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The use of surgery and yttrium 90 in the management of extensive and diffuse pigmented villonodular synovitis of large joints

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Abstract

Objective. The surgical treatment of extensive diffuse pigmented villonodular synovitis (PVNS) of large joints alone is unsatisfactory, with high rates of local recurrence. Post-synovectomy adjuvant treatment with external beam radiation therapy or intra-articular injection of yttrium 90 (^{90}Y) yielded better results. We report our experience with 10 cases treated with debulking surgery followed by intra-articular injection of ^{90}Y.

Patients and methods. Between January 1989 and June 1998, 10 patients (eight males and two females aged 15–49 yr) with extensive diffuse PVNS were treated. In six patients the knee joint, in three patients the ankle joint, and in one patient the hip joint were involved. The 10 patients underwent 15 operations, one patient had three surgical procedures, and three patients underwent two surgeries (the intervals between re-operations for local recurrence were 2–4 yr). All patients had an intra-articular injection of 15–25 mCi (555–925 MBq) ^{90}Y, 6–8 weeks after the last surgery.

Results. Mean follow-up time was 6 yr (range 2.5–12 yr). All patients were followed using repeated computerized tomography (CT) scans, magnetic resonance imaging (MRI), plain X-ray films and bone scans semi-annually. In nine patients, neither evidence of disease nor progression of bone or articular destruction were noted. In one patient, stabilization of disease was achieved with no further evidence of bony or articular damage. No complications were noticed after surgery or after the intra-articular ^{90}Y injection.

Conclusion. A combination of debulking surgery with intra-articular injection of ^{90}Y for extensive diffuse PVNS of major joints is a reliable treatment method, with good results.

KEY WORDS: Intra-articular injection, Yttrium 90, Pigmented villonodular synovitis, Large joints, External beam radiation therapy.

PVNS is a benign proliferative histiocytic disorder of the synovium. In 1941, Jaffe described it as a group of synovial, tenosynovial and bursal lesions [1]. Localized and diffuse forms of synovial involvement were reported [2]. PVNS affects people in their third or fourth decades of life [3]. In most cases the disease is monoarticular and involves mainly the knee joint; the hip and ankle joints follow in frequency [3]. The lesion is rarely polyarticular [4, 5]; it has the potential to invade extensively local structures such as muscles, tendons, bones and skin [6].

PVNS should be included in the differential diagnosis when arthritis with or without a mass presents in a single major joint in young people. Joint aspiration reveals a brownish discolouration of the fluid due to the breakdown of blood products (haemosiderin) within the joint [7].

The classical appearance of PVNS on plain X-ray films is of a soft-tissue swelling or mass about the joint, with joint-space preservation. No peri-articular osteoporosis is seen [3, 8, 9]. Erosions or subchondral cysts are common, and are more prevalent when PVNS occurs at 'tight' joints, such as the hip, ankle or elbow, than in the knee [3]. No intra-articular calcifications

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are seen. Osteophytes are rare. The effusion may appear dense on plain X-ray films or CT scan due to the high iron content. MRI will show the effusion, and the haemosiderin-laden soft tissue masses will be seen as areas of low signal intensity on T_1, and especially on T_2 sequences. This is more pronounced on gradient echo than on spin-echo images. The size of the region of abnormal tissue may appear larger than the real lesion ('blooming' phenomenon) due to the magnetic susceptibility effect caused by haemosiderin [8].

Pathologically, the lesion shows dense infiltrate of polygonal or spindle cells with abundant cytoplasm and vesicular nuclei; some of the cells contain haemosiderin. Multinucleated giant cells are sometimes present, either scarcely or in large numbers. Aggregation of foamy cells can also be seen. Abundant production of collagen, fibrosis and hyalinization may be evident in patients with long-standing disease [10] (Fig. 1).

The pathogenesis of PVNS is not clear, however most authors believe it is caused by chronic inflammation [11]. Others think it is a neoplastic disorder, such as a giant cell sarcoma arising near or inside the synovial space or tendon sheath. The latter theory is supported by monoclonality and chromosomal abnormalities [12–14]. Disturbances of metabolism, trauma and haemorrhage are other possible aetiologies.

Complete excision of the mass in the affected joint is the treatment of choice in the localized form [10]. In extensive diffuse cases total synovectomy is needed, but to carry out this procedure with 'acceptable' joint damage is difficult, and in many cases almost impossible to achieve [10]. This is the reason that other treatment modalities such as radiation and intra-articular injection of ^{90}Y have been tried and shown to be effective in reducing the rate of local recurrence with 'acceptable' joint damage [15, 16]. The main long-term goal is to avoid the need for joint replacement in young people.

In few publications, ^{90}Y was injected into the joint of diffuse or recurrent PVNS with good results [15, 17]. We report our experience in 10 cases treated by surgical debulking (subtotal synovectomy) followed by intra-articular ^{90}Y.

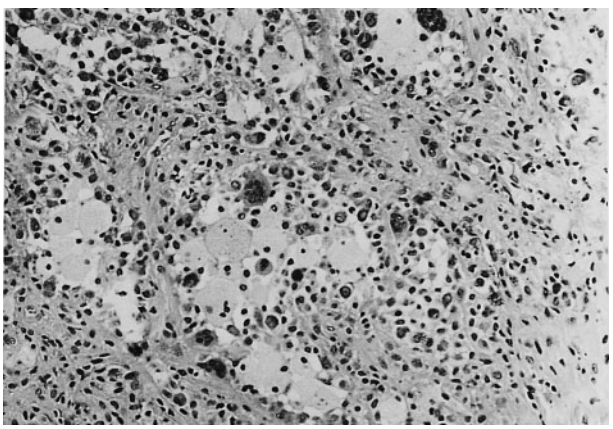

FIG. 1. Pathological specimen of pigmented villonodular synovitis. The histological picture shows mononuclear histiocytic cells, multinucleated giant cells, foamy histiocytes and haemosiderin deposits.

Patients and methods

Between January 1989 and June 1998 (9.5 yr), 10 patients with extensive diffuse biopsy-proven PVNS of a major joint were treated (Table 1; Figs 2 and 3). The patients underwent 15 surgical debulking procedures.

TABLE 1. Patient epidemiological data

Patient no.	Sex	Age at ^{90}Y injection (yr)	Anatomical location	Follow-up period (yr)
1	Male	15	Knee	12
2	Male	25	Knee	11
3	Female	35	Ankle	10.5
4	Male	29	Knee	9
5	Male	33	Hip	4.5
6	Male	40	Knee	4
7	Female	49	Knee	3
8	Male	33	Ankle	3
9	Male	27	Ankle	2.5
10	Male	38	Knee	2.5

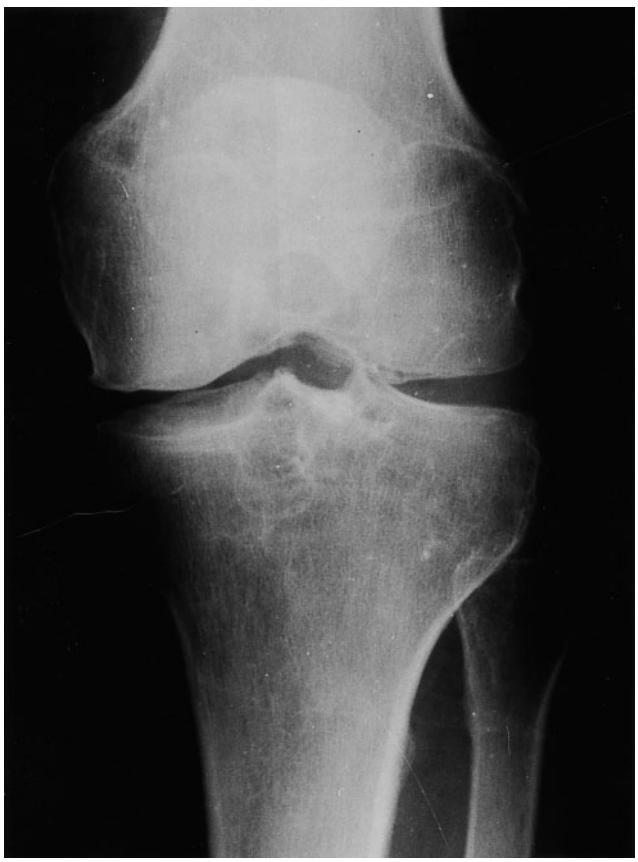

FIG. 2. Antero-posterior film of left knee: large sharply marginated erosions in both sides of the knee joint, with sclerotic rims. Normal joint space and normal bone mineralization are noted. No calcification of deposits is seen.

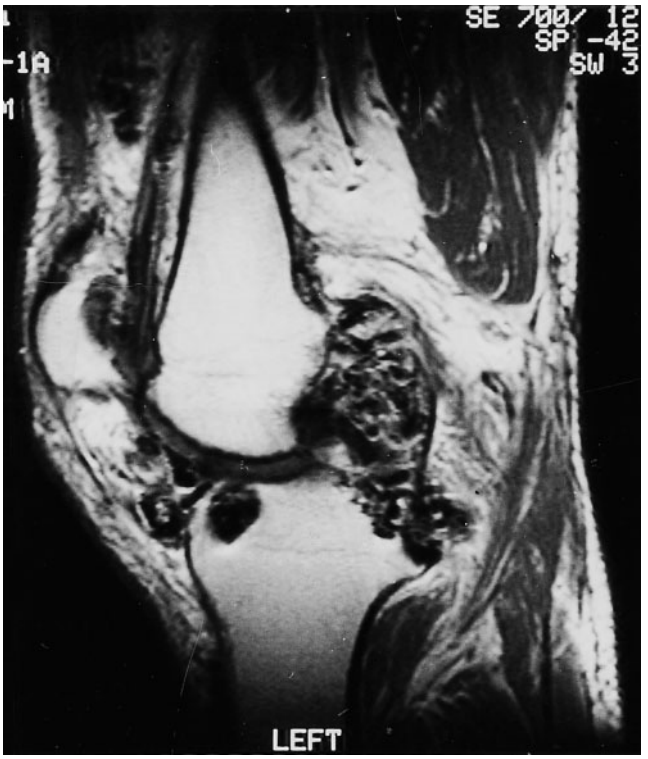

FIG. 3. Sagittal T_1-weighted MRI after gadolinium injection. Low signal nodules, indicating haemosiderin deposits, in the knee joint and within the erosions. Enhancing synovium surrounding the haemosiderin deposits indicates synovitis.

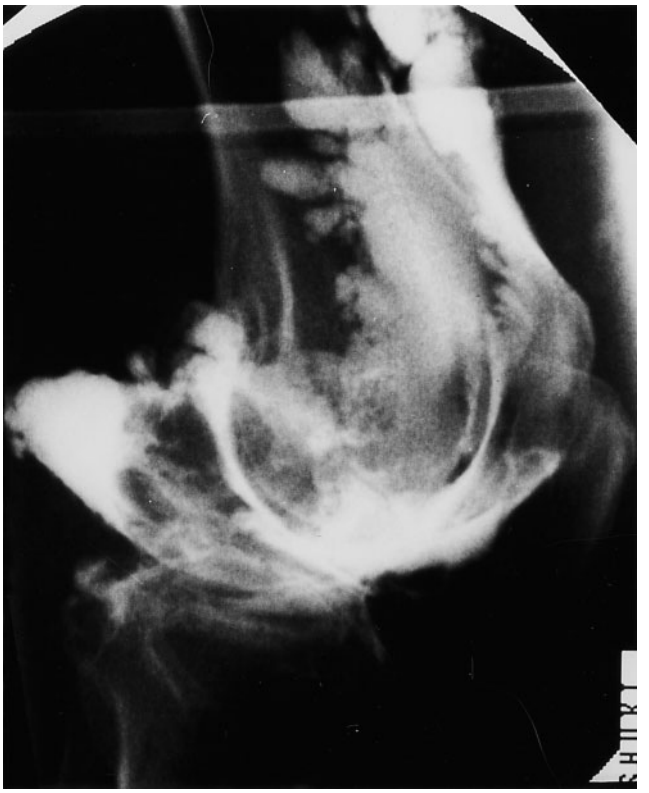

FIG. 4. Intra-operative arthrogram of a knee. Course, thickened synovium with filling defect can be seen.

Six patients underwent one surgical procedure, three patients underwent two surgical procedures (one recurrence; patients 3, 9 and 10) and one patient underwent three surgical procedures (two recurrences; patient 8). These four patients (3, 8, 9 and 10) were presented to us as a local recurrence after previous surgeries elsewhere. The intervals between surgeries were 2–4 yr, as reported by them. All of them received an intra-articular injection of 15–25 mCi (555–925 MBq) ^{90}Y (Amersham, UK) 6–8 weeks after last surgery (Fig. 4). The dose of injected ^{90}Y depends on the volume of the joint and body size. The functional and radiological status of the affected joints before last surgery and intra-articular injection of ^{90}Y were diffuse swelling and pains, with a range of motion that was reduced by approximately 25–50%. All patients used analgesic and non-steroidal anti-inflammatory drugs on a regular basis. In all cases, except for that of patient 5, only mild osteoarthritic changes were noted on plain X-ray radiographs.

^{90}Y is a beta emission colloid with a physical half-life of 64 h and a beta radiation of 2.27 MeV [18]. The maximal penetration in the synovium and cartilage is 11 and 8.5 mm, respectively [18].

The procedure was performed in the operating room. Under aseptic conditions, a needle was inserted into the affected joint and the fluid was aspirated. An arthrogram was performed in order to ensure the location of the needle and the integrity of the joint space, and only then was ^{90}Y injected. Passive movements of the joint were performed on the table to ensure spreading of ^{90}Y in the joint space. A Geiger counter, which was located around the affected joint, was used throughout the procedure to ensure no systemic leakage of ^{90}Y. A bulky dressing was placed over the joint for 48–72 h. Gradual movement of the joint and limb weight bearing were advocated after the first 3–4 days.

The patients were checked every month for the first 3–4 months using clinical joint examination for pain, tenderness, range of motion and plain X-ray films. After that, a semi-annual follow-up examination with the same protocol was performed. CT or MRI was performed 6 months after the injection and then once a year.

Results

In none of our patients was systemic leakage of ^{90}Y observed during the procedure. In nine patients, no evidence of local recurrence and no progressive bone and/or joint destruction were noted on clinical and imaging studies. No follow-up biopsies or arthroscopies were performed as it was simple to follow these patients with clinical examinations, plain X-rays, and CT and MRI in particular (see Patients and methods). In one

patient (patient 5, hip joint), stabilization of disease was achieved with no further joint damage for 4.5 yr. No complications were recorded after surgery or ^{90}Y injection: there were no post-operative infections, no wound healing problems, no deep vein thrombosis and no skin complications, such as radiation necrosis. In nine patients the functional outcome of the involved joint is excellent so far according to Enneking's criteria [19]. Patient No. 5 (hip) suffers pain and uses a cane from time to time. No difference has been found so far in terms of functional outcome between those who had one and those who had multiple previous surgeries, although the numbers of patients in this study are small.

Discussion

This series is small, with a regular distribution of ages and affected joints, but it includes only extensive diffuse PVNS of these joints in young patients. The final common pathway of this disease leads to total joint destruction, which eventually leads to the need for joint replacement [20]. This should be avoided if possible, especially in these young and healthy patients.

The traditional effective treatment for PVNS is surgical synovectomy [20]. It can be done either by arthroscopy or by arthrotomy. Arthroscopic synovectomy has reduced morbidity and is well tolerated by patients [21]. Open surgical synovectomy causes stiffness, pain and has a long recovery time, mainly after procedures involving the knee joint. Arthroscopic surgery, especially in diffuse cases, has a high recurrence rate in comparison to open synovectomy, which is still high in itself [10]. Although Flandry reported a recurrence rate of $<10\%$ in open surgical knee synovectomy over 5 yr of follow-up, in most papers the recurrence rate is between 25 and 45% [4].

Another solution should be considered if synovectomy alone might create more than reasonable damage or if the disease recurs. In either of these cases, two adjuvant treatments are available: the first is low dose radiotherapy and the second is intra-articular injection of ^{90}Y. Both methods have shown good results [15–17].

Radiation therapy is usually applied for malignant tumours as a definitive or adjuvant treatment. Radiation therapy for non-malignant conditions is infrequently used. This method of treatment has been suggested for PVNS following partial resection, where salvage of subsequent recurrence may compromise function [16].

There are few publications that deal with low-dose external beam radiation therapy for treatment of diffuse PVNS [10, 16]. The technique involves treatment of the entire circumference of the limb at joint level with $\sim$3000–4000 rad [16]. Most of these patients show improvement, although the average follow-up time is unclear. No long-term radiotherapy complications have been described. However, the long-term effects of radiation on soft tissues, bones or joints, including the risk of secondary cancer, are well known [22]. Since PVNS is still a benign disorder, the use of even low-dose radiotherapy should be considered with caution.

Approximately 40 patients who received intra-articular injection of ^{90}Y for PVNS have been described in six articles, the most recent of which was published in 1992 [15, 17, 23–26]. Most patients showed clinical improvement, which correlated in some publications to the timing of ^{90}Y injection, relative to the number of recurrences after previous surgical synovectomies. The results were better when ^{90}Y was used earlier.

The side effects of intra-articular injection of ^{90}Y are few, predictable and avoidable [26]. These include radionecrosis of the extraarticular soft tissues, febrile and local painful reactions, and leakage of radioactivity from the affected joint to the entire body via the lymph nodes [27]. The first two side effects are minor and easily treatable. Radionecrosis of the surrounding soft tissues rarely occurs if needle placement is confirmed by fluoroscopy and an arthrogram. Needle tract necrosis can be eliminated by flushing the needle with saline prior to removal. Febrile and painful reactions are usually mild, temporary and easily managed with antipyretic and analgetic drugs.

Systemic leakage of radioactivity theoretically has the potential to cause infertility [28]. With respect to ^{90}Y treatment for persistent synovitis or arthritis, with which many more patients were treated, there was no evidence of a cause and effect relationship between it and infertility [22]. None of those patients treated with intra-articular ^{90}Y injection developed infertility. Franssen measured the systemic leakage of radioactivity outside eight knees 48 h after injection of ^{90}Y [15]. Count rates were measured above the knee joint, the inguinal nodes, the liver and the heart, and were expressed as a percentage of the amount of radioactivity in the injected knee joint. The results showed that only 1% of ^{90}Y diffused outside the knee.

A theoretical problem is the risk of secondary malignant changes resulting from the treatment of a benign disease. Chromosomal damage to circulating lymphocytes is reported to occur following injection of intra-articular ^{90}Y [29]. The degree of damage closely reflected the comparative uptake of the isotope in regional lymph nodes 24 h after intra-articular injection. The risk of secondary malignant changes would be greater if the chromosomal damage in these patients were a true index of whole-body irradiation, and would suggest a possible increased incidence of leukaemia and solid neoplasms. In this situation the chromosomal changes do not represent a whole-body irradiation, but rather a selective irradiation of some lymphocytes in the regional lymph nodes [29]. Dolphin calculated that if 5 mCi of ^{90}Y are distributed evenly throughout the body, the total body irradiation would be 13 rad, and the risk of cancer induction following such a dose would be 0.4 per 1000 patients treated [30].

Among the small number of patients who were treated with ^{90}Y for PVNS and the larger number of patients who were treated for chronic synovitis or arthritis, none developed cancer. The long-term effects of ^{90}Y on the articular cartilage were considered, but review of the available literature (as performed) did not disclose any mention of such an effect until now. In our series (six out of 10 patients were <35 yr of age), no complications of any of the above mentioned types occurred. Treatment using ^{90}Y in teenagers and young adults, especially young women, is still under discussion in some quarters, where radiation therapy for non-malignant pathology is controversial. One of our patients was a 15 yr-old adolescent male, but with closed physes. We had two females in our series, the younger of whom was 35 yr old. No complications have yet occurred in this patient subgroup.

None of the reviewed articles compared low-dose radiotherapy with intra-articular injection of ^{90}Y for PVNS. Moreover, the number of patients who were treated using each method was small, and hence no firm conclusions can be drawn.

We combined ^{90}Y injection and a traditional open synovectomy, albeit a limited one, by performing debulking, leaving behind a microscopic amount of disease to be treated with intra-articular ^{90}Y. In this way we avoided the disadvantages of complete total synovectomy and the long-term hazards of external beam radiation therapy in such difficult cases.

Conclusion

In conclusion it seems that in selected patients with primary or recurrent extensive diffuse PVNS, the combination of debulking surgery followed by intra-articular ^{90}Y is a good and safe solution as a joint-saving procedure. Larger series with long-term follow-up results are needed in order to compare the available methods of treatment.

References

1. Jaffe HL, Lichtenstein L, Sutro CJ. Pigmented villonodular synovitis: bursitis and tenosynovitis. Arch Pathol 1941;31:731–65.
2. Flandry FC, Hughston JC. Current concepts review: pigmented villonodular synovitis [abstract]. J Bone Joint Surg 1987;69:942.
3. Dorwart RH, Genant HK, Johnston WH, Morris JM. Pigmented villonodular synovitis of synovial joints: clinical, pathologic and radiologic features. AJR Am J Roentgenol 1984;143:877–85.
4. Flandry FC, Hughston JC, Jacobson KE *et al.* Surgical treatment of diffuse pigmented villonodular synovitis of the knee. Clin Orthop 1994;300:183–92.
5. Wendt RG, Wolfe F, McQueen D *et al.* Polyarticular pigmented villonodular synovitis in children: evidence for a genetic contribution. J Rheumatol 1986;13:921–6.
6. Ray RA, Morton CC, Lipinski KK, Carson JM, Fletcher JA. Cytogenetic evidence of clonality in a case of pigmented villonodular synovitis. Cancer 1991;67:121–5.
7. Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant cell tumor of the tendon sheath and synovial membrane). A review of 81 cases. J Bone Joint Surg Am 1984;66:76–94.
8. Bravo SM, Winalski CS, Weissman BN. Pigmented villonodular synovitis. Radiol Clin North Am 1996; 34:311–26.
9. Lin J, Jacobson JA, Jamader DA, Ellis JA. Pigmented villonodular synovitis and related lesions: The spectrum of imaging findings. AJR Am J Roentgenol 1999;172:191–7.
10. Schwartz HS, Unni KK, Pritchard DJ. Pigmented villonodular synovitis. A retrospective review of affected large joints. Clin Orthop 1989;247:243–55.
11. Sakkers RJ, deJong D, van der Heul RO. X-chromosome inactivation in patients who have pigmented villonodular synovitis. J Bone Joint Surg Am 1991;73:1532–6.
12. Choong PF, Willen H, Nilbert M *et al.* Pigmented villonodular synovitis. Monoclonality and metastasis—a case for neoplastic origin? Acta Orthop Scand 1995; 66:64–8.
13. Fletcher JA, Henkle C, Atkins L, Rosenberg AE, Morton CC. Trisomy 5 and trisomy 7 are nonrandom aberrations in pigmented villonodular synovitis: confirmation of trisomy 7 in uncultured cells. Genes Chromosomes Cancer 1992;4:264–6.
14. Ohjimi Y, Iwasaki H, Ishiguro M *et al.* Short arm of chromosome 1 aberration recurrently found in pigmented villonodular synovitis. Cancer Genet Cytogenet 1996; 90:80–5.
15. Franssen MJ, Boerbooms AM, Karthaus RP, Buijs WC, van de Putte LB. Treatment of pigmented villonodular synovitis of the knee with yttrium-90 silicate: prospective evaluations by arthroscopy, histology and 99mTc pertechnetate uptake measurements. Ann Rheum Dis 1989;48:1007–13.
16. O'Sullivan B, Cummings B, Catton C *et al.* Outcome following radiation treatment for high-risk pigmented villonodular synovitis. Int Radiat Oncol Biol Phys 1995; 32:777–86.
17. Gumpel JM, Shawe DJ. Diffuse pigmented villonodular synovitis: non-surgical management. Ann Rheum Dis 1991;50:531–3.
18. Boerbooms AMT, Buijs WC, Danen M, van de Putte LB, Vandenbroucke JP. Radio-synovectomy in chronic synovitis of the knee joint in patients with rheumatoid arthritis. Eur J Nucl Med 1985;10:446–9.
19. Enneking WF, Spanier S, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106–20.
20. Byers PD, Cotton RE, Deacon OW. The diagnosis and treatment of pigmented villonodular synovitis. J Bone Joint Surg Br 1968;50:290–305.
21. Sim FH. Synovial proliferative disorders: role of synovectomy. Arthroscopy 1985;1:198–204.
22. Gumpel JM. Radiosynoviorthesis. Clin Rheumatic Dis 1978;4:311–26.
23. Williams PL, Gumpel JM. Use of yttrium 90 in diffuse pigmented villonodular synovitis after surgical synovectomy. J Orthop Rheumatol 1988;1:121–8.
24. Chen DY, Lan JL, Chou SJ. Treatment of pigmented villonodular synovitis with yttrium-90: changes in

immunologic features, Tc-99m uptake measurements, and MR imaging of one case. Clin Rheumatol 1992;11:280–5.
25. O'Sullivan MM, Yates DB, Pritchard MH. Yttrium 90 synovectomy—a new treatment of villonodular synovitis [letter]. Br J Rheumatol 1987;26:71–2.
26. Wiss DA. Recurrent villonodular synovitis of the knee. Successful treatment with yttrium-90. Clin Orthop 1982; 169:139–44.
27. Pavelka K, Meier-Ruge W, Muller W, Fridrich R. Histological study of effects of colloidal 90 yttrium on knee joint tissues of rabbits. Ann Rheum Dis 1975; 34:64–9.
28. De la Chapelle A, Oka M, Rekonen A, Ruotsi A. Chromosome damage after intra-articular injections of radioactive yttrium. Ann Rheum Dis 1972;31:508–12.
29. Gumpel JM, Stevenson AC. Chromosomal damage after intra-articular injection of different colloids of yttrium 90. Rheumatol Rehabil 1975;14:7–12.
30. Dolphin GW. Biological hazards of radiation. Ann Rheum Dis 1973;32(Suppl.):23–8.