Radiosynovectomy: Introduction and Overview of the Literature

6

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Contents

6.1 Introduction

Rheumatoid arthritis (RA) and local degenerative changes such as osteoarthritis (OA) are the most common reasons for synovitis that lead to chronic pain, swelling, destruction and dysfunction of the joints.

Systemic treatment including non-steroidal anti-inflammatory drugs (NSAIDs) as well as disease- modifying antirheumatic drugs (DMARDs), like biologicals, glucocorticoids (GC) and intraarticular GC injections is performed to control synovitis. In case with persisting synovitis, further therapy options are necessary.

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Studies have reported that surgical removal of the inflamed synovium can improve symptoms and function of the affected joints. However, due to insufficient removal of the inflamed synovial membrane in arthroscopic synovectomy, recurrence rate of synovitis was high [1–3].

Radiosynovectomy, also known as radiosynoviorthesis or RSO, is an important alternative to surgical or chemical synovectomy for the treatment of rheumatoid arthritis. The use of this therapy method had increased in the last years and is currently performed in about 100,000 joints per year in Europe.

A wide list of indications for RSO is reported in the literature, but the clinical outcome differs and depends on the primary disease, the type of the affected joint and the pre-existing degenerative changes.

6.2 Indications for Radiosynovectomy (RSO)

The indication for RSO is worked out in cooperation with the rheumatologists, orthopaedists and the nuclear medicine specialists. Only an expert in nuclear medicine is permitted to perform radiosynovectomy and is also responsible for the therapy.

RSO is reasonable if inflammation of the synovial membrane (synovitis) occurs. Therefore, before therapy diagnostic requirements such as arthrosonography and multiphase bone scintigraphy of the joints are mandatory to demonstrate synovitis (Fig. 6.1).

The main indications for RSO according to the European procedure guidelines for radiosynovectomy and with modifications to the German and Austrian

Fig. 6.1 A female patient, 72 years with rheumatoid arthritis of the hands. Before radiosynovectomy, scintigraphy is performed to clearly localize the inflamed joints. Tc-99m methylene diphosphonate (Tc-99m MDP) bone scintigraphy shows a typical symmetrical increased tracer uptake in both wrists and small finger joints due to synovitis (*right image*). Also in the distal interphalangeal joints, synovitis can be seen. The localization is not typical for rheumatoid arthritis and is secondary caused by degenerative changes

guidelines [4–6] are persisting synovitis after a 4- to 6-month systemic treatment in:

- Rheumatoid Arthritis
- Seronegative spondyloarthropathy (e.g. reactive or psoriatic arthritis)
- Other inflammatory joint diseases, e.g. Lyme disease and Behcet's disease
- Undifferentiated arthritis (where the arthritis is characterized by synovitis, synovial thickening or effusion)
- Persistent synovial effusion (e.g. after arthroscopic synovectomy)
- Persistent effusion after joint prosthesis
- Osteoarthritis (activated osteoarthrosis)
- Pigmented villonodular synovitis (PVNS)
- Haemophilic arthritis
- Contraindications
- Pregnancy
- Breast-feeding
- Local skin infection
- Acute rupture of popliteal cyst (Baker's cyst of the knee)
- Relative Contraindications
- The radiopharmaceuticals should only be used in children and young patients (<20 years), if the benefit of treatment is likely to outweigh the potential hazards.
- Extensive joint instability with bone destruction

6.3 Radiopharmaceuticals

The radionuclides that are injected into the articular cavity are phagocytized by the synovial cells. The irradiation leads to fibrotic and sclerosing changes of the synovial membrane and to an occlusion of the superficial capillaries. The inflammation as well as the proliferative and destructive process is stopped. Clinically, the pain and effusion of the treated joints, as well as the mobility get improved [7, 8].

In RSO β-emitting radionuclides are used.

Essential for the choice of the nuclides is the penetration depth of the emitted irradiation in correspondence to the thickness of the synovium and the nuclide's half-life. The most often used and approved nuclides for RSO in Europe are:

(Nuclide, half-life, mean/maximum penetration depth in tissue)

- Yttrium-90 citrate (Y-90, 2.7 days, 3.6/11 mm) – used for large joints like the knee joints

- Rhenium-186 sulphide (Re-186, 3.7 days, 1.2/3.7 mm) – used for medium-sized joints such as shoulder, elbow, wrist, hip and ankle
- Erbium-169 citrate (Er-169, 9.4 days, 0.3/1.0 mm) – used for small joints in the fingers and the toes, sterno- and acromioclavicular and temporomandibular

Furthermore, not so widespread used radionuclides for RSO are dysprosium-165 ferric hydroxide, holmium-166 hydroxyapatite and samarium-153 hydroxyapatite [9].

6.4 Radiosynovectomy in Rheumatoid Arthritis (RA)

The effectiveness of radiation synovectomy in rheumatoid arthritis was investigated by several authors.

In a meta- analysis 2,190 treated joints were evaluated [10]. There were 1,880 joints with rheumatoid arthritis and 37 patients with seronegative arthritis including psoriatic arthritis, ankylosing spondylitis and Reiter's disease. One hundred twenty-one had osteoarthritis. The period of observation was 1 year. The mean improvement rate for rheumatoid arthritis was 66.7 ± 15.4 %. For osteoarthritis the success rate was 56 ± 11 %. The results were dependent on the pre-existing morphological changes according to the American Association's staging criteria (Steinbrocker). The best results were achieved in patients without morphological changes. However, RSO in patients with changes according to Steinbrocker I was successful in 72.8 ± 12.3 % and in 64 ± 17.3 % in Steinbrocker II. Even in joints staged with Steinbrocker III and IV had a success rate of 52.4 ± 23.6 %.

Based on the clinical outcome after RSO, three groups were defined where RSO was indicated. In case of deformed or unstable joints, there was no clinical response. Therefore, RSO was not indicated (Table 6.1).

Most of the treated joints were large joints like knees (64 %). Medium-sized joints like shoulder, elbow, wrist, ankle and small finger joints were presented in 17 and 19 %.

Several studies were performed to determine the clinical response in the different types of joints.

6.4.1 Radiosynovectomy of Large Joints

Kampen et al. [11] reported in a summary of prospective studies in which 796 knee joints were treated using yttrium-90 colloid (Y-90) that the success rate ranged from 50 to 100 %. The overall follow-up duration was 6–36 months.

Several authors also compared yttrium-90 colloid (Y-90) with the intraarticular injection of corticosteroids. It turned out that RSO was effective in 78 and 70 % of RA patients in whom corticosteroids were ineffective [12, 13].

Furthermore, in a double-blind study by Urbanova et al. [14], the authors compared Y-90 in combination with corticosteroids. Corticosteroids alone and the

Table 6.1 Groups for RSO [10]

Group	Clinical response rate	Disease	Pre-existing morphological changes
A (appropriate)	>80 %	Rheumatoid arthritis Haemarthrosis in haemophilia Haemarthrosis in Willebrand's disease Villonodular synovitis	No changes
B (acceptable)	60–80 %	Rheumatoid arthritis Seronegative arthritis Osteoarthritis Repeating injection in previous responder	Steinbrocker I, II[a] Minimal or moderate
C (helpful)	<60 %	Rheumatoid arthritis Osteoarthritis	Steinbrocker III, IV[a] Severe destruction
D (not indicated)	No response	Need for surgical interventions Previous nonresponder Deformed joints Unstable joints	

[a]Classification according to the American Association's staging criteria (Steinbrocker)

combination with Y-90 colloid showed comparable efficacy in reduction of pain and effusion for a short time. But in the long term (after 12 months), Y-90 colloid was superior. The improvement was seen with the variables of pain, functional disability, joint tenderness and swelling.

Similar results were also found in a 6-year follow-up study by Grant et al. [15] in 21 patients with RA. After 6 years, 75 % of the patients that were treated initially with glucocorticoid (GC) needed other treatments (e.g. surgical synovectomy, knee arthroplasty, Y-90 reinjection) versus 66 % of patients in the RSO group ($p > 0.05$).

In another study [16] the combination therapy was also investigated in 15 patients with chronic pyrophosphate arthropathy of the knee. They found that all outcome parameters were significantly better for the combination of Y-90 and GC injection with regard to pain, stiffness, effusion, range of movement ($p < 0.01$) and joint circumference ($p < 0.05$). Therefore, the combination therapy was favoured in chronic pyrophosphate arthropathy.

It seems that the combination therapy is also the preferred therapy concept in clinical routine because, in a survey of radiation synovectomy in Europe, 60 % of the responders reported that they used corticosteroid co-injection with radiopharmaceuticals. Rheumatoid arthritis was the most prevalent disease in patients treated.

Regarding steroids, triamcinolone hexacetonide was most frequently used due of its relatively long residence time in joints.

It was also suggested that corticosteroids reduces lymph node uptake of radiocolloids [17, 18].

6.4.2 Surgical Synovectomy and Radiosynovectomy

Surgical synovectomy is well established in the local treatment of RA.

However, due to traumatization and insufficient removal of all pathological tissue with minimal arthroscopic synovectomy, the recurrence rate was high and amounted to 30 % in a long-term follow-up [2, 3].

Therefore, several authors reported the usefulness of the combination of arthroscopic subtotal synovectomy and radiosynovectomy.

In a recent study by Akmese et al. [19], the authors compared the combined arthroscopic synovectomy and RSO in the treatment of chronic non-specific synovitis of the knee. They found that the limitation of motion and effusion was significantly regressed. Also pain and synovial membrane thickness were significantly reduced (82 and 54 %). Clinically and radiologically on MRI, there was no recurrence after 3 years.

Similar results were also found from other authors. Kerschbaumer et al. [20] reported about significantly better long-term clinical results (8 years) in 141 knee joints that were treated with the combination therapy than patients that were treated with RSO alone.

Furthermore, in another study by Goetz et al. [21], 32 patients with RA of the knees were successfully treated with the combination therapy and also did not need any surgical re-intervention in 84, 44 and 34 % after 5, 10 and 14 years. Similar results were also found from other authors with better results for the combination therapy in the early stages of rheumatically swollen joints. Therefore, the authors suggested to perform the combined therapy for the treatment of early rheumatoid stages of the ankle joint. Additionally, open synovectomy should be preferred to arthroscopic synovectomy if tenosynovectomy is simultaneously required [22, 23].

Regarding the time of RSO, it was suggested to perform RSO 6 weeks after surgery, because after this time the postoperative edema had diminished and the surgical wound is almost closed to avoid any leakage of the injected radionuclide. Moreover, the postoperative inflammatory changes were at the maximum at this time and the efficacy of the anti-inflammatory effect of the RSO was thus increased [19].

Further studies are needed to establish this favourable therapy concept for the chronic non- specific synovitis in the long-term follow-up.

6.4.3 Radiosynovectomy in Knee Endoprosthesis

Radiosynovectomy was also under investigation for treating recurrent joint effusions after knee endoprosthesis.

First results about the usefulness of RSO in knee endoprosthesis were reported by Mödder et al. [24]. In their study 107 patients with chronic joint effusion due to "polyethylene disease" were treated with Y-90. In 93/107 (87 %) patients, joint effusion completely diminished after therapy.

In a recent study by Mayer-Wagner et al. [25], 55 patients with chronic joint effusion after endoprosthetic knee replacement were treated with Y-90 colloid.

Significant improvement in pain, effusion and function was seen in 54 %. Most of the patients in whom RSO treatment failed, complications like infection, loosening, allergy and trauma were detected.

In summary, RSO represents a valid therapeutic option in persistent effusion after joint prosthesis. However, in case of treatment failure, endoprosthetic complications should be excluded.

6.4.4 Radiosynovectomy of Medium- and Small-Sized Joints

Rhenium-186 is used for the hip, shoulder, elbow, wrist, ankle and subtalar joint and erbium-169 for finger and toe joints, acromio-/sternoclavicular joints and temporomandibular joints.

It was reported that the efficacy of RSO for medium-sized joints in RA varies from 60 to 90 % (Fig. 6.2a, b).

In two prospective studies by Göbel et al. [26, 27], the authors evaluated the efficacy of rhenium-186 for medium-sized joints ($n=50$) and erbium-169 for digital joints ($n=131$) in patients with RA. The injection of rhenium-186 and erbium-169 was combined with triamcinolonhexacetonid. The synovitis in the control groups was treated by the injection of cortisone alone. Follow-up time was 3 years. Pain, synovial swelling, joint motion and stage of radiological destruction (based on the staging by Larsen-Dale-Eek) were assessed.

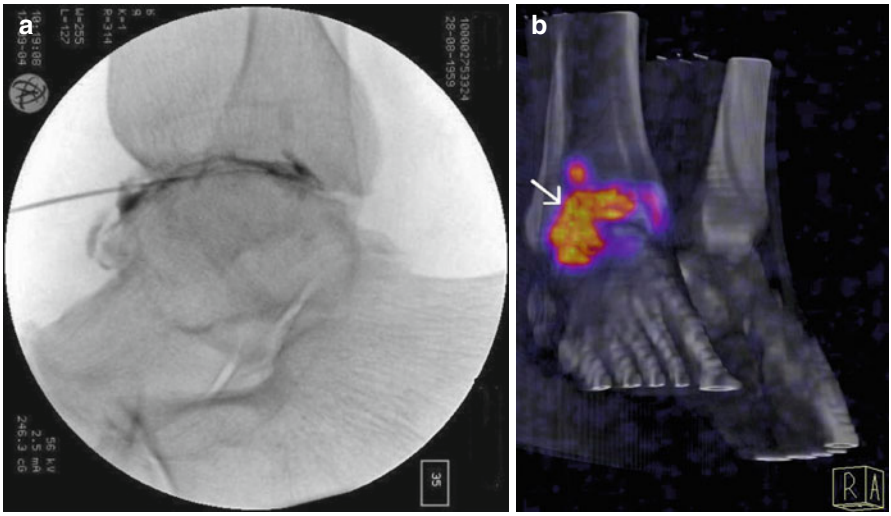

Fig. 6.2 (**a**) Arthrogram of the ankle joint during the RSO. The puncture needle can be seen on the left side. (**b**) Patient with rheumatoid arthritis was submitted for RSO of the right ankle joint. After the injection of 74 MBq rhenium-186, single-photon emission computed tomography (SPECT) is showing the distribution within the ankle joint (*arrow*)

Significantly better clinical results were achieved in the group with combined injection of radionuclide and cortisone. The results of the small metacarpophalangeal joints (MCP) and the medium-sized joints were comparably good. However, proximal interphalangeal joints (PIP) responded less than other joints, which was explained by a leakage of the nuclide due to increased movement during manual activities.

Therefore, a sufficient immobilization (up to 72 h) by using a finger splint is recommended to avoid leakage. However, according to the guidelines, if immobilization of the treated joint cannot be ensured, hospitalization is mandatory.

In the study mentioned above, the progression in radiological joint destruction correlated also with the clinical results and was significantly lower in comparison with the groups that were injected with cortisone alone.

The results are in concordance with other authors. In an international multicenter double-blind and placebo-controlled study on patients suffering from rheumatoid arthritis, 82 finger joints were investigated. After 6 months the results showed that pain and swelling significantly decreased (95 % vs. 42 %) and mobility increased (64 % vs. 42 %) after RSO [28].

In a similar study by van der Zant et al. [29], joints of the upper extremities were treated. The clinical effect was better when radionuclide plus cortisone was injected into the joints (69 %) than cortisone alone (29 %). Furthermore, there was no significant difference in clinical outcome for patients with RA and with non-RA. It seems that the destruction process of the joints as well as the localization also has an influence on the clinical effect of joint motion and pain.

In a study by Kraft et al. [30], the authors found that pain was significantly decreased after RSO, whereas the influence of joint motion was minimal. This was most likely due to the progressive destructive processes of the joints. Furthermore, the best results were observed for shoulders and elbows. Ankle joints responded worst.

Also other authors reported that the effect of RSO was higher for upper extremity than for lower extremity joints. It was supposed that this was due to mechanical forces in weight-bearing joints that could perpetuate the joint damage and recurrence of synovitis [12, 29, 31].

6.5 Radiosynovectomy in Osteoarthritis

Osteoarthritis (OA), which is also known as degenerative joint disease, is caused by mechanical abnormalities leading to a secondary synovitis with cartilage and subchondral bone destruction. Symptoms include joint pain, stiffness and sometimes joint effusion. Most often the weight-bearing joints of the lower extremities are affected. In finger polyarthrosis the distal interphalangeal (DIP) joints and/or proximal interphalangeal joints (PIP) and/or the first carpometacarpal (CMC) joints are involved.

RSO is indicated when synovitis occurs with pain and joint effusion.

In the literature the success rate ranges from 45 to 85 %. We also found in an own meta- analysis of 121 patients with OA that the mean success rate was 56 ± 11 %.

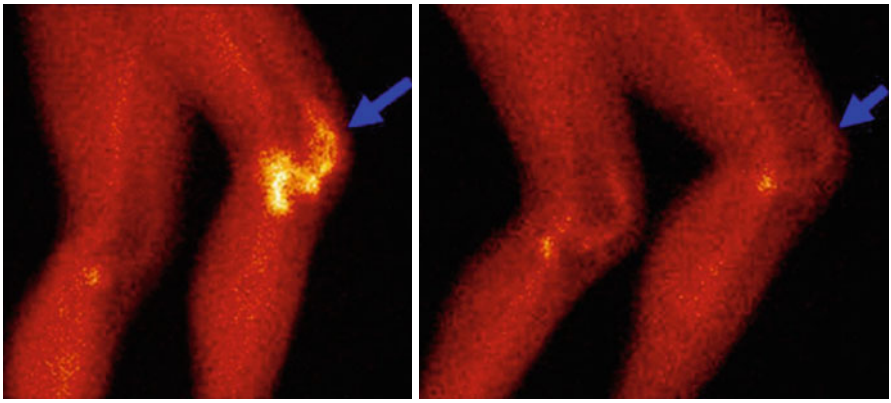

Fig. 6.3 A female patient, 50 years with chronic synovitis in osteoarthritis. Before radiosynovectomy, Tc-99m methylene diphosphonate (Tc-99m MDP) bone scintigraphy shows an increased tracer uptake in the early phase of scintigraphy of the right knee (*arrow* on the *left image*). Six months after radiosynovectomy, synovitis diminished and tracer uptake in Tc-99m MDP bone scintigraphy was significantly reduced (*arrow* on the *right image*)

The observation period was 1 year. Furthermore, it could be demonstrated that the improvement rate depended on pre-existing degenerative morphological changes. It turned out that the improvement rate was >80 % when there were no degenerative changes and 60–80 % in case of moderate changes (Fig. 6.3). However, the response rate decreased in cases of severe degenerative changes, but in clinical routine it was still classified as "helpful" with a success rate <60 % (Table 6.1).

Similar results were also found from other authors. It was reported that in patients with OA of the knee, the overall success rate in pain was 86 % and knee flexibility was improved in 65 %. Furthermore, the clinical improvement was inversely related to radiographic knee damage, patient's age and duration of the disease [32, 33].

Based on these results it seems that the therapy effect also depends on the underlying disease and the type of joint.

Zuderman et al. [34] reported that the success rate of RSO for the small-, medium- and large-sized joints were 89, 86 and 79 %. It was higher in RA (89 %) than in patients with OA (79 %). Furthermore, for the finger, ankle and wrist joints in RA, RSO was so promising that it should be preferred over the sole intraarticular corticoid injection.

Rau et al. [35] also found in a multicenter study that clinical outcome was significantly better in large joints for OA, but the response rate was similar for small- and large-sized joints in patients with RA.

However, in a study by Kampen et al. [36], the authors found that the therapy was also highly effective in digital joint OA with local synovitis. The best results were obtained in the thumb base joints. All patients also reported an improvement in their manual activities.

We also performed a double-blind controlled prospective study on 22 patients with local synovitis in OA of the thumb base joints. The effect of erbium-169 in

combination with corticosteroids was compared to corticosteroid injection alone. The follow-up duration was 1 year.

It turned out that RSO in combination with steroids was significantly effective regarding reduction of pain, inflammation and improvement of the motion. Corticosteroids showed a significant reduction of pain for a limited time up to 6 weeks after injection, but after this time the pain worsened. There was also a disease progression in this group after 1 year [37].

6.6 Radiosynovectomy in Haemophilic Patients

Haemophilia is a hereditary disorder which causes bleeding into joints. Repeated joint bleedings cause joint and cartilage destruction. RSO is indicated when chronic synovitis occurs in chronic haemorrhagic arthropathy.

Several studies reported that the frequency of bleeding is reduced after RSO. Therefore, also the factor usage is reduced.

In an own meta-analysis of 15 patients with Willebrand's disease and 116 with haemophilia, a reduction of joint bleedings and factor usage after RSO was found in 91 ± 4.3 % [10].

This is in concordance with a recent study about haemophilic synovitis by Turkmen et al. [38]. The authors investigated 82 knee joints in a 10-year retrospective analysis. After 1, 3 and 5 years, there was no repeated bleeding in 89, 73 and 63 %, respectively. In addition, RSO was effective independent of the type of joint and the degree of synovial hypertrophy. However, it was also reported that the more severe synovites and the knee joints reqiured more injections than the elbow or the ankle joints [39, 40].

Kastersen et al. [41] also reported a reduction of the frequency of joint bleeding after RSO in 94 % during the first year. Patients with minor or no radiological changes of the joints showed the best results. This is in concordance with other authors of more than 250 treated joints. Furthermore,RSO turned out to be safe and highly cost effective in comparison to surgical synovectomy and should be performed early before the appearance of articular cartilage damage [42–44].

Conclusion

Radiosynovectomy (RSO) represents an effective therapy method in the treatment regime of inflammatory joint diseases. Several indications for RSO according to the guidelines are reported in the literature.

RSO is appropriate in the treatment of rheumatic arthritis and haemophilic arthropathy with a high clinical response rate. RSO also provides acceptable clinical results in patients with osteoarthritis according to the degenerative changes.

Large- as well as medium- and small-sized joints are suitable for RSO.

The co-injection of glucocorticoids and radiation synovectomy provide favourable clinical results and is therefore most often performed in clinical routine.

In case of arthroscopic synovectomy, the combination with RSO provides significantly better clinical results than the surgical method alone.

Therefore, close cooperation with the rheumatologists and orthopaedists is necessary to consider RSO in each patient to ensure optimal medical care.

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