

## Radiotherapy for Pigmented Villonodular Synovitis

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### ABSTRACT

**Objective:** To report outcomes after radiotherapy used to treat diffuse pigmented villonodular synovitis.

**Patients and Methods:** Between 1969 and 2000, 4 patients with pigmented villonodular synovitis were treated with radiotherapy at the Department of Radiation Oncology, Health Science Center, University of Florida, Florida, USA. Three patients had benign disease while the fourth developed diffuse metastases. Mean follow-up was 196 months (range, 70 to 439 months). All patients had both intra- and extra-articular involvement. Joints involved included the knee (n = 2), hip (n = 1), and spine (n = 1). Extra-articular extension included involvement of bone, muscle, nerves, and/or vessels. Two patients received radiotherapy alone and 2 patients received postoperative radiotherapy. Two patients received 35 to 36 Gy in 18 fractions, 1 patient received 18.86 Gy in 15 fractions, and 1 patient received 45 Gy in 25 fractions.

**Results:** Two patients with benign pigmented villonodular synovitis were locally controlled; 1 patient progressed after 18.86 Gy. The patient with malignant pigmented villonodular synovitis developed a local recurrence and died with disseminated metastases 85 months after radiotherapy. No patient developed a late complication.

**Conclusion:** These limited data and a review of the literature suggest that moderate-dose radiotherapy may control benign diffuse pigmented villonodular synovitis. It is unlikely that radiotherapy alone will control malignant pigmented villonodular synovitis.

**Key words:** Synovitis, pigmented villonodular; Radiotherapy

### INTRODUCTION

In 1941, Jaffe et al defined pigmented villonodular synovitis (PVNS), bursitis, and tenosynovitis as yellow-brown villous or nodular, tumour-like lesions containing closely-compacted polyhedral cells, multinuclear giant cells, lipoid cells, and haemosiderin-containing cells.<sup>1</sup> While all 3 lesions are histologically and cytologically identical, they differ in their location. For simplicity, the lesions are commonly grouped under the term PVNS.

Lesions can be further classified into localised and diffuse forms. The localised form is often effectively treated with local excision. In contrast, diffuse PVNS is typified by widespread involvement of the synovium with

villous and coarse nodular outgrowths. Diffuse PVNS is usually treated with total or near total synovectomy and has a much higher rate of recurrence, often requiring multiple surgeries and additional therapy.

PVNS may arise in a tendon sheath (also referred to as giant-cell tumour of the tendon sheath or tenosynovial giant cell tumour) and usually occurs in the flexor tendon sheaths of the hands. Synovial lesions usually affect large joints such as the knee, hip, and shoulder, although these monoarticular lesions can affect any joint. Other documented sites include the foot and ankle,<sup>2,3</sup> temporomandibular joint,<sup>4,5</sup> sternoclavicular joint,<sup>6</sup> and spine. A few cases of multifocal involvement have been reported, all of them in children.<sup>7</sup>

PVNS is an extremely rare condition affecting only 1.8 people per million.<sup>8</sup> Therefore, treatment data are relatively sparse, especially concerning the use of radiotherapy (RT). The disease affects men and women equally<sup>8</sup> and may occur at any age, with reports describing patients as

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young as 4 years old,<sup>9</sup> although PVNS typically occurs in adults in their thirties and forties. The onset is usually insidious, often delaying diagnosis for several years. The most common presenting complaints are mild to moderate pain and swelling of the joint. Less often, patients present with a reduced range of motion.<sup>1,8,10</sup>

Biopsy of the lesion is necessary to establish the diagnosis. While computed tomography (CT) can be helpful in defining extrinsic bone erosions and excavations,<sup>11</sup> magnetic resonance imaging (MRI) is considered the best imaging modality for localised and diffuse PVNS,<sup>12,13</sup> especially during preoperative planning and postoperative follow-up. In particular, the ferromagnetic properties of haemosiderin in PVNS cause low signal intensity on T1- and T2-weighted images.<sup>11,14</sup> Occasionally, a definitive diagnosis of PVNS may be based on MRI and clinical correlation without a biopsy.<sup>15</sup>

The aetiology of PVNS has been widely disputed. Jaffe et al originally proposed an inflammatory aetiology, hence the ending 'itis'.<sup>1</sup> Other proposed aetiologies include trauma, abnormal lipid metabolism, and neoplasm. A malignant form of PVNS has been reported with metastases most often involving the lungs and lymph nodes. However, because malignant PVNS is extraordinarily rare, the aetiology remains unclear.

This report describes the authors' experience using RT to treat the diffuse form of PVNS. The pertinent literature is reviewed, with an emphasis on patients with malignant PVNS associated with metastases.

## PATIENTS AND METHODS

Between 1969 and 2000, 4 patients with biopsy-proven diffuse PVNS were treated at the Department of Radiation Oncology, Health Science Center, University of Florida, Florida, USA (Table 1).

The pathologic specimens were reviewed and reconfirmed as PVNS. One patient had previously untreated PVNS and 3 patients had PVNS that had recurred after prior surgery. The joints involved included the knee (2 patients), hip (1 patient), and spine (1 patient). Two patients were women and 2 were men. The mean age was 56 years (range, 41 to 66 years). The patients who were treated for recurrent PVNS underwent a median of 3 surgeries (range, 2 to 3 surgeries) before RT. All 4 patients had diffuse PVNS with intra- and extra-articular involvement, including local invasion of bone, muscle, nerves, and/or blood vessels.

All 4 patients had clinical and/or radiographic evidence of gross disease prior to treatment and all were irradiated with megavoltage external beam RT. Two patients were treated with subtotal resection and postoperative RT and 2 patients were treated with RT alone. Two patients received 35 to 36 Gy in 18 fractions, 1 patient received 18.86 Gy in 15 fractions, and the remaining patient received 45 Gy in 25 fractions. All patients were treated with once-daily fractionation. The mean follow-up was 196 months (range, 70 to 439 months).

## RESULTS

The treatment outcomes are summarised in Table 1. Two patients with benign PVNS were locally controlled and

**Table 1.** Clinical and pathologic data of 4 patients treated with radiotherapy.

Patient number	Joint	Age (years)/sex	History	Local invasion	Disease status at time of radiotherapy	Radiation dose/number of fractions	Final status
1	Hip	52/Female	1st recurrence 30-year history	Thigh	Gross residual (subtotal resection 1 year before RT)	18.86 Gy/15 fractions	Local recurrence necessitating total hip replacement Alive and disease free at 439 months
2	C3-C4 Vertebrae	41/Female	Previously untreated 8-month history	Paraspinus musculature and soft tissues	Gross residual (subtotal resection 4 months before RT)	45 Gy/25 fractions	Alive with no evidence of disease at 70 months
3	Knee	66/Male	1st recurrence 25-year history	Extension into calf muscles	Gross disease (previous resection 25 years before and biopsy 5 years before RT)	36 Gy/18 fractions	Dead with intercurrent disease at 90 months
4	Knee	66/Male	2nd recurrence 3-year history	Bone involvement Encasement of nerves and vessels	Gross residual (repeat total synovectomy 4 months before RT)	35 Gy/18 fractions	Dead with malignant disease at 85 months

Abbreviation: RT = radiotherapy.

one patient developed disease progression and required surgical intervention. The latter patient received the lowest RT dose in the series. The patient with malignant PVNS developed a recurrence necessitating surgery and subsequently experienced distant metastases, which proved fatal. A summary of his case follows. No patient developed significant complications due to RT.

### Case Report

A 66-year-old white male (patient 4) presented in May 1987 having undergone a repeat total synovectomy of his left knee in January 1987. His surgical history included total knee arthroplasty for arthritis, possibly secondary to PVNS, in 1983 and a synovectomy for a mass in the left knee in 1984, which revealed PVNS. The patient subsequently noted progressive enlargement of a mass involving the medial and anterior aspects of the left knee. He was asymptomatic and followed radiographically until January 1987 when bone destruction inferior to the medial aspect of the tibial plateau was observed. Preoperative MRI showed an extensive mass surrounding the left knee with invasion of both the distal femur and proximal tibia as well as encasement of the neurovascular bundle. The patient underwent a total synovectomy, and was found to have recurrent diffuse PVNS. Ninety percent of the tumour was removed; due to encasement of the neurovascular bundle, it was not possible to perform a limb-sparing gross total resection.

Examination prior to RT revealed an ill-defined soft tissue mass involving the medial aspect of the knee with extension to the popliteal fossa. Extension of the left knee joint was within 5° to 10° of normal; flexion was markedly reduced to 90°. There was 1+ pitting oedema of the left lower extremity.

The initiation of RT was delayed until May 1987 due to a family illness. The patient subsequently received 35 Gy in 18 fractions with once-daily RT. No regression of PVNS was observed at the completion of treatment.

A left above-knee amputation was performed in March 1988. The following year recurrent PVNS was observed in the left groin and resection was performed. Failure was subsequently observed in the groin and pelvis and another resection was performed in March 1991; pathology again revealed PVNS. The patient developed another recurrence in the left medial thigh and hip and the right lateral hip and underwent additional surgery in December 1991. The patient was also found to have

pulmonary metastases in 1991. Fine-needle aspiration verified that these metastases were likely due to PVNS and the patient underwent 2 short courses of palliative RT to the lung. The patient experienced a good response to the palliative RT and subsequently died in June 1994 with disseminated PVNS.

## DISCUSSION

### Surgery

Surgery is the mainstay of treatment for PVNS. Localised PVNS may be successfully treated with local excision,<sup>3,16,17</sup> whereas the standard treatment for diffuse PVNS is total synovectomy.<sup>2-6,11,16-19</sup> Both arthroscopic and open techniques have been employed. Recurrent lesions are sometimes treated with repeat excision followed by RT to treat residual disease. Amputation is reserved for uncontrollable progressive PVNS.

### Chemotherapy

Chemotherapy has not had a traditional role in the treatment of PVNS. However, Kroot et al recently reported a 30-year-old patient with recurrent disease treated with anti-tumour necrosis factor (TNF) monoclonal antibody (infliximab) for 54 weeks, after failing previous synovectomy and intra-articular yttrium 90 (<sup>90</sup>Y) treatment.<sup>20</sup> Infliximab was chosen because immunohistochemical analysis of the lesion had shown infiltrates of CD68-positive macrophages with abundant staining for TNF- $\alpha$ . By the end of treatment, the patient had improved activities of daily living, could stand without pain, and had stable PVNS documented by MRI.

Subsequently, Finis et al analysed the gene expression of 11 samples of PVNS using genome-wide complementary DNA microarrays, polymerase chain reaction, and immunohistochemical analysis.<sup>21</sup> A high expression level of TNF was found in the lesions, similar to the expression observed in rheumatoid arthritis. The PVNS samples were also found to have overexpression of both pro- and anti-apoptotic genes. The authors speculated that anti-apoptotic mechanisms predominate over pro-apoptotic mechanisms based on the high levels of DNA strand breaks and lack of apoptotic fractions. Thus, activation of apoptosis might have a role in the future treatment of PVNS.

### Radiotherapy

RT has traditionally been reserved for recurrent and/or incompletely resectable PVNS.<sup>2,4,19</sup> However, in the past decade, limited data indicate that RT may control PVNS with a low risk of long-term complications.

O'Sullivan et al reported 41 patients with PVNS treated with RT at the Princess Margaret Hospital, Toronto, between 1972 and 2003.<sup>22,23</sup> Eighteen patients presented with previously untreated PVNS and 23 had recurrent disease with prior treatment. All but one patient had both intra- and extra-articular disease and, without exception, the diffuse subtype of the disease. Patients received moderate-dose RT, usually 35 Gy in 14 fractions. With a mean follow-up time of 77 months, 40 of 41 patients (98%) had local control after RT. No patient required amputation or experienced a serious RT complication. The authors' recommendations for treatment of diffuse PVNS included gross total resection followed by moderate-dose RT to treat residual disease. Alternatively, they suggested that control of gross disease could be obtained with RT alone.

Kotwal et al reported their experience with 48 patients with PVNS of the tendon sheath treated with either surgery alone (34 patients) or followed by postoperative RT (14 patients).<sup>24</sup> Those patients selected for adjuvant RT had either mitotic figures or incomplete excision and received approximately 20 Gy in 10 fractions. No recurrences were seen in the RT group, whereas 2 patients in the non-irradiated group had a recurrence. No RT-related complications were observed.

Blanco et al conducted a prospective study on 22 patients with previously untreated diffuse PVNS treated with combined partial arthroscopic synovectomy and RT consisting of 26 Gy in 17 fractions.<sup>25</sup> Three patients (14%) experienced recurrence within 1 year and were treated with repeat arthroscopic synovectomy. No RT complications were observed.

Intra-articular injection of radioactive material has also proven effective. Shabat et al treated 10 patients (6 previously untreated and 4 recurrent lesions) with diffuse PVNS involving the knee, ankle, or hip.<sup>26</sup> All the patients were treated with surgical debulking (subtotal synovectomy) followed by intra-articular injection of 15 to 25 mCi (555-925 MBq) of <sup>90</sup>Y 6 to 8 weeks after surgery. With a mean follow-up of 6 years, 9 patients had no evidence of PVNS and 1 had stabilisation of disease. No significant complications were reported.

Chin et al reported 30 patients with recurrent PVNS who underwent total synovectomy followed by intra-articular instillation of 300 mCi of dysprosium-165.<sup>19</sup> With a mean follow-up of 5.3 years, 5 patients (17%) had a recurrence.

Kat et al used radiosynovectomy for 11 patients (7 previously untreated and 4 recurrent lesions).<sup>27</sup> <sup>90</sup>Y was used for knee lesions while rhenium 186 was preferred for hip lesions. Two patients underwent repeat radiosynovectomy within 4 months of the first treatment due to a relapse of symptoms. At the 1-year follow-up, PVNS was clinically and radiographically controlled in all patients.

### **Malignant Pigmented Villonodular Synovitis**

The aetiology of PVNS has been the subject of debate since Jaffe first described the disease in 1941.<sup>1</sup> Many investigators today believe the lesion to be a neoplasm based on the tendency to recur, lack of inflammatory features, presence of chromosome abnormalities and monoclonality, and invasive growth and (rarely) metastases.

In 1984, Rao and Vigorita analysed the histological features of 81 patients with lesions treated at the Hospital for Special Surgery, New York, USA, and concluded that PVNS is a benign synovial neoplasm.<sup>28</sup> Reasons given to refute the inflammatory theory included insignificant degree of inflammation, centrifugal growth pattern, propensity for recurrence after inadequate removal, lack of characteristic changes in adjacent tissues, and no relationship between the degree of fibrosis and duration of symptoms or size of the lesion.

Several chromosomal abnormalities have been reported to be associated with PVNS.<sup>29-32</sup> Ray et al,<sup>29</sup> Choong et al,<sup>32</sup> and Ohjimi et al<sup>31</sup> used karyotyping, while Layfield et al<sup>30</sup> used fluorescence in situ hybridisation (FISH) to analyse metaphases from short-term cultures demonstrating small but significant numbers of cells with trisomies involving chromosomes 7 and/or 5. Subsequently, Fletcher et al used FISH to demonstrate trisomy 7 in both cultured and uncultured PVNS cells.<sup>33</sup> However, non-neoplastic disease processes such as rheumatoid arthritis, osteoarthritis, and haemorrhagic synovitis may contain cells that exhibit trisomy 7.<sup>34</sup>

In contrast, Sackers et al<sup>35</sup> and Vogrinic et al<sup>36</sup> have demonstrated polyclonality in a patient with PVNS of the knee and 7 patients with giant cell tumour of the tendon sheath, respectively, using X-chromosome inactivation. These authors concluded that PVNS is more likely to be a reactive process rather than a true neoplasm. Another explanation for these findings is that polyclonality may be the result of heterogeneity within the tumour with a neoplastic-like process beneath the

synovial membrane and secondary inflammatory changes located at the periphery of the lesion,<sup>32</sup> as described by Rao and Vigorita.<sup>28</sup> Another explanation would be that localised lesions are actually reactive granuloma, while diffuse lesions might represent a separate neoplastic process.<sup>37</sup>

Criteria for 'malignant giant cell tumour of the tendon sheath' have been outlined by Enzinger and Weiss and included either a benign giant cell tumour/PVNS coexisting with frankly malignant areas or, alternatively, a malignant-appearing recurrence when the original lesion was typical benign giant cell tumour/PVNS.<sup>38</sup> Subsequently, Bertoni et al based their criteria for malignant PVNS on histologic appearance and whether or not benign disease coexisted with, or preceded, the diagnosis of cancer.<sup>39</sup> Bertoni et al's criteria for malignant PVNS included the following:

- a nodular, solid infiltrative pattern of the lesion
- large, plump, round or oval cells with deep eosinophilic cytoplasm and indistinct borders
- large nuclei with prominent nucleoli
- necrotic areas
- absence of a zonal pattern of maturation.

PVNS is widely known to have the propensity to invade extra-articular soft tissue and bone. On the other hand, metastatic disease is an extremely rare finding. The most common sites of metastases include the lungs and regional lymph nodes. Kahn summarised 5 papers on 'malignant giant cell tumour of the tendon sheath' with 8 cases of metastases.<sup>40</sup> All of the cases of PVNS involved either the hand, wrist, or foot and histologically resembled the benign giant cell tumour of the tendon sheath. Bertoni et al described 8 cases of malignant PVNS and added 7 other case reports<sup>39</sup> published since Kahn's review. Overall, 20 of 25 patients (80%) developed disseminated PVNS.

Localized PVNS can be effectively treated with local excision. In contrast, diffuse PVNS has a high likelihood of recurrence after total or subtotal synovectomy. Moderate-dose external beam RT may reduce the risk of recurrence in patients with recurrent and/or incompletely resectable PVNS with a low risk of complications. Patients with postoperative residual PVNS are considered for RT regardless of whether the lesion was previously untreated or recurrent after a prior operation. It is unclear whether the likelihood of local control is higher after a gross total resection with postoperative RT for microscopic residual PVNS compared with RT

for gross disease. In general, these authors' preference is to remove all gross PVNS prior to RT if it is resectable. Definitive RT is preferred for patients with incompletely resectable or unresectable PVNS.

Malignant PVNS is rare and is associated with a high risk of dissemination. RT may be used to palliate symptoms associated with metastases; the probability of controlling gross disease in the long term with RT alone is poor.

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