
ORIGINAL ARTICLE

The Role of Radiotherapy in the Treatment of Pigmented Villonodular Synovitis

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ABSTRACT

Background: This article reviews our 47-year experience of radiotherapy (RT) as adjuvant treatment for histologically confirmed pigmented villonodular synovitis (PVNS).

Methods: We identified seven women and two men with diffuse PVNS of the knee (n = 8) or hip (n = 1) who were treated with postoperative RT between 1969 and 2015 at the University of Florida. The median patient age was 59 (range, 39-79) years. The median follow-up was 5.5 (range, 2.1-26.0) years. All patients received megavoltage external-beam RT using three-dimensional conformal techniques. The median RT dose was 36 (range, 19-45) Gy in a median of 18 (range, 13-36) fractions; four patients received twice-daily fractionation, and five once daily.

Results: Of the nine patients, five had clinically and / or radiographically stable disease or were disease-free; three failed to achieve local control; and one had a questionable local recurrence based on magnetic resonance imaging 4 months later. None had acute or long-term complications from RT.

Conclusion: Synovectomy and watchful waiting remains the primary management for PVNS. In cases of extensive disease with incomplete excision and / or local recurrence, local RT should be considered.

Key Words: Radiotherapy; Synovitis, pigmented villonodular; Treatment outcome

中文摘要

放射治療在治療色素性絨毛結節滑膜炎的應用

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背景：本文回顧我們47年應用放療作為輔助手段治療色素性絨毛結節滑膜炎（PVNS）的經驗。

方法：回顧分析7名女性和2名男性患有膝（8例）或髖（1例）關節PVNS並在1969年至2015年在佛羅里達大學接受術後放射治療的患者。患者的年齡中位數為59歲（範圍：39-79歲）。中位數隨訪期為5.5年（範圍：2.1-26.0年）。所有患者接受兆伏級外束三維適形技術放射治療。劑量中位數為36 Gy（範圍：19-45 Gy）；分為13-36次給予照射（中位次數：18次）。4名患者接受每日2次的分次治療，5名接受每日一次分次治療。

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結果：在9名患者中，5名病情穩定或無疾病；3名未能控制局部病變；1名4個月後磁共振成像疑似局部復發。沒有患者發生放療導致的急性或長期併發症。

結論：滑膜切除和觀察等待仍然是治療PVNS的主要方法。在不完全切除和/或局部復發的大範圍病變的情況下，應考慮局部放射治療。

INTRODUCTION

Pigmented villonodular synovitis (PVNS) is a benign, locally aggressive, neoplastic process of the joints, particularly the synovial membrane or tendon sheaths. PVNS can affect various joints, with 1.8 new cases per million persons per year.¹ Studies from the US and UK report a greater prevalence among males,²⁻⁴ whereas retrospective studies in China report a female predominance,^{5,6} as do series from France, Portugal, and Italy.⁷⁻⁹ PVNS usually occurs in the age of 30s^{3,5,7} or 40s to 50s.^{6,10}

PVNS most commonly affects the large joints, such as the knees, hips, and ankles.⁶ There is a predilection for the knee, with rates as high as 74% and 88% of all cases.^{5,11} Rarely, PVNS occurs in the temporomandibular joint, presenting as trismus, clicking, and a painful pre-auricular mass.^{12,13} PVNS often presents with pain and swelling of the joint; proper diagnosis is often delayed from 16 months to even 5 years owing to the nonspecific symptoms.^{5,6,14-17} PVNS of the hip (the second most common site) typically presents with pain alone and does not exhibit noticeable swelling due to the deep nature of the joint.⁵

Radiographs may show effusions in the joint or a soft tissue mass. T2-weighted magnetic resonance imaging (MRI) can reveal the pathognomonic 'blooming' artefact caused by the magnetic properties of iron in the haemosiderin deposits.¹⁸ In the absence of haemosiderin deposits, MRI cannot clearly distinguish between PVNS and other types of synovial hyperplasias or arthritides; thus, pathological diagnosis is necessary.¹⁹

We reviewed our 47-year experience of treating PVNS with radiation therapy (RT) at the University of Florida and discussed RT in the management of PVNS.

METHODS

In accordance with protocols of our institutional review board, we identified seven women and two men with diffuse PVNS of the knee (n = 8) or hip (n = 1) who were treated between 1969 and 2015 at the Department of Radiation Oncology, University of Florida (Table). Seven patients were treated with postoperative RT, and two were treated with RT alone after multiple recurrences following surgical procedures. All lesions were ill-defined and composed of mononuclear, histiocyte-like cells admixed with multinucleated giant

Table. Patient and tumour characteristics.

Patient No.	Sex / age at diagnosis (years)	Tumour location	Surgical history before radiotherapy	Total dose / fractionation	Current status
1	M / 66	Right knee	1 unknown surgery 25 years earlier; 1 partial synovectomy	36 Gy / 18 fractions QD	Died of intercurrent disease at 90 months without disease progression
2	M / 66	Left knee	1 TKA; 2 synovectomies	35 Gy / 18 fractions QD	Died with disease progression at 85 months
3	F / 44	Right hip	1 synovectomy	18.86 Gy / 15 fractions QD	Disease progression until total hip replacement; disease-free for 240 months and died of intercurrent disease
4	F / 56	Right knee	3 synovectomies	35 Gy / 28 fractions BID	Stable disease at 65 months
5	F / 49	Left knee	2 synovectomies	36 Gy / 30 fractions BID	Disease recurrence at 35 months
6	F / 59	Right knee	1 arthroplasty; 2 synovectomies	45 Gy / 18 fractions QD	Disease-free at 61 months
7	F / 73	Left knee	1 TKA; 2 synovectomies	43.2 Gy / 36 fractions BID	Disease-free at 66 months
8	F / 79	Right knee	1 excision of presumed Baker's cyst; 1 TKA	36 Gy / 30 fractions BID	Stable disease at 36 months
9	F / 39	Left knee	4 synovectomies	32.5 Gy / 13 fractions QD	Questionable recurrence based on magnetic resonance imaging at 4 months

Abbreviations: BID = twice daily; QD = once daily; TKA = total knee arthroplasty.

cells, foamy histiocytes, and chronic inflammation with a prominent nodular or villous architecture and abundant haemosiderin pigment. The median patient age was 59 (range, 39-79) years. The median follow-up was 5.5 (range, 2.1-26.0) years. All patients presented with swelling, pain, or both.

All but one patient had multiple surgeries (mostly synovectomy), with a median of three (range, 1-4) surgeries prior to RT. Three patients underwent a total knee arthroplasty before RT. All patients received megavoltage external-beam RT using a three-dimensional conformal technique. Careful attention was paid to protect a longitudinal strip of tissue along the joint to preserve vascular and lymphatic collateral return and minimise risk of lymphoedema. The median RT dose was 36 (range, 19-45) Gy in a median of 18 (range, 13-36) fractions; four patients received twice-daily fractionation, and five once daily, at the discretion of the attending physician. Postoperative imaging, including MRI and bone detail radiography, was used to evaluate disease control.

RESULTS

Of the nine patients, five had clinically and / or radiographically stable disease or were disease-free; one died of intercurrent disease without progression of PVNS; and three failed to achieve local control (one died with metastatic disease progression at 85 months, one had disease progression necessitating a total hip replacement, and one recurred locally at 35 months). One patient had a questionable recurrence based on MRI at 4 months, and subsequent positron emission tomography and computed tomography. The 66-year-old man who died with metastatic disease had undergone a total knee arthroplasty for arthritic knee pain. He subsequently underwent two synovectomies that failed to control disease. RT was delivered to 35 Gy over 18 fractions once daily. The patient eventually had metastases in the left groin, hip, thigh, and lungs, and was treated with palliative RT to the lungs. He died 85 months after the initial RT. No patient had acute or long-term complications from RT.

DISCUSSION

Diagnosis of PVNS is often delayed, as its symptoms mimic arthritis. Furthermore, tissue diagnosis can be difficult to obtain with arthroscopy, and can be misinterpreted as soft tissue sarcoma.²⁰

The most common aetiology of PVNS is chronic

inflammation in the synovium, evidenced by the presence of iron deposits, macrophages, CD8 T cells, and fibrotic changes²¹ as well as elevated biomarkers such as C-reactive protein and erythrocyte sedimentation rate.⁵ PVNS has been associated with traumatic injury in as many as 75% of cases,^{2,3} probably caused by the associated inflammatory changes. When the disease is localised, it has been associated with traumatic injury in as many as 88% of cases.² One case report describes multiple tumours on the tendon sheaths of the hand linked to repetitive trauma.²² Although PVNS is characterised by polyclonality, thus ruling out a neoplastic process,²³ some lesions are characterised by monoclonality and chromosomal abnormalities, characteristic of neoplasms,²⁴ such as rearrangements and translocations on 1p11-13.^{25,26} More specifically, the translocation between 1p13, which encodes colony stimulating factor 1 (CSF1), and 2q37, which encodes (collagen type IV, alpha-3COL6A3),²⁷ results in overexpression of CSF1, which is thought to induce the chronic inflammatory process by attracting cells such as macrophages.¹⁹ Others have hypothesised that abnormal lipid metabolism is the aetiology of PVNS.^{28,29}

Synovectomy is the first line of treatment for local PVNS, whereas total synovectomy is reserved for diffuse PVNS. The issue of arthroscopic versus open surgery remains unsettled, with many reports of lower recurrence rates with arthroscopic surgery,^{6,30} possibly owing to improved visualisation and access for more complete excision.¹⁷ Arthroscopic surgery is also associated with shorter hospital stay and operation time, and less blood loss.³⁰ However, others report reduced recurrence with open surgery^{5,31-33} or no significant difference between the two approaches.⁹ The risk of relapse is greater after partial resection through arthroscopic surgery, compared with open surgery.³ The recurrence rate decreases in institutions that treat more patients with PVNS, thus suggesting the importance of an experienced surgeon in management of PVNS.³¹ Because recurrence is due to incomplete resection, especially in patients with diffuse PVNS, adjuvant therapy plays a very important role.^{34,35} In a retrospective study of 294 patients, the 5-year local control rate significantly decreased in those having an incomplete resection compared with those having a complete one (57% vs. 76%, $p = 0.0007$).⁹

Recurrence rates vary depending on the site of PVNS. Various retrospective series report a recurrence rate of PVNS in the temporomandibular joint of 9% with

synovectomy alone.^{5,13,36,37} Nonetheless, the recurrence rate in larger joints, such as the knee, has been reported to reach nearly 50%,^{35,38} with a median time to recurrence of 5 years and a 35-year recurrence rate of 35%. The recurrence rate is significantly greater with PVNS located in the knee than hip (24% vs. 6.98%, $p = 0.01$).⁵ Nonetheless, RT was not evaluated in those patients with recurrence.⁵ The recurrence rate was 40% in patients with ankle and foot PVNS treated with an excision and no adjuvant therapy.³⁹

The risk of recurrence significantly increases in the diffuse subtype over the local subtype.³¹ In a retrospective study of 294 patients, there was a significantly greater rate of local failure with the diffuse subtype compared with localised disease, with a median time to local relapse of 16 months.⁹ Given that 40% of patients with recurrence experienced multiple recurrences within 5 years of initial treatment, and that previous relapse was associated with local failure, the authors concluded that patients should not undergo curative-intent surgery after a first relapse. In a retrospective study of 107 patients, there was a precipitous fall in recurrence-free survival from 69% at 1 year to 32% at 5 years.¹¹ The discordance between a recurrence based on imaging and a recurrence based on symptoms has attributed to the difficulty in interpreting imaging due to multiple resections of synovium, radiation treatment, and disease progression that can be locally destructive.⁴⁰

RT is often reserved for recurrences after synovectomy and should be used early in the disease process before disease progression and recurrence cause destructive bone changes. In a survey by the German Cooperative Group on Radiotherapy in Benign Diseases, only 10 of 189 surveyed institutions used RT for PVNS; across 14 institutions nationwide and 41 treated sites of disease, radiation was used in 95.1% of cases after debulking surgery, with a good functional outcome in 82.9% and toxicity no worse than Radiation Therapy Oncology Group grade II.⁴¹ Many studies have demonstrated good local control and reduced risk of recurrence after surgical resection followed by external-beam RT at doses ranging from 16 to 40 Gy.^{40,42-48}

Disease may still be visible in the joint up to 12 months after radiation.⁴⁴ In a retrospective study of 173 patients, all those with primary PVNS who received postoperative adjuvant radiosynoviorthesis or RT did not recur, and 86% of patients who recurred and

subsequently received RT or radiosynoviorthesis did not recur again.³¹ Yttrium-90 silicate (⁹⁰Y) has been shown to improve inflammation but does not clear the PVNS completely.^{49,50} Nonetheless, results after synovectomy and intra-articular ⁹⁰Y are promising, with nine patients in remission and four patients exhibiting no evidence of disease after a mean follow-up of 48 months.⁵¹ Another study demonstrated local control in all 10 patients with diffuse PVNS of the knee, ankle, or hip treated with debulking surgery and ⁹⁰Y intra-articular injection.⁵² There was no recurrence in seven patients treated with debulking and ⁹⁰Y injection.⁵³ Intra-articular chromic phosphate (³²P) was used in nine patients with PVNS, three of whom had recurrence after treatment.⁵⁴

The role of chemotherapy in PVNS has not been thoroughly evaluated. There have been cases of intra-articular injections of infliximab followed by synovectomy in patients with relapsing PVNS of the knee with complete remission.⁵⁵ Infliximab, an inhibitor of tumour necrosis factor alpha (TNF-alpha), is thought to be effective due to the inflammatory state of synovial tissue in PVNS and the high levels of TNF-alpha.⁵⁶ There is evidence that imatinib, a tyrosine kinase inhibitor, may be effective for PVNS by inhibiting the CSF1 receptor, improving symptoms and reducing tumour size⁵⁷⁻⁵⁹; toxicity is associated with its chronic use.⁵⁸ One of our patients with right-knee PVNS had stable disease after RT and imatinib.

CONCLUSION

Based on the literature and our experience with diffuse PVNS, we recommend a synovectomy and close monitoring with serial MRI. Surgery and adjuvant RT should be considered if there is any radiological or clinical sign of recurrence. Patients with incompletely resected PVNS may be considered for treatment with RT alone. We use doses of 35 to 45 Gy at 1.8 Gy per once daily fraction or 1.2 Gy per twice daily fraction. We have used hyperfractionation when treating patients with soft tissue sarcomas with adjuvant RT to reduce the likelihood of late effects.

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