Introduction

The management of rheumatoid arthritis (RA), which is among the most common diseases, includes both systemic anti-rheumatic therapy and local articular treatment. Systemic (front-line) therapy usually comprises anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) (for reviews of anti-rheumatic systemic therapies, see references [1–3]). Local treatment may involve attempts to control inflammation and pain in individual joints conservatively by intra-articular application of analgesics or glucocorticoids; however, in many patients these fail to elicit a satisfactory response in the long term, and moreover they may lead to severe side effects. It is, therefore, often necessary to resort to ablation of the diseased lining of the joint, a step made indispensable by the excessive proliferation of the synovium that occurs as a basic feature of the pathology of RA. The oldest established ablative method, practised since the 19th century, is surgical resection of the synovium. Today, surgical ablation is generally performed by arthroscopic synovectomy [4]. This does not always give optimal results, because of incomplete removal of the diseased tissue and recurrence of inflammation [5, 6]. Attempts have, therefore, been made over many decades to remove the inflamed synovium by other methods, including the local application of chemicals or of radioisotopes.

The first published pre-clinical report of the administration and the action of a locally injected radionuclide on the synovial membrane dates back to 1924 [7]. A description of the local administration of radionuclides for the therapy of inflammatory alterations of the synovial membrane in clinical practice was published in 1952 [8] and was followed in the late 1960s by the introduction of colloids containing yttrium-90 (90Y) and the introduction of the term radiosynoviorthesis (RSO) [9, 10]. In RSO a β-emitting radiocolloid is injected into the articular cavity. The colloidal particles are phagocytized by the synovial lining cells; thereafter, the β-energy released effects a therapeutically active irradiation of the surrounding synovial tissue, resulting in a fibrotic and sclerosed synovial membrane [11]. The inflammatory process, including the proliferative and destructive processes, is stopped, which leads to an alleviation of the pain and effusion. This is accompanied by an occlusion of superficial capillaries [12].

A critical feature of RSO is the choice of nuclide to be used. The penetration depth of the emitted radiation is selected to correspond to the thickness of the synovium in the joint to be treated: inadequate penetration will give an inferior therapeutic effect, and excessive penetration depths may constitute a safety hazard. The nuclide’s half-life should suffice for adequate, but not correspond to the thickness of the synovium in the joint to be treated: inadequate penetration will give an inferior therapeutic effect, and excessive penetration depths may constitute a safety hazard. The nuclide’s half-life should suffice for adequate, but not excessively prolonged, exposure of the joint and should be substantially less than the retention time of the radiopharmaceutical in the region to be treated. Only β-emitters have penetration depths of the right order. The preceding criteria have led to the prevailing use in Europe of three isotopes for RSO. In soft tissue, β-rays from yttrium-90 (90Y; t1/2 2.7 days) have a mean/maximum penetration depth of 3.6/11 mm, and so 90Y is used for RSO of the knee. Rhenium-186 (186Re; penetration depth 1.2/3.7 mm; t1/2 3.7 days) is used for medium-sized joints such as hip, shoulder, wrist and ankle. Erbium-169 (169Er; penetration depth 0.3/1.0 mm; t1/2 9.4 days) is used only for the joints in fingers and in toes (complete data and doses are given in reference [13]). The therapeutic efficacy of RSO with 186Re-colloids and 169Er-colloids has been confirmed in large clinical trials meeting the strict criteria of evidence-based medicine [14, 15].

RSO has thus been in use for many years. However, although the favourable verdict of many studies has been supported by clinical experience of the benefits of RSO, early trials did not
accord with present-day standards of evidence-based medicine [16]. This review is intended to survey the present status of RSO with $^{90}\text{Y}$ and to assess the benefit-risk ratio of this therapy in light of all available data. For the purpose of this review, the relevant literature was duly researched, looking primarily at recent (since 1975) publications in German and English language from the data banks Medline, Embase, BIOSIS (from 1993), Derwent Drug File (from 1983) and SciSearch (from 1980).

**Indications and standard dose range for yttrium $^{90}\text{Y}$ colloid**

Indications for RSO include various inflammatory and degenerative joint diseases like RA, spondyloarthritis, psoriatic arthritis, pigmented villonodular synovitis, haemophilic arthritis, calcium pyrophosphate arthropathy, undifferentiated arthritis and (activated) osteoarthritis (OA). Additionally, the removal of residual inflamed tissue after incomplete arthroscopic synovectomy and treatment of chronic effusions after implantation of joint endoprostheses may also be performed by RSO. A survey between 1991 and 1993 [17] revealed that, at that time, 71% of RSO administrations were for RA, and that $^{90}\text{Y}$ was employed in about 45% of cases. While this picture is still largely true, there is today a trend towards increasing use of $^{90}\text{Y}$ RSO in other indications besides RA [18-20].

$^{90}\text{Y}$ RSO should only be used when all methods of conservative therapy have failed, including i.a. injections of long-acting corticosteroids. The recommended dose range [21] for initial RSO with the $^{90}\text{Y}$ citrate or silicate colloid is 185–222 MBq (5–6 mCi). For repeated RSO, a dose of 111–222 MBq (3–6 mCi) is recommended, depending on the thickness of the synovial membrane and the size of the joint [13, 22].

According to current guidelines [21], absolute contra-indications to any RSO are pregnancy, breast-feeding, local skin infection and ruptured popliteal cyst of the knee; relative contra-indications are extensive joint instability, advanced erosive joint disease or other forms of bone destruction, evidence of significant cartilage loss within the joint and, for patients below 20 years of age, an unfavourable risk–benefit ratio.

**Efficacy of treatment with yttrium $^{90}\text{Y}$ colloid**

**Rheumatoid arthritis**

Table 1 presents a summary of the published results of prospective trials on the application of $^{90}\text{Y}$ RSO in RA with a follow-up examination after at least 6 months. The clinical efficacy is stated as 51–100%; naturally, this depends inter alia on the success criteria used by the authors in each case. Results of some particularly relevant studies are summarized in the following text, followed by a review of three meta-analyses conducted to date.

In a double-blind study on RA patients, Delbarre et al. [9] observed a statistically significant superiority of 222 MBq $^{90}\text{Y}$ colloid over placebos (non-radioactive yttrium-89 colloid, NaCl) in 146 radiosynoviortheses of the knee. Bridgman et al. [23] performed a placebo-controlled study with mostly bilaterally affected patients, random selection of one knee to be treated actively for each patient and double-blinded assessment. More than 50% of patients benefited from RSO with a 111 MBq dose of $^{90}\text{Y}$ colloid 12 months after treatment, even though all other therapeutic procedures (except for surgical synovectomy), including i.a. injection of corticosteroids, had been ineffective. The relatively low response rate was attributed by the authors to an inadequate radiation dose. There was a sustained improvement in 57% of cases, and in 30% of patients the joint effusion had completely resolved.

In a double-blind three-arm study with 20 patients per arm, Urbanová et al. [24] compared a $^{90}\text{Y}$ colloid alone with a $^{90}\text{Y}$ colloid plus i.a. triamcinolone and with i.a. triamcinolone alone. The study showed in long-term (12 months) that $^{90}\text{Y}$ colloid was superior to corticosteroid. The authors recommended, on the basis of pure efficacy criteria, the administration of $^{90}\text{Y}$ colloid alone. However, the i.a. corticosteroid alone, or in combination with the $^{90}\text{Y}$ colloid, had in the short term an at least equally favourable influence on both pain and effusion.

In a randomized study [25], Menkes et al. investigated 97 joints in 72 patients after i.a. injection of 150 MBq of $^{90}\text{Y}$ colloid in comparison with 100 mg osmic acid and 40 mg triamcinolone. The authors reported that in 69.6% of the patients treated with the $^{90}\text{Y}$ colloid good and very good results were observed, compared with only 54.4% of the patients after osmic acid and 38.9% after triamcinolone.

Jahangier et al. [26] performed a study in which the inclusion criterion was insufficient reaction to at least two i.a. injections of a corticosteroid. After 12 months, 78% of the knees in RA patients had been effectively treated. This, and also other studies [26-31], confirmed the efficacy of RSO in RA, especially for those patients in whom i.a. corticosteroid injections were no longer sufficient.

From many publications [20, 28, 32-39], it may be concluded that $^{90}\text{Y}$ RSO achieves the highest efficacy in RA patients with low-grade morphological joint alterations (low Steinbrocker [40] or Larsen [41] stages). The use of RSO in joints that already show advanced erosive defects is, however, still regarded as helpful [20, 42].

Three meta-analyses have been carried out on the efficacy of $^{90}\text{Y}$ RSO, arriving, however, at contradictory results. These will be discussed in detail.

Heuft-Dorenbosch et al. [43] performed a systematic review of 297 publications, first assessing these on the basis of their relevance and of the Delphi criteria for methodologically sound randomised clinical trials [44]. Only seven trials measured up to these criteria, and five of these were not taken into account for other reasons (e.g. dwindling recruitment, lack of published detail), leaving only the publications of Bridgman et al. [23] and Grant et al. [45] as being deemed to be of sufficiently high quality. The unfavourable conclusions drawn by Heuft-Dorenbosch et al. about RSO with $^{90}\text{Y}$ colloids are based largely on the work of Grant et al. [45]. However, this paper does not stand up to a detailed critical consideration: this was a mixed-design study (including more than one randomization procedure), and the consequent lack of uniformity was not taken into account in their analysis. Thus, the only valid study that finally remains in the meta-analysis carried out by Heuft-Dorenbosch et al. is the work, cited earlier, by Bridgman et al. [23], in which effectiveness of the $^{90}\text{Y}$ colloid against a placebo was demonstrated—in fact, at a lower dosage than would be recommended today. The relatively low response rate is attributed by the authors of the paper to an inadequate radiation dose, and would presumably have been greater with present-day dosages. In summary, the paper by Heuff-Dorenbosch et al. can only be regarded as showing that there are only a few studies on the efficacy of RSO in knee arthritis if one adopts the strict Delphi criteria.

Jones [46] covered only 10 publications, of which the only studies satisfying the inclusion criteria for a comparison of $^{90}\text{Y}$ colloids with a placebo or no treatment were those by Bridgman et al. [23] and Szanto [47]. For this small selection, Jones confirmed that RSO with $^{90}\text{Y}$ colloids was superior to placebo or no treatment [odds ratio (OR) 2.42]. In a comparison of the $^{90}\text{Y}$ colloids against i.a. corticosteroids, on the other hand, Jones found no difference (OR 1.89), but again, this comparison was based upon only two studies that satisfied the inclusion criteria—one of which [48] was broken off because of insufficient patient recruitment and therefore cannot be regarded as valid [43], and the other [25], in contrast, showed a considerable advantage of $^{90}\text{Y}$ colloid over i.a. administration of a corticosteroid.

It is important to note that the meta-analyses of Heuff-Dorenbosch et al. and of Jones were based on only 20–50 patients.
<table>
<thead>
<tr>
<th>No. of knees&lt;br&gt;(N)</th>
<th>Intra-articular&lt;br&gt;corticoid failures?</th>
<th>Dose (MBq)</th>
<th>Success (%)</th>
<th>Follow-up duration&lt;br&gt;(months)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Good or very good</td>
<td>Moderate</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Yes</td>
<td>111</td>
<td>57 (motility)</td>
<td>–</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>Yes</td>
<td>185</td>
<td>Pain: 90Y, 90Y + LC &gt; LC</td>
<td>–</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>20b</td>
<td>Yes</td>
<td>185</td>
<td>76 for all RA 68 for all knees</td>
<td>–</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>169</td>
<td></td>
<td></td>
<td>59</td>
<td>37</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>150</td>
<td>Yes</td>
<td>185</td>
<td>60</td>
<td>37</td>
<td>3</td>
<td>12</td>
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<td>Yes</td>
<td>185</td>
<td>50</td>
<td>32</td>
<td>18</td>
<td>36</td>
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<tr>
<td>84</td>
<td>Yes</td>
<td>185</td>
<td>62</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>185</td>
<td>70% responded</td>
<td>–</td>
<td>–</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>Yes</td>
<td>300</td>
<td>Overall moderate</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>45</td>
<td>Not stated</td>
<td>222</td>
<td>53.3</td>
<td>22.2</td>
<td>24.5</td>
<td>6</td>
</tr>
<tr>
<td>23</td>
<td>Uncertain</td>
<td>150</td>
<td>69.6</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>25</td>
<td>Uncertain</td>
<td>150</td>
<td>72</td>
<td>12</td>
<td>16</td>
<td>6–12</td>
</tr>
<tr>
<td>36</td>
<td>No</td>
<td>185–275</td>
<td>78c</td>
<td>41.7</td>
<td>–</td>
<td>6–12</td>
</tr>
<tr>
<td>24</td>
<td>No</td>
<td>185</td>
<td>51.3</td>
<td>–</td>
<td>–</td>
<td>6–12</td>
</tr>
<tr>
<td>22</td>
<td>No</td>
<td>111–222</td>
<td>Improvement in pain and swelling</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>23</td>
<td>No</td>
<td>Not stated</td>
<td>56</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>63</td>
<td>No</td>
<td>Not stated</td>
<td>46</td>
<td>25</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td>51</td>
<td>17</td>
<td>22</td>
<td>36</td>
</tr>
</tbody>
</table>

Results calculated by the authors from data in the publications cited.

aOnly those knees treated in the indication of RA are counted.
bWith corticoids as co-medication.
cResult independent of age and duration of disease.

avg: average; Phys. + pat.: physician and patient; LC, long-acting corticosteroid.
in the studies that were considered acceptably rigorous—or considered at all—by these authors. This very small sample size in the pursuit of experimental rigour has inherent problems, particularly in view of the extensive positive experience of $^{90}$Y in clinical practice, derived from reports on thousands of patients in some cases [17], which, even if they are not evaluable according to current best standards of evidence-based medicine (e.g. [16]), must still somehow be taken into account.

In contrast to the two meta-analyses summarized here, the one by Kresnik et al. [20] reflects extensive clinical experience with RSO. This work contains data on 2190 joints, at least 1417 of them being knees treated with $^{90}$Y colloid. The study selection criteria were broad, and other indications were also considered in addition to RA. Indications were grouped into ‘appropriate’ (including early clinical RA without radiographic changes), ‘acceptable’ (including RA with minimal or moderate radiographic changes; Steinbrocker I/II), ‘helpful’ (including RA with severe joint destruction; Steinbrocker III/IV) and ‘not indicated’. Respective response rates according to the American Association’s criteria (Steinbrocker) were >80%, 60–80%, <60% and ‘no response’. Thus, for RA without any morphological alterations, RSO can have a response rate of over 80%, but even in the presence of severe morphological alterations, it is still helpful. Kresnik et al. concluded that RSO provides better results in RA than in OA and that, apart from the underlying disease, local inflammation may develop, thus contributing to the formation at the margins of the joints. Already early in the breakdown of articular cartilage for various reasons and new bone appears to be rising [18, 19]. OA is characterized by progressive OA, i.e. erosive inflammatory OA of the distal finger joints. Rates of response to RSO depend on the extent of inflammatory involvement, and vary between 35 and 78% (Table 2).

Osteoarthritis

OA is a less common indication for RSO, but its proportion appears to be rising [18, 19]. OA is characterized by progressive breakdown of articular cartilage for various reasons and new bone formation at the margins of the joints. Already early in the disease, local inflammation may develop, thus contributing to the symptoms of joint pain, limitation of movement, joint swelling and effusion. The degree of inflammation may vary considerably from mild intermittent irritation to a clinical picture resembling RA, i.e. erosive inflammatory OA of the distal finger joints. Rates of response to RSO depend on the extent of inflammatory involvement, and vary between 35 and 78% (Table 2).

A prospective study by Farahati et al. [18], who carried out a multivariate analysis of factors influencing therapeutic outcome (age, disease duration, underlying disease, sex, type of joint), showed in the 6-month investigation period a marked alleviation of pain in 78% of the patients independently of their underlying disease. In a multicentre study by Rau et al. [19], 56% of the patients with activated OA of the knees benefited from RSO. In a broad survey, Kresnik et al. [20] report an acceptable response rate in the range of 60–80% for OA with slight to moderate morphological alterations, but even when the morphological alterations are severe they assess RSO as ‘helpful’ (see earlier discussion).

Other indications

Other indications for RSO are listed earlier (see section ‘Indications for $^{90}$Y RSO’). The primarily inflammatory conditions among them, apart from RA, are the spondyloarthritides, a group that includes for example ankylosing spondylitis, psoriatic arthritis and reactive arthritis. Pathologically, these diseases are characterized by axial involvement including sacroiliitis, synovitis of peripheral joints and enthesitis. Therefore, in many respects their therapy follows the same principles and methods as the treatment of RA, and the efficacy of RSO in this group of diseases essentially resembles that in RA. In many studies, these conditions have been treated and assessed in common [19, 29, 31, 49–51]. Jahangier et al. [49] observed good effects in psoriatic arthritis in 75% of cases and in ankylosing spondylitis in 76%.

In opposition to these results and another monocentric study [26] in which RSO ‘seemed to be a successful, moderately effective method’, the same group recently published a double-blind, randomized, Placebo-controlled multi-center-study with a negative judgement on the efficacy of RSO [52]. In 97 patients with predominantly undifferentiated and RA, RSO with $^{90}$Y and glucocorticoid showed an unusually low efficacy of 50% and was not superior to placebo and glucocorticoid 6 and 12 months after injection. However, a critical consideration does reveal several inconsistencies [53, 54]. The prospectively defined Composite Change Index (CCI) used in the former study was changed for the latter one, but its individual results like tenderness, swelling, etc., were not documented. Moreover, important statistical data are missing. The duration of remission is much longer in the RSO group (27±29 months) compared with the GC group (18±25 months) and also the mean CCI in the RSO group after 12 months with 7.7 is notably higher than in the GC group with 4.9, which is an increase of 164%. For both comparisons, no P-values are given. Finally, the prospectively defined inclusion criterion of two ineffective glucocorticoid injections was ignored to some extent (‘number of i.a. GC injections ≥1’) and the two treatment groups were not homogeneous. The RSO group had an average duration of synovitis of 38±38 months with a huge range between 6 and 240 months, whereas the GC group ranged from 35±32 months but with a range between 2 and 120. Thus, the study group treated with RSO consisted of two extremes: patients in the early beginning of the disease without resistance to i.a. GC injections (RSO is not indicated) and another subgroup in very advanced stages of arthritis, where RSO is known to be of lower success. It is anticipated that the average of these two subgroups will not show a significant advantage over GC injection, and thus this study is not suitable to disclaim the usefulness of $^{90}$Y RSO for treatment of joint knee arthritis.

Table 2. Efficacy of $^{90}$Y colloids in treating OA

<table>
<thead>
<tr>
<th>No. of knees&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intra-articular corticoid failures?</th>
<th>Dose (MBq)</th>
<th>Success (%)</th>
<th>Follow-up duration</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Yes</td>
<td>185</td>
<td>46</td>
<td>–</td>
<td>–</td>
<td>[29]</td>
</tr>
<tr>
<td>200</td>
<td>Yes</td>
<td>185</td>
<td>61</td>
<td>–</td>
<td>–</td>
<td>[19]</td>
</tr>
<tr>
<td>17</td>
<td>Yes</td>
<td>222</td>
<td>71</td>
<td>29</td>
<td>Retrospective, multicentre study</td>
<td>[51]</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>185</td>
<td>50</td>
<td>90</td>
<td>–</td>
<td>[26]</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>185</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>[30]</td>
</tr>
<tr>
<td>36</td>
<td>Not stated</td>
<td>185–275</td>
<td>78 for all indications</td>
<td>–</td>
<td>6</td>
<td>Prospective study, pain relief</td>
</tr>
<tr>
<td>17</td>
<td>Not stated</td>
<td>185</td>
<td>40</td>
<td>–</td>
<td>–</td>
<td>[58]</td>
</tr>
<tr>
<td>20</td>
<td>Not stated</td>
<td>180</td>
<td>35</td>
<td>–</td>
<td>–</td>
<td>[42]</td>
</tr>
<tr>
<td>47</td>
<td>Not stated</td>
<td>185–200</td>
<td>43</td>
<td>–</td>
<td>ca. 12 Prospective study</td>
<td>[102]</td>
</tr>
</tbody>
</table>

The criteria adopted by the respective authors are used; percentages are calculated by the present authors from data in the publications. In the reference column, only the first author is given.

<sup>a</sup>Only those knees treated in the indication of RA are counted.
Results obtained from various other inflammatory joint diseases include crystal arthritis, with typical improvement rates of 40–70% [55–57]; lyme arthritis, with variable responses between 25% and 82% [29, 30, 42, 49, 58]; pigmented villonodular synovitis, with success rates between 25 and 100%, but with very small sample sizes [38, 59–63]; haemophilic arthritis, with improvement rates between 50 and 90% [64–70]; chronic effusion after implantation of endoprostheses, improved in more than 60% of all cases [71–74]; and removal of residual inflamed tissues following incomplete arthroscopic synovectomy [6].

Safety of RSO with yttrium [90Y] colloid

Exposure to radiation in/from the knee

Considering radiation effects, a distinction must be drawn between the action of β radiation, which because of its short penetration distance reaches only structures in the immediate vicinity of the joint cavity, and the effects of bremsstrahlung (X-rays produced indirectly by braking of the electrons), which can reach more remote organs but whose biological activity is very weak.

On the basis of the penetration distances given before, the local exposure to β radiation from 90Y can be estimated. For example, according to Johnson et al. [75], after an injection of 185 MBq of 90Y, for a cartilage thickness of 2 mm, a dose of 1 Gy is reached at a depth of 1.5 mm in the adjoining bones. Thus, the β radiation induces no systemic effect. Local effects beyond the synovial membrane are clinically tolerable.

The question of harmful effects of β radiation on other diarthrodial tissues, especially the articular cartilage has always been a subject of debate. In a three-dimensional culture system with bovine articular cartilage in alginate beads exposed to increasing activities up to 3 MBq 90Y/ml medium, Ailland et al. [76] found a dose dependent decrease of collagen type II synthesis which might account for a pre-arthrotic breakdown of the structural integrity of articular cartilage. Five weeks after exposure to radioactivity, they described a near-total cell death of these data to the situation in vivo is not possible. In the patient’s joint, the contact time between the radiopharmaceutical and the cartilage surface is much shorter than in the model due to the phagocytosis of the radiocollids by the synovial macrophages [77]. Moreover, the patient eligible for RSO suffers from arthritis with a variety of i.a. pro-inflammatory enzymes and cytokines, which are potentially hazardous for the articular cartilage and will destroy the tissue if the inflammatory activity is not antagonized. However, these in vitro data should be kept in mind especially if the indication for RSO is discussed in young patients in earlier stages of arthritis.

Various authors have carried out estimates of radiation exposure of the gonads due to bremsstrahlung from the knee; all in all, these effects have been estimated as minor [78, 79]. For example, Wagener [79] conducted phantom and in vitro scintigraphy and measured a radiation dose in the gonad region of 1.1 μGy/MBq, corresponding to 0.000244 Gy after RSO with the maximum recommended dose of 222 MBq 90Y. As this did not include exposure of the gonads to radiation from accumulated 90Y in nearby lymph nodes, which Wagener et al. could not detect, they made a worst-case calculation assuming that all the applied 90Y was taken up by the lymph nodes; even then, the exposure was only 0.0006 Gy, a value not considered dangerous in adults.

Leakage from the knee

Ideally, the rate of leakage of the nuclide vehicle from the treated region should be negligible in comparison with the rate of decay of the nuclide. For colloidal particles injected into the joint cavity, a major factor determining the leakage rate is the size of the particles. Early studies with gold-198 with particles of 20–30 nm revealed considerable leakage of 3–18% [80–82], greater than when the particle size was 300 nm (leakage into lymph nodes and the liver on average 1%, a value considered acceptable) [83]. The commercial 90Y citrate colloid has a particle size of about 2000 nm [84], with a range of 1000–3000 nm (information supplied by the manufacturer); a corresponding figure for the 90Y silicate has not been published.

Another important factor reducing leakage is immobilization of the joint after treatment. In a study with 90Y citrate colloid used in treating inflammatory rheumatic diseases [78], there was no statistically significant difference between out-patient and in-patient RSO regarding the leakage of radioactivity as long as immobilization was adequate (splitlim). The median activity leakage was in this study 1.8%, and this value is used here (see below) as a basis for estimating radiation exposure due to leakage.

In the recent study mentioned earlier [85], 142 out-patient radiosynovitheses with immobilization of the knee for 3 days showed generally small leakage, with a median value of 0.8%. The important part played by bed rest in preventing leakage was also found by Lloyd and Reeder [86]. Thus, the question of performing RSO as an in- or out-patient procedure is more dependent on local legislation on radiation protection, as long as an appropriate immobilization of the treated joints is secured. If this is not trusted in an out-patient setting, i.e. in otherwise handicapped patients, treatment should be performed as an in-patient protocol.

A final potential factor to be considered in connection with leakage is the chemical identity and particle size of the 90Y colloid used. It is generally accepted that a particle size above 300 nm is necessary to minimize spontaneous leakage, and that particles up to 10000 nm are taken up by phagocytosis [87]. In a comparison of the commercially available citrate and silicate colloids in 142 knees that were immobilized for three days after RSO [85], both colloids showed a clustering of leakage values at the level zero with a small number (around 25%) of higher values and without statistically or clinically significant difference between the two. The highest values were found for patients who received RSO following surgical synovectomy.

It is possible to estimate the radiation exposure after RSO of the knee. The distribution of colloids in the body after systemic administration is known [88]. It may be assumed that the leakage of colloidal radiopharmaceutical out of the knee occurs through the lymph circulation and that the colloid is first transported to the inguinal lymph nodes, from where it is transported to subsequent lymph nodes and eventually into the bloodstream. It is then very quickly taken up by the reticulo-endothelial system. According to this and a leakage of 1.8%, the highest activity that reaches the knee (apart from the treated knee) is in the regional lymph nodes, liver, spleen and bone marrow. The overall effective exposure corresponds to a radiation dose of 0.038 mSv/MBq—that is, 8.44 mSv following the administration of the maximum recommended dose of 90Y colloid (222 MBq). This estimate was based on the assumption of the most unfavourable case and is therefore probably a significant overestimate [89].

Biological dosimetry

The absence of a γ-component in the decay emission of 90Y makes direct dosimetry difficult. Therefore, indirect dosimetry, based upon biological findings, is the method of choice. A suitable biological variable to assess whole-body radiation exposure is the incidence of chromosomal aberrations, though it should be noted...
that these can arise from causes other than ionizing radiation. In a recent study [90], the frequency of dicentric chromosomes in peripheral lymphocytes was determined immediately before RSO with $^{90}$Y colloid and 4 weeks after the treatment. Before RSO, 25 dicentric chromosomes were found in 10,000 cells (incidence rate 0.25%); after RSO, 41 were found in 10,000 cells (0.41%). This difference was not statistically significant; thus, there is no evidence that RSO causes an increase in the number of dicentric chromosomes in peripheral lymphocytes. This method is the most sensitive available today, and so its failure to detect any radiation effect confirms the very low extent of whole-body radiation exposure engendered by $^{90}$Y RSO. The use of accurate, state-of-the-art biological dosimetry in vivo makes this result trustworthy, and it must be regarded as superseding those of Gumpel et al. [91, 92], which were based upon very small, non-randomized studies where results did not reach statistical significance, without correction for baseline values or confounders in case of biological dosimetry.

Risk of malignoma

In about 180 published studies and reports that were reviewed, with more than 9300 patients treated with $^{90}$Y, only one case each with chronic myelocytic and lymphatic leukaemia has been reported [93]. This case was diagnosed 4 yrs and the latter 6 months after RSO. These are not commented upon as having been potentially related to the $^{90}$Y treatment, but the short intervening period makes this seem unlikely. The present authors are not aware of any other cases in which malignancy of a type known to be potentially radiation-induced was reported following RSO with $^{90}$Y. Thus, in 30 yrs of $^{90}$Y-RSO, no case of treatment-related malignancy has been established [94]. In a recent seven-year study of 1228 hospital patients, 143 of whom received $^{90}$Y RSO and 1085 did not, it was found that those receiving yttrium in fact had a lower rate of malignancies than those who did not [95].

Other adverse effects

A nationwide survey in Germany [96] has shown that RSO is associated with only very few complications (the survey covered all nuclides currently used in RSO). Radiogenic injection-site necrosis, joint infection and thrombosis of the respective limb due to immobilization, were estimated to be roughly 1%, and the majority of complications proved to be amenable to standard therapy. Necrosis can occur by reflux of the administered colloid through the needle track. This is best prevented by saline or corticosteroid flushing and by immobilization of the treated joint. Similarly, necrosis can also occur if the injection is not administered correctly. Such necrosis heals slowly (months) and usually leaves a small scar and a depigmented skin area.

RSO with yttrium ($^{90}$Y) colloid in the context of knee synovitis

Irrespective of the individual disorder for which RSO may be considered appropriate in a given case, RSO should never be regarded as a first-line therapy; other methods must first have been given adequate opportunity to succeed before their clear failure—not sooner than after a period of at least 6 months—makes the patient a candidate for RSO.

RSO with a $^{90}$Y colloid offers the option of a local, minimally invasive treatment of synovitis in arthritic knee conditions of various origins. RSO can thus, in many cases of sometimes highly debilitating arthritis of the knee, relieve pain and restore the quality of life even in those patients, who do not sufficiently respond to other treatments. The accumulated evidence of the numerous trials and surveys conducted to date, leaves little room for doubt that, from the clinical point of view, RSO is an effective treatment.

Specifically, RSO is indicated in patients who have not been helped by i.a. injection of long-acting steroids (so-called ‘corticosteroid failure’). To avoid deterioration of the joint, the transition from corticosteroids to RSO should be made promptly after corticosteroid failure has been established.

Nevertheless, as a general rule, $^{90}$Y-RSO should always be co-administered with corticoid. Apart from any intrinsic therapeutic effect—and here a synergy with $^{90}$Y cannot be ruled out—corticoids are recommended as they help obtain a rapid improvement of the acute complaints and reduce side effects. A typical dose would be 10–20 mg triamcinolon, best administered as a crystalline suspension. Administration of the corticosteroid leads to less extra-articular leakage of the radionuclide, owing to a reduction in the hyperperfusion and increased vascular permeability that are associated with arthritis [26]. The corticosteroid also helps to minimize any reactive synovitis that may be provoked by the injected $^{90}$Y-emitter [97]. Furthermore, if the corticoid is administered directly after the injection of the radiocolloid (while the needle is still in the joint), then the consequent rinsing of the needle ensures that all the radionuclide is flushed into the joint cavity. This helps to prevent radiation-induced necrosis [98] by reflux of the activity through the puncture channel. If corticosteroid is not used, then the flushing should be performed with saline [13].

Practical details for the administration of $^{90}$Y and the avoidance of unwanted side effects can be found in the current European [21] and German [99] RSO guidelines. Adherence to these guidelines—which are similar in all relevant points—will ensure the routine attainment of the full effectiveness of this method in a safe manner. A practical summary of nuclear medicine related details of RSO has recently been published [100].

Conclusion

RSO with a $^{90}$Y colloid offers a local and relatively non-invasive therapy for treating synovitis of the knee joint. There is a great weight of accumulated evidence both for the efficacy of this treatment and for its safety if administered properly. The theoretical danger arising through exposure to radiation is minimal, and there are no known cases of malignancies caused by $^{90}$Y RSO. Other adverse side effects are uncommon and are in almost all cases acceptable in view of the benefit of the therapy.

W. E. K. has received consultancy fees and speakers fees from Schering, the former owner of Cis Bio (supplier of Y-90 citrate).

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J. P. is an employee of Schering Germany, the local distributor for radiocolloids for RSO in Germany.

A. K. has received consultancy fees and speaker’s fees from Abbott and Wyeth.

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