# EANM Procedure Guidelines for Radiosynovectomy

## I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in

1. Evaluating patients who might be candidates for intra-articular treatment using colloidal preparations of $^{90}$Y, $^{186}$Re or $^{169}$Er
2. Providing information regarding the performance of these treatments.
3. Understanding and evaluating the sequelae of therapy.

## II. Background information and definitions

### *A. Definitions*

1. Radiation synovectomy/radiosynoviorthesis (RS) in this context means radionuclide therapy of joint synovitis or synovial processes by intra-articular injection of $^{90}$Y silicate/citrate *or* $^{186}$Re sulphide *or* $^{169}$Er citrate. Synovitis means inflammation of the specialised connective tissue lining of a joint cavity (synovium).
2. i) $^{90}$Y emits a beta particle with a maximum energy of 2.27 MeV, a mean energy of 0.935 MeV and an average soft tissue range of 3.6 mm. The physical half-life is 2.7 days.
   ii) $^{186}$Re emits a beta particle with a maximum energy of 1.07 MeV, a mean energy of 0.349 MeV, an average soft tissue range of 1.1 mm and a 9% abundant gamma emission with a photopeak of 0.137 MeV. The physical half-life is 3.7 days.
   iii) $^{169}$Er emits a beta particle with a maximum energy of 0.34 MeV, a mean energy of 0.099 MeV and an average soft tissue range of 0.3 mm. The physical half-life is 9.4 days.

### *B. Background*

Intra-articular injection of $^{90}$Y silicate/citrate, $^{186}$Re sulphide and $^{169}$Er citrate is approved in Europe for the treatment of a range of refractory painful arthropathies. Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with other forms of therapy and should be able to liaise closely with other clinicians involved in managing the patient. The treating clinician should either see the patient jointly with the rheumatologist or orthopaedic surgeon assuming overall management of the patient's condition or be prepared to assume that role. The treating clinician should be appropriately trained and experienced in the safe use and administration of $^{90}$Y silicate/citrate, $^{186}$Re sulphide and $^{169}$Er citrate therapy.

Clinicians involved in unsealed source therapy must be knowledgeable about, and comply with, all applicable national and local legislation and regulations. The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, and procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread.

## III. Common indications

$^{90}$Y silicate/citrate, $^{186}$Re sulphide and $^{169}$Er citrate are indicated for the treatment of joint pain arising from arthropathies including:

- Rheumatoid arthritis
- Spondylarthropathy (e.g. reactive or psoriatic arthritis)
- Other inflammatory joint diseases, e.g. Lyme disease, Behcet's disease
- Persistent synovial effusion
- Haemophilic arthritis
- Calcium pyrophosphate dihydrate (CPPD) arthritis
- Pigmented villonodular synovitis (PVNS)
- Persistent effusion after joint prosthesis
- Undifferentiated arthritis (where the arthsritis is characterised by synovitis, synovial thickening or effusion)

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*Contraindications*

1. Absolute

- Pregnancy
- Breast-feeding
- Local skin infection
- Ruptured popliteal cyst (knee)

2. Relative

- 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.
- Evidence of significant cartilage loss within the joint.

## IV. Procedure

### *A. Facility*

The facilities required will depend on national legislation for the administration of pure beta-emitting therapy agents. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities. The administration of $^{90}$Y silicate/citrate, $^{186}$Re sulphide and $^{169}$Er citrate should be undertaken in a dedicated room, equipped for sterile injection procedures, by appropriately trained medical staff with supporting scientific and nursing staff.

### *B. Patient preparation*

1. Patients considered for intra articular $^{90}$Y silicate/citrate, $^{186}$Re sulphide or $^{169}$Er citrate therapy will have failed at least one intra-articular injection of long-acting glucocorticoid (e.g. methylprednisolone acetate or triamcinolone). Pain will usually be severe enough to limit normal activities and/or require regular analgesics.
2. Radiographs of the joints to be treated should be obtained and reviewed prior to undertaking RS. Weight-bearing views of lower limb joints should be requested specifically. Symptoms largely or exclusively attributable to cartilage damage are unlikely to benefit from RS.
3. Additional imaging procedures may be useful but are not essential in planning RS:
   - Scintigraphic assessment of soft tissues and severity of active inflammation [e.g. by 3-(2-)phase $^{99m}$Tc MDP/HDP/HEDP bone scintigraphy and/or $^{99m}$Tc-HIG scintigraphy] of the affected joints.
   - Ultrasound – to evaluate synovial structure and thickness and exclude ruptured Baker's cyst.
   - Magnetic resonance imaging of the affected joint.
4. The time interval between arthroscopy or joint surgery and radiosynovectomy should be (2–) 6 weeks and that between joint puncture and radiosynovectomy should be 2 weeks. The minimum interval between repeated treatments in the same joint is 6 months.

### *C. Information regarding the procedure*

Patients should receive both written and verbal information about the procedure prior to receiving therapy, including the importance of immobilising the affected joint for up to 48 h post injection. Informed written consent must be obtained from the patient.

1. Patients should be told that 60–80% of patients benefit from $^{90}$Y silicate/citrate, $^{186}$Re sulphide or $^{169}$Er citrate therapy.
2. Patients should be told that response is unlikely within 14 days of injection and may be delayed until up to 1 month.
3. Patients should be warned of the risk of a temporary increase in synovitis following treatment.
4. Patients should understand that radiopharmaceutical will not benefit other non-treated joints but some overall positive effect on other joints may be noticed if steroid is co-injected (see later).
5. Patients should be informed of the potential complications of treatment:
   i) Risks associated with joint puncture: local haemorrhage, bruising, infection (very rare), extravasation
   ii) Theoretical risk of exposure to beta-emitting radiation including radiation necrosis (rare) and future malignancy.
   iii) Risk of post-injection pyrexia or radiopharmaceutical allergy (very rare).

### *D. Administration*

1. Joint puncture for radiosynovectomy carries the same risk as any joint puncture and should follow the rules of strict asepsis.
2. Local skin anaesthesia is advisable.
3. Correct deposition and homogeneous distribution of the radiopharmaceutical agent in the joint space is essential. Puncture of all joints other than the knee should be performed under fluoroscopic (X-ray screening) or ultrasound guidance. The knee can routinely be injected without imaging guidance.
4. If imaging guidance is not used (e.g. knee) then radiopharmaceuticals should not be injected unless intra-articular needle placement has been ensured by aspiration of joint fluid through the needle which is being used to inject the radiopharmaceutical.

5. A particle size of at least 5–10 nm is essential to avoid leakage.
6. Absolute immobilisation of the treated joint(s) for 48 h using splints or bed rest is recommended as this will reduce transport of particles through the lymphatics to the regional lymph nodes.
7. Where possible, simultaneous administration of intra-articular long-acting glucocorticoids (e.g. methylprednisolone or triamcinolone) is recommended to reduce the risk/severity of acute synovitis and to improve treatment response. [e.g. triamcinolone acetonide 40 mg (1 ml) for the knee, hip or shoulder or 20 mg (0.5 ml) for elbow, ankle, wrist or subtalar joints].
8. The needle through which the radiopharmaceutical has been injected should be flushed before and during withdrawal with 0.9% saline.

### *E. Instructions for patients*

The importance of joint immobilisation following treatment should be emphasised. The treating clinician must advise the patient on reducing unnecessary radiation exposure to family members and the public. Written instructions should be provided where required.

Following treatment, patients should avoid pregnancy for at least 4 months.

If in-patient treatment is required, nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

### *F. Precautions*

Urinary radiopharmaceutical excretion is of particular concern during the first 2 days post administration. Patients should be advised to observe rigorous hygiene in order to avoid contaminating groups at risk using the same toilet facility. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post injection and to wash significantly soiled clothing separately. A double toilet flush is recommended after urination. Patients should wash their hands after urination.

Incontinent patients should be catheterised prior to radiopharmaceutical administration. The catheter should remain in place for 3–4 days. Catheter bags should be emptied frequently. Gloves should be worn by staff caring for catheterised patients.

### *G. Radiopharmaceuticals*

1. $^{90}$Y colloids are suitable for the knee joint only. The recommended activity per joint is 185–222 MBq (5–6 mCi).

2. $^{186}$Re sulphur colloid is suitable for hip, shoulder, elbow, wrist, ankle and subtalar joints.

   Both the administered activity and the injected volume of $^{186}$Re sulphide colloid vary according to the volume of the joint to be treated as follows:

| Joint | Adm. activity [MBq (mCi)] | Recommended volume (ml) |
|---|---|---|
| Hip | 74–185 (2–5) | 3 |
| Shoulder | 74–185 (2–5) | 3 |
| Elbow | 74–111 (2) | 1–2 |
| Wrist | 37–74 (1–2) | 1–1.5 |
| Ankle | 74 (2) | 1–1.5 |
| Subtalar | 37–74 (1–2) | 1–1.5 |

   The total activity of $^{186}$Re at a single session should not exceed 370 MBq (10 mCi).

3. $^{169}$Er citrate colloid is suitable for metacarpophalangeal, metatarsophalangeal and digital interphalangeal joints.

   Both the administered activity and the injected volume of $^{169}$Er citrate vary according to the volume of the joint to be treated as follows:

| Joint | Adm. activity [MBq (mCi)] | Recommended volume (ml) |
|---|---|---|
| Meta-carpophalangeal | 20–40 (0.5–1) | 1 |
| Meta-tarsophalangeal | 30–40 (0.8–1) | 1 |
| Proximal interphalangeal | 10–20 (0.3–0.5) | 0.5 |

   The total $^{169}$Er citrate activity injected at a single session should not exceed 750 MBq (20 mCi).

4. Doses of radiocolloids delivered to synovium have been estimated from models of joints using a series of assumptions. Physicians are referred to: Johnson and Yanch, *Arthritis Rheum* 1991; 34:1521–1530; Bowering and Keeling, *Br J Radiol* 1978; 51:836–837; Husák et al. *Phys Med Biol* 1973; 18:848–54; Johnson et al. *Eur J Nucl Med* 1995; 22:977–988.

5. Extra-articular (unwanted) radiation exposure and consequent doses have been estimated as follows:

| Radio-pharma-ceutical (reference) | Numbers of patients/ diagnoses | Joints/ injected activity | Post-injection management | Organ imaged | % injected activity detected | Estimated organ absorbed dose in organ |
|---|---|---|---|---|---|---|
| $^{90}$Y colloids (Gumpel et al., *Br J Radiol* 1975; 48:377–381) | 27/"persistent synovitis" | Knees/ 185 MBq | Bed rest for 3 days. Some wore a light splint | Local lymph nodes | Mean 3.9–5.5% for different colloids | No estimate |
| $^{90}$Y citrate colloid (Gratz et al., *J Rheumatol* 1999; 26:1242-1249)* | Not specified/ RA but ? some with spondyl-arthritis | 6 knee joints/ 185 MBq | Removable brace applied for at least 72 h. Patients told not to move the joint. „If ever possible patients kept in bed". | Liver, spleen and kidneys | Not specified | Liver= 27±13 cGy Spleen= 12±10 cGy Kidneys= 67±33 cGy Whole body= 16±9 cGy |
| $^{169}$Er colloid (Gratz et al., *J Rheumatol* 1999; 26:1242–1249)[a] | As above | 7 finger joints/ 37 MBq | As for $^{90}$Y (above) | Whole body and single nodes | Not specified | Whole body= 0.4±0.3 cGy; nodes= up to 4.3 Gy |
| $^{186}$Re colloid (Gratz et al., *J Rheumatol* 1999; 26:1242–1249)[a] | As above | 23 joints various/ 74–111 MBq | As for $^{90}$Y (above) | Liver, spleen, kidneys and local lymph nodes | Not specified | Liver= 10±8 cGy; spleen= 20±23 cGy; kidneys= 9±11 cGy; nodes= up to 54 Gy |

[a] Significantly greater extra-articular radiation detection in patients within the group who did/could not manage to immobilise joints after injection

### *H. Guidelines for measuring the activity to be administered*

Use a dose calibrator specially configured to quantify beta emissions. Pre- and post-administration measurements should be made to establish the exact injected activity.

### *I. Side-effects*

1. Early: Increased synovitis: temporary
2. Late: Radionecrosis: rare

### *J. Follow-up*

1. Post-therapy imaging should be undertaken, where possible, to confirm appropriate radiopharmaceutical distribution within the treated joint space.
2. Patients should be reviewed 6–8 weeks after injection. Review should include clinical and laboratory indices of treatment response, and assessment of synovial inflammation and possible radionecrosis.
3. In cases where clinical evaluation cannot provide reliable indication of failure/response and where appropriate pre-injection MR/ultrasound data are available, further MR/ultrasound may be of value to document changes in synovial volume and/or vascularity.
4. Clinical examination and ultrasound should be repeated at 3–4 months/6 months and 12 months after treatment.
5. Pain reduction typically occurs 1–3 weeks post injection. Treatment failure is likely if no response is detected by 6 weeks post injection.
6. A few patients who have failed to respond to the first radionuclide injection report pain reduction and improvement of joint function following re-treatment 6 months later. Two failed injections should not be followed by subsequent RS treatments.

## V. Issues requiring further clarification

1. Presumed mechanism of action: After intra-articular administration the radioactive particles are absorbed by the superficial cells of the synovium. Beta radiation leads to coagulation necrosis and sloughing of these cells.
2. Many authors recommend combined corticosteriod and radionuclide administration to reduce local inflammation and to prolong the residence time of the radiopharmaceutical agent in the joint. The efficacy of combined steroid/radiocolloid therapy should be compared with steroid alone in sufficiently powered randomised controlled studies.

## VI. Concise bibliography

There are few well-designed trials to evaluate the efficacy of radiosynovectomy. Only a minority are prospective and most are not well-defined regarding joint disease, stage or sample size.


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## VII. Disclaimer

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost effective use of high quality nuclear medicine therapeutic procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of guidelines should always be considered in determining their current applicability.

## VIII. Description of the guideline development process

The EANM Radionuclide Therapy Committee has been involved in the process of guideline development for undertaking radionuclide therapies since 1995. A multinational group of therapy experts developed a series of monographs on the radionuclide therapy agents licensed for use throughout Europe. Subsequently a series of protocols was published on the Internet for use by members of the European Association of Nuclear Medicine. The monographs and protocols were achieved through a process of consensus taking note of the evidence available at the time of writing. The monographs and protocols have been in the public domain for 4 years and comments have been received from members of the nuclear medicine community. The guidelines have been developed using material within the monographs and protocols and have been formatted to harmonise with the Society of Nuclear Medicine Therapy Guidelines format.

This guideline has been developed in close collaboration with Dr. G. Clunie and Prof. M. Fischer, who jointly contributed to the original text and provided an invaluable source of practical advice on radiosynovectomy.

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