

## Long term follow-up after radiosynovectomy with yttrium 90 in patients with different rheumatic diseases

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*The aim of the retrospective study was to evaluate the efficacy of radiosynovectomy (with yttrium 90) mainly in patients with rheumatoid arthritis, less with some other rheumatic diseases. The evaluation period varied from half to nine years. The procedure was performed in 273 patients (225 females, 48 males) or in 463 joints (402 knees, 61 shoulders and ankles). The effect was evaluated by change in degree of morning stiffness, pain and swelling (score from 0 to 9). Very good results were obtained in 69 (15 %), good in 142 (30.5 %), moderate in 197 (42.5 %) and no effect in 55 (12 %) joints. Six months after the procedure 38 joints (8 %), half to two years after 221 joints (48 %) were in good remission, after 3 to 4 years 95 joints (20 %), after 5 to 6 years 57 joints (12%) were well, 7 to 9 years later 52 joints (11 %) showed no signs of arthritis. Joint pain and swelling were the most frequent procedure complications (5.6 %). In two patients with additional immunomodulating therapy chronic myeloid and lymphocytic leukaemia were diagnosed. Radiosynovectomy is considered to be an effective and safe treatment for synovitis in different rheumatic diseases.*

**Key words:** arthritis rheumatoid, synovial membrane-surgery; yttrium radioisotopes

### Introduction

Synovitis is a frequent cause of pain, swelling and functional joint impairment in different rheumatic diseases. For more than 100 years the removal of an inflamed synovial membrane (surgical synovectomy) has been a cornerstone in management of joint inflammation refractory to standard medical treatment. However, the difficulty of removing all the diseased synovium often leads to regrowth, surgical reintervention is often contraindicated because of fibrosis and scar tissue from the previous surgery. The interest for the non-invasive methods of synovectomy was raised and stimulated by easier procedure, lack of complications and lower

costs. Many isotopes have been therefore suggested and tested as the potential synovial ablative agents.<sup>1</sup> The development of open arthroscopic, chemical and radiosynovectomy was the consequence of better knowledge of the pathophysiology of synovitis. Radiosynovectomy became an alternative to a surgical method. The interest in this procedure markedly increased in 1950, especially as a prevention method against recurrent and progressive damage in rheumatoid arthritis (RA).<sup>2</sup> It can in principle also be applied to joints in the variety of other inflammatory joint diseases, most frequently in haemophilic synovitis, osteoarthritis and pigmented villonodular synovitis. The first reported use of radiosynovectomy was in 1952 with gold-198.<sup>3</sup> Most often yttrium-90 with tissue penetration 3.6 mm is applied in large joints, rhenium-186 with 1.2 mm tissue penetration in medium sized joints, erbium-169 with tissue penetration of 0.3 mm in small joints. Phosphorus-32,

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radium-224 and dysprosium-165 are also used. All are high-energy  $\beta$ -emitting radio-pharmaceuticals.<sup>4,5</sup> The average absorbed radiation dose for 180 MBq of administered yttrium-90 is about 100 Gy to 100 g of synovium. Radiosynovectomy is suitable local treatment of synovitis in the case of unresponsiveness to conventional at least half a year long antirheumatic therapy and when surgical synovectomy is contraindicated. It is well known that at early stage the response is better than at late or end-stage of the disease.<sup>6-8</sup> The advantage of radiosynovectomy compared to surgical synovectomy is the relative simplicity of the procedure, lower cost, shorter hospitalisation, quicker rehabilitation, less surgical complications and complications due to anaesthesia especially in elderly patients. Its drawbacks are radiation dose delivered to non-target organs due to leakage of radioactive material from joint cavity to liver, spleen and regional lymph nodes and occasional side effects.

## Patients and methods

### *Indication for <sup>90</sup>Y-citrate synovectomy*

<sup>90</sup>Y-citrate was applied to patients over 45 years old with synovitis caused by RA and in some cases of synovitis in the course of other rheumatic diseases such as ankylosing spondylitis, osteoarthritis and haemophilic haemarthropathy. In rheumatic diseases <sup>90</sup>Y-citrate was used when the response to previous conventional at least half a year long antirheumatic therapy was insufficient. The procedure was also performed when surgical synovectomy was contraindicated

### *Inclusion criteria*

The patients in whom radiosynovectomy was performed between 1985 and 1994 and were followed for at least 6 months after the application of <sup>90</sup>Y-citrate were included and evaluated in the retrospective study. Conventional radiographs of the treated joints were performed before procedure for exclusion of the patients with very severe secondary osteoarthritic changes.

Two hundred and seventy three patients (225 females and 48 males) have been selected for the evaluation. The mean age of the patients was  $57 \pm 10$  years. Mean time of the disease duration was  $8.5 \pm 6.5$  years. In 261 patients (448 joints) RA was

present, 3 patients had osteoarthritis, 8 ankylosing spondylitis and one haemophilic haemarthrosis (12 patients, 15 joints). Four hundred and two knees and 61 ankles or shoulders were treated and evaluated. The mean number of treated joints per patient was  $1.7 \pm 0.9$ . In knees and shoulders 185 MBq (5 mCi) and in ankles 111 MBq (3 mCi) of <sup>90</sup>Y-citrate was applied.

### *Method of application*

The procedure was performed under strict aseptic conditions. The joint was punctured without prior application of local anaesthetic. Synovial fluid if present in excessive amount was removed from the joint and discarded. Subsequently <sup>90</sup>Y-citrate was injected intraarticularly. No corticosteroids were given and no additives were admixed to the radiopharmaceutical. After withdrawing the needle the joint was passively flexed and extended several times. Afterwards it was immobilised with semi-compressive bandage. Patients were hospitalised for three days and were advised to stay in bed for 48 hours. They had access to bathroom facilities but they were not allowed to bear any weight on the joints.

### *The evaluation of therapeutic effect*

The evaluation of therapeutic effect was retrospective. The data about pain, swelling and morning stiffness in the joint before and after therapy were collected from in- and out-patients files. The period between the procedure and the last visit was considered as the follow-up period. The average frequency of patients' visits was 2 - 4 times yearly, the evaluation of the treatment effect was made by physician in charge.

Each of the three parameters were graded according to the severity of signs and symptoms as normal (0), mild (1), moderate (2) or severe (3). The three scores were summarized to get the overall improvement which was graded with regard to achieved score (from 0 to 9).

No improvement after treatment was considered if the change of score has been less than 1, moderate if the change was between 1.1 and 3, good between 3.1 and 6, and excellent between 6.1 and 9.

The duration of the improvement was measured as well. The treatment was considered unsuccessful if improvement lasted less than 6 months. The side effects of radiotherapy were concurrently recorded.

## Results

The mean follow-up period was  $4 \pm 2.6$  years, with the range of 0.5 to 9 years. Mean morning stiffness score before therapy was  $1.85 \pm 0.93$  and after therapy it was  $1.10 \pm 0.75$  ( $p > 0.001$ ).

Mean pain score was  $2.84 \pm 0.39$  before and  $1.47 \pm 0.7$  after therapy ( $p > 0.001$ ). Mean joint swelling score was  $2.59 \pm 0.56$  and  $1.43 \pm 0.7$  before and after therapy respectively ( $p > 0.001$ ).

The improvement was achieved in 88 % of treated joints. No significant improvement was noticed in 12 % of joints. Excellent effect of the treatment was achieved in 15 % of joints (Table 1).

The patients were followed-up in average for  $4.03 \pm 2.6$  years. The mean duration of observed therapeutic effect was  $2.79 \pm 2.3$  years. In 8 % of treated joints the effect lasted about 6 months and in 11 % the improvement lasted for 7 to 9 years. In majority of patients the effect was observed from six months to 7 years (Table 2).

The complications of therapy were noted in 23 patients. Joint pain and swelling were the most frequent side effects (17 patients or 5.6 %). In one transient fever and in two cases radiation necrosis at the injection site developed. In two patients chronic myelogenous and lymphatic leukaemia, respectively, was diagnosed, in one four years and in the other six months after radiosynovectomy. In a single patient hypernephroma and liposarcoma less than one year after radiotherapy were incidentally found.

## Discussion

Since the introduction radioisotope synovectomy remained one of the few possible radical treatments of severe joint pain due to chronic synovial inflammation in RA and some other chronic rheumatic diseases. According to the joint size yttrium-90 colloid for large joints, rhenium-186 sulphide for me-

**Table 1.** Patients according to degree of improvement.

Follow-up (years)	Number of joints	Without effect*	Moderate effect	Significant effect	Excellent effect
1	122	16	48	36	22
2	43	7	15	15	6
3	55	7	19	23	6
4	46	9	21	8	8
5	33	0	19	10	4
6	53	7	27	15	4
7	58	5	29	15	9
8	25	2	9	9	5
9	28	2	10	11	5
sum (%)	463 (100%)	55 (12 %)	197 (42,5 %)	142 (30,5 %)	69 (15 %)

Legend: \*This group is considered as "no effect" according to score of improvement of less than 1.1.

**Table 2.** Duration of improvement according to the years of follow-up.

Follow-up (years)	Number of joints year*	Effect <0.5 years	Effect 0.5 - 2 years	Effect 3 - 4 years	Effect 5 - 6 years	Effect 7 - 9 years
1	122	21	101	0	0	0
2	43	0	43	0	0	0
3	55	5	15	35	0	0
4	46	5	12	29	0	0
5	33	0	10	7	16	0
6	53	1	12	11	29	0
7	58	3	19	8	4	24
8	25	2	4	3	6	10
9	28	1	5	2	3	17
sum (%)	463 (100%)	38 (8%)	221 (48%)	95 (20%)	58 (13%)	51 (11%)

Legend: \*This group is considered as "no effect" according to too short duration of improvement.

dium sized joints, erbium-169 citrate for small joints are usually applied.<sup>5</sup> Allergic reactions, fever and radiation necrosis at the injection canal are considered the early complications.<sup>5</sup> Radiation necrosis was reported after synovectomy with yttrium-90 in an ankle. The authors warn against injecting this radioisotope in small and medium sized joints.<sup>9</sup> Yttrium-90 was used in our patients without serious side effects in spite of few medium sized joints included. In only two cases self-limited radiation necrosis was noticed in needle canal after yttrium injection in the ankle. Side effects were rare in our group as well as in the reports of others where flare up of synovitis is most often reported.<sup>10, 11, 5</sup> Myelogenous and lymphatic leukaemia after 4 years and after six months of radiotherapy occurring in our patients, could be considered as the late complications, although according to the literature they have not been reported anywhere else with the exception of chromosomal aberrations in lymphocytes.<sup>5</sup> On the other hand it is known that lymphatic leukaemia occurs with higher frequency in patients with RA.<sup>12</sup> Besides, the immunomodulatory treatment given to those patients in course of their disease could possibly play a role in development of leukemia. Hypernephroma and liposarcoma occurring in one of our patients less than one year after radiotherapy, cannot be considered as a consequence of radiation exposure after synovectomy.

As already mentioned most of the radiation dose emanates from leaking of the radioactivity from the joint cavity. Leakage of radioactivity to the regional lymph nodes is considered to cause chromosomal aberrations.<sup>13</sup> It is not possible to measure the leakage when yttrium-90, pure  $\beta$  emitter, is used. Therefore the dose to lymph nodes was calculated for dysprosium-165. Doses of 13 Gy in the immobilised and over 80 Gy in mobilised patient were measured. The leakage is higher if the particles are very small.<sup>1</sup> To reduce the leakage our patients were immobilised for 2 to 3 days.

Although 40 years of use of radiosynovectomy have already passed the reports on long term effects of this therapy are not numerous.<sup>10, 14</sup> Although our study was large and long term it has a drawback of being retrospective. The natural course of inflammatory rheumatic disease is quite variable and especially in retrospective studies it is sometimes not possible to tell the influence of different factors on rheumatic disease progress.<sup>15</sup> In spite of this the evaluation of therapeutic effects in patients with RA could be satisfactorily performed because they

keep visiting rheumatologist regularly on long term basis when the mentioned criteria of efficacy of radiosynovectomy are evaluated, thus enabling conscientious follow-up.

Most of the authors report favourable results of the radiosynovectomy in 60 to 80%.<sup>1, 16, 17</sup> We were able to see the favourable effects of the radiosynovectomy in significant number of our patients. The results of our study are satisfactory compared with the results of others.<sup>14, 18, 19</sup> Our experience is mostly limited to the patients with RA, since the number of patients with ankylosing spondylitis, osteoarthritis and haemophilic arthropathies was quite small. The effect of treatment in a single patient, a young boy, with haemophilic arthropathy of the ankle was excellent and in accordance with the report of Van Kasteren et al.<sup>10</sup> In our patients the recommended age limit of 45 years<sup>20</sup> was respected with the exception of the patient with haemophilic arthropathy. Hemophiliacs who need treatment are of younger age since chronic arthropathy is the major complication of haemophilia.<sup>21</sup> Fortunately the radiation dose for gonads is 1.05  $\mu\text{G}/\text{MBq}$  which is not high.<sup>22</sup>

In conclusion we can tell that the results of our study are in agreement with the reports in the literature. We consider radiosynovectomy effective, safe and suitable non-invasive therapy for inflamed joints in rheumatoid arthritis and in some other rheumatic diseases that are not responding to conventional antirheumatic therapy. The long-term effects are satisfactory, the side effects after synovectomy are not numerous and not severe. The method seems promising in haemophilic arthropathy as well. Less favourable results were achieved in osteoarthritis.

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