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ORIGINAL ARTICLE

The results of 394 consecutive cases of knee joint radiation synovectomy (radiosynoviorthesis) using ^{90}Y

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Abstract

Objective The aim of this study was to assess the treatment results of ^{90}Y radiation synovectomy for chronic exudative synovitis of knee joints.

Methods The retrospective data consist of 394 consecutive knee radiation synovectomies performed using 6 mCi (222 MBq) of ^{90}Y. The assessment included 3-point custom pain and joint mobility scale, evaluation of joint's circumference, binary joint's temperature evaluation, patellar ballottement test, indications for puncture and its volume in applicable cases. 21 cases had to be forfeited due to missing data regarding follow-up.

Results The final analysis of 373 treatment procedures performed in 253 patients yielded following results—at 6 months after treatment, 80.9% of the patients reported at least partial pain relief (including 33.3% with complete pain relief), which increased to 86.7% at one year. The pain intensity decreased over time, however, the outcomes were worse in older patients. The probability of pain recurrence was 15% at 6 months, and 28% at one year. It was highest in post-traumatic synovitis, and lowest in pigmented villonodular synovitis. The circumference of the treated knee joints decreased over the course of follow-up, however, the decrease was significantly lower in older patients. The fraction of patients with full knee joint mobility increased from 34.6 to 40.6% at 6 months and 49.2% at one year. The percentage of patients that required articular puncture decreased from 62.8% at baseline to about 35.6% at 6 months, and 32.8% at one year. Positive patellar ballottement was found in 68.5% before treatment and remained at about 40–50% during the course of follow-up. The increased temperature of the joint was reported in 51.2% at baseline and decreased to 33% at 6 months and 28.3% at one year.

Conclusions (1) Radiation synovectomy is a safe and effective method of treatment in patients with exudative synovitis, however, the pain recurrence rate is significantly higher in post-traumatic exudative synovitis compared to pigmented villonodular, undifferentiated, and rheumatoid arthritis. (2) Our results suggest that older patients have worse treatment results with radiation synovectomy compared to younger patients.

Keywords Hypertrophic-exudative synovitis · Knee joint · Radiosynovectomy · Radiation synovectomy · Radiosynoviorthesis · Yttrium-90

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Introduction

The therapeutic use of radionuclides in exudative synovitis dates back to 1952 [1]. The founding father, an Austrian doctor called Karl Fehlinger [2], used injections of gold isotopes in treatment of rheumatoid arthritis. Currently, radiation synovectomy (radiosynoviorthesis) is a common treatment modality, applicable in a wide range of arthropathies manifested by exudative, proliferative chronic synovitis [3-8]. Among common indications for this treatment modality, there are autoimmunological diseases such as rheumatoid arthritis [9-12] (which is also the most common indication for such treatment [13]), proliferative disorders including pigmented villonodular synovitis [14-16], post-traumatic joint effusions with synovial hypertrophy or undifferentiated arthritis syndromes [17-21], seronegative spondyloarthropathies (such as psoriatic arthritis [22], Lyme's borreliosis, colitis ulcerosa and ankylosing spondylitis) and haemophilia-related synovitis [23, 24].

A majority of patients qualified for this procedure are those that did not respond to corticosteroid or hyaluronate injections. In some cases, radiation synovectomy can also be used as a cheap, fast, non-invasive and relatively effective (60–80%) alternative for surgery, which does not exclude its application at a later stage.

The European Association of Nuclear Medicine (EANM) guidelines for radiation synovectomy indicate three radionuclides [4]. The choice of agent depends on the size of the joint treated [25]—^{90}Y silicate/citrate is used for the treatment of knee, ^{186}Re sulphide for medium-sized joints and ^{169}Er citrate for fingers and metatarsophalangeal joints. ^{90}Y emits beta particles with a maximum energy of approximately 2.27 MeV, soft tissue range of 3.6 mm and $T_{1/2}$ of 2.7 days. Each injection delivers approximately 6 mCi (222 MBq), which according to the available literature, yields a clinical effect in 60–80% of the patients, usually after a 2–4 weeks delay. The procedure can be repeated provided at least 6 months gap between injections [4, 5].

That considered, practice-based rationale behind radioisotope injections remains unsatisfactory [26]. We believe that reports regarding treatment results are necessary, and could help us better understand the clinical applications and contraindications for radioactive yttrium radiation synovectomy.

Patients and methods

Patients

The initial study group consisted of retrospectively collected, prospectively gathered data regarding 394 radiation synovectomies performed on 303 treated knee joints. 21 cases were excluded due to the lack of follow-up. The final analysis includes 373 ^{90}Y injections performed in one clinic on 282 knee joins, in a total of 253 patients. The mean and median age were 50.9 and 52.1 years, and the mean and median follow-up were 14.5 and 6.1 months, respectively. 52.1% of the patients were female. The distribution between right and left knee joints was even (49/51%). Muscle atrophy was reported in 19 cases (6.6%). The pharmacotherapy of the patients included corticosteroids (10.5%), other immunosuppressive (1.4%), both combined (1.4%), nonsteroidal anti-inflammatory drugs (NSAID, 7.8%), corticosteroids combined with NSAID (5.3%), NSAID combined with immunosuppressive (0.7%) and a combination of these three components in 2.8%, 23.4% of the patients received no systemic therapy, and the data is missing in about 46.7% of the cases. Almost half (47%) of the patients received surgical treatment prior to radiation synovectomy. The median time from the onset of symptomatic chronic arthritis to radiation synovectomy was 2 years, and ranged from 1 month to 25 years.

Due to the fact that radiation synovectomy is a strictly localized modality of treatment, treatments of separate knee joints were regarded as separate cases in this study. However, since the analysis aimed at assessing the practical application of this treatment method, multiple injections in a single knee joint were regarded as one, long observation.

The prevalence of different arthropathies in treated patients is shown in Table 1. The most common diagnosis were undifferentiated arthritis, autoimmunological diseases including rheumatoid arthritis and pigmented villonodular synovitis.

Methods

Each synovectomy was performed using 6 mCi (222 MBq) of ^{90}Y citrate by IBA CIS Bio International, France. According the our local protocol, the procedure was performed in ambulatory setting. Depending on the site of injection, the patient was either seated with legs hanging down, or lying on the back. A physical examination, and USG (if necessary) was performed before the procedure. At first, if excessive fluid was present—a joint puncture through suprapatellar recess was performed. Then the needle was injected through the anterior and lateral aspect of the knee joint gap, the joint fluid was aspired to confirm the proper location of the needle in the joint space, and the radionuclide was injected. The procedures were performed in strict asepsis, followed by a sterile dressing, and the treated joint was immobilized for up to 48 h after injection. Simultaneous injection of glucocorticoids was not routinely implemented, however, it was encouraged in repeated synovectomies, and in cases with high risk of recurrence.

Table 1 Characteristics of the study group

Treatment indication	Synoviectomies performed	Knees treated	Patients treated
Total	373	282	253
Proliferative			
Pigmented villonodular synovitis	97	71	65
Autoimmunological			
Rheumatoid arthritis	73	60	48
Psoriasis	15	13	11
Ankylosing spondylitis	9	4	4
Colitis ulcerosa	3	3	3
Systemic lupus erythematosus	3	2	1
Other			
Undifferentiated arthritis	130	98	91
Post traumatic arthritis	37	27	26
Gout-induced chronic synovitis	6	4	4

The data regarding follow-up was collected retrospectively from two places, The Maria Sklodowska-Curie Institute—Oncology Center, Gliwice Branch and District Hospital of Orthopedics and Trauma Surgery in Piekary Slaskie—the first where the injections were performed, and the second where patients were initially qualified for the treatment, and check-up visits took place. The data was gathered retrospectively, based on control visits performed in accordance with our institutional protocol. The assessment included 3-point custom pain and joint mobility scale, evaluation of joint's circumference, temperature (increased/normal), patellar ballottement, indications for puncture of the treated knee joint and it's volume in applicable cases, together with additional punctures performed outside control visits in each consecutive 3-months period.

The 3-level pain assessment scale was as follows:

0: no substantial pain
1: partial reduction of pain
2: pain comparable to baseline or worse

The simplification of pain-reporting scale was due to the clinical setting of data-gathering, to ensure that the pain is measure in relation to initial symptoms, and to minimize inter-observer variability.

"Time to pain relapse" was regarded as time to first reported pain comparable or worse than baseline, after a 1.5 months post-treatment blanking period.

The joint mobility scale measured knee flexion, and used thresholds of 90° (able to climb stairs), and 130° (no clinical restriction of movement).

The data was gathered at 2 weeks after treatment, at 1.5 and 3 months, then every three months till 1.5 years after treatment and twice a year afterwards.

Surgical synovectomy was performed in 16 patients during follow-up, including two cases in which the surgical synovectomy was performed twice. Knee arthroplasty was performed in 11 cases. Among these, there was one case of a patient that has had both surgical synovectomy and knee arthroplasty during follow-up after radiation synovectomy. In these patients, such procedures were regarded as end of follow-up.

Statistical analysis

In this study, a change of the analysed clinical events over time for each participant was assessed. Since a repeated measures' design was taking into account in the statistical analysis, a multilevel (hierarchical) modelling was applied. In particular, multilevel models are generalizations of linear models relying on nested random analysis of variance, and they recognize the existence of data hierarchies by allowing for residual components at each level in the hierarchy (when a design includes both fixed and random effects, it is often called a mixed effects' model).

The following clinical events (response variables) were modelled in the study: patellar ballottement, puncture (volume and quantity), total puncture volume in 3-month periods, pain, and joint mobility, based on the selected available set of risk factors (explanatory variables): months since beginning of the therapy, muscular dystrophy, sex, age, bilateral knee treatment, diagnosis, and length of follow-up.

Additionally, an analysis of censored data using endpoint of pain equal or worse to baseline (recurrence or exacerbation) at any of the visits during follow-up after a 1.5-months post-treatment blanking period was performed. This analysis regarded each patient as one longitudinal

observation, and did not account for improvement after further synovectomies.

In the analysis, Gaussian, binomial logistic, and ordinal logistic regression were used depending of the statistical type of response variables. The statistically significant results of the stratified and interaction regression coefficients ($p < 0.05$) were considered.

In the analysis of censored observations regarding time to first event of pain recurrence or exacerbation, Kaplan–Meier curve and log-rank tests were used.

The statistical analysis was performed using StatSoft Statistica 13.1 (basic statistical tools, graphs, Kaplan–Meier curves, log-rank test) and 'MASS' package (Version 7.3–51.4) using the R platform (Version 3.5.3).

Results

The general results are presented in Table 2.

Pain was one of the most common symptoms. Majority (84.7%) of patients reported moderate to severe pain exacerbated by ambulation, and in 7 cases (2.5%) the pain was severe and continuous. About 12.8% reported no pain at the beginning of the treatment. At 6 months after treatment, 80.9% of the patients reported at least partial pain relief, including 33.3% with complete pain relief, and these values changed to 86.7% and 23.5% respectively at 12 months. The pain intensity reported by patients significantly decreased over time during follow-up—odds ratio (OR) of 0.93 (0.89–0.97; $p = 0.0008$), and increased with the age of the patients—OR of 1.01 (1.001–1.02; $p = 0.0336$). The interaction analysis of these parameters suggests that the age of the patients has a negative impact on the pain reduction over time—OR of 1.002 (1.001–1.003; $p = 0.0002$) (Fig. 1a). Patients in the 3rd and 4th quartile of age reported significantly higher pain intensity compared to 1st quartile, with OR of 1.94 (1.23–3.05; $p = 0.004$) and OR of 1.75 (1.11–2.77; $p = 0.017$) respectively (Fig. 1b). The reported pain intensity was lower in cases where both knee joints were treated—OR of 0.58 (0.33–0.996, $p = 0.0482$).

The likelihood of pain relapse after first synovectomy, defined as an occurrence of pain equal or worse to baseline at any of the visits during follow-up of each case after a blanking period, was 15% at 6 months, and 28% at 1 year of observation (Fig. 2). It is important to note, that this analysis used censored data, and regarded the occurrence of such endpoint without accounting for further improvement if synovectomy was repeated or other methods of treatment employed. There was a statistically significant differences between patients with four most common diagnosis ($p = 0.03$). The likelihood of pain relapse was 9% for patients with undifferentiated arthritis, 12% for pigmented villonodular arthritis, 15% for rheumatoid arthritis, and 36%

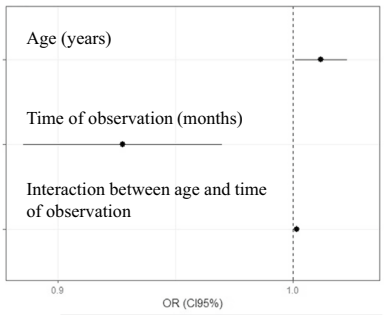
Table 2 General results: pain intensity, joint mobility, joint effusion, knee circumference and excessive joint temperature over the course of follow up

Time	# of cases	Pain				Joint mobility (degree of flexion)						Joint effusion									
0[a]	282	Complete pain relief	12.8	Partial reduction	84.7	Worse/equal to baseline	2.5	Full (>130)	34.6	Impaired (90–130)	60.6	Stiff (<90)	4.8	Positive patellar ballotement	68.5	Necessity of puncture	62.8	Puncture volume (mean value, cc)	22	Mean knee circumference [cm]	42.3	Excessive joint temperature	51.2
0.5	249		15.7		62.4		21.9		29.1		68.7		2.2		45.5		21.7		11.3		42.8		25.6
1.5	144		30.1		57.1		12.8		41.9		54.2		3.9		50.7		38.3		20.8		43		28.2
3	155		21.6		66.7		11.7		38.3		56.2		5.5		46.6		30.8		15.1		42.6		20.2
6	110		33.3		47.6		19.1		40.6		55.4		4		46.2		35.6		18.5		42.5		33
9	68		29		51.6		19.4		43.1		53.4		3.5		54.7		48.5		19.7		40.8		32
12	67		23.5		63.2		13.3		49.2		50.8		0		42.6		32.8		15		42.6		28.3
15	33		30		53.3		16.7		40		46.7		13.3		45.8		29.2		10.1		42.6		20
18	45		29.3		58.5		12.2		44.2		55.8		0		48.7		34.1		11.6		41.7		25.8
24	37		35.3		38.2		26.5		38.2		55.8		3		39.4		20.7		10.2		42.3		35.7

All values except "knee circumference" and "puncture volume" are presented as % of patients

[a]The pain measurements for baseline are as follows: neglectable pain, pain at ambulation, constant pain

A. The pain intensity reported by patients significantly decreased over time during follow-up, and increased with the age of the patients. The interaction analysis of these parameters suggests that the age of the patients has a negative impact on the pain reduction over time.



B. The age of the patients had an inverse impact on the reported pain intensity. Patients in the 3rd and 4th quartile of age reported significantly higher pain intensity compared to 1st quartile.

Q1 – ref
Q2 – OR 1.28 (0.82-1.99) p=0.27
Q3 – OR 1.94 (1.23-3.05) p=0.004
Q4 – OR 1.75 (1.11-2.77) p=0.017

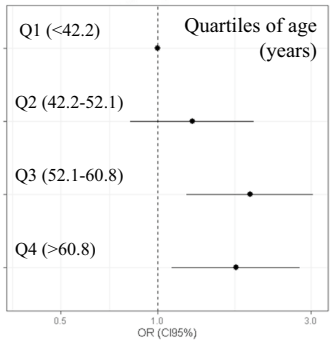


Fig. 1 Interactions between pain intensity, time and age of the patients

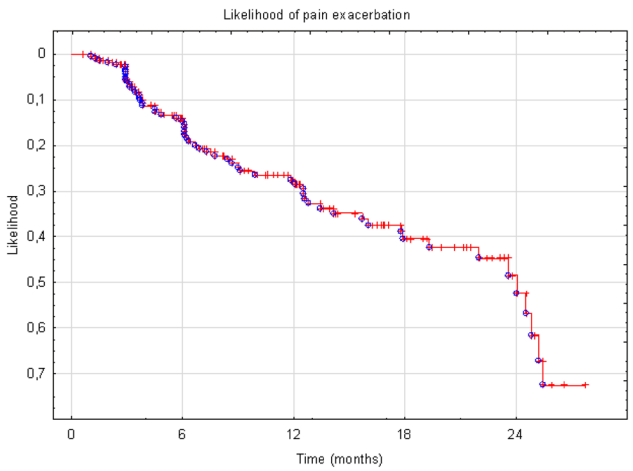


Fig. 2 The likelihood of pain relapse (defined as first occurrence of pain comparable to or worse that baseline after a blanking period) over time in the whole group

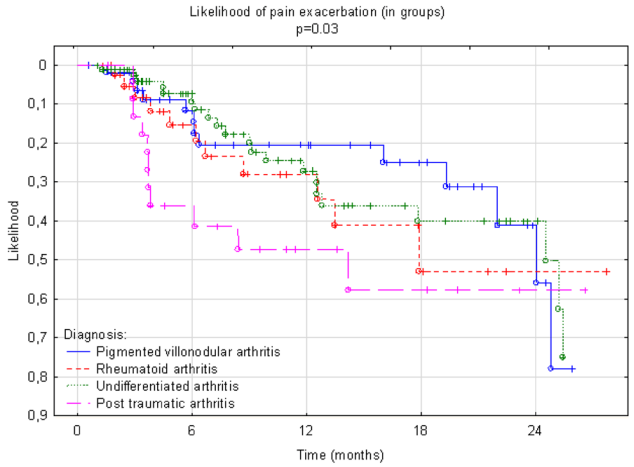


Fig. 3 The likelihood of pain relapse over time in four subgroups of patients with four most common diagnosis in the study group

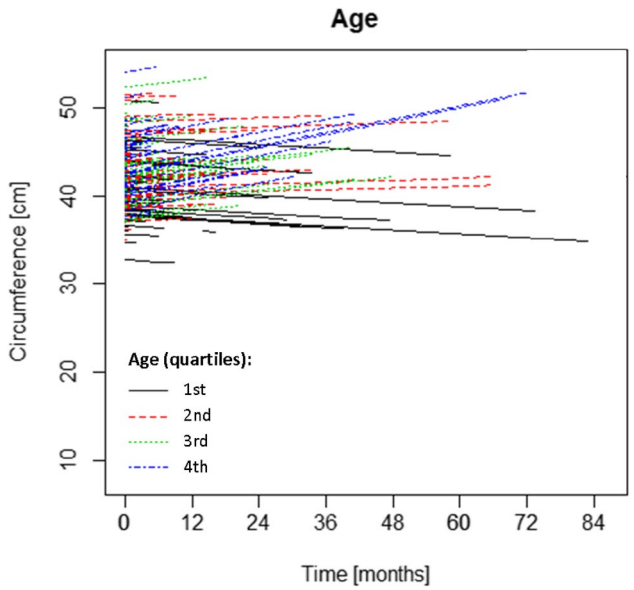


Fig. 4 A statistical model representing decrease of joints' circumference over time, stratified by age into four groups

for post-traumatic arthritis at 6 months, and 20% for patients with pigmented villonodular arthritis, 27% for rheumatoid and undifferentiated arthritis, and 47% for post-traumatic arthritis at 1 year, which is shown on Fig. 3.

The circumference of the treated knee joints decreased over the follow-up by about 0.03 cm per month ($p < 0.0001$). After adjusting for age, the decrease was 0.13 cm per month, and was significantly lower in older patients ($p < 0.0001$, Fig. 4). The joint circumference was lower in patients with muscle atrophy by 3.15 cm on average ($p = 0.0047$).

The knee joint mobility was retained in most cases, however many patients had a restriction of knee flexion to a maximum flexion degree between 90 and 130′. At baseline, 34.6% of the patients had a full mobility of the treated knee joint, which increased to 40.6% at 6 months and 49.2% at one year. The percentage of patients that had sufficient knee mobility for basic everyday ambulation (at least 90′ knee flexure) remained over 95% thorough observation, except for 3rd (94.5%) and 15th month (86.7%).

As presented in Fig. 5, the percentage of patients that required articular puncture significantly ($p < 0.0001$) decreased from 62.8% at baseline to about 35.6% at

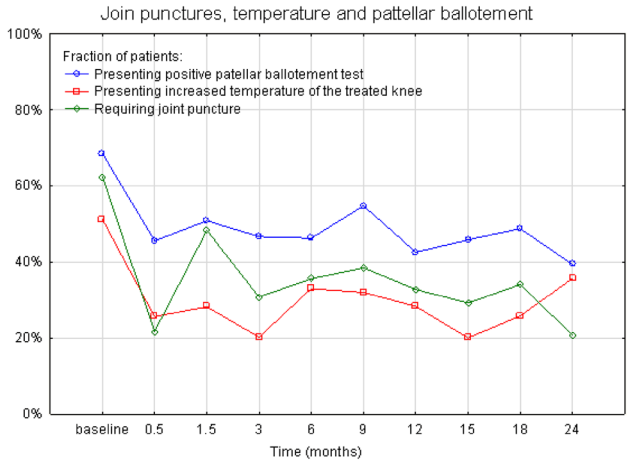


Fig. 5 Fraction of patients requiring join punctures, presenting increased temperature of the joint and presenting positive patellar ballottement test over time

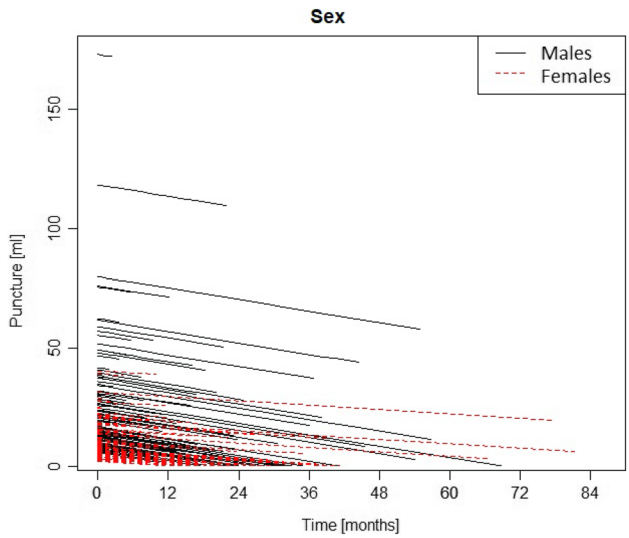


Fig. 6 A statistical model representing decrease of volume of effusion aspired during articular punctures over time, stratified by sex into two groups

6 months, and 32.8% at one year of observation. The volume of effusion decreased over the course of follow-up ($p=0.0001$), and was significantly higher in patients with clinical muscle atrophy by 13.1 cc ($p=0.036$) and males by 14.6 cc ($p=0.0001$) (Fig. 6). When analysed as sum of punctured effusion for each consecutive 3-months period, the difference was even more pronounced—47.3 cc more in males compared to females, and 73.8 cc more for patients with muscle atrophy.

Positive patellar ballottement was found in 68.5% before treatment and remained at about 40–50% during the course of follow-up (Fig. 5). The patellar ballottement symptom was nearly two times less common with OR of 0.52 (0.37–0.73, $p=0.0002$) and the number of punctures was almost twice as low with OR of 0.45 (0.28–0.73, $p=0.0011$) in females compared to men.

The increased temperature of the join was found in 51.2% at baseline, dropped down to 25.6% as soon as after 2 weeks, and then further decreased to 20.2% at 3 months. After 6 months 33% of the patients had clinically increased temperature of the treated joint and this value remained around 30% for the rest of follow-up (Fig. 5).

Regarding side effect of the treatment, besides transient exacerbation of symptoms during the first 1–3 weeks, in vast majority of cases no significant adverse effects were reported. There was a single case of skin necrosis, however the patient was lost to follow-up and no further data could be obtained.

We have found worse joint mobility in undifferentiated arthritis ($p=0.0181$), and lower joint circumference in rheumatoid arthritis ($p=0.0004$) compared to pigmented villonodular synovitis.

Discussion

Even though radiation synovectomy has a well-established place in the contemporary nuclear medicine, and is currently the second most common performed nuclear medicine procedure in Germany [25], the up-to-date research regarding its effectiveness is rather of low-quality. There is plenty of series with modest study groups, but often aimed at assessing particular, sublime endpoints (i.e. on biological level), few prospectively collected data regarding clinical efficacy and a great deal of uncertainty in the descriptions of material and methodology [4]. We believe that since our methods, and most of all—demographics of the treated population are changing, there is a necessity for verification of effectiveness of commonly applied treatment methods on larger, clinical cohorts. However, we are also aware of the limitations of our analysis—typical for retrospective studies, such as missing data (i.e. clinical data regarding concomitant medications missing in 46.7%) or certain choices being left to the attending doctors' discretion and experience instead of being performed with strict accordance to a protocol (i.e. indications for articular puncture), which can influence treatment results. Therefore we believe that further studies, especially prospective, randomized trials are necessary and justified.

In our study, partial reduction of pain at 6-months occurred in 47.6% cases, and complete pain relief was found in 33.3% of the patients, which is consistent with available literature. In our previous publications, we reported 37.5%/37.5% and 33%/40% partial/complete pain relief at 6 months [5, 7]. It is suggested in EANM guidelines that patients should be informed about 60–80% efficacy of the treatment [4]. Liepe et al. reported 31% excellent response

rate and 45% moderate to good response rate in a series of 100 treated knee joints [25]. Deutsch et al. achieved 40–85% response rate in patients treated for knee joints, however the results might have been affected by a higher percentage of patients with osteoarthritis [27]. Chrabański reports an increase of patients reporting intensity of pain as measured by Visual Analogue Scale (VAS) equal to 0 during ambulation from 1% to 24.3%, and VAS 0–4 from 24.3% to 76.7% over the course of 5 months [28]. A meta-analysis by Kresink et al. showed 73% ± 17% response rate, however the article regarded treatment of different joints, not only knee [29]. Modder, in his monography, reports pain reduction in 88% at 2 years [6]. A comparison of different radiosynovectomy agents by Liepe et al. showed decrease from VAS 6 ± 2 at baseline to VAS 3 ± 2 at 6 months [30]. Kim et al. reported at least fair reduction of pain in 77.5% of treated knee joints after 6 months based on a group of 40 treated knee joints [31].

We found a correlation between reported pain and age of the patients, but no correlation between the reported pain and sex, which is similar to findings by Farachati et al. [32] and Chrabański [28]. In general, older patients responded worse to treatment (had a higher pain scale result on average).

There was a correlation between patients with both knee joins treated and a lower pain measurements on average. Perhaps this could be connected with higher pain tolerance in patients with more extensive disease, however, we haven't found similar results in other publications.

Although there were no statistically significant findings regarding joint's mobility, the fraction of patients retaining at least 90° knee flexure remained over 95% for the majority of follow-up. Similarly Chrabański reports an improvement of knee joint functions after radiation synovectomy in his group [28]. Perhaps a more precise scale would be required to observe statistically significant differences in our study.

The volume of the punctures significantly decreased with consecutive visits, which is different from our prior publications. Previously, we have observed a trend of decreasing mean volumes of punctures, but it wasn't statistically significant [5, 7]. The current results may be a result of longer follow-up and larger database, and are consistent with literature findings [28, 31]. We found a significant correlation between puncture volumes and clinically apparent muscle atrophy prior to treatment as well as puncture volume and male sex. Both of these factors increased the average puncture volumes. Such correlation could have been caused by larger size of knee joints in males on average. However, females were also almost twice less likely to undergo punctures, regardless of the volume.

Although certain authors claim that the diagnosis does not significantly affect the pain-related treatment outcome [8], we have found a correlation suggesting that patients diagnosed with post-traumatic synovitis have a significantly higher chance (40% +) of early pain relapse. Some publications indicate that haemophilia-induced synovitis responds better to radiation synovectomy, but we haven't had such patients in our study group.

Acknowledgements Treatment described in this manuscript is a routine modality performed in accordance with locally approved treatment protocol. The data was gathered retrospectively. Therefore, according to our local regulations, no additional IRB approval was necessary for this study.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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