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ORIGINAL ARTICLE

A prospective observational study on the long-term results of ^{90}Yttrium citrate radiosynoviorthesis of synovitis in osteoarthritis of the knee joint

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Abstract

Objectives Radiosynoviorthesis (RSO) is used for the treatment of inflammatory joint diseases. However, there are no long-term results published comparing it to conservative therapy. Therefore, the aim of this prospective observational study was to evaluate response rates after radionuclide therapy in patients suffering from knee osteoarthritis over a time period of 10 years.

Methods Radionuclide therapy with intra-articular administration of colloidal ^{90}Yttrium citrate was performed in osteoarthritic patients [Kellgren–Lawrence grades I/II ($n = 69$) and Kellgren–Lawrence grade III ($n = 72$)].

Results In patients with early-stage disease, an excellent/good response with respect to pain, joint mobility, and function was observed in 82.5% for 1 year and in 73.7% for 8 years after therapy. Responses declined to 50% at 10 years post treatment. In grade III patients, an excellent/good response was observed in 45.9%; a decline to 41.2% was observed in the first 8 years. In this group, the number of patients available for follow-up after 9 and 10 years dropped significantly from 51 patients after 8 years to only 30 patients after 9 years, and to nine patients after 10 years. As a result, these response rates were not appraisable.

Conclusion Long-term results of radiosynoviorthesis in knee osteoarthritis are excellent/good in many patients. The response rate depends on Kellgren–Lawrence stages, and early-stage radionuclide therapy for osteoarthritis is suggested.

Keywords Radiosynoviorthesis · Osteoarthritis · ^{90}Yttrium citrate · Intra-articular radionuclide therapy

Introduction

In elderly patients, osteoarthritis (OA) is the common degenerative joint disease, causing pain and disability in about 34% of the population > 65 years of age in the US [1]. In Europe, at least 40 million people might be affected [2]. Similar data are published for Asia. These data reflect a rapidly aging population in all parts of the world [3], which will further increase the incidence of osteoarthritis and will cause a significant socioeconomic burden. Musculoskeletal diseases cost the economies of Western countries such as US, Canada, Great Britain, or France between 1 and 2.5% of the gross national product [4], with osteoarthritis being the most frequent diagnosis [5].

For many years, osteoarthritis was characterized by alterations in the composition of cartilage and joint-related bone solely from a disproportion between mechanical load and loading capacity of the involved anatomical structures. Inflammation was classified as a secondary phenomenon and was considered "nonclassical" [6]. In general, the diagnosis of osteoarthritis was made using X-ray imaging based on clinical symptoms such as pain and disability, and often in late disease stages with advanced bone alterations. More recently, osteoarthritis has been defined as a disease of the whole joint, including the juxta-articular soft tissues.

Joint pain is the leading clinical symptom of OA, but the pain intensity is not always concordant with the radiological degree of bone alterations in the affected joints. Therefore, another pain generator in addition to the structural changes of cartilage and bone was assumed. Recent studies on animal models of OA demonstrated blood vessels penetrating the osteochondral junction into the cartilage [7]. Nociceptive nerve fibers accompanying these vessels might contribute to

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the joint pain. This hypothesis is supported by clinical studies which show pain relief from pharmacological blockade of the nerve growth factor (NGF) in patients with OA [8]. Moreover, the ongoing nociceptive input from joint pain leads to central sensitization, and synovitis has been described as the determining factor for this neuronal sensitization [9]. Therefore, early treatment of synovitis should prevent central pain chronification in patients with OA.

In general, normal healthy cartilage tissue has no vascular and lymphatic supply, and it relies on nutrient supply from the adjacent bone and synovial membrane. However, inflammation of the synovial membrane will compromise the normal physiologic state of the joint [1]. Synovitis plays an important role in clinical symptoms and progression of osteoarthritis, but it was difficult to diagnose previously. However, currently with the development of new diagnostic tools such as high-resolution ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET), it is possible to diagnose synovitis at an early stage. In about 33–52% of patients suffering from osteoarthritis of the knee joint, inflammatory changes of the synovium have been demonstrated by ultrasound. Using MRI, the positive results were even higher [10]. In patients with rheumatoid arthritis, PET with a macrophage-specific radioactive tracer diagnosed synovitis even in subclinical, MRI-negative stages [11]. Due to the correlation between synovial inflammation and disease severity and its relevance for central pain sensitization, the synovial tissue should be the target for any therapy of knee joint osteoarthritis [12]. Therapeutic modalities targeting this component of the disease might be beneficial not only for the clinical symptoms but also for prevention or delaying the disease progression.

In 1952, Fellinger and Schmidt [13] published results after an intra-articular administration of radionuclides (3.7–7.4 MBq ^{131}I or 37 MBq ^{198}Au) for the first time. They observed a significant reduction of pain in patients suffering from rheumatoid arthritis. For more than 60 years, radiosynoviorthesis using radioactive colloids was recognized as a safe, therapeutic modality for inflammatory joint diseases. However, published results are mainly limited to several months to 1 year of monitoring.

The aim of this prospective observational study is to collect and assess data for the long-term effects of radiosynoviorthesis in patients with osteoarthritis of the knee joint. These results were compared with clinical data prior to and 1 year after radiosynoviorthesis.

Materials and methods

Patients with symptomatic osteoarthritis of one knee joint referred for radiosynoviorthesis were offered a long-term follow-up to 10 years post treatment (at year 1, year 5, and then every year up to 10 years). One hundred and forty-one patients consented to be part of this trial.

Inclusion criteria for radiosynoviorthesis were: chronic synovitis persisting for more than 4–6 months, defined by clinical signs such as joint pain and swelling without response to conventional therapy, including intra-articular administration of corticosteroids; Kellgren–Lawrence grades I–III. Exclusion criteria: pregnancy, continuing breastfeeding, bacterial infection, ruptured popliteal cyst, Kellgren–Lawrence grade IV.

The mean age of the patients (45 males, 96 females) was 61.5 years (range 40–86). Joints to be treated were 71 right and 70 left knee joints. Mean duration of osteoarthritis prior to radiosynoviorthesis was 12.3 years (range 5–20), the mean number of joint punctures was 8.7 (range 1–150). At the time of radiosynoviorthesis, rheumatoid arthritis was excluded in all patients due to the criteria of the American Rheumatism Association (ARA) [14].

In all patients, soft-tissue scintigraphy with ^{99m}Technetium pertechnetate of both knee joints was performed before the radiosynoviorthesis to confirm active synovitis of the affected joint. 100–150 MBq were injected, and planar blood pool images of both knees in anterior and posterior projections and a lateral view of the affected knee were performed. Two identical regions of interest (ROI) were placed on both knees in both anterior and posterior projections, one on the knee and one on the proximal tibia, the latter being used for background correction. A synovial index was calculated for both knees on the basis of background corrected count numbers within the knee ROI. The lateral view was used to diagnose/exclude a Baker's cyst and for correlation with ultrasound.

All patients underwent a diagnostic ultrasound. The quantity of synovial fluid and the synovial thickness in the midline, lateral, and medial part of the capsule were estimated. The femoral condyles, menisci, ligaments, and the cartilage status were examined. We confirmed or excluded a Baker's cyst, its wall thickness, and a possible rupture, which would exclude radiosynoviorthesis. These studies were carried out in order to clinically confirm the inclusion criteria of the patients. Long-term follow-up studies by ultrasound were not routinely performed. However, ultrasound measurements were additionally recorded in 25 sample patients to complete the clinical data.

In order to grade morphological joint changes, X-ray images of the affected joints were performed under load in the anterior-posterior and lateral view, including an axial image of the patella. Classifications were made based on the following:

Kellgren and Lawrence (KL) criteria [15]:

Grade I: doubtful narrowing of the joint space and possible osteophytic lipping.

Grade II: definite osteophytes, definite narrowing of the joint space.

Grade III: moderate multiple osteophytes, definite narrowing of the joint space, some sclerosis, and possible deformity of bone contour.

Grade IV: large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of bone contour.

Patients with Kellgren–Lawrence grade IV were not included in this long-term observational trial for ethical reasons. The probability of progressive morphological degeneration of cartilage and bony structures in these joints is high. In the guidelines of the European Association of Nuclear Medicine (EANM) [33], radiosynoviorthesis is not indicated (in fact it is listed as a relative contraindication) if "extensive joint instability with bone destructions and evidence of significant cartilage loss within the joint" are obvious.

Based on this classification, nine patients had Kellgren–Lawrence grade I, 60 patients had grade II, and 72 patients had grade III.

Since our patients had had a long history of knee joint osteoarthritis, they underwent different therapeutic procedures prior to radiosynoviorthesis: the mean number of intra-articular corticosteroid administrations per patient was 9.3. Eighty-six patients had external radiotherapy, four patients were treated by chemical synovectomy, and 21 patients by surgical synovectomy; only 30 patients did not undergo interventional anti-inflammatory therapy before radiosynoviorthesis.

The methodology of radiosynoviorthesis

The knee joint of the patient was punctured under sterile conditions. In patients with joint effusion, the joint fluid was drained prior to injection of 188–222 MBq ^{90}Yttrium-colloid. A mixture of 40 mg triamcinolone-acetonide and 1 ml lidocaine was used to flush the needle while carefully withdrawing it from the joint. The injection site was compressed with a sterile swab and the joint was carefully moved to improve tracer distribution within the joint cavity. To avoid extra-articular radionuclide leakage, the treated joint was immobilized for 48 h with a bandage and the patient was confined to bed.

For the evaluation of the effectiveness of radiosynoviorthesis, the treating physician used a points system for objective assessment, and all patients used a points system for subjective assessment of pain [16], representing the clinical changes compared to the situation before radiosynoviorthesis (Tables 1 and 2).

This was done 1 year after radionuclide therapy, at 5 years, and for each year to 10 years follow-up. Patients were asked to rank their subjective assessment of pain alteration compared to their pretherapeutic complaints on a 10-cm visual analog scale (VAS). These values were transformed into a 5-point scale: very good improvement or no complaints (VAS 8–10) = 4 (points); major improvement (VAS 5–7) = 3; moderate improvement (VAS 3–4) = 2; minor improvement (VAS 1–2) = 1; no change or worsening of complaints (VAS 0) = 0.

In the objective assessment, joint pain was evaluated for each patient by the physician twice (at rest and under load). Other symptoms such as changes in joint movement, walking capacity, and the number of arthrocenteses after radiosynoviorthesis were reported during each control, to evaluate the differences to previous control results. In this way, the total objective and subjective assessment of ^{90}Yttrium-colloid radiosynoviorthesis was found to be: 31 points (examination done by the physician) + 4 points (VAS by self-evaluation) = 35 points.

The grading was: excellent (no complaints) = 29–35 points; good (major improvement) = 22–28 points; medium (moderate improvement) = 15–21 points; weak (minor improvement) = 8–14 points; bad (no change or worsening) = 0–7 points.

The effectiveness of radiosynoviorthesis was analysed using the points system and comparing the values during the follow-up appointments. For the analysis of long-term response rates compared to 1-year results, Statistica version 5.0 from StatSoft Inc. was used for statistical evaluation.

Results

The evaluation of the scintigraphic synovial index showed a normal value of 0.8 ± 0.2 in healthy knee joints. The mean synovial index of the knee joints to be treated was 1.79 ± 0.5 before radiosynoviorthesis, the mean synovial index was 1.18 ± 0.3 in those patients controlled 10 years after radiosynoviorthesis.

In our prospective, long-term observational study, the response rate values for year 1 after radiosynoviorthesis were taken as basal values to be compared with the response rate values from 5 up to 10 years after radionuclide therapy as shown in Tables 3, 4, and 5.

Because of the low number of patients with Kellgren–Lawrence (KL) grade I ($n = 9$), data of these patients were combined with those of the Kellgren–Lawrence grade II group. As shown in Table 3, 1-year data compared to long-term response rates up to 10 years did not show significant differences. In subgroup Kellgren–Lawrence I/II (Table 4), the statistical analysis of data did not show a significant difference for 1 year vs 5 to 8 years, whereas between 1 year and the 9- and 10-years control, there was a significant difference ($p = 0.0063$ and $p = 0.0019$ respectively). The same was true for subgroup Kellgren–Lawrence grade III (Table 5), with stable clinical results up to 8 years after treatment. The response rates after 9 and 10 years were not appraisable due to the low number of patients available for these controls.

The mean number of joint punctures prior to radiosynoviorthesis was 8.7 with a range of 1–150. None of the OA patients had less than 1–3 punctures in the disease history. After radiosynoviorthesis, 78 of the treated 141

Table 1 Scoring system of objective clinical and functional parameters

Parameters	Objectives	Points	Parameters	Objectives	Points
Decrease of joint circumference (cm)	> 7, no more swelling	4	Joint hyperthermia	no	1
	5.1–7.0	3		yes	0
	3.1–5.0	2			
	0.1–3.0	1	Ability to walk	yes	1
				no	0
Improvement of joint function (flexion)	20° total function	4			
	15°	3	Walking capacity (hours)	unlimited	5
	10°	2		5–10	4
	5°	1		2–5	3
	0° or worsening	0		1–2	2
				0.5–1	1
Contracture after RSO (measure of fixed flexion)	0° /total extension	4		0–0.5	0
	1°–5°	3			
	6°–10°	2	Joint punctures post RSO (n =)	0	2
	11°–15°	1		1–2	1
	≥ 16°	0		> 2	0
Improvement of pain in load VAS 1–10 cm scale	8–10 or no pain	4	Surgery post RSO	no	2
	5–7	3		yes	0
	3–4	2			
	1–2	1			
	0 or worsening	0			

patients (55.3%) underwent no further puncture during the control period, with a range of 1–10 for the other 63 patients.

To assess histological changes of the synovial membrane after radiosynoviorthesis, we examined the arthroscopic and histological appearance before and after intraarticular radionuclide treatment in patients suffering from rheumatoid arthritis from an earlier trial [17]. The results of 20 of these patients (14 female, six male, with Kellgren–Lawrence grades I/II in 18 patients and Kellgren–Lawrence grade III in two patients) were also exemplified in this study to support the clinical data. We performed arthroscopy prior to and up to 1 year after radiosynoviorthesis and took biopsies of the synovium for histology, even in a few patients treated for osteoarthritis. The arthroscopic images before radiosynoviorthesis showed a hyperaemic membrane and grape-like proliferated synovia. In histology, the synovium was covered by 3–4 layers of lining cells and showed diffuse inflammatory infiltrations. After radionuclide therapy, the synovial surface was silk-like, covered only by a single cell layer. Less inflammatory infiltrations, but signs of fibrosis were seen histologically.

Fig. 1: Images of arthroscopy and histology before and after RSO.

Ultrasound estimations in 25 patients before and 5 years after radiosynoviorthesis showed a significant reduction of the amount of synovial fluid and of synovial tissue thickness, respectively, which supports the clinical efficacy of intraarticular radionuclide treatment in the long term.

Table 2 Subjective patient pain-scoring system

Parameter	Objective	Points
Improvement of pain VAS 1–10cm scale	8–10 or no pain	4
	5–7	3
	3–4	2
	1–2	1
	0 or worsening	0

Discussion

An increased prevalence of osteoarthritis is seen worldwide in an aging population; however, there is no definitive preventive or curative therapy. Synovitis is increasingly recognized to have a strong aetio-pathological role in osteoarthritis, being more a precursor in the initial stage of the disease than a consequence of joint failure, and having a high impact on an individual's pain sensation. Therefore, this inflammatory tissue should be the main target of therapeutic strategies [18].

The Royal College of Physicians list only intraarticular corticosteroids and hyaluronans in "Osteoarthritis — National Clinical Guideline for Care and Management in Adults" [19]. Moreover, the American Academy of Orthopaedic Surgeons (AAOS) published a recommendation for non-arthroplasty treatment of osteoarthritis of the knee in 2008 [20]. They evaluated

Table 3 Response rate of radiosynoviorthesis in all treated osteoarthritis patients

Years after RSO	Number of patients: *n*	Excellent: *n* (%)	Good: *n* (%)	Medium: *n* (%)	Weak: *n* (%)	Bad: *n* (%)	Excellent + good: *n* (%)	Significance
1	141	45 (31.9)	45 (31.9)	36 (25.5)	15 (10.6)	0	90 (63.8)	
5	141	42 (29.8)	45 (31.9)	33 (23.4)	18 (12.7)	3 (2.1)	87 (61.7)	ns[1]
6	138	54 (39.1)	27 (19.5)	30 (21.7)	24 (17.4)	3 (2.2)	81 (58.6)	ns
7	132	60 (45.5)	15 (11.4)	33 (25)	21 (15.9)	3 (2.3)	75 (56.9)	ns
8	108	45 (41.7)	18 (16.7)	24 (22.2)	18 (16.7)	3 (2.8)	63 (58.4)	ns
9	66	24 (36.4)	15 (22.7)	12 (18.2)	15 (22.7)	0	39 (58.3)	ns
10	33	9 (27.27)	9 (27.27)	6 (18.2)	9 (27.27)	0	18 (54.54)	ns

ns[1] = no significance to basal value, 1 year after radiosynoviorthesis

systemic reviews and other publications with AAOS level II of evidence, resulting in only a small amount of evidence for long-term benefits of intra-articular administration of corticosteroids. The mean duration of symptomatic pain relief was only about 3–4 weeks and did not influence or improve joint function [21]. Similar results were published by the Royal College of Physicians [19].

The discussion about the dosage and frequency of corticosteroid injections is controversial. Weber [22] recommends limiting the number of intra-articular corticosteroid therapies to three injections per year only. Wernecke et al. [23] published a systematic review of the effects of intra-articular corticosteroids on articular cartilage in both animal and human chondrocyte cultures after incubation with triamcinolone acetonide.

Two in-vitro investigations showed the chondrotoxic effect of triamcinolone, whereas in-vivo studies support cartilage protective effects by low-dose triamcinolone administration. One of the human trials included in this review was published by Raynold and co-workers [25], who administered 40 mg triamcinolone acetonide for 2 years every 3 months. The results supported a long-term protective effect on cartilage. This protective effect was only demonstrated by X-ray images of the knee joints, which showed only the rough anatomical structures. The authors concluded that the effects of corticosteroids on intra-articular cartilage might be dose- and time-dependent: low-dose and short-time may be beneficial, high-dose and long-time could be detrimental. In another randomized clinical trial, the effect of intra-articular corticosteroid injection versus saline was studied in knee osteoarthritis patients. Over 2 years, patients were administered with intra-articular 40 mg triamcinolone acetonide or saline every 3 months. In MRI imaging, the corticosteroid group showed increased cartilage loss compared to the saline group who showed no loss, without any difference in pain severity between the two groups [24]. More details of possible adverse events caused by intra-articular corticosteroid injections were published by Tracy and Edison in 2015 [21]. Thus, the overall incidence of adverse events following intra-articular administration of corticosteroids is relatively low, but the abovementioned risks should be taken into account.

With regard to clinical effectiveness, data from the Cochrane Database Systematic Review with regard to intra-articular corticosteroids for knee osteoarthritis confirm that “no effect of intra-articular corticosteroids remains after 6 months” and less confidently that there is a clinically relevant "short-term effect regarding pain palliation, joint function, and quality of life” [26].

Radiosynoviorthesis of inflammatory joints disease with acute or chronic synovitis, including rheumatoid arthritis, spondylarthritis, reactive arthritis, pigmented villonodular synovitis, and hemophilic arthropathy, has been used for about

Table 4 Response rates of radiosynoviorthesis in Kellgren–Lawrence grades I+ II osteoarthritis patients ($n = 69$).

Years after RSO	Number of patients: *n*	Excellent: *n* (%)	Good: *n* (%)	Medium: *n* (%)	Weak: *n* (%)	Bad: *n* (%)	Excellent + good: *n* (%)	Significance
1	69	33 (47.8)	24 (34.7)	12 (17.4)	0	–	57 (82.5)	
5	69	30 (43.5)	24 (34.8)	12 (17.4)	3 (4.3)	–	54 (78.3)	ns[1]
6	66	42 (63.6)	9 (13.6)	9 (13.6)	6 (8.7)	–	51 (77.2)	ns
7	66	45 (68.1)	6 (9.1)	12 (18.2)	3 (4.5)	–	51 (77.2)	ns
8	57	36 (63.2)	6 (10.5)	12 (21.0)	3 (5.2)	–	42 (73.7)	ns
9	36	18 (50)	3 (8.3)	9 (25)	6 (6.7)	–	21 (58.3)	$p = 0.0063$
10	24	9 (37)	3 (12.5)	6 (25)	6 (25)	–	12 (50)	$p = 0.0019$

ns[1] = no significance to basal value, 1 year after radiosynoviorthesis

Table 5 Response rate of radiosynoviorthesis in Kellgren–Lawrence grade III osteoarthritic patients ($n = 72$).

Years after RSO	Number of patients: *n*	Excellent: *n* (%)	Good: *n* (%)	Medium: *n* (%)	Weak: *n* (%)	Bad: *n* (%)	Excellent + good: *n* (%)	Significance
1	72	12 (16.7)	21 (29.2)	24 (33.3)	15 (20.8)	0	33 (45.9)	
5	72	12 (16.7)	21 (29.2)	21 (29.2)	15 (20.8)	3 (4.2)	33 (45.9)	ns[1]
6	72	12 (16.7)	18 (25)	21 (29.2)	18 (25)	3 (4.2)	30 (41.7)	ns
7	69	15 (26.1)	9 (13)	21 (30.4)	18 (26.1)	3 (4.4)	24 (39.1)	ns
8	51	9 (17.7)	12 (23.5)	12 (23.5)	15 (29.4)	3 (5.9)	21 (41.2)	ns
9	30	6 (20)	12 (40)	3 (10)	9 (30)	0	18 (60.0)	
10	9	0	6 (66.7)	0	3 (33.3)	0	6 (66.7)	

ns[1] = no significance to basal value, 1 year after radiosynoviorthesis

65 years, and has proven to be a valid therapeutic modality in these patients. Literature data regarding radiosynoviorthesis of osteoarthritis of the knee joints are rare. Many of the studies are hampered by either small-study effects or inclusion of high-grade osteoarthritic patients. Trials using colloidal radionuclides and corticosteroids as a comparator often did not observe a significant difference between the two therapeutic modalities after a follow-up time of weeks. These trials are biased by the fact that the corticosteroid effect will decrease during this time period and on the other hand, the optimal time point for evaluating the effect of radiosynoviorthesis is > 6 months.

To the best of our knowledge, data from prospective, observational, long-term results of radiosynoviorthesis of osteoarthritic knee joints have not been published so far. In only one trial treating digital joint osteoarthritis, the mean follow-up time was 41 months [27], reporting a good to excellent response rate in 68%. In 1996, our own group presented response rates after radiosynoviorthesis in patients suffering from rheumatoid and non-rheumatoid arthritis. Excellent and good results were observed in 70% within the first 4 years, declining to 65% in the 5th year without a significant difference between the different primary diseases [28]. In a meta-analysis from 2002 [29], a total number of 2190 joints treated by radiosynoviorthesis with a minimal follow-up time of 1 year were analysed. Only 121 osteoarthritic knee joints were included. The mean response rate for all joints was 72.5 ± 17%; for the osteoarthritic knee joints the response rate was 56 ± 11% with a clear trend to better results in those cases with minimal radiological changes. The same trend was observed in patients suffering from rheumatoid arthritis with 72.8 ± 12.5% in Steinbrocker stage I vs 64 ± 17.3% in Steinbrocker stage II. Comparing the response rate regarding pain relief and/or improvement of joint function of all treated joints, a difference between rheumatoid arthritis (> 80%) and osteoarthritis (60–80%) was observed [29].

In another prospective trial, the degree of inflammation was evaluated by 2-phase bone scintigraphy with ^{99m}Tc-MDP in patients suffering from osteoarthritis with inadequate control by systemic or local conservative therapy and treated by radiosynoviorthesis. Follow-up examinations 6 months and 1 year after radiosynoviorthesis showed pain relief in > 50% of patients. Evaluating the assessment score during follow-up, 67.7% versus 64.5% had a satisfactory response 6 and 12 months respectively after treatment. Comparable to other studies, differences in the clinical response rates depended on the degree of morphological changes: grade I with a response rate of 76.3 ± 15.6%, grade II with 62.3 ± 25.6%, and grade III with 54.2 ± 29.8% of success [30].

Different response rates of radiosynoviorthesis between patients with rheumatoid arthritis and osteoarthritis were also published by Zuderman et al. [31]. In 136 patients, refractory to systemic and/or local conservative therapy, a total of 424 joints were treated by radiosynoviorthesis. Three hundred and thirteen joints were affected by rheumatoid arthritis (RA) and 111 by osteoarthritis (OA). In all joints, regardless of the size (large size — knee; mid size — ankle, wrist, shoulder; small size — finger joints) a significant difference was observed with a response rate in all RA joints of 89% and 79% in OA joints. The differences in knee joints were even more pronounced (88% vs 70%). In 2014, retrospective data were published by an Australian group [32]. From a total of 129 patients suffering from osteoarthritis, 116 reached an endpoint of 36 months follow-up. In addition to knee joints, one hip joint, one ankle, and 19 elbow joints were also treated with ^{90}Yttrium-colloid, which is only indicated/approved for radiosynoviorthesis of knee joints (see EANM guideline) [33]. Patients were controlled at 3 months and then each year following radiosynoviorthesis. A clinical response was shown by 68/116 patients (59%); 90% of these patients with initially complete response after 3 months maintained this until a control at 36 months. Only 55% of patients with a moderate response after 3 months and 23% of patients with initially mild response showed response maintenance. One single osteoarthritic knee showed a moderate response, which was sustained for more than 3 years.

In our study, both local signs of joint inflammation and function of the joints were evaluated by an objective and a subjective points system. By inclusion of the objective assessment points

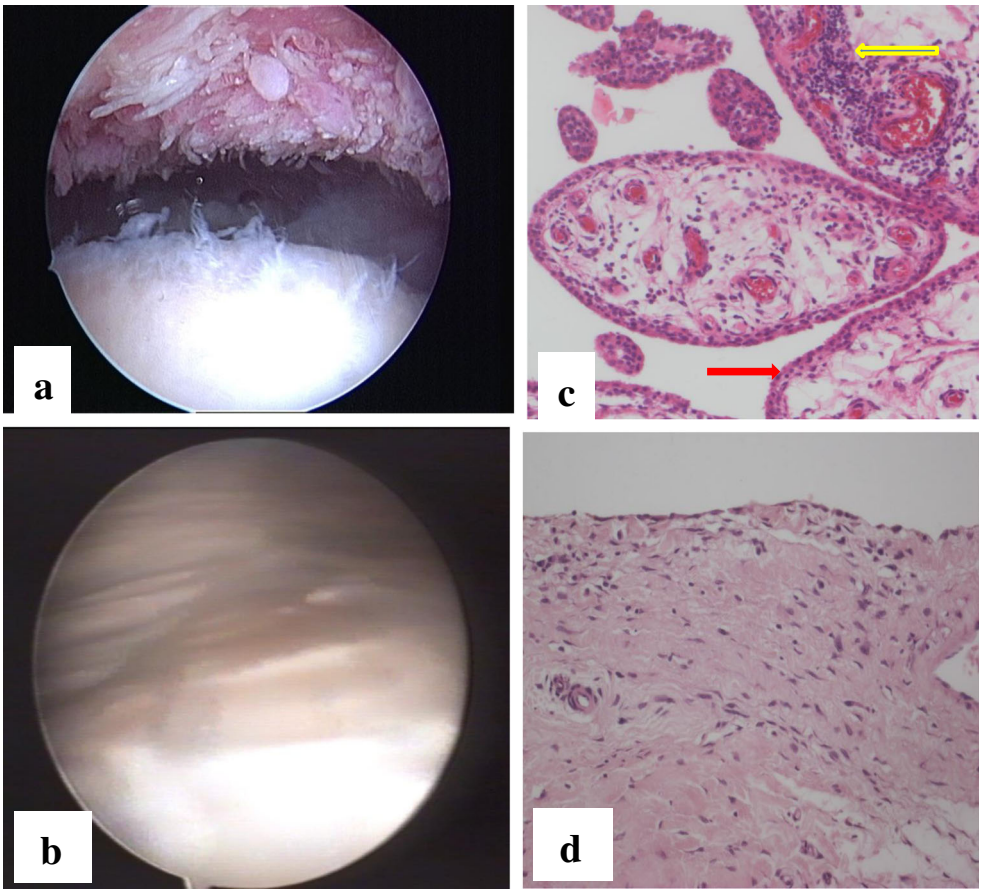
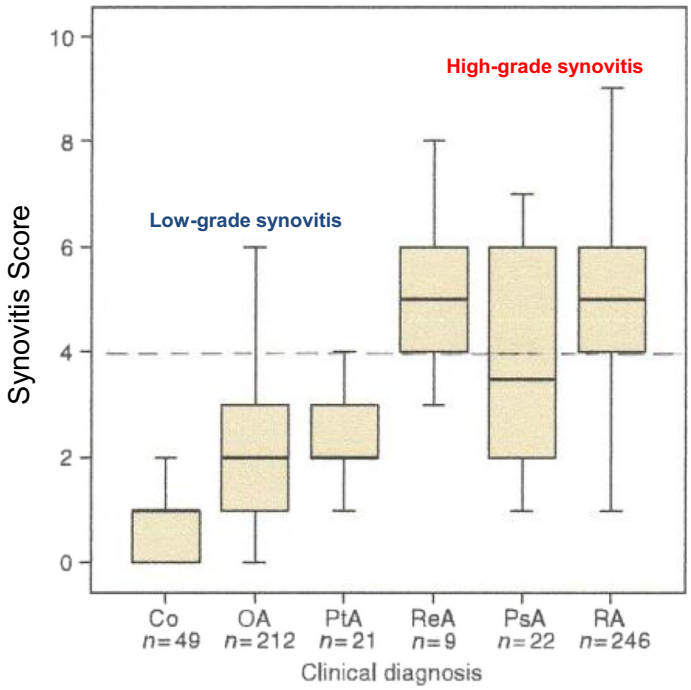


Fig. 1 Arthroscopical image (**a**) and histology (**c**) of a knee with Kellgren–Lawrence grade II osteoarthritis before radiosynoviorthesis showing grape-like clusters of the synovium, enlargement of the lining cell layer (*red arrow*) and inflammatory infiltrations (*yellow arrow*). After radiosynoviorthesis, the synovial surface is silk-like without clusters (**b**); histology: no hyperplasia of synovial lining cell layer and significantly less inflammatory infiltration in the synovial tissue (**d**)

system together with the subjective and patient-based self-evaluation of pain, we tried to reach a clearer evaluation of the treatment efficacy. The index we used was based on several response criteria. Clinical parameters such as joint circumference and joint hyperthermia were used as parameters for inflammation. Joint movement and the ability to walk were used for the assessment of joint function, and pain was also included in the subjective self-evaluation. For the objective parameters, we included the treating physician's comparative evaluation of the subjective pain data depending on time after treatment. These data were collected after 1 year, at 5 years after radiosynoviorthesis, and then every year for a further 5 years. The subgroup analysis, total group vs Kellgren–Lawrence I/II and III patients, showed similar results to those reported by other groups [29–31] with regard to the dependence of clinical response rates from morphological joint changes. In the total group of 141 patients, no significant differences in response rates over time were observed. The excellent/good response in all our patients was stable between 63.8% 1 year after radiosynoviorthesis and 54.5% after 10 years. In the subgroup Kellgren–Lawrence grades I/II, excellent/good results were observed in 73.7% after 8 years. The response rates of 58.3% after year 9 and 50% after year 10 were significantly lower. In the subgroup Kellgren–Lawrence grade III, there was no significant declining of the response rates 1 year after the radiosynoviorthesis until year 8 (45.9% vs 41.2%). Due to a large number of patients who were lost from follow-up after 8 years in this subgroup, the data for the last 2 years should not be taken into account.

In 2006, Jahangier et al. [34] published data regarding the dependence of clinical treatment effects on pre-treatment macrophage infiltration in the synovium after radiosynoviorthesis and corticosteroids versus corticosteroids alone in patients with rheumatoid arthritis and non-rheumatoid arthritis. Higher response rates were observed in patients with marked synovial inflammation, regardless of the clinical diagnosis. Krenn and co-workers [35] published a synovitis score in 2006, separating different rheumatoid diseases (Fig. 2) and showing that some patients with osteoarthritis might have high-grade synovitis, causing higher uptake of the radioactive tracer. However, the differences of mean synovitis score values explain the variable response rates published for different inflammatory joint diseases. The synovitis score might be influenced positively by radiosynoviorthesis. As published earlier, the macro- and microscopic changes of arthroscopy and histology of synovial biopsy, which developed within 6 months after radiosynoviorthesis in those patients responding to treatment, did not change in the following years [17].

Severe side-effects and adverse events from radiosynoviorthesis are very rare in all trials and surveys published so far. Following the drug safety reports for all radiocolloids approved for intraarticular treatment in Europe,



n = 559 (Co: controls; OA: osteoarthritis; PtA: post-traumatic arthritis; ReA:reactive arthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis

Fig. 2 Synovitis score [35] for discrimination of inflammatory joint diseases by the degree of inflammatory alterations of synovial tissue. Co = control group, OA = osteoarthritis, PtA = posttraumatic arthritis, ReA = reactive arthritis, PsA = psoriatic arthritis, RA = rheumatoid arthritis

in a total of approximately 900,000 joints treated between 1990 and 2011, only 30 serious complications were documented [36]. Even if a high estimated number of unreported cases is assumed, the true incidence of severe side–effects will be below 1‰.

The lack of a control group might be considered a limitation to this study; however, osteoarthritis is a progressive disease. The lack of any curative or long-term effective therapy for osteoarthritis would not have been acceptable for an ethical committee for running a control group for up to 10 years.

Conclusion

The aim of radiosynoviorthesis is to improve joint function by decreasing joint effusion, swelling, pain, and stiffness. This is achievable, especially in the early stage of osteoarthritic joint disease. The locally administered beta energy radiation leads to a reduction of inflammatory activity of the synovium, resulting in a delay or even a reduction in damage to cartilage and bone by inflammatory mediators.

The therapy response depends on the morphological changes in the joints, and radiosynoviorthesis in knee joint osteoarthritis should be performed preferably in early stages with Kellgren–Lawrence grades I and II. In Kellgren–Lawrence grades III/IV, the intraarticular beta radiation may reduce pain caused by synovitis, and might be indicated only in inoperable patients or may help to delay endoprosthetic joint replacement.

Our results demonstrate the long-term clinical efficacy of radiosynoviorthesis in patients with knee osteoarthritis. Excellent and good response rates were seen in patients with Kellgren–Lawrence grades I/II after a single radiosynoviorthesis and relatively lower response rates in patients with Kellgren–Lawrence grade III.

While long-term results of pharmacological treatment of osteoarthritis are not satisfactory, radiosynoviorthesis shows a long-term promising and maintained response rate. Radiosynoviorthesis should be an integral part of the therapeutic strategy.

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Compliance with ethical standards

Disclosure of potential conflicts of interest The authors have nothing to disclose.

Ethical approval This prospective study was approved the Research Ethics Committee of the Polyclinic of the Hospitaller Brothers of St. John in God, Semmelweis University Budapest on Sept. 2nd, 2008,

confirmed on March 27th, 2019 (Dr. R. Bernadette, Dr. G. László). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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