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A survey of radiation synovectomy in Europe, 1991–1993

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Abstract. The prevalence of radiation synovectomy practice is unknown. As new particulate radiopharmaceuticals offering many potential advantages are being developed, it seems prudent to appraise the extent, frequency and variation in radiation synovectomy practice. We have evaluated radiation synovectomy practice in Europe over the period 1991–1993 by means of a postal questionnaire. More than 2300 European members of the European Association of Nuclear Medicine were questioned about the number of treated patients and joints, disease prevalence in their patients and the use of radiopharmaceuticals. Overall, 119/490 (24%) of centres replying to the survey practised radiation synovectomy during the 3 years. There were 13 450 different joint injections in 8578 patients. Rheumatoid arthritis was the most prevalent disease in patients treated (71%) and the most frequently treated joints were knee (46%) and finger joints (20%). Eight different radiopharmaceuticals were employed. Yttrium-90 colloids were most frequently and widely (100/119 centres) used, mainly employed for knee synovectomy but were also used to treat most appendicular joints. Erbium-169 colloid was almost exclusively used to treat finger joints (31/33 centres). Corticosteroid was routinely co-injected in 36/60 (60%) centres. Radiation synovectomy was widely practised throughout Europe during 1991–1993. There are variations in practice illustrated by the diversity of treated arthritides and injected joints and by the use and application of different radiopharmaceuticals.

Key words: Radiation synovectomy – Radiosynoviorthesis – European survey – Questionnaire

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Introduction

The technique of radiation synovectomy (radiosynoviorthesis) has been available for more than 40 years for the management of joint disease. It is generally understood that there is a geographical variation in the practice of the technique. It is practised in Europe, Australia and Canada more than in the United States for example, where no radiopharmaceuticals are licensed for clinical radiation synovectomy by the Food and Drug Administration. There have been no published data on the prevalence of this technique.

Recently, there has been renewed interest in radiation synovectomy [1]. Since the introduction of the particulate radiopharmaceutical, dysprosium-165 ferric hydroxide macroaggregate [2], it has been clear that consistently lower levels of extra-articular activity accumulation are attainable with particulate radiopharmaceuticals than occur with radiocolloids [2–8]. Particulate radiopharmaceuticals, therefore, offer a theoretically safer and more precise therapeutic alternative to radiocolloids and if proved efficacious will provide valuable therapeutic options in the future.

There has been a paucity of well-controlled randomised studies assessing the outcome following radiation synovectomy [1]. It is, therefore, not surprising that in the literature there is no clear evidence of the efficacy of one of the most widely reported radiopharmaceuticals in current use: yttrium-90 radiocolloid [9]. Clearly, if new agents are to be successfully developed, they must survive the scrutiny of the results of carefully conducted randomised studies.

With the emergence of "new" agents and questioning of the "old", it therefore seems an appropriate time to appraise the practice of radiation synovectomy. The initial step is to document the extent and frequency of radiation synovectomy practice and to evaluate any potential variation in technique. We have undertaken a survey to record radiation synovectomy practice in Europe by means of a postal questionnaire.

Materials and methods

Questionnaire. In May 1994, all members of the European Association of Nuclear Medicine (EANM) were sent a postal questionnaire together with an explanatory letter, both written in English. Members were asked about radiation synovectomy practice from

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1991 to 1993 inclusively. As letters were sent to both occupational and private addresses registered with the EANM, recipients were asked to liaise with colleagues in the centre ("department/clinic") where they worked and return one questionnaire from each centre. The questionnaire, written on one A4 sheet, consisted of three main sections: (1) frequency of radiation synovectomy; (2) patients and joints treated; (3) radiopharmaceuticals used. If a centre did not undertake radiation synovectomy in any of the 3 years, they were asked to return a blank questionnaire. The questions in section 1 were: "How many injections have you/your department given in 1991–1993? How many patients is this? Do you give more than one injection to the same joint? If yes, what is the maximum given? Which joint(s) was this?" In section 2 the questions were: "Which joints do you/have you injected (answer yes/no): ... knee, ... ankle, ... wrist, ... elbow, ... fingers, ... others? What % of total joints injected are: ... knee, ... ankle, ... wrist, ... elbow, ... fingers, ... other? Do you/your department treat patients with (yes/no and % of total injections): ... rheumatoid arthritis, ... psoriatic arthritis, ... reactive arthritis, ... osteoarthritis, ... gout/CPPD, ... haemophilic arthritis, ... other?" In section 3 the questions were: "Do you/your department use (yes/no): ... ^{90}Y/silicate colloid, ... ^{90}Y citrate colloid, ... ^{90}Y resin colloid, ... ^{90}Y Fe hydrate colloid, ... ^{169}Er, ... ^{165}Dy-FHMA, ... ^{32}P, ... ^{198}Au, ... ^{186}Re, ... other? Do you use one agent specifically for (yes/no): ... one particular joint, ... or diagnosis?"

Positive respondents were asked in a second letter about corticosteroid co-injection. The questions were: "Do you routinely co-inject corticosteroid (yes/no)? If yes, which corticosteroid do you inject?" Also, if questions had been left unanswered, positive respondents were contacted again by letter and specifically asked about the relevant practice.

Repeat sampling. To assess whether the replies were returned by a representative sample of European Nuclear Medicine centres, non-respondents from six different countries were contacted by letter written in their native language. The letters were sent 6 months after the original questionnaire and included a copy of the questionnaire. Fifteen members from each of the six countries were chosen at random from the EANM membership database. Four of the countries were chosen because they had the lowest initial response rate of all European countries and two by virtue of having the greatest number of recorded members.

Results

Questionnaires

Questionnaires were sent to 2306 European members of the EANM (including members in Israel and Turkey). There were initially replies from 458 different centres in 29 countries. From the estimate of centres using radiopharmaceuticals in Europe (according to EANM re-

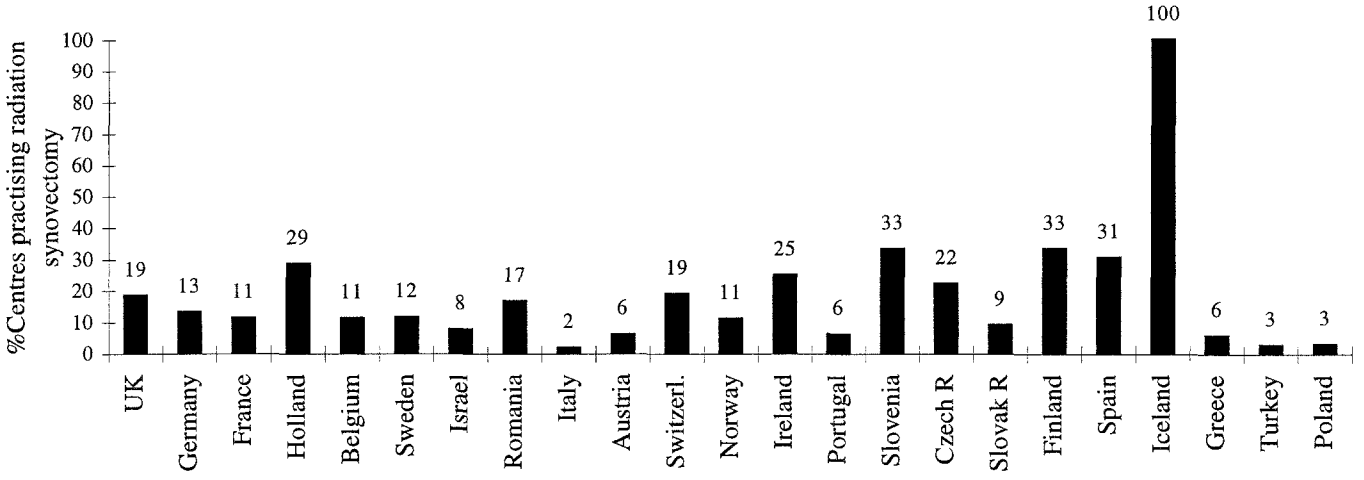

Fig. 2. Estimated number of centres/country (identified by the EANM membership database) practising radiation synovectomy in Europe (1991–1993)

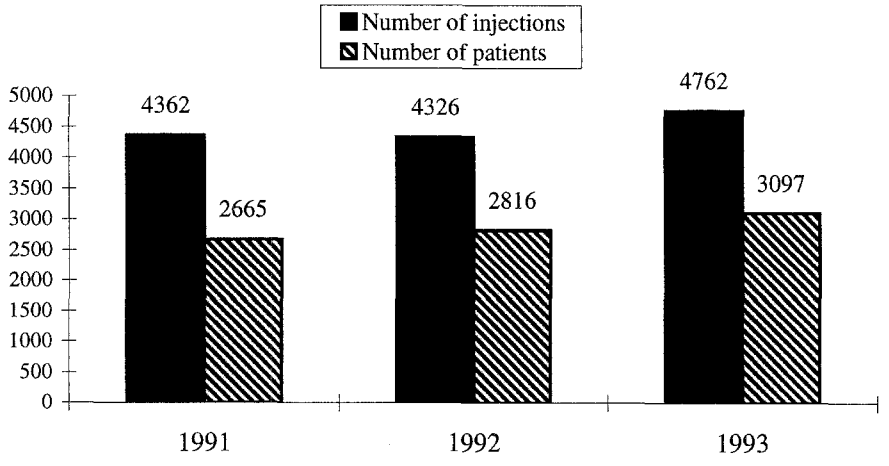

Fig. 3. Number of radiation synovectomy joint injections and number of patients treated in Europe (1991–1993)

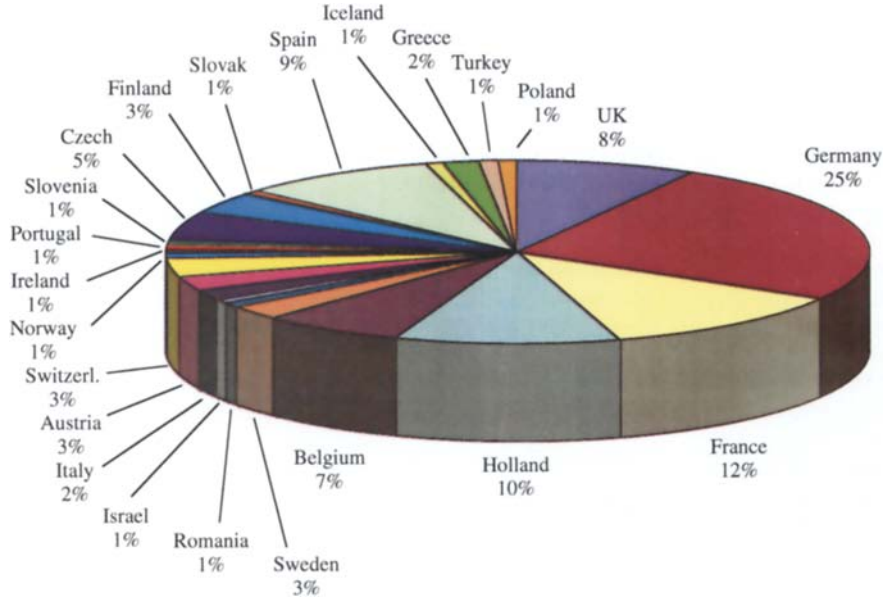

Fig. 1. Distribution of 119 centres practising radiation synovectomy in Europe (1991–1993)

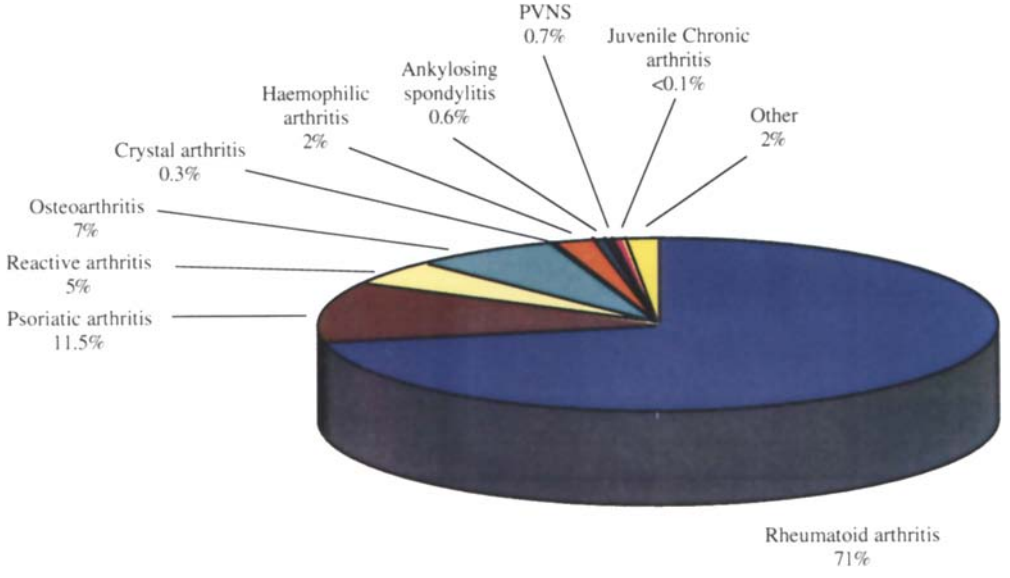

Fig. 4. Disease prevalence in patients treated by radiation synovectomy in Europe (1991–1993)

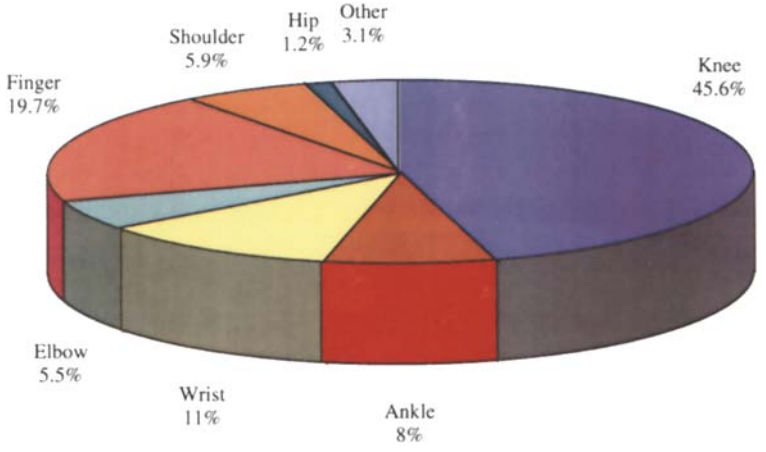

Fig. 5. Frequency of joint treatment in Europe (1991–1993)

cords), this represented an initial response rate of 458/1004 (46%). Of the responding centres, 112/458 (24%) in 23 different countries practised radiation synovectomy over the period 1991–1993.

Repeat sampling

The reply rate from original non-responders was 32/90 (36%), replies being received from all six countries sampled. Of the responders, 11/28 (39%) did not receive the

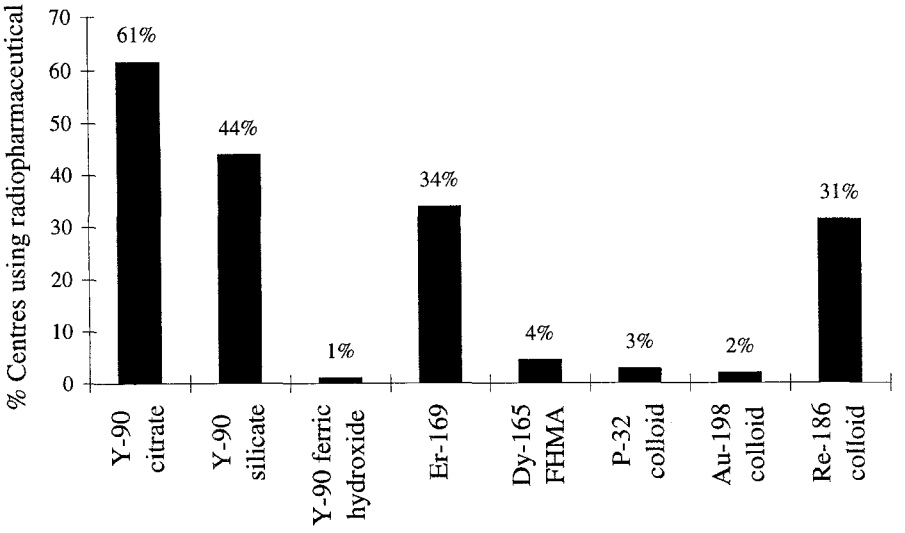

Fig. 6. Extent of use of radiopharmaceuticals for radiation synovectomy in Europe (1991–1993)

original questionnaire and 4/28 (14%) worked in centres from which a colleague had already returned the questionnaire. Of the responding centres, 7/32 (22%) in four countries practised radiation synovectomy. Data from repeat sampling were pooled with that from the original questionnaire. All subsequent results refer to the pooled data.

Distribution of centres

In total there were 119 institutions in 23 different countries where radiation synovectomy was practised during 1991–1993. The geographical distribution of centres is shown in Fig. 1. Using the membership database as an indication of the number of centres in each country administering radiopharmaceuticals, an estimate was made of the percentage of centres in each country where radiation synovectomy was undertaken (Fig. 2).

Patients and diseases

Over the 3 years, 8578 patients had one or more radiation synovectomy treatment (Fig. 3). There appeared to be a small increase in patients treated over the 3 years. Rheumatoid arthritis was the most prevalent arthritis in treated patients (71%) and was the only type of arthritis treated in 22/119 (19%) centres. There were four centres where treatment was exclusively given for haemophilic arthritis (18% of all haemophilic arthritis patients treated). The prevalence of different arthritides in patients treated by radiation synovectomy is shown in Fig. 4.

Injections and joints

There were 13 450 different joint injections in the 8578 patients (Fig. 3). Repeat joint injections or multiple joint injections in the same patient were not uncommon. There were 65/119 (55%) centres where joint injections had been repeated and in 21/65 (32%) centres this had been done 3 or more times in at least one patient. The most frequently re-treated joint was the knee (65% centres) although finger, wrist, elbow, shoulder and ankle joints were also reported to have been re-treated. Multiple joint injections had been given in the same patient in 60/119 (50%) centres. Generally, these patients had received from two to six joint injections, though in one centre up to 13 different joints had been injected in a single patient. The most frequently treated joints overall were knee (46%) and finger joints (20%). The frequency of treatment of these and other appendicular joints is shown in Fig. 5.

Radiopharmaceuticals

Over the 3 years, there were eight different radiation synovectomy radiopharmaceuticals in clinical use (Fig. 6). The most widely used was yttrium-90 citrate colloid (73/119) centres). In total, three different ^{90}Y radiopharmaceuticals were employed though ^{90}Y resin colloid was not in use. Overall a ^{90}Y radiocolloid had been used in 112/119 (94%) centres.

In centres where more than one type of joint was treated, different radiopharmaceuticals were often used. The specificity of use of a radiopharmaceutical for certain joints was greatest for ^{90}Y colloids and ^{169}Er. These were employed for the treatment of knees (64% joints treated) and finger joints (76%) respectively (Table 1).

Corticosteroid co-injection

From the 119 positive respondents, 60 (50.4%) were subsequently asked by letter about routine corticosteroid co-injection with radiopharmaceuticals. There were 36/60 (60%) centres where corticosteroid was routinely co-injected. Triamcinolone hexacetonide was most fre-

Table 1. Application of the four radiopharmaceuticals most commonly used for radiation synovectomy

Joint[a]	Number of centres using radiopharmaceutical for joint injection[b]			
	^{90}Y colloids	^{186}Re colloid	^{169}Er colloid	^{165}Dy FHMA
Shoulder	12	14	–	2
Elbow	19	28	3	1
Wrist	5	24	6	1
Finger joints	2	–	31	–
Hip	6	7	–	–
Knee	100	–	–	5
Ankle	12	25	1	1

[a] Joints from "other" category in questionnaire are not included
[b] 4/119 centres not included owing to insufficient data

quently used (46% of centres). The range of corticosteroids used for co-injection is shown in Fig. 7.

Discussion

To our knowledge, this is the first reported survey of radiation synovectomy practice. Choice of target population was based on maximising the chance of contacting workers responsible for handling radiopharmaceuticals. Access to the member database of a European organisation such as the EANM made this choice of method practicable. However, was this method likely to underestimate the prevalence of the technique in Europe? Whilst it is recognised that in some countries there may be smaller centres with few staff, none of whom may be EANM members, it was assumed that radiation synovectomy would primarily be practised in larger centres where staff membership of the EANM was more likely.

It is possible that in some countries rheumatologists or orthopaedic surgeons administer the joint injections but reaching sufficient numbers may have proved prohibitively difficult. This latter route of investigation would have been possible only by contacting members of a rheumatological society in each country. Based on 1994 figures from the European League Against Rheumatism (EULAR), this approach would have required contacting 10618 people in 35 countries (F Wyss, executive secretary EULAR, personal communication).

The response rate from repeat sampling was slightly less than that from the original questionnaire (36% vs 46% respectively). The percentage of positive replies from the secondary questionnaire was comparable to that from the original (22% vs 24% respectively). This indicates that it was unlikely that response to the original questionnaire was significantly biased in favour of either users or non-users of radiation synovectomy; however, it also suggests that the prevalence of radiation synovectomy practice overall may have been slightly underestimated.

Radiation synovectomy was widely practised throughout Europe during 1991–1993. We also received replies from around the world. Other countries where radiation synovectomy is practised are: Australia, Canada, South Africa and Mexico. Taken together, 71% of the European centres in our survey practising radiation synovectomy were concentrated in six countries (Belgium, France, Germany, Holland, Spain and the United Kingdom). This is likely to reflect a number of factors including differences in population density and resource distribution. We did not attempt to survey variations in the expense of the technique or in logistical or administrative factors influencing the supply and handling of a radiopharmaceutical. It is likely that these are important factors in determining radiation synovectomy practice in some European countries.

More than 71% of patients treated had rheumatoid arthritis. The management of rheumatoid arthritis will vary

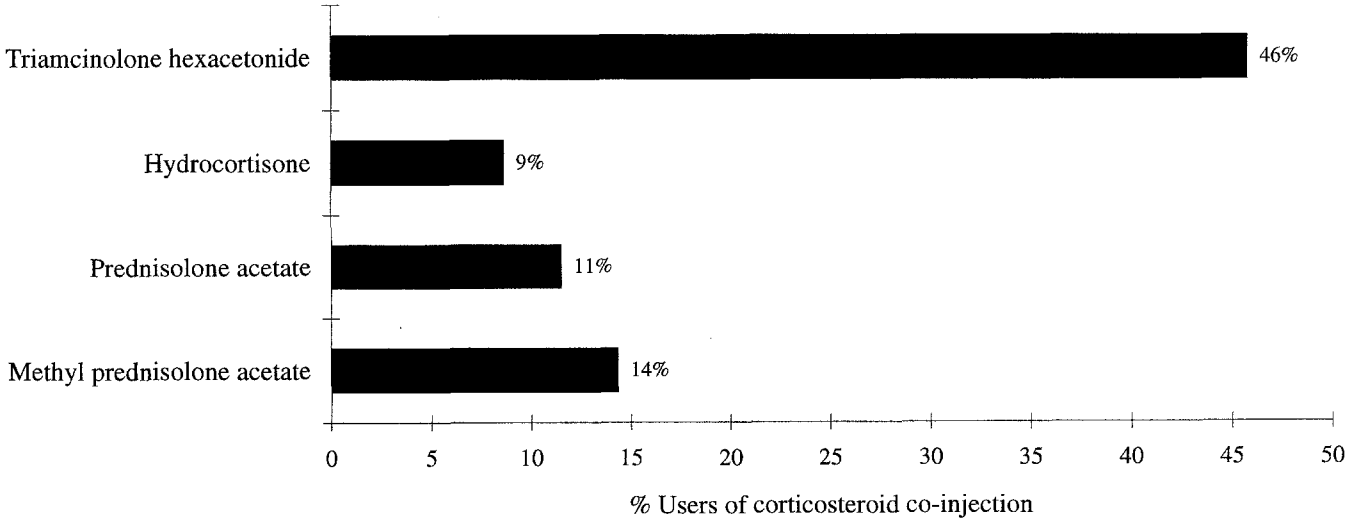

Fig. 7. The most commonly used corticosteroids for routine intra-articular co-injection with radiopharmaceuticals in Europe (1991–1993). (Data from 36/60 centres)

according to the availability of drugs, drug monitoring and surgery. Where these resources are scarce, radiation synovectomy may be perceived as an especially useful treatment option. However, approximately 13% of the patients treated had seronegative arthritides (ankylosing spondylitis, psoriatic and reactive arthritis). Compared to patients with rheumatoid arthritis, in whom arthropathy is most commonly polyarticular, these patients classically have an oligoarticular pattern of arthritis [10]. The impact of local joint therapy such as corticosteroid injection or radiation synovectomy might be expected to be greater in this group of patients than in patients with polyarticular arthritis. Although it appears there are many patients with seronegative arthritis being treated by radiation synovectomy, there are surprisingly few, if any reports in the literature studying outcome in this particular group of patients.

The frequency of finger joint injections was high (19.7% treated joints). Almost exclusively finger joints were injected with ^{169}Er colloid. ^{169}Er was also occasionally used for injecting other joints. The results from ^{169}Er colloid finger joint injection have been compared with those from intra-articular corticosteroid injection in three studies [11–13]. Two of the three studies [12, 13] showed no benefit of ^{169}Er over corticosteroid therefore leaving reasonable doubt as to whether ^{169}Er is more efficacious than intra-articular corticosteroid injection for small finger joints. Despite these findings and the absence of subsequent published data suggesting efficacy over corticosteroid, it appears that ^{169}Er is still widely employed for finger joint treatment.

A relatively large number of radiopharmaceuticals are used throughout Europe. Use may partially be reflected by ease of supply and expense. To our knowledge, no comparative evaluation of the joint retention and extra-articular leakage of different ^{90}Y colloids has been made since the study of Gumpel et al. [14] and no comparison of clinical outcome has ever been made. Significantly, Gumpel's data suggested that ^{90}Y resin colloid was associated with the least amount of regional lymph node irradiation as a result of joint leakage of activity compared to citrate, silicate and ferric hydroxide colloids. At the time of this study the production of ^{90}Y resin colloid had just been discontinued. It is unknown whether differences in efficacy exist between the ^{90}Y colloids.

Knowledge of the β^- penetration of various radionuclides has led to the rationale that average β^- penetration is tailored to joint size thus ^{90}Y preparations are used for larger joints, ^{169}Er for small joints and ^{186}Re for joints of intermediate size [15]. There seems to be broad agreement with this approach in Europe. It is pertinent to note, however, that these generalisations may only apply if the radiopharmaceutical remains in the synovial fluid or on the surface of the synovial lining [1]. Movement of a radiopharmaceutical into the synovial subintima either within the matrix or within phagocytes would suggest that as long as a radionuclide half-life was sufficient, cells throughout the tissue would be irradiated, even by radionuclides with relatively less penetrative β^- emissions.

Many centres do not routinely co-inject corticosteroids with radiopharmaceuticals. Those which do, favour triamcinolone hexacetonide – a preparation which is relatively insoluble and recognised to have a relatively long residence time in joints [16]. There are no published data on whether co-injection of corticosteroids influences clinical outcome following radiation synovectomy, however, there is some evidence to suggest that prior administration of corticosteroid reduces lymph node uptake of radiocolloid [17]. The role of corticosteroid co-injection with either colloidal or larger particulate radiopharmaceuticals clearly has not been adequately addressed.

Summary

This survey has emphasised the extent of radiation synovectomy practice throughout Europe. We hope that this survey may form a reference from which European physicians may identify issues which are important in deciding the most appropriate use of radiation synovectomy. We have touched briefly on a number of these issues in the discussion, for example, need we be using so many different radiopharmaceuticals? Does corticosteroid co-injection reduce extra-articular activity spread or improve outcome? Will particulate radiopharmaceuticals prove more efficacious than radiocolloids, and if so, for which joints? For the knee, do combined procedures such as saline irrigation with radiopharmaceutical and corticosteroid injection improve outcome over synovectomy alone?

Perhaps the most important unanswered question is: Are radiopharmaceuticals more efficacious than conventional intra-articular corticosteroid injection? If so, which? A definitive answer to this question would perhaps be the single most important factor in predicting radiation synovectomy practice in the future. It is clear from this survey that there are many physicians in many centres throughout Europe using the technique of radiation synovectomy. This indicates that there may be a core of interest in endeavouring to determine the answer to many of these questions.

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