Original article

Nuclear Medicine Communications

Yttrium-90 radiation synovectomy in knee osteoarthritis: a prospective assessment at 6 and 12 months

Dimitrios Chatzopoulos[a], Efstratios Moralidis[c], Pavlos Markou[d] and Vassilios Makris[b]

Objective **To assess the outcome of yttrium-90 radiation synovectomy at 6 and 12 months in patients with knee osteoarthritis unresponsive to systematic or local medical treatment.**

Methods **Consecutive patients with osteoarthritic knee pain resistant to conventional therapy and submitted to intraarticular yttrium-90 treatment because of synovial inflammation, as demonstrated by early-phase bone scintigraphy, were prospectively evaluated at 6 and/or 12 months. The assessment of the outcome of treatment was based on self-reporting of relief of knee pain limiting daily activities, measured as percentage reduction of the pretherapeutic joint discomfort with a Visual Analogue Scale. Resting and nocturnal pain also were considered, together with knee flexibility and ultrasonographic changes.**

Results **Among a total of 97 patients, a $\geq$ 50% Visual Analogue Scale pain palliation was experienced by 64 of 90 (71.1%) patients at 6 months and 50 of 69 (72.5%) at 12 months ($P=0.992$). Moreover, nocturnal and resting pain alleviation, gain in knee flexibility and regression of large joint effusions and Baker's cysts were observed in considerable proportions. In the evaluation of the outcome of treatment in 62 patients with serial assessments using a composite criterion, 42 (67.7%) versus 40 (64.5%) had a satisfactory response at 6 and 12 months, respectively ($P=0.850$). The probability of a favourable therapeutic result was inversely related to the severity of radiographic joint changes.**

Conclusion **Yttrium-90 synovectomy exerts a beneficial therapeutic effect in a substantial proportion of patients with osteoarthritic knee pain and synovial inflammation, inadequately controlled by pharmacotherapy. Clinical improvement is inversely related to radiographic knee damage.** ***Nucl Med Commun*** **30:472–479** © **2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Nuclear Medicine Communications 2009, **30**:472–479

Keywords: knee pain, osteoarthritis, radiation synovectomy, synovitis, yttrium-90

[a]Department of Nuclear Medicine, [b]3rd Department of Orthopaedics, Aristotle University, Papageorgiou Hospital, [c]Department of Nuclear Medicine, Aristotle University, AHEPA Hospital, Thessaloniki and [d]Department of Medical Physics, Health Care Unit Management, Edessa, Greece

Correspondence to Dr Efstratios Moralidis, PhD, Department of Nuclear Medicine, AHEPA University Hospital, 1 Stilp. Kyriakidi Street, Thessaloniki 54636, Greece
Tel: +30 2310 994688; fax: +30 2313 016969;
e-mail: emoral@hol.gr; emoral@med.auth.gr

Received 1 December 2007 **Revised** 12 March 2008
Accepted 12 March 2008

Introduction

Osteoarthritis of the knee is a common form of arthritis in synovial joints, is characterized by progressive loss of hyaline cartilage and periarticular bone remodeling and constitutes a major medical concern in terms of pain, disability and handicap in ageing populations [1–3]. Synovial membrane inflammation may play a critical role in disease process and it is likely that synovitis is present in most patients with symptomatic osteoarthritis, which contributes in the development of pain, limitation of movement, joint swelling and effusion [1,3–7].

The management of knee osteoarthritis aims at pain control, functional improvement and prevention or retardation of its progression [8]. Despite systemic pharmacotherapy with analgesics and anti-inflammatory drugs, intraarticular corticoid or hyaluronic acid injections in the affected joint are frequently demanded, which may afford some patients a modest and short-lived palliation of pain [8,9]. On the grounds of the inflammatory component of osteoarthritis, intraarticular treatment with β-emitting radioisotopes (radiation synovectomy) would offer a therapeutic option when other nonsurgical modalities cannot relieve symptoms.

The most extensive experience in radiation synovectomy of the knee joint has been obtained with yttrium-90 [10,11]. However, conflicting results have been reported in knee osteoarthritis with this form of treatment [12–18]. Earlier reports usually included limited numbers of patients [12–15], insufficient data were provided as often knee osteoarthritis was examined as part of a general evaluation of ^{90}Y treatment [14,16,17], dissimilar criteria for patient selection and clinical improvement

0143-3636 DOI: 10.1097/MNM.0b013e32832b52b9

were used and success rates varied over a wide range and at different follow-up intervals. Moreover, evidence of synovitis with an early-phase bone scan was not always pursued [12,15,17,18], whereas ultrasonographic findings after treatment have not been reported before.

Owing to modest results from previous publications, radiation synovectomy has been relatively rarely used in knee osteoarthritis [11]. Wider acceptance of intraarticular ^{90}Y therapy in this disease would be substantiated by stronger evidence in favour of this treatment. Therefore, this study was conducted to assess the safety and the overall efficacy at 6 and 12 months of ^{90}Y radiation synovectomy in the treatment of knee osteoarthritis and also to investigate for predictors of response.

Materials and methods

Patients' enrollment and assessment

Consecutive patients submitted to ^{90}Y radiation synovectomy for knee osteoarthritis over an 18-month period were asked to attend our outpatient clinic at 6 and 12 months after the treatment for a prospective follow-up evaluation. Some of those patients did not attend the planned posttreatment appointments regularly and other returned for reassessment between the scheduled visit dates or were lost to follow-up. Travelling distance and further management in private practice were the main reasons for incomplete outcome data. Among all patients having undergone ^{90}Y synovectomy during the study period, those assessed in our clinic at 6 or 12 months were enrolled in the study, whereas patients with inadequate documentation of the outcome of treatment at the defined time points were disregarded.

In all patients presenting with knee joint complaints and a diagnosis of osteoarthritis, the baseline assessment included a careful review of medical records and relevant blood tests, a knee orientated history, physical examination, ultrasonography, plain radiography and early-phase bone scintigraphy. This array of examinations conforms to standard evaluation of patients assessed for radiation synovectomy and in our facility it is typically carried out within the day of a patient's appointment or on the next day [19,20]. It was ensured that no patient enrolled had a history of knee joint injury or surgery, knee disorders secondary to infection or metabolic abnormalities or recognized familial disease. The diagnosis of knee osteoarthritis was independently confirmed, using widely accepted criteria [21].

Knee pain palliation after therapy and associated improvement of functional ability was based on patients' subjective judgement and expressed as percentage reduction of the pretreatment discomfort, using a Visual Analogue Scale (VAS) with endpoint markings '0 (no relief at all) to 100 (complete pain elimination)'. In an effort to limit subjectivity in self-reporting pain, before grading knee discomfort, patients were interrogated in a standardized manner including questions regarding the quality of life and the degree of handicap during daily activities, such as walking, climbing stairs, standing up, lifting weights or picking up things from the ground. The duration of symptoms was estimated from the time point patients first asked for medical attention. Resting or nocturnal pain were used as surrogate markers of disease activity and their presence or absence at baseline examination and after treatment was recorded according to patients' statement on a dichotomous scale ('absent' or 'present'). The range of motion of the affected knees was employed as an objective indicator of disease and measured from full extension to maximum flexion using a goniometer. A limitation in knee flexibility $\geq 15^{\circ}$ (maximum expected 130°) was categorized as range of motion impairment and an increase $\geq 15^{\circ}$ between the baseline and the posttreatment assessment was classified as improvement.

Patients were submitted to real-time ultrasonography for the evaluation of knees before and after ^{90}Y treatment, concerning joint effusions and Baker's cysts. The presence and amount of a joint effusion was assessed from scans through the suprapatellar recess and measurement of its maximum anteroposterior width [22]. Knee joint effusion was classified as large when this dimension was greater than 5 mm and in follow-up assessments, a measurement equal to or less than this cut-off point was accepted as large effusion regression. Moreover, the popliteal region was examined for the presence of a Baker's cyst and its longest diameter was measured. All ultrasonographic acquisitions were performed by a trained and experienced physician. Measurements were taken in duplicate and the mean value was entered in analysis. Synovial membrane thickness was not considered herein, as in our experience inflammatory hypertrophy of the synovium commonly is markedly asymmetrical and, apart from a visual impression, measurements are impractical.

At baseline evaluation, participants underwent weight-bearing posteroanterior and lateral radiography of the knees and the severity of the disease was classified according to the standard radiological Kellgren–Lawrence scale for osteoarthritis [23]: 0, no signs of osteoarthritis; 1, minute osteophytes of doubtful importance; 2, definite osteophytes but preserved joint space; 3, definite osteophytes and moderate narrowing of joint space; 4, greatly impaired joint space and sclerosis of subchondral bone. In addition, blood pool images of the knees from an early-phase bone scan were acquired to assess for elevated perfusion in the joints, reflecting synovitis. The degree of inflammation in the affected joint was assessed visually and categorized as 'mild' or 'intense' (tracer accumulation equal to or more than the adjacent soft tissues,

respectively). Knee radiographs and bone scans were interpreted by two experienced independent observers, blinded to other data; in cases of discrepancy, a consensus reading was obtained.

The criteria used to proceed to radiation synovectomy in patients with knee osteoarthritis were: (i) knee pain at stress severe enough to prevent engagement from daily activities for at least 3 months before the therapeutic procedure, resistant to systematic intake of analgesics, anti-inflammatory medication and intraarticular corticosteroid injections; (ii) early-phase bone scan findings consistent with synovial inflammation. Radionuclide treatment was not denied in patients with debilitating knee pain and advanced radiographic alterations, if they were unwilling to undergo knee arthroplasty or were poor candidates for surgery because of significant comorbidities and ill health.

Radiation synovectomy procedure

The procedure was carried out under sterile conditions with 185 MBq ^{90}Y silicate (Yttriumsilicat, Nycomed Amersham, UK) instilled in the joint cavity in combination with triamcinolone hexacetonide 20 mg to minimize reactive synovitis provoked by irradiation [11]. Then, the injected joint was immobilized in extension by an elastic knee brace and ^{90}Y bremsstrahlung scintigraphy was obtained to verify homogeneous distribution of the radioactive material within the joint cavity. Subsequently, patients were advised to rest and abstain from weight bearing of the respective knee for at least 3 days after the injection and discharged with instructions regarding radiation protection and follow-up visits. Early posttreatment presentation to the clinic was encouraged, if unusual symptoms or signs occurred.

Assessment of the outcome of treatment

The outcome of radiation synovectomy was evaluated at 6 and 12 months in terms of relief of knee pain limiting daily activities, alleviation of resting or nocturnal pain and also the change in the range of motion. In addition, for the overall assessment of the response to treatment, these primary outcome measures were combined in a composite criterion, which is described below. Ultrasonographic changes after ^{90}Y treatment were used as secondary outcome measures. Variables recorded at the baseline assessment were analyzed for the determination of factors that might have influenced responsiveness to treatment.

Statistical analysis

Continuous variables were expressed as mean ± 1 standard deviation and categorical variables as numbers or proportions. Mann–Whitney rank-sum test was used to compare two independent samples of patients and Kruskal–Wallis statistic was used in the comparison of three or four independent groups of patients, followed by Dunn's formula for further paired comparisons. The χ^2 statistic and Fischer's exact test were used for categorical data comparisons and Bonferoni's adjustment was applied as appropriate. Potential predictors of VAS improvement scores were assessed by univariate analysis and subsequently, variables with a $P \leq 0.20$ were entered in stepwise regression analysis. A P value of less than 0.05 was required for covariates to be included in the regression equation. Logistic regression analysis was used to assess the independent contribution of factors in the determination of the radiation synovectomy outcome with a $P \leq 0.10$ required for variables to enter in analysis. Statistical significance was accepted for P values less than 0.05.

Results

Patients' characteristics

There were 109 patients with single ^{90}Y treatment for knee osteoarthritis during the study period. Twelve patients had inadequate follow-up data (three with complete loss to follow-up, five with a single assessment earlier than 6 months and four returning for posttreatment evaluation in-between the planned dates). Among the remaining 97 patients, 62 had serial assessments at 6 and 12 months, 28 were assessed at 6 months only and seven had a single 12-month assessment. The baseline features of all patients are listed in Table 1. Owing to the similarities in the three groups of patients with adequate, prospectively collected, follow-up data, those patients were summed up into two groups: a population consisting of 90 patients with a 6-month assessment and a second cohort comprising 69 patients assessed at 12 months (Table 1).

During the monitoring period, no patient increased concomitant medication or was treated with intraarticular agents. Conversely, symptoms modifying drugs were discontinued after treatment in most cases. However, as some patients continued to receive a drug regimen because of disease activity in joints other than the treated knee, this information was not included.

Side effects

There was no case with compartmentation of the injected radioactive material into the joint cavity. A moderately increased joint effusion was observed in three patients within few days after treatment and arthrocentesis was performed to resolve knee discomfort. An allergy occurred immediately after one procedure, which responded promptly to antihistaminic medication and lasted for 2 days. There were no instances of needle-track or skin burns or other adverse physical effects detected at clinical visits.

The outcome of treatment

The outcome of radiation synovectomy, including ultrasonographic changes, is summarized in Table 2.

Table 1 Patients' characteristics at baseline assessment

	Patients assessed					All patients with adequate outcome data	
	At 6 and 12 months ($n=62$)	Only at 6 months ($n=28$)	Only at 12 months ($n=7$)	At other time points or lost ($n=12$)	P^a	At 6 months ($n=90$)	At 12 months ($n=69$)
Age (years)	68.5 ± 8.8	67.0 ± 8.6	69.4 ± 4.8	66.9 ± 6.8	0.760	68.0 ± 8.8	68.6 ± 8.5
Female, *n* (%)	53 (85.5)	24 (85.7)	6 (85.7)	10 (83.3)	0.998	77 (85.6)	59 (85.5)
Right/left joint, *n*	36/26	13/15	6/1	5/7	0.204	49/41	42/27
Resting pain, *n* (%)	12 (19.4)	4 (14.3)	1 (14.3)	1 (8.3%)	0.784	16 (17.8)	13 (18.8)
Nocturnal pain, *n* (%)	40 (64.5)	12 (42.9)	4 (57.1)	7 (58.3)	0.294	52 (57.8)	44 (63.8)
Pain duration (months)	30.2 ± 21.1	36.9 ± 20.5	34.3 ± 25.2	42.5 ± 20.4	0.213	32.3 ± 21.0	30.6 ± 21.4
Impaired range of motion, *n* (%)	38 (61.3)	16 (57.1)	2 (28.6)	9 (75.0)	0.248	54 (60.0)	40 (58.0)
K–L 0, *n* (%)	4 (6.5)	0	1 (14.3)	0	0.270	4 (4.4)	5 (7.3)
K–L 1, *n* (%)	19 (30.6)	14 (50.0)	2 (28.6)	4 (33.3)	0.339	33 (36.7)	21 (30.4)
K–L 2, *n* (%)	21 (33.9)	5 (17.9)	1 (14.3)	4 (33.3)	0.352	26 (28.9)	22 (31.9)
K–L 3, *n* (%)	17 (27.4)	8 (28.5)	2 (28.6)	4 (33.3)	0.982	25 (27.8)	19 (27.5)
K–L 4, *n* (%)	1 (1.6)	1 (3.6)	1 (14.3)	0	0.242	2 (2.2)	2 (2.9)
Intense blood pool, *n* (%)	31 (50.0)	18 (64.3)	2 (28.6)	9 (75.0)	0.138	49 (54.4)	33 (47.8)
Large effusion present, *n* (%)	13 (21.0)	8 (28.6)	1 (14.3)	1 (8.3)	0.511	21 (23.3)	14 (20.3)
Baker's cyst present, *n* (%)	21 (33.9)	8 (28.6)	2 (28.6)	3 (25.0)	0.911	29 (32.2)	23 (33.3)
Baker's cyst diameter (mm)	11.6 ± 18.4	13.1 ± 21.6	6.9 ± 16.9	10.8 ± 20.2	0.971	12.1 ± 19.3	11.1 ± 18.2

There were no significant differences in the comparison between all study participants assessed at 6 months versus those with an assessment at 12 months.
K–L, Kellgren–Lawrence radiographic grade.
[a]Comparison of the first four groups of patients.

Table 2 The outcome of yttrium-90 synovectomy at 6 and 12 months

	Patients with serial assessments			All study participants		
	6 months ($n=62$)	12 months ($n=62$)	*P*	6 months ($n=90$)	12 months ($n=69$)	*P*
VAS improvement (%)	65.3 ± 21.3	59.5 ± 27.4	0.148	62.4 ± 25.1	60.6 ± 26.9	0.697
VAS improvement ≥ 10%, *n* (%)	62 (100)	59 (95.2)	0.244	86 (95.6)	66 (95.7)	1.000
VAS improvement ≥ 30%, *n* (%)	60 (96.8)	54 (87.1)	0.095	83 (92.2)	61 (88.4)	0.588
VAS improvement ≥ 50%, *n* (%)	46 (74.2)	45 (72.6)	1.000	64 (71.1)	50 (72.5)	0.992
VAS improvement ≥ 70%, *n* (%)	34 (54.8)	33 (53.2)	1.000	50 (55.6)	38 (55.1)	1.000
VAS improvement ≥ 90%, *n* (%)	13 (21.0)	7 (11.3)	0.222	20 (22.2)	9 (13.0)	0.201
Resting pain improvement, *n* (%)	7/12 (58.3)	6/12 (50.0)	1.000	10/16 (62.5)	7/13 (53.8)	0.927
Nocturnal pain improvement, *n* (%)	38/40 (95.0)	38/40 (95.0)	1.000	49/52 (92.3)	42/44 (95.5)	1.000
Range of motion improvement, *n* (%)	27/38 (71.1)	26/38 (68.4)	1.000	36/54 (66.7)	28/40 (70.0)	0.905
Large effusion regression, *n* (%)	9/13 (69.2)	12/13 (92.3)	0.322	16/21 (76.2)	13/14 (92.9)	0.366
Baker's cyst elimination, *n* (%)	14/21 (66.7)	16/21 (76.2)	0.734	19/29 (65.5)	18/23 (78.3)	0.369
≥ 50% Baker's cyst diameter reduction, *n* (%)	17/21 (81.0)	16/21 (76.2)	1.000	22/29 (75.9)	18/23 (78.3)	1.000

VAS, Visual Analogue Scale.

Univariate and stepwise regression analysis of all study participants provided the following models for covariates in the prediction of VAS improvement scores (K–L grade, Kellgren–Lawrence radiographic grade):

$$\%\,\text{VAS improvement at 6 months} = 84.0 - 11.6\times\text{K–L grade}\ (r = 0.439,\ P < 0.001) \quad (1)$$

and

$$\%\,\text{VAS improvement at 12 months} = 90.5 - 15.9\times\text{K–L grade}\ (r = 0.587,\ P < 0.001) \quad (2)$$

Other potentially explanatory variables by univariate analysis (age, degree of tracer accumulation in blood pool scintigraphy, presence of a large effusion or a Baker's cyst) did not contribute significantly in the prediction of VAS improvement in stepwise regression analysis.

Among patients with serial assessments and impaired range of motion, those with an improvement in knee flexibility at 12 months had a VAS improvement score of 70.8 ± 17.6% and those without 33.3 ± 27.1% ($P = 0.000$). At that time point, patients with or without nocturnal pain elimination had VAS scores of 61.3 ± 27.4 versus 5.0 ± 7.1%, respectively ($P = 0.023$) and the values of those with or without resting pain alleviation were 85.0 ± 10.5 versus 41.7 ± 32.5%, respectively ($P = 0.009$).

In the formulation of a composite criterion for the overall assessment of ^{90}Y treatment, an upper threshold of VAS improvement was set at $\geq 70\%$, based on the weighted mean of this variable in patients with improved surrogate markers, whereas a lower cut-off point was selected at the $\geq 50\%$ level, a value used extensively in the past [24]. Thus, knees fulfilling any of the following points were considered to have a satisfactory therapeutic response: (i) VAS improvement $\geq 70\%$ alone; (ii) a VAS improvement score of $\geq 50\%$ combined with alleviation of resting or nocturnal pain or improvement in the range of motion. Joints without any of the above requirements were classified as having an unsatisfactory clinical result.

In the 62 patients with serial assessments, 42 (67.7%) of them had a satisfactory therapeutic response at 6 months, whereas at 12 months 36 had a sustained therapeutic result and six deteriorated. Among the 20 patients with an unsatisfactory result of treatment at 6 months, there were four cases with an upgraded clinical response at 12 months. Thus, late assessment included 40 (64.5%) satisfactory responses and 22 unsatisfactory therapeutic results ($P = 0.850$, compared with the 6-month assessment). The baseline characteristics of patients separated into those with and those without a satisfactory response at 6 and 12 months are presented in Table 3. In logistic regression analysis, a radiographic grade K–L ≥ 2 ($\chi^2 = 6.737$, $P = 0.009$) and a grade K–L ≥ 3 ($\chi^2 = 19.855$, $P = 0.000$) were the best discriminators of the outcome of treatment at 6 and 12 months, respectively. Moreover, a radiographic grade K–L ≥ 3 ($\chi^2 = 8.863$, $P = 0.003$) was the only independent predictor of a sustained or improved outcome of treatment over the examined period of time.

An analysis of the outcome of treatment in patients with serial assessments based on the severity of radiographic alterations is presented in Table 4. In knee joints with advanced radiographic abnormalities (K–L 3–4), there was a significant decline in VAS improvement scoring between 6 and 12 months ($P = 0.020$). In this cohort, the diameter of Baker's cysts was longer in patients with a satisfactory response at 6 months (19.4 ± 21.6 mm) compared with those without (1.1 ± 2.4 mm, $P = 0.048$) and the duration of symptoms was shorter in patients with a sustained outcome (27.0 ± 14.0 months) compared with those with deterioration (48.0 ± 15.7 months, $P = 0.021$).

Finally, it should be added that similar findings were observed in the investigation of characteristics of responders and in the analysis according to radiographic grading when the composite criterion was applied in all participants of the study.

Discussion

This study assessed the outcome of ^{90}Y radiation synovectomy in knee osteoarthritis at 6 and 12 months, using primary outcome measures similar to the objectives of medical management, and is one of the largest published series from a single centre heretofore. The results suggest that this form of therapy represents a safe and competent treatment option in osteoarthritic knee pain with scintigraphically established synovial inflammation, inadequately controlled by pharmacotherapy.

Synovial inflammation and yttrium-90 treatment

^{90}Y is a pure β-emitter capable of delivering a therapeutic radiation dose to the synovium with inflammatory hypertrophy. However, owing to the multifactorial aetiology of osteoarthritis evolution, ablation of the inflamed synovium may not be expected to influence significantly the entire pathological process, but it can contain local progression and lead to an alleviation of pain, functional improvement and regression of effusion. Moreover, as the degree of inflammation in osteoarthritis may vary from a mild intermittent irritation to marked synovitis, the response rates to radiation synovectomy would depend on the extent of inflammatory involvement [11,25–27]. Hence, a pretreatment early-phase bone scan has obvious appeal.

Table 3 Baseline characteristics of patients with serial assessments grouped according to the outcome of treatment based on the composite criterion

	Response at 6 months			Response at 12 months		
	Satisfactory ($n=42$)	Unsatisfactory ($n=20$)	P	Satisfactory ($n=40$)	Unsatisfactory ($n=22$)	P
Age (years)	67.0 ± 9.0	71.7 ± 6.6	0.049	68.3 ± 8.8	68.8 ± 9.1	0.735
Female, *n* (%)	37 (88.1)	16 (80.0)	0.453	35 (87.5)	18 (81.8)	0.709
Right/left joint, *n*	26/16	10/10	0.540	26/14	10/12	0.221
Pain at rest, *n* (%)	10 (23.8)	2 (10.0)	0.306	9 (22.5)	3 (13.6)	0.512
Nocturnal pain, *n* (%)	29 (69.0)	11 (55.0)	0.426	28 (70.0)	12 (54.5)	0.347
Pain duration (months)	27.9 ± 20.2	35.1 ± 22.6	0.120	26.3 ± 19.3	37.4 ± 22.7	0.025
Impaired range of motion, *n* (%)	27 (64.3)	11 (55.0)	0.672	26 (65.0)	12 (54.5)	0.592
K–L 2–4, *n* (%)	22 (52.4)	17 (85.0)	0.023	19 (47.5)	20 (90.9)	0.001
K–L 3–4, *n* (%)	8 (19.0)	10 (50.0)	0.027	4 (10.0)	14 (63.6)	0.000
Intense blood pool, *n* (%)	24 (57.1)	7 (35.0)	0.174	25 (55.6)	8 (33.3)	0.132
Large effusion present, *n* (%)	6 (14.3)	7 (35.0)	0.124	8 (20.0)	5 (22.7)	1.000
Baker's cyst present, *n* (%)	17 (40.5)	4 (20.0)	0.154	14 (35.0)	7 (31.8)	0.063
Baker's cyst diameter (mm)	14.8 ± 19.7	4.9 ± 13.3	0.091	12.5 ± 18.8	10.1 ± 18.1	0.780

K–L, Kellgren–Lawrence radiographic grade.

Table 4 The outcome of yttrium-90 synovectomy in knee joints serially assessed, according to the radiographic classification

	K–L 0–1 (n=23)	K–L 2 (n=21)	K–L 3–4 (n=18)	P
Assessment at 6 months				
VAS improvement (%)	74.6 ± 17.1*	64.3 ± 19.4	54.7 ± 23.9*	0.019
Satisfactory therapeutic result, n (%)	20 (87.0)*	14 (66.7)	8 (44.4)*	0.006
Resting pain improvement, n (%)	1/3 (33.3)	5/7 (71.4)	1/2 (50.0)	0.516
Nocturnal pain improvement, n (%)	14/14 (100)	14/14 (100)	10/12 (83.3)	0.086
Range of motion improvement, n (%)	11/12 (91.7)*	11/12 (91.7)**	5/14 (35.7)*,**	0.001
Large effusion regression, n (%)	3/5 (60.0)	3/3 (100)	3/5 (60.0)	0.420
Baker's cyst elimination, n (%)	2/7 (28.6)*	6/8 (75.0)	6/6 (100)*	0.020
$\geq$ 50% Baker's cyst diameter reduction, n (%)	5/7 (71.4)	6/8 (75.0)	6/6 (100)	0.367
Assessment at 12 months				
VAS improvement (%)	75.7 ± 13.4*	63.3 ± 26.7**	34.4 ± 24.1*,**	0.000
Satisfactory therapeutic result, n (%)	21 (91.3)*	15 (71.4)**	4 (22.2)*,**	0.000
Resting pain improvement, n (%)	1/3 (33.3)	5/7 (71.4)	0/2 (0)	0.164
Nocturnal pain improvement, n (%)	14/14 (100)	14/14 (100)	10/12 (83.3)	0.086
Range of motion improvement, n (%)	11/12 (91.7)*	10/12 (83.3)**	5/14 (35.7)*,**	0.004
Large effusion regression, n (%)	5/5 (100)	3/3 (100)	4/5 (80.0)	0.420
Baker's cyst elimination, n (%)	4/7 (57.1)	6/8 (75.0)	6/6 (100)	0.194
$\geq$ 50% Baker's cyst diameter reduction, n (%)	4/7 (57.1)	6/8 (75.0)	6/6 (100)	0.194

K–L, Kellgren–Lawrence radiographic grade; VAS, Visual Analogue Scale.
In paired comparisons: *P<0.05 in K–L 0–1 versus K–L 3–4; **P<0.05 in K–L 2 versus K–L 3–4.

The assessment of knee pain

Pain is the most prominent and disabling symptom in knee osteoarthritis, but the assessment of its severity may present difficulties [21]. It is likely that certain features of pain can be judged more reliably while retaining their clinical usefulness, such as pain at rest and pain that disrupts sleep, whereas the impact of pain on functioning represents another essential part of the assessment [28]. In our study, these issues were taken into account in the assessment of knee pain and also in the implementation of the composite criterion.

The outcome of treatment

Side effects in ^{90}Y synovectomy were rare, harmless and easy to manage. On the basis of VAS scoring, the probability of a $\geq$ 50% alleviation of knee pain limiting daily activities amounted to 71.1 versus 72.5% at 6 and 12 months, respectively, in all participants of the study (Table 2). Moreover, there was a favourable effect in knee flexibility, while nocturnal pain was almost completely eliminated, though the response rate was less good in the remission of resting pain. Notably, although there was a declining trend in the response to treatment between early and late assessment in terms of VAS scoring and resting pain, no statistically significant difference was attained, indicating that the therapeutic result largely was sustained up to 12 months. Pain palliation and associated functional improvement were significantly related to the grade of radiographic alterations, as shown by regression equations (1) and (2).

The overall outcome of ^{90}Y treatment based on the composite criterion was similar at 6 and 12 months, with 67.7 and 64.5% of patients with serial assessments attaining a satisfactory response at those time points, respectively (Table 3). Radiographic grading was the best predictor of the clinical outcome and the sole discriminator of a sustained result by logistic regression analysis. A plausible explanation would be that radiographic alterations incorporate the effect of many factors influencing the progressive damage of joint architecture. It is also worth noting that the intensity of tracer accumulation in blood pool images could not contribute significantly in the prediction of VAS improvement scores and it could not determine a satisfactory therapeutic result (Table 3). These findings imply that in osteoarthritic knees with scintigraphically established synovitis, the degree of inflammation may not influence significantly the outcome of treatment.

Ultrasonographic findings

Repeat ultrasonography at 6 and 12 months showed substantial regression of large joint effusions (76.2 vs. 92.9%, respectively) and elimination of Baker's cysts (65.5 vs. 78.3%, respectively). The former is a recognized response and an indication for radionuclide therapy [12,19]. The prevalence of Baker's cysts is associated with synovial inflammation (unpublished data from our institution) and their regression may reflect an effective anti-inflammatory treatment. Interestingly, ultrasonographic results at 12 months tended to be better than those at 6 months, but this observation was not supported by statistical significance (Tables 2 and 4).

Radiographic grading

On the basis of both VAS scoring and the composite criterion, patients with no or minimal radiographic abnormalities (K–L 0–1) tended to have a better response to treatment in comparison to patients with only definite osteophytes on radiographs (K–L 2), but at no statistical significance (Table 4). Conversely, compared with patients with nonsevere radiographic joint damage (K–L 0–1 or 2), patients with higher-grade morphological alterations (K–L 3–4) experienced a lower

degree of pain palliation and functional improvement. In addition, those patients gained less in knee flexibility and also had a decreased probability for a satisfactory or sustained therapeutic outcome. In this context, VAS improvement score decreased significantly from 54.7 to 34.4% between 6 and 12 months. However, in that population, alleviation of nocturnal pain and favourable ultrasonographic changes were observed in considerable proportions, similar to those of patients with less joint damage. Overall, these findings indicate that radiation synovectomy may be helpful in an appreciable number of osteoarthritic knees with advanced radiographic deformation. In that cohort, increased dimensions of Baker's cysts at baseline assessment and a short duration of symptoms were associated with a beneficial or sustained response, respectively, though the sample was small to generalize.

Comparisons to previous work

In literature, no uniform validated system has been used for the assessment of the clinical efficacy of radiation synovectomy and the selection criteria differ in various studies; thus, comparison with other data is difficult. Furthermore, in virtually all previous reports, only a fraction of the entire population consisted of patients with knee osteoarthritis, so that their demographic or outcome data usually are impossible to separate. In earlier publications encompassing knees treated in the indication of osteoarthritis, the improvement rates range from 35 to 71% with the outcome evaluated 6–30 months after therapy [12–18]. Most previous series were retrospective [12,13,17], one of them in a multicenter setting [16], while there is one follow-up study [14] and another broad survey of literature [18]. The assessment of the outcome was based on a standardized questionnaire [13,14,16], patients' subjective judgement and the status of joint effusions [12], improvement of pain [17], or a global opinion from the physician or the patient and further need for intraarticular steroid injections [15]. There are studies enrolling patients unresponsive to medical treatment [14,17], one publication required resistance to intraarticular steroid injections but included a small number of joints previously submitted to arthroscopic synovectomy [12] and other patients underwent radiation synovectomy according to published guidelines [16] or with no specified criteria [15]. Few investigators provide information on the duration of symptoms [12,15], which is longer than that of our population. In publications reporting on participants' age, this is comparable to that of our sample in some studies [14,16,17], but the population is younger in other [12,15]. Concordant to our methodology, synovitis was proven by blood pool scans in some studies [13,14,16], whereas knee flexibility was considered in other publications [15,16]. Congruent to our results, a better clinical outcome with minimal radiographic changes has been reported previously [15,18], although there are data disputing this observation [17]. One work supports that even when the radiographic alterations are severe, radiation treatment is helpful [18], which is in agreement with our findings. There are also published data concurring in that the clinical outcome is not influenced by age, sex and the duration of symptoms, which is consistent with our results [15,16]. Finally, an intraarticular ^{90}Y dose of 185 MBq was injected in all previous series, except a single study using 222 MBq [12]. Notably, in our study, 57 out of 97 knees (59%) had definite osteophytes and also in 30 cases (31%) joint space was narrowed, but such information cannot be extracted from earlier work.

Potential limitations

Among all patients submitted to radiation synovectomy, those with inadequate documentation of the outcome of treatment at the defined time points were excluded. It should be mentioned, however, that consecutive patients were enrolled and assessed prospectively, while the reasons for loss to follow-up were not related to the outcome of treatment. Moreover, the baseline characteristics were similar between patients with inadequate outcome data, those with a single follow-up visit and those with serial assessments (Table 1), whereas the response to treatment was trivially affected when the latter two groups were summed up (Table 2). These facts would obviate selection bias.

It would be preferable for the outcome to rely on explicit measures endorsed by international bodies [24]. However, the criteria used in our study reflect our experience and routine practice for many years, the rationale in applying them was discussed above, and the conclusions were based on substantially improved scores and objective measurements.

The efficacy of a therapy ideally is evaluated by a controlled randomized trial. It should be added, however, that the progression of osteoarthritis may vary and be influenced by a number of factors, so that in this situation, the formation of a matched group by randomization is not always likely and the usefulness of a control sample would be debatable [29]. Moreover, the continuation of an ineffective therapeutic regimen or injections of intraarticular placebo, despite evidence of synovial inflammation on bone scintigraphy (which, in turn, entails non-negligible radiation exposure), may prevent the consent of candidates. Nevertheless, although this study was not powered by a control arm, it retains the validity of a prospective assessment of the effect of intraarticular ^{90}Y in a random population of patients with osteoarthritic knee pain and associated synovitis, refractory to systematic and local pharmacotherapy. In this context, the recorded response rates at 6 and 12 months (Table 2) support that ^{90}Y treatment provides a substantial therapeutic benefit when conventional treatment has been ineffective.

Conclusion

This study shows that radiation synovectomy is a safe and effective therapeutic option in knee osteoarthritis with concurrent synovial inflammation established by early-phase bone scintigraphy, when other nonsurgical therapies have failed. A substantial proportion of patients submitted to ^{90}Y treatment experience significant and sustained remission of knee pain limiting daily activities, alleviation of nocturnal and resting pain and gain in knee flexibility. The probability of a favourable outcome of treatment is inversely related to the severity of radiographic damage in the affected joints. However, even in patients with advanced osteoarthritic abnormalities on radiographs and burdensome knee replacement surgery radiation synovectomy may be helpful.

References

1 Felson DT. Osteoarthritis of the knee. *N Engl J Med* 2006; **354**:841–848.
2 Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001; **60**:91–97.
3 Poole AR. An introduction to the pathology of osteoarthritis. *Front Biosci* 1999; **4**:D662–D670.
4 Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. *J Rheumatol* 1997; **24**:365–371.
5 Hedbom E, Hauselmann HJ. Molecular aspects of pathogenesis in osteoarthritis: the role of inflammation. *Cell Mol Life Sci* 2002; **59**:45–53.
6 Martel-Pelletier J, Pelletier JP. New insights into the major pathophysiological processes responsible for the development of osteoarthritis. *Semin Arthritis Rheum* 2005; **34** (**6 Suppl 2**):6–8.
7 Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, *et al.* Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage* 2007; **15**:516–523.
8 Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al.* EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; **62**:1145–1155.
9 Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD005328. doi: 10.1002/14651858.CD005328.pub2.
10 Clunie G, Ell PJ. A survey of radiation synovectomy in Europe. *Eur J Nucl Med* 1995; **22**:970–976.
11 Kampen WU, Voth M, Pinkert J, Krause A. Therapeutic status of radiosynoviorthesis of the knee with yttrium [^{90}Y] colloid in rheumatoid arthritis and related indications. *Rheumatology* 2007; **46**:16–24.
12 Stucki G, Bozzone P, Treuer E, Wassmer P, Felder M. Efficacy and safety of radiation synovectomy with Yttrium-90: a retrospective long-term analysis of 164 applications in 82 patients. *Br J Rheumatol* 1993; **32**:383–386.
13 Kröger S, Sawula JA, Klutmann S, Brenner W, Bohuslavizki KH, Henze E, *et al.* Effect of radiosynovectomy in patients with inflammatory joint disorders not caused by rheumatoid arthritis. *Nuklearmedizin* 1999; **38**:279–284.
14 Kampen WU, Brenner W, Kroeger S, Sawula JA, Bohuslavizki KH, Henze E. Long-term results of radiation synovectomy: a clinical follow-up study. *Nucl Med Commun* 2001; **22**:239–246.
15 Taylor WJ, Corkill MM, Rajapaske CN. A retrospective review of yttrium-90 synovectomy in the treatment of knee arthritis. *Br J Rheumatol* 1997; **36**:1100–1105.
16 Rau H, Lohmann K, Franke C, Goeretzki G, Lemb MA, Müller J, *et al.* Multicenter study of radiosynoviorthesis: clinical outcome in osteoarthritis and other disorders with concomitant synovitis in comparison with rheumatoid arthritis. *Nuklearmedizin* 2004; **43**:57–62.
17 Will R, Laing B, Edelman J, Lovegrove F, Surveyor I. Comparison of two yttrium-90 regimens in inflammatory and osteoarhtropathies. *Ann Rheum Dis* 1992; **51**:262–265.
18 Kresnik E, Mikosch P, Gallowitscth HJ, Jesenko R, Just H, Kogler D, *et al.* Clinical outcome of radiosynoviorthesis: a meta-analysis including 2190 treated joints. *Nucl Med Commun* 2002; **23**:683–688.
19 Clunie G, Fischer M. EANM procedure guidelines for radiosynovectomy. *Eur J Nucl Med Mol Imaging* 2003; **30**:BP12–BP16.
20 Fischer M, Mödder G. Radionuclide therapy of inflammatory joint disease. *Nucl Med Commun* 2002; **23**:829–831.
21 Altman R, Asch E, Bloch D, Bole D, Borenstein K, Brandt K, *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986; **29**:1039–1049.
22 Tarhan S, Unlu Z, Goktan C. Magnetic resonance imaging and ultrasonographic evaluation of the patients with knee osteoarthritis: a comparative study. *Clin Rheumatol* 2003; **22**:181–188.
23 Kellgren J, Lawrence J. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957; **16**:494–501.
24 Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, *et al.* OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004; **12**:389–399.
25 Goldenberg DL, Egan MS, Cohen AS. Inflammatory synovitis in degenerative joint disease. *J Rheumatol* 1982; **9**:204–209.
26 Schwarz A, Elbracht T, Jeschke A, Weseloh G, Swoboda B, Kuwert T. Bone scintigraphy and clinical outcome in rheumatoid gonarthritis. *Nuklearmedizin* 2003; **42**:94–98.
27 Gratz S, Göbel D, Behr TM, Herrmann A, Becker W. Correlation between radiation dose, synovial thickness, and efficacy of radiosynoviorthesis. *J Rheumatol* 1999; **26**:1242–1249.
28 Peat G, Croft P, Hay E. Clinical assessment of the osteoarthritis patient. *Best Pract Res Clin Rheumatol* 2001; **15**:527–544.
29 Kampen WU, Czech N. Methodologic issues in the assessment of the efficacy of radiation synovectomy for arthritis of the knee: comment on the article by Jahangier *et al. Arthritis Rheum* 2007; **56**:385.