9 Local Complications After Radiosynovectomy and Possible Treatment Strategies: A Literature Survey

Willm Uwe Kampen

Contents

9.1 Introduction

Radiosynovectomy (RSO) is performed by intra-articular injection of three different radiocolloids, normally guided by fluoroscopy; the radiopharmaceuticals are phagocytized by the synovial lining cells leading to a radiogenic sclerosis and fibrosis of the inflamed synovial membrane and thus to a significant reduction of joint effusion and pain. Apart from unavoidable systemic side effects like the low whole-body radiation load and a transient flush associated with coadministered intra-articular corticosteroids, possible serious local side effects or complications after radiosynovectomy are:

1. Superficial skin or needle track ulceration
2. Radionecrosis of the juxta-articular soft tissue
3. Intra-articular infection
4. Thromboembolic complications due to posttreatment joint immobilization

W.U. Kampen
Nuklearmedizin Spitalerhof, Spitalerstr. 8, Hamburg 20095, Germany
e-mail: kampen@nuklearmedizin-spitalerhof.de

W.U. Kampen, M. Fischer (eds.), *Local Treatment of Inflammatory Joint Diseases: Benefits and Risks*, DOI 10.1007/978-3-319-16949-1_9

Most of these side effects are preventable if the injection is carefully done under aseptic conditions, if the intra-articular needle placement is secured, and if the correct radionuclide in an appropriate activity is chosen for therapy. However, some cases are documented in the literature and should be discussed in this chapter.

9.2 Radiogenic Tissue Damage of Different Severity

Local skin and needle track ulceration or even severe necrosis of periarticular soft tissues are the most serious complications of radiosynovectomy. A reflux of the radiocolloid during retraction of the needle with concomitant deposition of a small amount of activity in the subcutaneous tissues is probably the most frequent reason for superficial skin lesions or a so-called needle track ulceration. In a retrospective study covering 83 RSO procedures in 45 patients, 1 local skin lesion was documented [1]. Ruotsi et al. described "bullous eruptions" in two finger joints 3 weeks after RSO and one case of a "slight erythema" after 1 month in a total of 83 finger joints treated with Er-169 colloid [2]. Another case of a local skin necrosis was described at the site of injection of Y-90 colloid in a patient with severe bone destruction [3]. However, no details are mentioned on the need of a special treatment or the clinical course in these cases.

The author has observed one case of local skin redness and pain after treatment of a hip joint with 150 MBq Re-186 colloid which occurred 2 days after RSO. The distribution scan showed no abnormality and, thus, there was not a fear of a severe necrosis of deeper tissue layers. The symptoms regressed over a period of 3 weeks under increased resting and frequent local cooling using ice packs (see Fig. 9.1).

Savaser and colleagues reported a case of needle track ulceration after RSO of an ankle joint with Re-186 in 1999 [4]. The lesion showed scarred healing after a few weeks without any further treatment. In a series of 38 knee joints treated with Yttrium-90, three patients showed "minor pigmentation at the injection site"; a needle track ulceration was documented in two other patients [5] which required treatment with skin grafting in one case.

While superficial lesions often show (scarred) healing without any special therapy, larger necroses with radiogenic damage of deeper tissue layers should be promptly treated to shorten the course of the disease and to minimize the complaints of the respective patients. Necrosis of para-articular tissue by accidental para-articular injection of the radionuclide is indeed the worst local complication after radiosynovectomy. Due to a restricted blood supply of the necrotic area, the healing process is additionally hampered by a low oxygen content.

The frequency of larger skin or soft tissue necroses is generally assumed to be very low which is proven by the analysis of the periodic safety update reports (see chapter by Fischer et al. in this book). Two necroses from a total of 11,000 RSO procedures were reported by Kolarz and Thumb in 1982 [6]. In another study which involved interrogation of both 260 nuclear medicine physicians performing radiosynovectomy throughout Germany and 20 insurance companies engaged in medical liability using a standardized questionnaire and covering 5 years, a total of

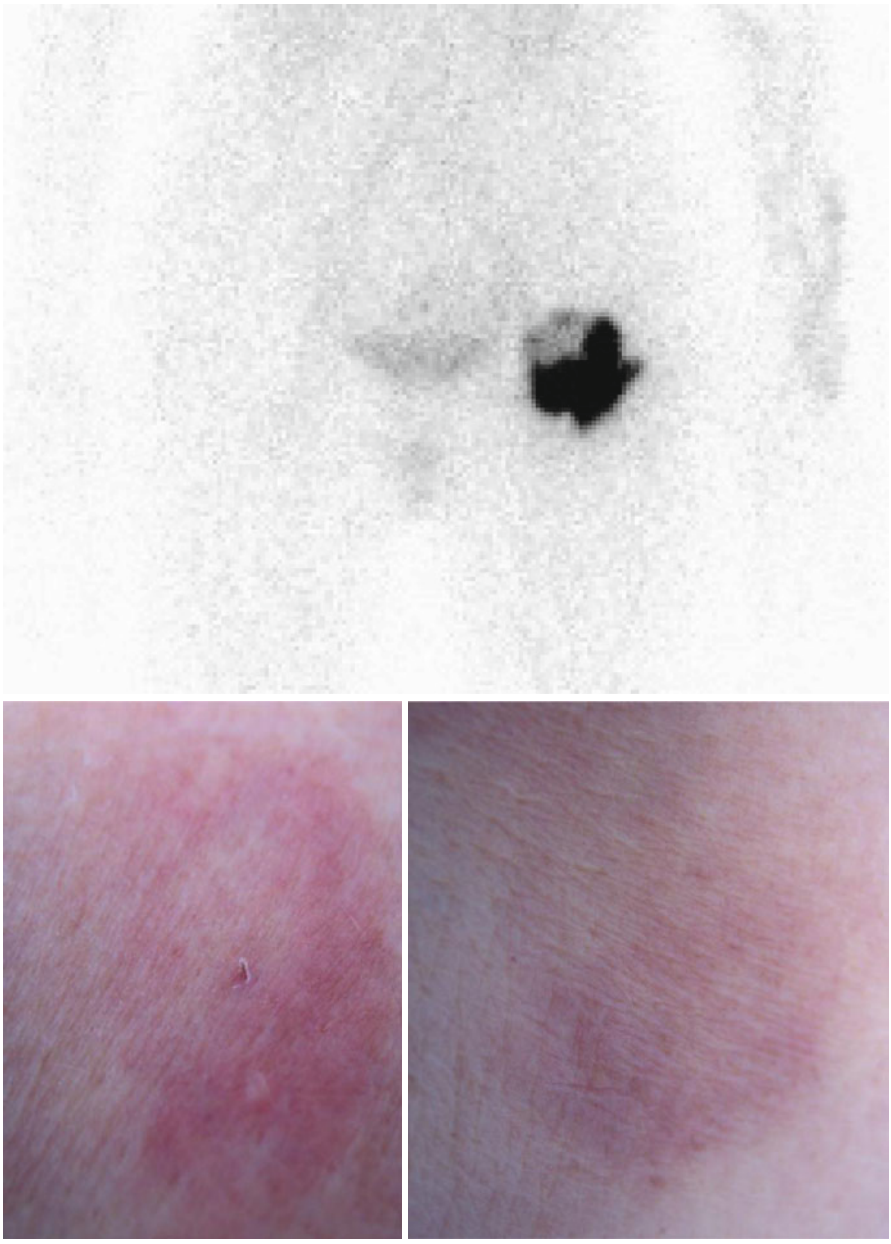

Fig. 9.1 Distribution scan after injection of 150 MBq Re-186-colloid into the left hip joint. *Lower left*: Circumscribed redness of the skin with a small moistened blain at the site of puncture 4 days after therapy. *Lower right*: Considerable fading of inflammatory activity 10 days after RSO, central defect is completely closed without any secretion

29 necroses were documented [7]. However, the response rate was only 25.7 % after 9 months. Thus, the true number of radionecroses after para-articular radionuclide application is probably higher but will never be reliably documented.

Deeper skin necroses have been documented in case reports [8, 9]. Due to the more pronounced deterioration of deeper tissue layers, a spontaneous healing cannot be expected, and surgical debridement and closure of the defect by skin grafting seems to be the adequate treatment.

Besides an insufficient injection technique, the choice of an inappropriate radionuclide and/or an excessive activity may be the reason for a radionecrosis. The choice of the appropriate radionuclide for a joint depends mainly on the tissue penetration depth of the beta particles which is particularly dependent on the energy of the radionuclide. This penetration depth must be suitable for the size of the joint which should be treated. Yttrium-90 has a maximum beta energy of 2.2 MeV resulting in a maximum tissue penetration depth up to 11 mm (mean value 3.6 mm). Thus, Y-90 is expected to be the most hazardous radionuclide used for radiosynovectomy and is approved for treatment of the knee joint only. Small joints (finger or toe joints, acromioclavicular, sternoclavicular, temporomandibular) must be injected with the low-energy beta emitter Erbium-169 (mean beta energy 0.34 MeV) which has a mean penetration depth of only 0.3 mm. Rhenium-186 is approved for treatment of mid-sized joints like wrist, elbow, ankle, or hip joint and has a mean penetration depth of 1.2 mm.

A further alignment to the different joints is accomplished by using different activities for joints of different sizes. This is documented in both national and international guidelines for radiosynovectomy, although not a legal requirement [10, 11].

Examples of radiogenic damage of the surrounding soft tissue following inappropriate choice of a radionuclide with an energy too high for the treated joint are published in the literature. Two necroses from RSO using Yttrium-90 in finger joints (metacarpophalangeal joint and proximal interphalangeal joint) were documented in an old study from 1972, covering a total of 250 treatment sessions [12]. However, no further information on the clinical course or treatment modalities is given in this paper. More recent studies showed severe complications with large, deep tissue ulcerations in ankle joints treated with Yttrium-90. Two cases of severe necroses were seen in a series of 7 RSO procedures of ankle joints treated with 555 MBq Yttrium-90 [13]. Another case report showed the same complication after RSO using Yttrium-90 in an ankle joint; however, the injected activity is not documented in this publication [14]. Thus, the combination of the “wrong” radionuclide (Yttrium-90 instead of Rhenium-186) and an excessive activity led to these serious complications which needed aggressive treatment with surgical excision of the necrotic soft tissue and closure with a fasciocutaneous flap.

The treatment of choice for these complications is still under debate. Some advice may be gained from therapy of radiogenic lesions after external beam radiation therapy. The common problem in both clinical settings is that radiation leads to parenchymal stem cell and vascular damage. This results in a reduced capacity of tissue regeneration from local hypoxia, finally leading to tissue necrosis [15]. Apart from a “wait-and-see” strategy or local conservative treatment, hyperbaric

oxygen therapy may be used to overcome the local oxygen shortage. The higher oxygen partial pressure induces revascularization of irradiated tissue and thus promotes its self-healing mechanisms [16] with clinical success rates up to 93 % in treatment of radiation-induced edema, ulceration, and bone necroses [15]. In our own survey, hyperbaric oxygen therapy was used in three cases of tissue necrosis after para-articular injection of Re-186 colloid with clinical success in two of them. However, in one patient with a local radiogenic tissue defect from Yttrium-90, 40 sessions of hyperbaric oxygen did not prevent tissue necrosis, and surgical therapy was needed [7].

Successful treatment requires complete resection of the damaged tissue with consecutive closure of the defect with well-vascularized, nonirradiated tissue. Depending on the severity and the dimensions of the local defect, either regional pedicled flaps or free-tissue transfer has been used [7, 9]. Despite appropriate surgery, complications with local wound dehiscence, seroma, or blood vessel thrombosis are seen, sometimes resulting in complete flap loss [17]. Due to the very low beta energy, skin ulcers from Er-169 colloids are likely to heal spontaneously with less pronounced tissue damage.

9.3 Intra-articular Infection

Joint infection is a severe complication which is not related to the radiopharmaceutical agent itself but might occur from any joint puncture performed either for diagnostic or therapeutic purposes. The individual risk for intra-articular infection depends on several predisposing factors, e.g., systemic inflammatory disease (rheumatoid arthritis), immunocompetence, ongoing pharmacotherapy, existence of joint replacement, and others. The frequency of joint infections after intra-articular injections is generally assumed to be very low and ranges from 1:3000 down to 1:100.000 [18]. In a survey covering 126.000 arthrographies, only three intra-articular infections were documented [19].

Apart from poor non-aseptic injection technique or contamination of the injected drug preparation, an infection may arise from bacterial infection of deeper tissue layers not eliminated by skin disinfection [20] or from hematogenous spread along the needle track [21].

Published data concerning joint infections after RSO are very rare. Three cases with intra-articular infection were documented in a very early paper by Menkes in 1979 [22], reviewing a total of >9,000 RSO procedures between 1969 and 1975. One case of a septic arthritis after repeated RSO was described by Taylor et al. [23] in a series of 121 knee joint treatments using Yttrium-90. However, there is no further information about any treatment strategy or the clinical course of such complication.

In our data pool [7], a total of 13 intra-articular infections were documented. In seven of these patients, oral antibiotics did not lead to restitution and, thus, intra-articular antibiotics were needed. An endoscopic joint lavage was performed in four additional patients.

In our experience, two patients developed severe pain and massive joint swelling with redness and skin hyperthermia a few hours after treatment with RSO for chronic effusion after endoprosthetic knee joint replacement. As the clinical symptoms were typical for joint infection, the patients were immediately treated with oral antibiotics (fixed combination of amoxicillin 875 mg and clavulanate 125 mg twice a day) and showed complete regression of complaints and symptoms after 3 weeks.

Early and intense therapy is necessary in case of septic arthritis to prevent severe joint damage and ankylosis or even systemic complications. According to the guidelines, aspiration of joint fluid must be done if an intra-articular infection is suspected. This is mandatory for establishing the diagnosis and the choice of an appropriate pharmacotherapy according to the antibiogram. If the symptoms increase within 24–48 h or if repeated aspiration is unsuccessful, surgical treatment is indicated [24]. An early ("primary") surgical therapy was also recommended in the literature [25]. A lower intra-articular bacterial count rate, the clinical decompression after joint lavage, and the avoidance of a possible "non-responding" to the antibiotic treatment are possible advantages compared to the primary antibiotic therapy.

9.4 Thromboembolic Complications

As with intra-articular infections, thromboembolic complications are not specific for radionuclide joint treatment but may occur following the mandatory immobilization of the treated joint using a tight bandage and a splint. This holds especially true for radiosynovectomy of lower limb joints in old and immobile patients or for those with a concomitant high risk of thrombosis, e.g., varicose veins or coagulopathies for any reasons. However, there are no documented cases of a thromboembolic complication in the literature so far, which is definitely linked to the radiosynovectomy procedure.

In our survey, a total of 12 cases of thrombosis after radiosynovectomy of lower limb joints were documented: 1 of them after treatment of both the knee and the hip joint in the same patient. An elevated risk profile was documented in 6 of 12 patients, and no prophylactic anticoagulation was performed. Most of these patients (8/12) were successfully treated with routine anticoagulation pharmacotherapy. A guideline for effective treatment of venous thromboembolic disease recommends short-term treatment with subcutaneous low-molecular-weight heparin or unfractionated heparin given intravenously [26].

Provided there are no preexisting risk factors in the individual patient, the risk of a thromboembolic complication must be carefully weighed against possible side effects from anticoagulation therapy, and thus, a general thromboembolic prophylaxis cannot be recommended. If RSO is performed in two adjacent joints of the lower limb (knee and hip joint or knee and ankle joint), the immobilization of both joints leads to an increased ("medium") risk with 10–20 % deep venous thromboses of the shank, 2–4 % of more proximal thromboses, 1–2 % of clinically relevant pulmonary embolism, and 0.1–0.4 % of lethal pulmonary embolism [27]. In such

patients and in those with two or more predisposing risk factors, an effective antithrombotic prophylaxis is mandatory [28]. Ready-to-use syringes containing low molecular heparin should be used for this purpose if the respective patient does not display any contraindications like bleeding abnormalities and cerebral or dissected aortic aneurysms.

9.5 Other Possible Complications: A Critical Review

Other complications published in the literature which are not direct results of RSO procedure and of minor severity include a transient and frequently self-limiting radiogenic effusion which has been documented in 2 % of patients several hours after radionuclide instillation [29]. A co-injection of a corticosteroid during radiosynovectomy helps to avoid this adverse event in the vast majority of patients [30]. Probably due to a tight bandage after RSO with compression of the local nerves, a transient fibular nerve paresis and symptoms mimicking Sudeck's dystrophy and carpal tunnel syndrome were documented in our survey, but there was no information on the further clinical course. A case of a radiogenic dermatitis has been documented which was probably a result of extended fluoroscopy during radiosynovectomy in a severely destroyed joint [7].

In a recently published study, a very high rate of osteonecroses (ON) and joint infections was found after RSO in patients suffering from osteoarthritis [31], and the authors stated that radiosynovectomy might not be as safe as it has been described before. However, this paper contained several methodological flaws which could have led to potentially incomplete or misleading conclusions.

First of all, the selection of patients is highly questionable. Kisielinski evaluated only 93 patients with 161 RSOs from a total of 80.000 RSOs within 12 years. The conclusion in the publication was thus made on a very small subgroup of 93/80.000 treatments (0.2 %), and nothing is stated about the eligibility criteria. Out of these 93 patients, 22 (with 49 of 80.000 RSOs) = 0.05 % suffered from ON and/or infection which is a very low rate of these serious events.

Most patients (50/79) had a Kellgren-Lawrence stage 4 with pronounced mutilations of the treated joint. Due to the considerably increased bone turnover in osteoarthritis, bone scanning cannot differentiate exactly between osteonecrosis and osteoarthritis if performed prior to RSO. To exclude preexisting osteonecrosis, a normal bone scan (or MRI) must be postulated but is never seen in patients with osteoarthritis in a Kellgren-Lawrence stage 3 and 4. In addition, osteonecrosis after RSO was diagnosed by methods with higher sensitivity and specificity (even intraoperatively or by histopathology). Therefore, it is not possible to point out whether osteonecrosis has developed after RSO or has been already present prior to RSO.

Osteonecrosis is a disease characterized by disturbance of local blood circulation but in many patients connected with several risk factors: cortisone for rheumatoid arthritis or COPD, cytostatics, abuse of alcohol and nicotine, trauma, irradiation, diabetes mellitus, and osteoporosis [32]. One main bias of the retrospective evaluation by Kisielinski et al. is the lack of a control group suffering from same risk

factors. Franchi and Bullough [33] reported on 11.7 % avascular necroses in femoral heads removed because of osteoarthritis; in about 20 % of specimens with ON, there was evidence of microfractures in the trabecular bone. In the publication of Kisielinski et al., 13 of 22 patients suffering from ON were postmenopausal women, only 2 of them less than 60 years. The probability of osteoporosis in this group is quite high. In most patients included in this study, Kellgren Lawrence stage 4 disease was confirmed. By definition, stage 4 is characterized by an advanced narrowing up to total loss of the joint space; articular cartilage is destroyed widely. This may lead to a loss of functioning buffer capacity resulting in traumatic microfractures in these parts of the bone, especially in osteoporotic patients. Seven of them had additional risk factors (RA on continuous corticosteroid therapy, COPD, and/or diabetes mellitus) enhancing the risk of ON.

To judge the risk of radiation to the subchondral bone with possible induction of local osteonecroses, no exact data about radiation doses to bone surface are discussed. The calculated radiation dose to bone surface after RSO of the knee joint using Yttrium-90 was 27–30 Gy [34]. The threshold for causing ON is 30 Gy [35]. Höller et al. reported ON of the pelvis after irradiation dose exceeding 50 Gy in 14 % [36]. Thus, local radiation of the bone is a clear risk factor for osteonecrosis, but radiation dose to the bone surface in RSO with Yttrium-90 is below threshold and with Rhenium-186, far less.

The authors argued that intra-articular infection was caused by RSO in five patients. Infection following RSO was strongly correlated to arthroplasty with a high degree of significance. However, a possible “low-grade” infection was never excluded prior to RSO, especially in patients with total knee replacement (three of five). In 2009, Jämsen et al. [37] published an incidence of 0.9 % surgical revisions in a register-based analysis of 43,149 otherwise uncomplicated cases. Hyperglycemia is also known to be significantly associated with infected knee replacement [38].

In the publication of Kisielinski, there are no data given relative to clinical signs of infection in joints that showed a positive bacteriology. Especially in patients with proven *Staphylococcus epidermidis* and *S. oralis*, it seems possible that infection was caused by diagnostic puncture and not during RSO. Thus, a clear correlation between intra-articular infection and joint puncture during RSO is not proven by the authors.

In addition to RSO, the patients showed many other factors that may have cause a higher risk for osteonecrosis. Therefore, a multifactorial analysis should have been done. The authors simply used Spearman’s rank test. This is a test to find correlations, but simple correlation gives no information about causality.

Therefore, in this retrospective study, it is not possible to conclude that RSO leads to osteonecrosis or infection. The general problem of any retrospective evaluation is the quality of data and how they can be controlled. In the publication of Kisielinski et al., a small number of patients with a large number of different variables are evaluated. Moreover, the variation of diagnostic procedures with different sensitivity and specificity prior to and after RSO confirming osteonecrosis probably is attributable to the quality of the study. The methodology used has significantly biased the presented results which should not be taken too seriously.

Conclusion

Radiosynoviorthesis is a safe local treatment option for patients suffering from inflammatory joint disease. However, appropriate patient selection, the choice of the correct radionuclide with an adequate activity for the respective joint, a skillful and aseptic injection technique, and a reasonable follow-up are indispensable to achieve a maximum of therapeutic efficacy with a minimum of possible hazards.

In case of any complications, the following *treatment recommendations* can be stated from literature data and own experiences:

- Any complaints of the patients must be taken for serious.
- Early surgical therapy with broad excision of the necrotic tissue and closure of the defect should be done in case of tissue damage from Yttrium-90.
- Hyperbaric oxygen therapy may be sufficient for treatment of Rhenium-186-induced ulcers. In case of therapeutic failure, surgery seems advisable.
- Lesions from Erbium-169 will probably heal by conservative treatment.
- Clinical signs of intra-articular infection after RSO should be secured by immediate fluid aspiration and bacterial culture. If an initial oral antibiotic treatment does not improve the situation significantly within 24–48 h, the infection should be treated by joint lavage or endoscopy together with the local application of intra-articular antibiotics.
- Prophylactic anticoagulation against thromboembolism from posttreatment immobilization is recommended only in patients after RSO of two adjacent joints of the lower limb and in patients with at least two risk factors.

References

1. Jahangier ZN, Jacobs JW, von Isselt JW, Bijlsma JW. Persistent synovitis treated with radiation synovectomy using yttrium-90: a retrospective evaluation of 83 procedures for 45 patients. Br J Rheumatol. 1997;36:861–9.
2. Ruotsi A, Hypen M, Rekonen A, Oka M. Erbium-169 versus triamcinolone hexacetonide in the treatment of rheumatoid finger joints. Ann Rheum Dis. 1979;38:45–7.
3. Molho P, Verrier P, Stieltjes N, Schacher JM, Ounnoughene N, Vassilieff D, Menkes CJ, Sultan Y. A retrospective study on chemical and radioactive synovectomy in severe haemophilia patients with recurrent haemarthrosis. Haemophilia. 1999;5:115–23.
4. Savaser AN, Hoffmann KT, Soerensen H, Banzer DH. Die Radiosynoviorthese im Behandlungsplan chronisch-entzündlicher Gelenkerkrankungen. Z Rheumatol. 1999;58:71–8.
5. Jacob R, Smith T, Prakasha B, Joannides T. Yttrium^{90} synovectomy in the management of chronic knee arthritis: a single institution experience. Rheumatol Int. 2003;23:216–20.
6. Kolarz G, Thumb N. Methods of nuclear medicine in rheumatology. Stuttgart: Schattauer-Verlag; 1982.
7. Kampen WU, Matis E, Czech N, Soti Z, Henze E. Serious complications after radiosynoviorthesis. Survey on frequency and treatment modalities. Nuklearmedizin. 2006;45(6):262–8.
8. Sojan S, Bartholomaeusz D. Cutaneous radiation necrosis as a complication of yttrium-90 synovectomy. Hell J Nucl Med. 2005;8:58–9.

9. Öztürk H, Öztemür Z, Bulut O. Treatment of skin necrosis after radiation synovectomy with yttrium-90: a case report. Rheumatol Int. 2008;28:1067–8.
10. Farahati J, Reiners C, Fischer M, Moedder G, Franke J, Mahlstedt J, Soerensen H. Guidelines for radiosynovectomy. Nuklearmed. 1999;38:254–5.
11. Clunie G, Fischer M, EANM. EANM procedure guidelines for radiosynovectomy. Eur J Nucl Med Mol Imaging. 2003;30:BP12–6.
12. Menkes CJ, Aignan M, Ingrand J, Lego A, Roucayrol JC, Belbarre F. La synoviorthese par les radio-isotopes a la main et au poignet. Rev Chir Orthop. 1972;58(59):432–9.
13. Bickels J, Isaakov J, Kollender Y, Meller I. Unacceptable complications following intra-articular injection of yttrium 90 in the ankle joint for diffuse pigmented villonodular synovitis. J Bone Joint Surg. 2008;90:326–8.
14. Peters W, Lee P. Radiation necrosis overlying ankle joint after injection with Yttrium-90. Ann Plast Surg. 1994;32:542–3.
15. Tibbles PM, Edelsberg JS. Hyperbaric oxygen therapy. N Engl J Med. 1996;334:1642–8.
16. Borg M, Wilkinson D, Humeniuk V, Norman J. Successful treatment of radiation induced breast ulcer with hyperbaric oxygen. Breast. 2001;10:336–41.
17. Guerlek A, Miller MJ, Amin AA, Evans GRD, Reece GP, Baldwin BJ, Schusterman MA, Kroll SS, Robb GL. Reconstruction of complex radiation-induced injuries using free-tissue transfer. J Reconstr Microsurg. 1998;14:337–40.
18. Holland C, Jaeger L, Smentkowski U, Weber B, Otto C. Septic and aseptic complications of corticosteroid injections. Dtsch Ärzteblatt Int. 2012;109:425–30.
19. Newberg AH, Munn CS, Robbins AH. Complications of arthrography. Radiology. 1985;155:605–6.
20. Charalambous CP, Tryfonidis M, Sadiq S, Hirst P, Paul A. Septic arthritis following intra-articular steroid injection of the knee – a survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. Clin Rheumatol. 2003;22:386–90.
21. von Essen R, Savolainen HA. Bacterial infection following intra-articular injection. A brief review. Scand J Rheumatol. 1989;18:7–12.
22. Menkes CJ. Is there a place for chemical and radiation synovectomy in rheumatic diseases? Rheumatol Rehabil. 1979;18:65–77.
23. Taylor WJ, Corkill MM, Rajapaske CAN. A retrospective review of Yttrium- 90 synovectomy in the treatment of knee arthritis. Br J Rheumatol. 1997;36:1100–5.
24. Hedstroem SA, Lidgren L. Septic bone and joint lesions. In: Klippel JH, Dieppe PA, editors. Rheumatology, vol. 4. London: Mosby; 1994. p. 3.1–3.10.
25. Donatto KC. Orthopedic management of septic arthritis. Rheum Dis Clin North Am. 1998;24:275–86.
26. Bueller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskop GE. Antithrombotic therapy for venous thromboembolic disease. Chest. 2004;126:401S–28.
27. Clagett GP, Anderson FA, Geerts W et al. Prevention of venous Thromboembolism. Chest. 1998;114:531S–560S.
28. Fischer M, Ritter B. Prevention of thromboembolism during radiosynoviorthesis. Der Nuklearmediziner. 2006;29:33–6.
29. Gratz S, Goebel D, Becker W. Radiosynovectomy in inflammatory joint disease. Orthopaede. 2000;29:164–70.
30. Gratz S, Goebel D, Behr TM, Herrmann A, Becker W. Correlation between radiation dose, synovial thickness, and efficacy of radiosynovectomy. J Rheumatol. 1999;26:1242–9.
31. Kisielinski K, Bremer D, Knutsen A, et al. Complications following radiosynoviorthesis in osteoarthritis and arthroplasty: osteonecrosis and intra-articular infection. Joint Bone Spine. 2010;77(3):252–7.
32. Mahmoudi M. Therapie der nicht-juvenilen, aseptischen Osteonekrose und des symptomatischen Knochenmarkoedems mit dem Prostazyklinanalogon Iloprost.-Eine MRT-kontrollierte klinische Verlaufsstudie. Düsseldorf. 2009. http://docserv.uni-duesseldorf.de/servlets/.

33. Franchi A, Bullough PG. Secondary avascular necrosis in coxarthrosis: a morphologic study. J Rheumatol. 1992;19:1263–8.
34. Johnson LS, Yanch JC. Calculation of beta dosimetry in radiation synovectomy using Monte Carlo simulation (EGS4). Med Phys. 1993;20:747–754754.
35. Murray K, Dalinka JE, Finkelstein JB. Complications of radiation therapy: adult bone. Semin Roentgenol IX. 1974;1:29–40.
36. Höller U, Hoecht S, Wudel E, Hinkelbein W. Osteonekrose nach Strahlentherapie gynäkologischer Tumoren. Strahlenther Onkol. 2001;177:291–5.
37. Jämsen E, Huhtala H, Puolakka T, Moilanen. Risk factors for infection after knee arthroplasty. J Bone Joint Surg Am. 2009;91:38–47.
38. Jämsen E, Nevalainen P, Kalliovalkama J, Moilanen T. Preoperative hyperglycemia predicts infected total knee replacement. Intern Med. 2010;21:196–201.