular synovitis of the knee after synovectomy with or without adjuvant radiotherapy

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Abstract

Background Diffuse pigmented villonodular synovitis (PVNS) of the knee is a rare benign disease that has a destructive clinical course. Reported treatment options include arthroscopic or open synovectomy with or without adjuvant radiotherapy of various doses. This study compared the long-term functional outcomes and disease control among treatment modalities and discussed 22 years of experience with radiotherapy (RT) as an adjuvant treatment for PVNS of knee.

Methods A single-center database was searched for patients who received synovectomy of knee with the pathologic diagnosis of PVNS. General data, treatment modalities, and recurrent status were retrospectively collected from medical records. Functional outcomes were evaluated by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) through phone interviews by an independent orthopedist.

Results From January 1995 to December 2017, 24 patients with diffuse PVNS of knee were identified, including 19 receiving open synovectomy (OP) and 5 undergoing arthroscopic surgery (AS). Adjuvant RT was performed on 14 patients with a median dose of 34.25 Gy (range 20-40 Gy). After median follow up of 6 years, clinically or radiographically confirmed recurrences were recorded in 10 cases. The local recurrence rate was significantly lower in the OP+RT group than the OP group (8.3% vs. 57.1%, p =0.038). Among those with preserved knee joints, there was no significant difference in the WOMAC score and stiffness score between patients in the OP+RT and OP groups.

Conclusions In conclusion, for patients with diffuse PVNS of knee, the addition of moderate-dose adjuvant RT to open synovectomy provided excellent local control while maintaining good joint function with limited treatment-related morbidity. Our study emphasized the importance of moderate dose of RT in diffuse PVNS of knee joint.

Background

Pigmented villonodular synovitis (PVNS) is a mono-articular proliferative process that originates from the synovial membranes and is also characterized by articular cartilage invasion. It is a rare, sarcoma-like, benign disease, and its incidence is about 1.8 cases per million people [1, 2, 3]. Younger patients seem to be predominantly affected, and the incidence peaks at the age of 30 to 40 years [3].
There are two distinct types of PVNS: localized and diffuse. The two types are histologically similar, but differ in the extent of synovial involvement. Diffuse PVNS presents with more pronounced symptoms and is more destructive. It has a high tendency to invade extra-articular structures, such as muscles, tendons, bones, neurovascular structures, and skin. Complete tumor removal may be challenging in patients with diffuse PVNS. The recurrence rates after surgical resection ranged from 8 to 56%, depending on the extent of surgery according to the previous study [4]. Therefore, although classified as a benign disease, diffuse PVNS could cause severe disability at a relatively young age. Despite having a high recurrence rate and possible severe joint function decline, there is a lack of strong evidence of the optimal treatment for diffuse PVNS [1, 2]. Open or arthroscopic synovectomy with or without adjuvant external beam radiotherapy (EBRT) have been reported as treatment options for diffuse PVNS. According to previous studies, the recurrence rate is higher for diffuse PVNS patients receiving arthroscopic synovectomy when compared to those who undergo open synovectomy [5, 6, 7, 8, 9, 10, 11]. Furthermore, PVNS of different anatomical locations should be analyzed separately since it influences the choices of treatment and surgical techniques. Hence, surgical modalities and affected joints should be taken into consideration when comparing clinical outcomes of diffuse PVNS. For the past decades, researches have focused on the treatment outcomes of diffuse PVNS after synovectomy with adjuvant external beam radiotherapy (RT) [12, 13, 14, 15]. Most of them are retrospective cohort studies with small sample sizes or even case reports. The results might be affected by confounding factors, such as localized versus diffuse types, affected joints, treatment modalities (open or arthroscopic synovectomy) and surgical approaches (anterior only or anterior combined posterior approach), if no proper stratification or analytical correction was done with limited case numbers [14, 15]. Furthermore, the goals of PVNS treatment are not only preventing disease recurrence, but also relieving pain and stiffness, and preserving joint function. A recent cohort study reported the long-term functional outcomes for PVNS patients, but the result of stiffness was lacking [15]. Therefore, the efficacy and long-term functional outcomes of adjuvant RT in treating diffuse PVNS of knee remained unclear [14, 15].

The purpose of the present study was to evaluate the efficacy and long-term functional outcomes in
treatments of diffuse PVNS of knee in a single medical center. Arthroscopic and open synovectomy with or without subsequent external-beam RT were compared. We hypothesized that open synovectomy with subsequent external-beam RT in treating diffuse PVNS of knee would lead to the less disease recurrence rate but more stiffness in the knee joint.

Methods

Data source and study subjects

After we received approval from the research ethics board, the pathology database of our institute was searched for patients who received synovectomy of knee with the pathologic diagnosis of PVNS. Those who had diffuse PVNS of the knee joints were enrolled. PVNS originating from joints other than knee and localized PVNS were excluded. Clinical data were retrospectively collected from medical records, image studies, surgery notes, and radiotherapy charts. The data collected included the patient’s age, sex, whether the disease was primary or recurrent, treatment modalities, radiation treatment technique, radiation dose regimens, and current disease status.

PVNS type

Localized or diffuse PVNS was determined by pre-operative magnetic resonance imaging (MRI) or operative findings. The major features of the localized PVNS were localized nodules with a clear boundary and a single or no pedicle. In diffuse PVNS, the surface of the synovial membrane is villous, and there is an extensive involvement of the adjacent vessels and nerves.

Study endpoints

The primary endpoint was functional outcomes and the secondary endpoints included local control and skin reaction. Functional outcomes were evaluated by the standardized questionnaire of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC score) through phone interviews by an independent orthopedist. The degree of hyperpigmentation, hypoalgesia, and any skin changes of the affected knee were scored by the RTOG (Radiation Therapy Oncology Group) scoring system.

The WOMAC score is widely used in the evaluation of hip and knee osteoarthritis. It is a self-administered questionnaire consisting of 24 items that are divided into three subscales: pain,
stiffness, and physical function. It is scored from 0 to 100, with higher the score denoting less perceived disability. The WOMAC score provides a more comprehensive assessment of patients’ subjective perception than the Four Functional Categories Assessments which was previously applied [15]. It is also easier to understand than the Toronto Extremity Salvage Score (TESS) and functional rating systems of the Musculoskeletal Tumor Society (MSTS), especially in conversations through a phone interview [15]. Therefore, the WOMAC score was used.

Local control was defined as: 1) the absence of clinical evidence of disease (including joint effusion, swelling sensation, and locking of the joint) for at least 2 years after treatment or 2) stable disease in MRI imaging for at least 2 years after treatment.

Statistics

Data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS, version 22.0). Considering the small sample size, nonparametric statistics with Fisher’s exact test was performed for categorical variable with a 95% confidence interval (CI). The mean WOMAC score of 90 was used to stratify the study cohort for analysis (WOMAC >90 vs. WOMAC <=90). A mean stiffness score of 6 was also used as a cut-off (stiffness score>6 vs. <=6). The correlation between WOMAC score and RT dose as continuous variables was evaluated by logistic regression.

Results

Study population and treatment modalities.

From 1995 to 2017, 40 consecutive histologically proven cases of PVNS were found. Seven cases were excluded due to localized PVNS, and nine were excluded due to origins other than knee joint. Twenty-four patients with diffuse PVNS of knee were included, including 13 women and 11 men. The mean age was 40.4 years (range 19-65 years) (Table 1). Of the 24 patients, the majority were treatment-naïve without previous surgical interventions or RT before the index operations to the affected knee. Only one patient had undergone a previous synovectomy.

Twelve patients underwent open synovectomy and received adjuvant RT (OP+RT), seven underwent open synovectomy alone (OP), two underwent arthroscopic synovectomy and received postoperative RT (AS+RT), and three underwent arthroscopic synovectomy alone (AS).
After synovectomy, 58.3% (14/24) of the patients received adjuvant external-beam RT by three-dimensional (3D) conformal or intensity-modulated radiation therapy (IMRT) technique. The median RT dose delivered was 36 Gy (range, 20-40 Gy) with a median of 16 fractions (range, 10-20 fractions). Most patients (n=11) received 30-36 Gy in 14-18 fractions (Table 2). No patient was treated with intra-articular yttrium-90. No patient suffered from wound breakdown, and there was no episode of deep infection. There was also no case of severe skin reaction (skin reaction greater than grade 2 on the RTOG grading system).

**Incisions of open synovectomy**

In our hospital, posterior synovectomy was not a routine procedure for diffused PVNS. The choice between treatment of open anterior with or without posterior approaches of synovectomy was mainly based on the pre-operative MRI. The combined posterior approach of synovectomy was adapted when the anterior or posterior cruciate ligament was extensively invaded by PVNS. Among the study cohort, there were 11 cases receiving combined open anterior and posterior synovectomies. There was no case of combined anterior arthroscopic and posterior open synovectomy.

**Local recurrence**

After a median follow-up of 6 years (range 2-15 years), the overall local recurrence rate was 41.7% (10 of 24 patients), including 6 demonstrating progression with gross disease on post-treatment MRI and 5 receiving re-operation of the affected knee with documented recurrences. Comparing the outcomes among treatment modalities, there was a significantly higher local control rate with open synovectomy and adjuvant RT (Supplementary Table 1). When focusing on those receiving open synovectomy, the local control benefit of adjuvant RT was still apparent, with a local recurrence rate of 8.3% in the OP+RT group versus 57.1% in the OP group (p=0.038) (Table 3).

**Adverse effects**

With moderate dose and the use of 3D conformal and IMRT technique, the acute and long-term toxicities of external beam radiotherapy were relatively mild in our study. There was no case of surgical wound breakdown nor deep wound infection recorded in those receiving adjuvant RT.
Furthermore, there was no grade 2 or greater long-term skin reaction nor soft tissue edema.

**Overall Functional outcomes**

Among the 24 cases, 4 patients were excluded from WOMAC score evaluation due to receiving total knee arthroplasty of the affected joints for progressive osteoarthritis after the index treatments, including 3 receiving open synovectomy and 1 arthroscopic synovectomy, all without adjuvant radiotherapy. There were 20 patients with preserved knee joints at recruitment and 19 completed functional outcome measures through phone interviews while 1 refused the interview. Their mean WOMAC score was 88 (range 48-100) (Tables 3-4). After long-term follow-up, neither the total WOMAC score nor stiffness score was significantly different between those who received adjuvant RT and those who did not, in both overall and the open synovectomy group (Table 4, Supplementary Table 1). Overall, the mean WOMAC score for the 4 patients receiving OP alone was 84. (Table 3.) An extremely poor functional outcome was reported in a 59-year-old female presented (WOMAC score=48). She first received open anterior and posterior synovectomy without adjuvant RT. However, local recurrence was noted and she underwent re-operation once in other hospital. According to the statement of the patient, there are difficulties going up and down the stairs, as well as arising from a sitting position. She also reported persistent joint pain and stiffness at the 5-year post-operative follow-up with a WOMAC stiffness score of 4, WOMAC pain score of 9, and WOMAC physical function score of 35. On the other hand, the mean WOMAC scores of the 6 patients receiving OP+RT was 91.6. (Table 2. and Table 3.) Extremely poor function was not observed.

To analysis the impact of adjuvant RT and disease recurrence on joint function, further analysis was performed, excluding those who received TKA. The proportion of patients with good functional outcomes (WOMAC score >90) was higher among those without recurrent disease (8/12 without recurrent PVNS versus 3/7 for those with recurrent PVNS). However, the correlation between recurrence and poor WOMAC score was not statistically significant ($p=0.226$). When testing the effect of adjuvant RT, rates for good functional outcomes were 61.5% (8/13) for those receiving adjuvant RT, which was higher than 50% (3/6) for those without adjuvant RT, though no statistically significant difference found. Regressions between the WOMAC score as continuous variable and the dose of
Discussion

The main finding of our study clearly showed that for diffuse PVNS of knee, 1) arthroscopic synovectomy resulted in a higher recurrence rate than open synovectomy; 2) adjuvant RT might improve local control, which is also true for those who undergo open synovectomy; 3) after long-term follow-up, adjuvant RT was not associated with worse stiffness or worse WOMAC functional outcomes, which is also a new contribution to the current literature.

**Open or arthroscopic synovectomy**

In previous studies, arthroscopic synovectomy was linked with higher PVNS recurrence rate when comparing to open synovectomy. A retrospective study published in 2011 indicated that there was limited access to the affected joint during arthroscopic surgery in 52.9% (9/17 cases) of patients [14]. Blanco et al. has reported that arthroscopic synovectomy alone was insufficient to eliminate all affected tissue, which was consistent with the finding in our study [10]. In another retrospective cohort study in 2015, recurrence rate of 36% (35/97), 58% (69/118), and 50% (5/10) were reported for open, arthroscopic, and arthroscopically-assisted mini open synovectomy, respectively [11]. These studies support the necessity of evaluating the effects of different surgical modalities, open or arthroscopic synovectomy. However, limited studies had compared patient outcomes according to different treatment modalities that they received [5, 11,12,13,14,15]. Having such different local control outcomes, the surgical modalities should be taken into consideration when comparing the clinical results.

**Adjuvant RT**

A meta-analysis including 35 retrospective studies comparing treatment outcomes of PVNS indicated that post-operative RT had additional local control benefit following synovectomy for diffuse PVNS. However, some of the included studies were low-quality evidences with high heterogeneity, including various affected joints, different evaluation tools of stiffness, and distinct diagnostic criteria of recurrences [16]. Griffin et al. assessed the efficacy and long-term functional outcomes of adjuvant RT in 50 patients with diffuse PVNS, including 60% of them having multiple surgeries before receiving
EBRT [15]. Local control was achieved in 94% patients after a mean follow-up of 94 months, which compared favorably with others reported in recent literatures. Nevertheless, this study did not evaluate the difference of open versus arthroscopic synovectomy and there were only a small portions of patients (14 out of 50) completed the evaluation of functional outcomes. Among the 14 patients, 4 cases were rated as having poor function, leaving some concerns about long-term adverse effects of RT.

Comparing to previous studies, our study focused on the functional outcomes of patients with diffuse PVNS of knee with or without EBRT after receiving open surgery [5,11,12,13,14,15]. Having 95% of those with preserved affected knee joints completing functional evaluation with WOMAC score, adjuvant EBRT was not associated with worse knee function nor poorer stiffness. The local control benefit of adjuvant EBRT was still present for those receiving open synovectomy. Furthermore, the results also showed a non-significant decrease in stiffness and poor activity following EBRT, which are contrary to the previous understanding. This might be explained by a reduced rate of recurrence and thus prevent soft tissue scarring resulting from multiple surgeries, although no statistical significance was observed between recurrence and WOMAC score according to Fisher’s test ($p=0.226$). (Table 5.)

The lack of statistical proof of the association between disease recurrence and poor functional outcome might cause by small sample size and possible selection bias. By excluding the 4 patients receiving total knee arthroplasty having the worse clinical conditions, the analytic power of association between recurrence and poor function might be weakened.

**Radiation toxicity and radiation dose**

Progress in RT techniques, such as 3D conformal or IMRT techniques, might improve the complication rate of adjuvant RT over time. With the 3D conformal and IMRT technique, the radiation toxicities in our study were relatively mild. No acute wound complication was noted, and the long-term toxicity of radiation did not significantly affect functional outcome. Griffin et al. studied 50 patients who received surgery and adjuvant RT [15]. Only one patient receiving synovectomy followed by RT with 30 Gy in 15 fractions was reported to have septic arthritis of the involved knee joint 2 years after the index treatment. Mollon et al. reported similar results to our study [16]. Although there have been concerns
about the adverse effects of RT on joint function, overall stiffness was comparable between groups (3.6% in those who received RT vs. 8.0% in those who did not).

The benefit of postoperative EBRT for diffuse PVNS is well recognized, but there is no consensus on the total dose of RT at present. Berger et al. reported on 7 patients who were treated with a total dose of 30 to 50 Gy postoperatively [12]. They were followed up for 29 months and showed no recurrence or late radiation reactions. Park et al. reported that the effect of low-dose radiation therapy at 20 Gy was similar to that of a moderate dose about 35 Gy [14]. Griffin et al. used EBRT with a mean dose of 39.8 Gy (range 24-50 Gy in 13-25 fractions) [15]. Most patients (26 of 50 patients) received 35 Gy in 14 fractions. And 23 of the 26 patients achieved local control at a mean follow-up of 94 months. Overall, 41 of 50 patients had good or excellent functional outcome. Therefore, it is believed that a low to moderate dose of postoperative RT can achieve a satisfactory local control rate and preserve the limb function.

Limitations
The limitations of our study included small sample size and possible selection bias due to retrospective nature. Five patients were excluded from the final functional analysis due to incomplete WOMAC scores. According to our medical records, four excluded patients received arthroplasty due to pain and difficulty in joint activity. In other words, our study excluded patients with extremely severe stiffness from the functional outcome evaluation, resulting in findings of a non-significant decrease in stiffness and poor activity following RT.

Conclusion
The addition of moderate-dose adjuvant EBRT following open synovectomy provided excellent local control while maintaining good function with low treatment-related morbidity for patients with diffuse PVNS of knee joint.

Abbreviations
pigmented villonodular synovitis (PVNS)
radiotherapy (RT)
external beam radiotherapy (EBRT)
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
open synovectomy (OP)
arthroscopic surgery (AS)
intensity-modulated radiation therapy (IMRT) technique

Declarations

**Ethics approval and consent to participate**

Our study was approved by the institutional review board of Kaohsiung Veteran General Hospital (VGHKS19-CT12-07). All patients provided signed informed consent to allow their clinical data to be used for research programmes.

**Consent for publication**

Informed consents were taken from all the patients for the publication.

**Availability of data and material**

The data supporting the conclusions of this article is included within the article and the supplement file.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

YP analysed and interpreted the patient data. YP and JC were major contributors to manuscript writing. CY and SW performed all the surgeries. All authors read and approved the final manuscript.

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Tables

Table 1. Patient and disease demographics

| Characteristic               | No. of Patients (%) |
|-----------------------------|---------------------|
| **Gender**                  |                     |
| Men/ female                 | 11(45.8%)/ 13(54.2%)|
| Mean age [range]            | 40.4 [19-65]        |
| **Presenting status**       |                     |
| Primary                     | 23                  |
| Local recurrence            | 1                   |
| **Disease recurrence**      |                     |
| Image proof                 | 6 (1 patient received MRI at other hospital) |
| Clinical symptoms           | 4 (3 of them received the total joint arthroplasty) |
| No evidence of recurrence   | 14                  |
| **Treatment**               |                     |
| Open synovectomy alone (OP) | 7                   |
| Open synovectomy and postoperative RT(OP+RT) | 12 |
| Arthroscopic synovectomy alone (AS) | 3 |
| Arthroscopic synovectomy and postoperative RT (AS+RT) | 2 |

Table 2. Radiotherapy delivered
EBRT: external-beam radiotherapy

*Four of the ten patients finally received the total joint arthroplasty of the affected joints because of progressive osteoarthritis post-treatment.

**One of the five patients refused to complete the WOMAC score on the telephone access, and the patient denied suffering from the clinical symptoms (joint effusion, swelling sensation, and locking of the joint) after treatment.

The correlation between WOMAC score and RT dose was checked by logistic regression, and showed no significant finding. (p=0.577)

### Table 3. Efficacy and functional outcome of the four treatment modalities

| Treatment Modality | Local recurrence rate | Mean WOMAC score of the affected knee joint (range) | Mean stiffness score in WOMAC score (range) | Fisher’s p value |
|--------------------|-----------------------|---------------------------------------------------|-------------------------------------------|-----------------|
| OP+RT              | 1/12                  | N=11                                               |                                           | 0.038***        |
|                    |                       | 91.6 (79-99)                                       |                                           |                 |
|                    |                       |                                                   |                                           |                 |
|                    |                       |                                                   |                                           |                 |
| OP                 | 4/7                   | N=4*                                               |                                           | 5.5 (4-8)       |
|                    |                       | 84 (48-100)                                        |                                           |                 |
| AS                 | 3/3                   | N=2**                                              |                                           | 8               |
|                    |                       | 69.5 (57-82)                                       |                                           |                 |
| AS+RT              | 2/2                   | N=2                                                |                                           | 7 (6-8)         |
|                    |                       | 94.5 (89-100)                                      |                                           |                 |

*Three of the seven patients finally received the total joint arthroplasty of the affected joints.

**One of the three patients finally received the total joint arthroplasty of the affected joints.

*** Comparison OP group with OP+ RT group in local recurrence at follow-up by Fisher’s test.

### Table 4. Comparison OP with OP+ RT in functional outcomes
| Treatment Modality | Approach                        | No. of patients | WOMAC score          | Stiffness score in WOMAC | WOMAC score | Fisher’s p value | V |
|--------------------|--------------------------------|-----------------|----------------------|--------------------------|--------------|------------------|---|
| OP+RT              | Anterior approach              | 5               | 79,80,96,98,98       | 6,4,6,7,8                | 7/11         | 4/11             | 5 |
|                    | Anterior and Posterior approach| 7*              | 75,90,97,98,98,99    | 8,6,6,6,8,7              | 5/11         | 4/11             |   |
| OP                 | Anterior approach              | 3**             | 100                  | 7                        | 3/4          | 1/4              | 1 |
|                    | Anterior and Posterior approach| 4***            | 48,93,95             | 4,6,4                    | 3/4          | 1/4              |   |

*One patient refused to complete the WOMAC score.
** Two patient finally received the total joint arthroplasty.
*** One patient finally received the total joint arthroplasty.

Table 5. The correlation between recurrence and WOMAC score

| Recurrence | WOMAC score | Total |
|------------|-------------|-------|
|            | <=90        | >90   |       |
| no         | 4           | 8     | 12    |
| yes        | 4           | 3     | 7     |
| Total      | 8           | 11    | 19    |

Exact significance: 0.226

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