Long-term results of multiple synovectomy for patients with refractory rheumatoid arthritis. Effects on disease activity and radiological progression

H. Nakamura[1], H. Tanaka[2], S. Yoshino[2]

[1]Institute of Medical Science, St. Marianna University, [2]Department of Joint Disease and Rheumatism, Nippon Medical School, Kanagawa, Japan.

Abstract

Objectives

We developed a radical multiple synovectomy (RaMS) procedure designed to reduce disease activity in refractory RA patients involving the excision of all inflamed synovial tissues. In this study we examined the long-term outcome of RaMS in terms of disease activity and articular destruction.

Methods

Forty-two patients with refractory RA underwent RaMS and were followed up for an average of 7.3 years. Clinical findings and radiological outcome were evaluated and compared to a control group.

Results

More than 40% of patients continued to maintain improvement up to 4 years after the operation. The number of swollen joints and painful joints, the erythrocyte sedimentation rate, CRP and rheumatoid factor quickly decreased after the operation. The beneficial effects continued for 4 years compared to patients treated with combination disease modifying anti-rheumatic drug therapy. The damage score worsened less rapidly in patients undergoing RaMS than in the control group. Articular destruction was less marked in the PIP, MP, wrist and ankle joints of patients who responded well to RaMS.

Conclusions

RaMS was effective for refractory RA in the short term and seemed to offer some advantages over other therapies in terms of slowing articular destruction. However, RaMS did not radically alter the natural disease course of RA.

Key words

Rheumatoid arthritis, synovectomy, long-term results, radiological findings.

Hiroshi Nakamura, MD, Associated Professor; Hidekazu Tanaka, MD; Shinici Yoshino, MD, Professor.

Please address correspondence and reprint requests to: Prof. Hiroshi Nakamura, MD, Institute of Medical Science, St. Marianna University, 2-16-1 Sugao, Miyamae-ku, Kawasaki-shi, Kanagawa 216-8512, Japan.
E-mail: nakamura@marianna-u.ac.jp

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Introduction

Synovectomy is performed to relieve pain, improve function, and suppress synovitis in the affected joints in rheumatoid arthritis (RA), with the aim of preventing further articular destruction. However, after a report by MacEwen (1) published in the 1980s, rheumatologists seem to have lost enthusiasm for synovectomy except in arthroscopic procedures. In their article, the authors concluded that synovectomy conducted on the finger or knee joints had little or no long-term value in the general treatment of RA, the prevention of recurrences of disease activity, or the progression of articular damage. Nevertheless, some reports on the results of synovectomy have been published, mainly concentrating on the clinical and radiological findings in individual joints independent of disease activity and the natural disease course (2-7).

As catabolic cytokines and proteases are produced in the inflamed synovium in RA (3-10), continuous synovitis can cause articular destruction and therefore the suppression of synovitis is important. In the early 1990s we developed a radical multiple synovectomy (RaMS) procedure for refractory RA patients unresponsive to disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) when rheumatologists were just starting to use MTX for the treatment of RA in Japan (11, 12). The purpose of RaMS is to reduce disease activity by excising as much inflamed synovial tissues as possible in all the swollen joints. We obtained an excellent outcome, including a remission rate of over 40% within 3 years after the operation (12).

The main objective of this study was to clarify the long-term outcome of RaMS in terms of disease activity and articular destruction to determine whether RaMS can radically alter the prognosis of RA.

Patients and methods

Patients

Fifty-two patients with RA underwent RaMS from 1992 to 1993 after granting an informed consent. The patients were diagnosed as RA according to the ACR criteria (13) and their physicians decided that their disease activity was severe enough to warrant surgery. Of this series, 42 patients were followed up for more than 5 years and analyzed in the present study. Patients had more than 6 swollen joints (average 14 joints) and/or high disease activity (mean ESR 60.5 mm/hour, mean CRP 4.0 mg/dl) which were unresponsive to medical treatment. Fourteen patients were selected from medical records as a control group, who had begun combination DMARD therapy to suppress RA activity in the same period and were followed up more than 5 years. Their demographic characteristics, and clinical and laboratory findings are listed in Table I; there were no statistically significant differences between the two groups.

Medications being taken before and after the operation is listed in Table II. In the RaMS group, the patients were unresponsive to medication for at least 6 months prior to the operation. Corticosteroids were administered in 93% of the patients in both groups and continued with no change after the operation. MTX was prescribed in 76% of the patients and 35% of the patients were treated with combination DMARD therapy prior to surgery in the RaMS group, whereas MTX was used in 50% of the patients and only one patient was treated with combination DMARD therapy in the control group. Thus, the medication was more intense in the RaMS group. The weekly dosage of MTX was 2.5-7.5mg and the daily dosages of salazosulfapyridine (SASP) and bucillamine (BU) were 1000 mg and 100–200 mg respectively. BU is a sulfhydryl compound with a similar chemical structure to tiopronin and D-penicillamine (14) and BU alone or in combination with other DMARDs has been shown to be effective in treating RA(15).

Surgical procedures

RaMS involved open synovectomy for all swollen joints in one or two stages (11). The following joints were operated on: 39 proximal interphalangeal (PIP) joints, 200 meracarpophalangeal (MP) joints, 58 wrist joints, 51 elbow joints, 43 knee joints, 57 ankle joints and 20

Table I. Characteristics of the patients.

	RaMS (n = 42)	Controls (n =14)	P
Treatment	RaMS (+ medical treatments)	Triple combination (MTX + SASP+ BU)	
Age (yrs.)	56.2 (43-73)	54.2 (22-73)	ns
Gender (M/F)	6/36	2/12	ns
Duration (yrs.)	14.8 (2-34)	16.7 (5-26)	ns
Swollen joints	14.0 ± 6.5	13.6 ± 4.9	ns
Painful joints	4.9 ± 4.5	6.4 ± 4.5	ns
ESR (mm/hr)	60.5 ± 33.1	70.8 ± 23.9	ns
CRP(mg/dl)	4.0 ± 3.7	3.7 ± 2.4	ns
RF (IU/ml)	224 ± 343	144 ± 38	ns

Values indicate the average (range) or the average ± SD. Statistical differences are calculated using Student's t-test. MTX: methotrexate; SASP: salazosulfapyridine; BU: bucillamine.

Table II. Medication before and after RaMS.

		RaMS (n=42)		Control (n=14)	
Before	Prenisolone	39	(93%)	13	(93%)
	Average dosage	4.7 mg/day		4.1 mg/day	
	DMARD				
	Methotrexate (MTX)	32	(76%)	7	(50%)
	Gold	5	(12%)	0	
	Salazosulfapyridine (SASP)	10	(24%)	2	(14%)
	Bucillamine (BU)	9	(21%)	3	(21%)
	Combination of DMARDs				
	double(MTX + SASP, BU, Gold)	14	(33%)	1	(7%)
	triple(MTX + SASP+ BU)	1	(2%)		
After	Predonisolone	39	(93%)	13	(93%)
	DMARD				
	Methotrexate (MTX)	36	(86%)		
	Gold	2	(5%)		
	Salazosulfapyridine (SASP)	16	(38%)		
	Bucillamine (BU)	26	(62%)		
	Combination of DMARDs				
	double (MTX + SASP, BU, Gold)	21	(50%)		
	triple (MTX + SASP+ BU)	9	(21%)	14	(100%)

Values are number of patients unless indicated. Prednisolone was continued unchanged. Postoperative medication was increased in 19 patients and remained unchanged in the rest of patients in the RaMS group. All of the control patients started triple combination therapy composed of MTX+SASP+BU.

other joints. An average of 11.1 joints were synovectomized in a single patient. In the RaMS group, medication was increased to combination therapy with two or three drugs in 19 patients (Table II). Though some of the patients undergoing RaMS started combination DMARD therapy or increased DMARD (Table II), our previous study showed that the surgical outcome was unaffected by the post-surgery change in medication (12), so the effect of any such drug change was not taken into consideration in this study. The post-operative medication was continued unchanged during the follow-up period except in 6 patients who experienced side effects or no beneficial response.

Measurements

The number of swollen joints and painful joints, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) level, serum rheumatoid factor (RF) titer, fatigue, duration of morning stiffness and grip strength were estimated at 3, 6, 12 and 18 months and then every year after the operation. We defined a less active condition of the disease as "remission" according to the preliminary criteria for remission outlined by the ACR (16). The criteria allow classification of a patient as in "remission" when they show no arthritic symptoms or fatigue even if the ESR or CRP remain high. The remission rate (RR) was calculated as follows: RR = the number of patients who fulfilled the criteria for remission divided by the total number of patients. For the radiological evaluation, X-rays of the hands and the joints undergoing synovectomy were taken at baseline, at 3 years and at the final examination, and read by well-trained, blinded rheumatologists. Overall radiological progression was expressed as the Damage Score (DS) (17) and carpal height ratio (CHR) (18). The damage score measures articular destruction of the MP and PIP joints, and CHR measures collapse of the carpal bones. Radiological findings for individual joints were expressed using the Larsen score (19). The difference in DS (ΔDS) was calculated as the Larsen score at 3 years or the final examination subtracted by the Larsen score at baseline. The decrease in the CHR ratio (%CHR) was calculated as follows: %CHR = (CHR at 3 years or the final examination – CHR at the baseline) / CHR at baseline x 100.

Patients who fulfilled the criteria for clinical remission at more than 4 yearly examinations were defined as having well-controlled disease and others were classified as having insufficiently controlled disease.

Statistical analysis

The Wilcoxon signed-ranks test was used for the variables of paired samples. The Mann-Whitney test or Student's t-test was used for the intergroup analysis. The ratios were analyzed by the chi-square test.

Results

Clinical and laboratory manifestations

RRs were 69%, 64%, 45%, 50%, 57% and 55% at 3, 6, 12, 18, 24 and 36 months after the operation respectively. More than 40% of patients maintained remission during 4 years after RaMS. The RRs in the synovectomy group

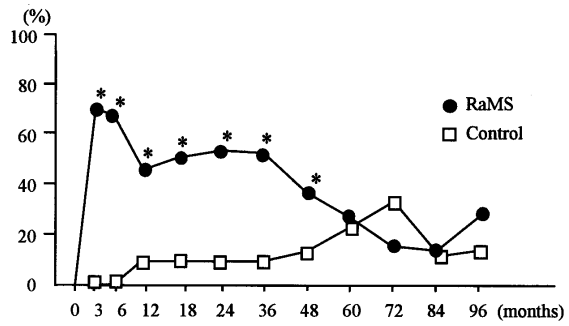

Fig. 1. Remission rates in the patients who underwent radical multiple synovectomy (RaMS) compared to the control group on combination DMARD therapy. The percent of patients who fulfilled the criteria for clinical remission was estimated at each examination. The difference between RaMS and control patients was analyzed by the $\chi 2$ test (*$p < 0.05$).

were significantly superior to those in the control patients who were treated with combination DMARD therapy. After 5 years, the RR in the controls increased and any significant difference between the two groups disappeared (Fig. 1).

The number of swollen joints decreased dramatically in the RaMS group and continued to be low during the follow-up, whereas the decrease was gradual in the control patients. The difference between the RaMS group and the controls was significant within 3 years after the operation and at 7 years (Fig. 2A). The number of painful joints showed a similar tendency and the difference between the two groups was significant within 2 years after the operation (Fig. 2B). The improvement in ESR began quickly after the operation and continued during the follow-up, whereas the improvement in the control group was not as marked (Fig. 2C). A decrease in CRP was measured in the synovectomy group at the time-points from 3 months to 7 years, whereas it started at 2 years in the controls (Fig. 2D). Grip strength improved at 6 and 12 months, but decreased gradually as time passed (Fig. 2E). Interestingly, RaMS was associated with a decrease in the RF titer soon after the operation (Fig. 2F).

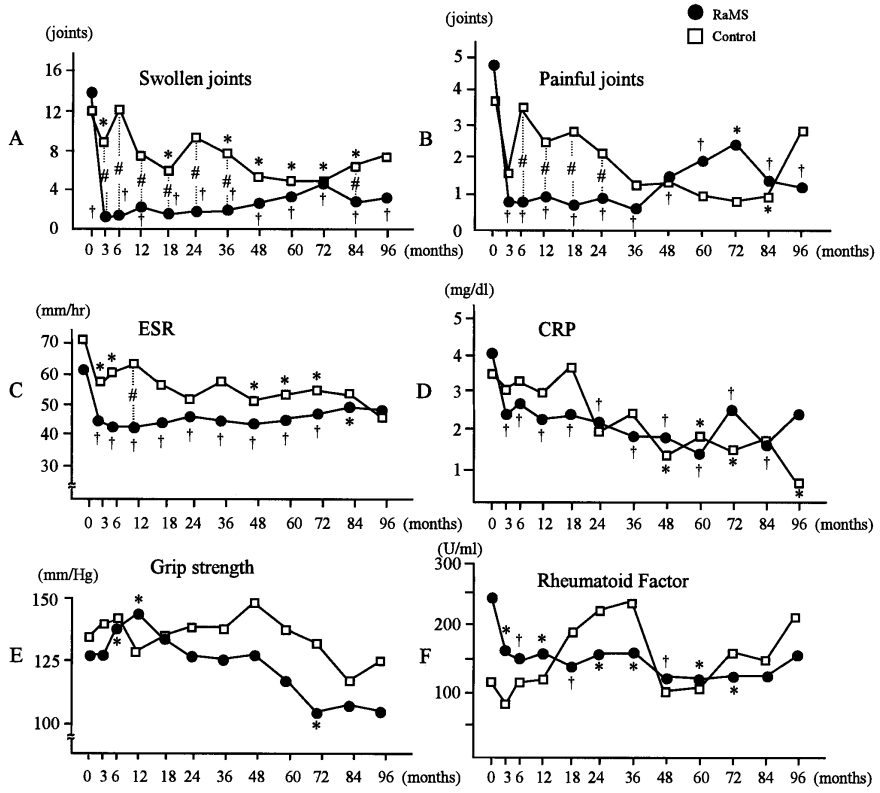

Fig. 2. Changes in the clinical and laboratory findings. (**A**) The number of swollen joints; (**B**) the number of painful joints; (**C**) erythrocyte sedimentation rate (ESR); (**D**) C-reactive protein (CRP); (**E**) grip strength; and (**F**) rheumatoid factor. Changes from the baseline values were analyzed by the Wilcoxon signed-ranks test (*$p < 0.05$, † $p < 0.01$) and comparisons between RaMS and control were made by the Mann-Whitney test (# $p < 0.05$).

Overall radiological progression

Articular destruction evaluated by DS and CHR tended to progress in both the well controlled and insufficiently-controlled groups. ΔDS at 3 years and at the final examination was less in the RaMS group, whereas %CHR showed no significant difference between the two groups (Fig. 3).

Radiological progression in individual joints

We further examined the radiological findings for individual joints that underwent synovectomy. Images showing mutilating deformity or severe destruction were excluded from evaluation. The average Larsen score progressed significantly in each joint; however, the progression was not significant in the PIP, wrist and ankle joints in well-controlled patients. In the elbow joints, articular destruction progressed during the first 3 years both in well-controlled and insufficiently-controlled patients, whereas no significant progression was found at the final examination in the well-controlled patients. This result indicates that the elbow joints deteriorate after synovectomy, followed by recovery to some extent in the well-controlled patients (Fig. 4).

A number of joints did not show radiological progression after synovectomy as defined by the Larsen score. Radiological findings remained unchanged in about 50 – 65% of the joints at 3 years and in 30 – 60% of the joints at the final examination. When the joints were classified according to whether the patients were well-controlled or not after the operation, the MP, wrist and ankle joints showed a better outcome in the well-controlled patients compared to insufficiently-controlled patients at 3 years and at the final observation (Table III).

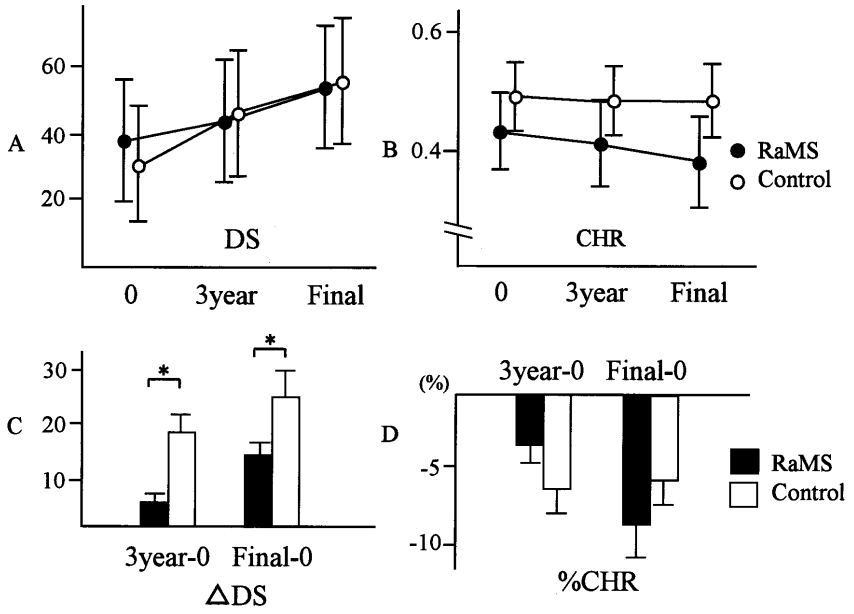

Fig. 3. Radiological progression estimated by damage score (DS) and carpal height ratio (CHR). The changes in DS (**A**) and CHR (**B**). The difference in DS (ΔDS) was higher in the controls both at 3 years and at the final examination (**C**).The change in the carpal height ratio (CHR) showed no significant difference (**D**). Values are expressed as the mean ± SD. Comparisons between RaMS and control patients were performed using the Mann-Whitney test.

Prognosis of RaMS

Six patients (14%) who underwent RaMS needed to increase or change their medication because of an unsatisfactory outcome, compared to 3 patients (21%) in the control group. Twenty-one patients (50%) with RaMS underwent further surgery (synovectomy in 6 patients and arthroplasty in 19 patients, including 22 total knee arthroplasties, 5 total hip arthroplasties, 2 total ankle arthroplasties and 1 total elbow arthroplasty) either on the synovectomized joints or untreated joints and 6 (43%) in the control group. Further synovectomy in the RaMS group was conducted on previously synovectomized joints, especially in the knee, elbow and wrist joints an average of 3.6 years after the initial surgery. Four control patients underwent RaMS an average of 2.8 years after the combination DMARD therapy. Two patients developed amyloidosis and one patient died of renal failure in each group (Table IV).

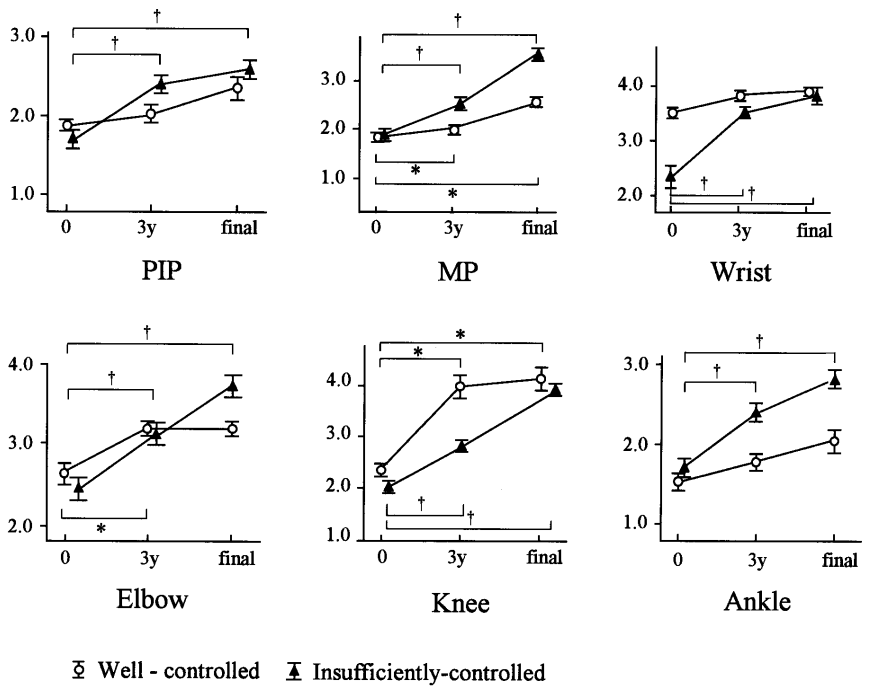

Fig. 4. Radiological progression in individual joints. Larsen scores were evaluated for the the well-controlled and insufficiently-controlled patients who underwent radical multiple synovectomy (RaMS). Values are expressed as the mean ± SE. Changes from the baseline values were analyzed by the Wilcoxon signed-ranks test (*p < 0.05 for well-controlled, † p < 0.05 for insufficiently-controlled).

Discussion

Surgical procedures are usually undergone to recover joint function in RA patients. The objectives of synovectomy however are to suppress synovitis and pain, and to prevent articular destruction rather than to reconstruct the joints. Though total joint replacement is an option for joints with severe destruction, synovectomy is preferable for the joint with severe refractory synovitis and less erosion, since joint replacements are aggressive and sometimes associated with complications such as infection or loosening. In other words, synovectomy seems to function like a medical treatment. We developed an RaMS procedure to extend the effect of conventional synovectomy, hoping to see suppression of RA activity and alteration of the natural disease course.

As synovial tissues are a source of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) which are some of the therapeutic targets of therapy in RA, antirheumatic effects are to be expected from the removal of synovial tissue. Similarly, RF probably originates mainly from synovial plasma cells and we observed RF titer decreases after RaMS. Theoretically, remission may be achieved by the complete removal synovial tissue. In our study, 69% patients fulfilled the criteria for remission at 3 months after the operation; however, the remission rate decreased to 54% at 3 years, 43% at 4 years, 31% at 5 years and 21% at 6 years. Development of synovitis in the other joints, relapse of

Table III. Radiological progression in each joint after synovectomy evaluated by the Larsen score.

	Radiological progression	PIP			MP			Wrist			Elbow			Knee			Ankle		
		Total	W	I	Total	W	I	Total	W	I	Total	W	I	Total	W	I	Total	W	I
	n =	*35*	*13*	*22*	*133*	*59*	*74*	*45*	*26*	*19*	*38*	*18*	*20*	*41*	*13*	*28*	*45*	*21*	*24*
3 year	yes	12	2	10	44	12	32	16	6	10	13	8	5	21	8	13	17	3	14
	no	23	11	12	89	47	42	29	20	9	25	10	15	20	5	15	28	18	10
	% of non-progression	*65.7*	*84.6*	*54.5*	*66.9*	*79.7*	*56.8*	*64.4*	*76.9*	*47.4*	*65.8*	*55.6*	*75.0*	*48.8*	*38.5*	*53.6*	*62.2*	*85.7*	*41.7*
	p		ns			<0.01			<0.05			ns			ns			<0.05	
Final	yes	17	6	11	97	35	62	25	10	15	22	10	12	29	11	18	22	7	15
	no	18	7	11	36	24	12	20	16	4	16	8	8	12	2	10	23	14	9
	% of non-progression	*51.4*	*53.8*	*50.0*	*27.1*	*40.7*	*16.2*	*44.4*	*61.5*	*21.1*	*42.1*	*44.4*	*40.0*	*29.3*	*15.4*	*35.7*	*51.1*	*66.7*	*37.5*
	p		ns			<0.01			<0.01			ns			ns			0.05	

W: well-controlled, I: insufficiently-controlled. Patients who fulfilled the criteria for clinical remission more than 4 times at yearly examinations were defined as well-controlled and others were classified as insufficiently-controlled. Chi-square test was used for statistical analysis.

Table IV. Prognosis of the patients.

	RaMS (n=42)	Control (n=14)
Change of medication*	6 (14%)	3 (21%)
Surgery	21 (50%)	6 (43%)
Synovectomy	6 (14%)	4 (29%)
Arthroplasty	19 (45%)	2 (14%)
Amyloidosis	2 (5%)	2 (14%)
Death**	1 (2%)	1 (7%)

* Change or increase of drugs due to side effects of lack of response.
** One patient in each group died of renal failure.

synovitis in the treated joints in some cases, and failure to suppress the inflammatory reaction expressed as an elevated ESR or CRP, were considered to be the reasons for partial remission and a gradual decrease in RRs. Extra-articular organs may also be involved in the pathogenesis of RA. Bone marrow stem cells are one of the candidates that provide ongoing active disease after RaMS (20).

Although there was no significant difference in disease activity between the two groups at the baseline, prior medical treatment was different. Considering the fact that about half of the patients with RaMS had been treated with combination DMARD therapy prior to surgery and that the patients in the control group were naive to the combination therapy, there might have been a bias in that the latter patients were more responsive to the medical treatment. The effects of RaMS as measured by the clinical and laboratory findings appeared very quickly and were superior to the controls in a short term follow-up, without any adverse events. Anti-rheumatic effects continued for more than 5 years; however, the difference in outcome compared with intensive medical treatment disappeared after 5 years. Two patients developed amyloidosis and another died of renal failure. These outcomes could have been the result of the natural course of RA.

Regarding synovectomy, McEwen conducted a well designed control study (1) and reported that there was little long-term value in surgical synovectomy for the treatment of RAand it failed to prevent articular damage. However, some favorable results have been reported by others in the wrist and elbow joints that were not included in McEwen's study. Chantelot (7) reported that 97% of patients showed satisfactory pain relief after synovectomy in the wrist joints. Tulp (2) reported that about 70% of patients showed satisfactory results after early and late synovectomy in the elbow. Synovectomy for the ankle joints resulted in no radiological deterioration in less erosive RA (6). On the other hand, synovectomy for the knee joints exhibited disappointing results even in the early stage (3,4). Pain relief was recorded as an effect of synovectomy in all reports, besides prevention of articular damage. In our study the radiological outcome of synovectomy for individual joints was influenced by type of the joint and disease activity. For example, radiological results of the PIP, wrist, elbow and ankle joints were better than the other joints, and those of the MP, wrist and ankle in the well-controlled patients were better than in the insufficiently-controlled patients.

Although it was hoped that our "radical multiple synovevctomy" procedure might offer a radical cure of RA, RaMS was unable to alter natural course of the disease radically. Nevertheless, it should be underlined that RaMS was beneficial in the short-term and resulted in some improvement of the underlying disease process. In terms of expense and invasiveness, RaMS could be considered more expensive and aggressive than conventional treatment. Chemical synovectomy using radioisotope or steroid injection on multiple joints are other options when multiple synovec-

tomy is being planned.

In conclusion, RaMS was effective in improving the clinical findings, especially joint swelling and joint pain in the short-term and offered some advantages with regard to articular destruction in refractory RA. The radiological outcome of synovectomy depended on the type of joint and the disease activity of the patient. Overall, RaMS did not alter the long-term natural course of RAradically.

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