

## Postoperative Loco-Regional Radiation Therapy for Breast Cancer Patients with Four or More Involved Lymph Nodes or Extracapsular Extension

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**Key words:** breast cancer, radiation therapy, breast loco-regional irradiation

### Abstract

**Background:** Post-mastectomy loco-regional radiation to the chest wall and draining lymphatics, combined with adjuvant chemotherapy and hormonal therapy, significantly improve survival in patients with node-positive breast cancer. However, the actual benefit of post-mastectomy radiotherapy and the desired extent of treatment are still debatable.

**Objectives:** To examine the effect of postoperative loco-regional radiotherapy on local and regional recurrence and survival in breast cancer patients with four or more involved lymph nodes or extracapsular tumor extension.

**Methods:** This controlled clinical trial included 258 breast cancer patients with four or more involved nodes or ECE. Eighty-nine patients in the control group had modified radical mastectomy and received adjuvant chemotherapy with melphalan and 5FU, but no radiation therapy. The 169 patients in the study group (87 with MRM and 82 with lumpectomy and axillary dissection) received various adjuvant chemotherapy regimes and radiation therapy to the chest wall/breast, supraclavicular region and full axilla.

**Results:** With an average follow-up of more than 5 years, loco-regional radiation significantly reduced local and regional disease recurrence. The median disease-free survival was significantly longer in radiated patients (59.2 months and 63.3 months in the MRM and L+AXLND groups, respectively, vs. 28.4 months in the control group;  $P < 0.01$ ). There was no difference in the rate of systemic recurrence and overall survival. The median overall survival was 71.2 and 67.5 months in the study groups (MRM and L+AXLND, respectively) and 70.5 months in the control group ( $P = 0.856$ ).

**Conclusions:** Radiotherapy to the breast/chest wall and to the draining lymphatics, in addition to surgery and adjuvant therapy, significantly reduced the risk of local and regional recurrence in high risk breast cancer patients with four or more involved lymph nodes or ECE.

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after lumpectomy and is therefore a part of breast-conserving therapy. For patients undergoing mastectomy, there is little doubt that radiation reduces the risk of chest wall recurrence. Furthermore, recent large trials also demonstrated a significant improvement in survival for node-positive patients who received post-mastectomy loco-regional radiation to the chest wall and draining lymphatics as well as adjuvant chemotherapy and hormonal therapy [1,2]. However, there is still substantial controversy regarding the actual benefit of post-mastectomy radiotherapy for certain subgroups of patients, and the desired extent of regional treatment. Thus, although nearly all PMRT trials included the internal mammary chain and the full axilla, the value of that strategy is still debatable.

Axillary recurrence is relatively uncommon in patients undergoing level I/II or complete (level I-III) axillary dissection. The risk may be higher in patients with four or more positive nodes [3], extracapsular tumor extension [4], and large involved nodes of more than 2 cm [5]. The extent of axillary dissection, as measured roughly by the total number of recovered nodes, may also have an impact on the risk of recurrence [6,7]. Long-term results from a major trial revealed that in clinically node-negative patients either axillary dissection or axillary irradiation provided identical long-term survival [8]. Another trial that compared radical mastectomy with total mastectomy (without axillary dissection) and loco-regional radiation also showed no difference in long-term survival [9].

Recently published guidelines by ASCO (American Society of Clinical Oncology) recommended PMRT to the chest wall and supraclavicular region for patients with four or more involved axillary lymph nodes. The expert panel further suggested that full axillary radiotherapy not be given to patients who had complete or level I/II axillary dissection. They found insufficient evidence to make suggestions for patient subgroups that might benefit from such treatment [10]. On the other hand, indications for postoperative full axillary irradiation, according to the recommended standards by Bartelink [11], were involvement of four or more nodes or more than 50% of the resected nodes,

The current management of invasive breast cancer involves several modalities – surgery, adjuvant chemo- and hormonal therapy, and radiation. It was clearly shown that radiation therapy reduces the risk of in-breast recurrence for patients

ECE = extracapsular tumor extension

MRM = modified radical mastectomy

L+AXLND = lumpectomy and axillary dissection

PMRT = post-mastectomy radiotherapy

the presence of a large involved lymph node of more than 2 cm, and ECE.

In the present work we studied the effect of postoperative loco-regional radiotherapy on local and regional recurrence and on disease-free and overall survival in breast cancer patients at high risk of relapse.

## Patients and Methods

The study population included 258 breast cancer patients: 89 patients in the control group and 169 in the study group. The control group comprised patients with four or more involved lymph nodes or ECE who were treated in our medical oncology unit during 1980–1984. They all had modified radical mastectomy and received adjuvant chemotherapy with melphalan and 5FU, but no radiation therapy. The control group was previously reported by Rakowsky et al. [12]. The study group comprised consecutive patients with four or more involved lymph nodes or ECE who were treated in our radiation therapy unit during 1988–1997. They had MRM (87 patients) or lumpectomy and axillary dissection (82 patients), and received various adjuvant chemotherapy regimens. Few patients with hormone-responsive tumors also received tamoxifen. Unlike the control group, patients in the study group received loco-regional radiation therapy to the chest wall/breast, the supraclavicular region and the full axilla.

Radiotherapy was delivered to the breast or chest wall by medial and lateral tangential fields; the posterior edges of the fields were aligned. The supraclavicular region and full axilla were treated with an anterior field that matched the tangential fields inferiorly and were half-beam blocked, abutted the bony spine medially and extended to split the humeral head laterally. A block was added over the humeral head laterally and over the spine and upper esophagus medially. The fields were treated with 50.0 Gy in 2 Gy daily fractions with 6 MV photons. A 10 Gy electron boost was added to the tumor bed for patients who had L+AXLND.

All the information was obtained from the medical charts. Local recurrence was defined as recurrent disease in the mastectomy scar (for patients with MRM) or in the ipsilateral breast (for patients with L+AXLND). Regional recurrence was defined as recurrent disease on the same side of the chest wall (other than the scar), supraclavicular region, or axilla. In order to study the role of loco-regional radiation in this setting, we evaluated and compared the disease-free survival, specific sites of first recurrence, and overall survival.

## Statistical analysis

For comparison of means, univariate analysis of variance (ANOVA) was used in case of one dependent variable, and multivariate analysis of variance (MANOVA) for more than one dependent variable. When those analyses revealed

significant differences, paired comparisons according to Scheffe were used as well. Chi-square test was used to compare between the groups on categorical variables. In addition, analysis of covariance (ANCOVA) was used to check if various variables contributed to differences between the groups. SPSS software was used for all the statistical analyses.

## Results

The average follow-up of the control and study groups was 65.5 months (range 7–112.5 months) and 70 months (range 4–171.5), respectively. The patients' demographics and disease characteristics are shown in Table 1. The mean number of obtained axillary nodes was 10.6 in the control group and 17.1 in the study groups, and the mean number of positive nodes was 6.8 and 7.1, respectively. In the control group 89.9% of patients had four or more positive nodes, as compared to 86.2% in the MRM group and 63.4% in the L+AXLND group. The other patients in the study had ECE. As can be seen, a significant difference was found in the size of the tumors, because only patients with T1 and T2 entered the control group, while few patients with T3 and T4 entered the study group. The adjuvant therapy received by the patients also differed. All patients in the control group received combination chemotherapy with melphalan and 5FU (FUME). Patients in the study groups received various chemotherapy regimens including anthracyclines (34.3%) and few received tamoxifen (9.2% of MRM and 17.1% of L+AXLND).

There were significantly fewer regional recurrences in patients receiving radiation as compared with the controls (10.3% and 7.3% in the MRM and L+AXLND study groups, respectively, and 28.1% in the control group;  $P < 0.01$ ,  $\chi^2 = 16.725$ ) [Figure 1]. Local recurrences were also significantly reduced in radiated patients (4.6% and 3.7% in the MRM and L+AXLND groups, respectively, and 16.9% in controls;  $P < 0.01$ ,  $\chi^2 = 12.125$ ) [Figure 1]. In order to check if these differences were not a function

**Table 1.** Patient and tumor characteristics

	Control (n=89)	MRM (n=87)	L+AXLND (n=82)	P	$\chi^2$
Age <50 yrs	34 (38.2%)	27 (31.0%)	27 (32.9%)	0.583	1.080
ER+	39 (43.8%)	50 (57.5%)	45 (54.9%)	0.224	2.993
PR+	37 (41.6%)	43 (49.4%)	48 (58.5%)	0.052	5.897
ER+ or PR+	47 (52.3%)	54 (62.0%)	55 (67.1%)	0.277	2.564
<b>Tumor (TNM)</b>					
T1	36 (40.4%)	18 (20.9%)	41 (50.5%)	<0.01*	46.191
T2	53 (59.6%)	45 (52.3%)	37 (45.1%)		
T3		10 (11.5%)	3 (3.7%)		
T4		13 (15.1%)	1 (1.2%)		
<b>Involved lymph nodes</b>					
1–3	9 (10.1%)	12 (13.8%)	30 (36.6%)	<0.01*	21.813
≥ 4	80 (89.9%)	75 (86.2%)	52 (63.4%)		
ECE	19 (21.3%)	56 (64.4%)	58 (73.4%)		
<b>Chemotherapy</b>					
Anthracyclin	0	38 (43.7%)	20 (24.4%)	<0.01*	53.363
Tamoxifen	0	8 (9.2%)	14 (17.1%)		

\* Statistically significant

ER = estrogen receptor, PR = progesterone receptor, TNM = tumor, node, metastasis staging classification.

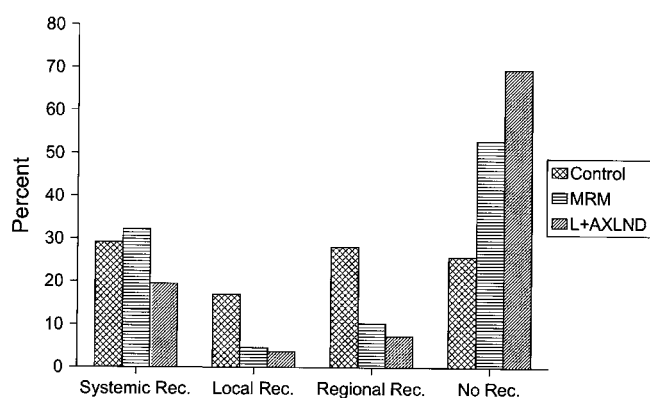


Figure 1. Site of first disease recurrence (%).

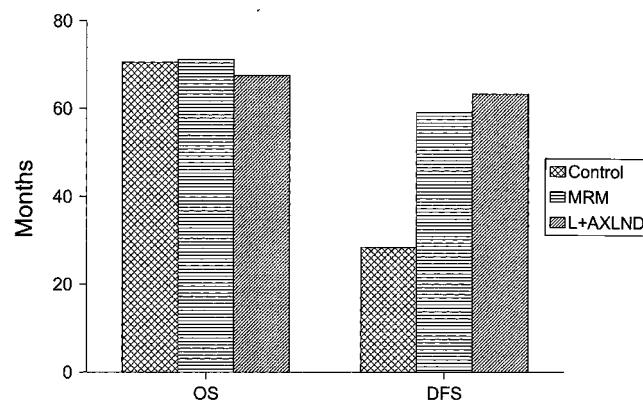


Figure 3. Median disease-free and overall survival.

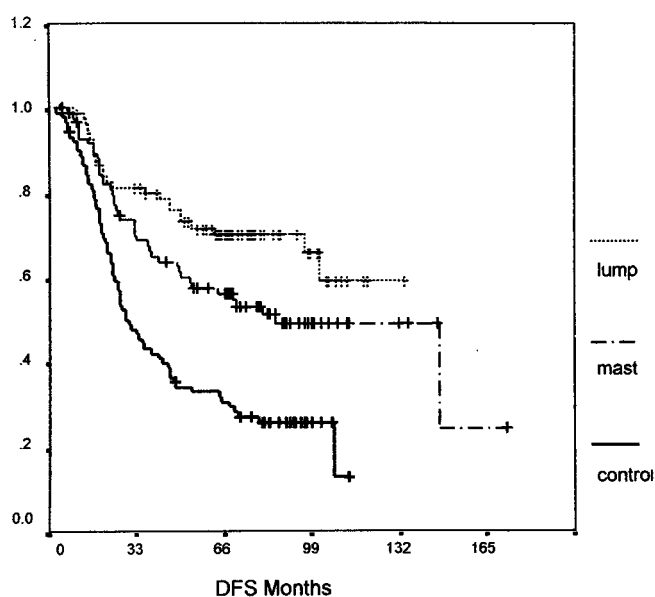


Figure 2. Kaplan-Meier estimate of disease-free survival ( $P < 0.001$ ).

of other variables, an ANCOVA test was used, with tumor size, number of involved nodes, ECE and receptors status as covariates. This analysis also revealed a significant difference in local and regional recurrences between the groups [ $F(1,199)=15.66$ ;  $P < 0.001$ ]. Thus, radiotherapy had an independent effect on loco-regional recurrence. As expected, because of fewer loco-regional recurrences, the median disease-free survival was significantly longer in radiated patients (59.2 months and 63.3 months in the MRM and L+AXLND groups, respectively, vs. 28.4 months in the control group;  $P < 0.01$ ) [Figure 2]. In contrast, loco-regional radiation had no effect on systemic relapse and overall survival. The median overall survival was 71.2 and 67.5 months in the study groups (MRM and L+AXLND, respectively) and 70.5 months in the control group ( $P = 0.856$ ) [Figure 3]. Of note, paired comparison tests according to Scheffe revealed no significant differences between the two study groups.

## Discussion

We showed that radiation therapy to the breast/chest wall, supraclavicular region and full axilla reduced the loco-regional recurrence rate in breast cancer patients with four or more involved axillary lymph nodes or extracapsular extension. There was no difference in systemic relapse or overall survival. This was a prospective historic, controlled, single-institution clinical trial of 258 patients. The control group consisted of 89 consecutive patients who had MRM and adjuvant chemotherapy. The study group consisted of 169 consecutive patients, 87 patients who had MRM and 82 patients who had breast-conserving surgery. Unlike the control group, all patients in the study group received loco-regional radiation therapy to the chest wall/breast and to the supraclavicular region and full axilla. The choice of radiation therapy was directed by the institute policy at the time, irrespective of patient or physician preference.

The role of radiation therapy in early-stage breast cancer is primarily to reduce the risk of loco-regional recurrence [13], as well as modestly improve survival in certain subgroups [1,2]. For patients who have breast-conserving surgery, radiation to the breast is complementary to their therapy. In those patients, indications for extending the radiation fields are based on trials evaluating PMRT. Most available data support PMRT to the chest wall and draining lymph nodes for patients at high risk for loco-regional relapse. However, these patient subgroups have not been clearly defined and the contribution of that therapy to loco-regional control and survival is not clear.

From 1988, we delivered radiation therapy to the chest wall/breast, the supraclavicular region and the full axilla in our breast cancer patients with four or more involved axillary lymph nodes or ECE, in line with the guidelines published later by Bartelink [11]. This policy differed slightly from ASCO guidelines, which suggested not giving full axillary radiotherapy after complete or partial (level I/II) axillary dissection [10]. Although full axillary radiation was used in almost all randomized trials

ASCO = American Society of Clinical Oncology

that examined the role of PMRT, the value of such treatment in the face of increased risk for complications is unclear and the issue has not been directly assessed.

The groups in this trial were well matched. All the patients received adjuvant therapy. However, because they were treated at various time periods, they received different regimens. Thus, only patients in the study group received anthracyclines and few were treated with tamoxifen. These differences are expected to affect systemic relapse and survival more than local control. Furthermore, a multivariate analysis revealed that radiation was an independent variable for reduction of loco-regional recurrence. Complications from radiotherapy were not evaluated in this study. It has been reported that loco-regional radiotherapy involving the full axilla significantly increased the risk of arm edema when given after complete axillary dissection (level I-III) [14]. However, in patients with level I-II dissections only, as widely accepted today, the risk of arm edema, even with full axillary irradiation, is much lower [1,15]. Finally, given the limited number of patients in each group, it should be remembered that a small survival advantage might not be apparent in this analysis.

In summary, we have shown that radiotherapy to the breast/chest wall and draining lymphatics, including the supraclavicular region and full axilla, significantly reduced the risk of local and regional lymph nodes recurrence in high risk breast cancer patients. These findings support the widespread approach of administering loco-regional radiation therapy to patients with four or more involved lymph nodes or ECE, in addition to surgery and systemic adjuvant therapy. This study contributes further to understanding the role of loco-regional radiotherapy in the modern treatment of early-stage breast cancer.

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### *Santa Claus has the right idea... Visit people only once a year.*

Victor Borge (1909-2000), Danish-born American entertainer. Borge, a Jew, escaped Nazi Germany where Hitler had placed him at the top of his personal list of Enemies of the Fatherland. Known as the "Un-Melancholy Dane" and the "Clown Prince of Denmark," Borge spent more than 70 years delighting audiences with his unique blend of comedy and classical music. Able to read and play music score backwards, forward, and often upside down, he appeared with the world's most acclaimed orchestras. He was knighted several times in several nations, but his sense of modesty and whimsy were such that he declared himself equally honored to appear as a guest on Jim Henson's "Muppet Show" and the children's educational program "Sesame Street."

## Spa Therapy for Ankylosing Spondylitis at the Dead Sea

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**Key words:** spa therapy, balneotherapy, ankylosing spondylitis, Dead Sea

### Abstract

**Background:** The efficacy of spa therapy in ankylosing spondylitis has not been investigated extensively.

**Objective:** To study the efficacy of balneotherapy and climatic therapy (climatotherapy) at the Dead Sea area in patients with ankylosing spondylitis.

**Methods:** In a single-blind randomized controlled study, 28 patients suffering from ankylosing spondylitis were allocated into two groups of 14 patients each. The first group (the combined treatment group) received balneotherapy (mud packs and sulfur pool) and exposure to the unique climatic conditions of the Dead Sea. The second group (the climatotherapy group) used the fresh water pool and experienced the same climatic conditions. The duration of treatment was 2 weeks and the follow-up period 3 months.

**Results:** For both patient groups a significant improvement was found in the outcome measures: Bath AS Disease Activity Index ( $P = 0.002$ ), Visual Analog Scale for pain ( $P = 0.002$ ) and VAS for spinal movement ( $P = 0.011$ ). The variability was explained by the effect of time (within group effect) rather than the type of treatment (between group effect). Quality of life, assessed by the SF-36 questionnaire, was very low prior to the study, but improved in terms of pain amelioration in the combined treatment group.

**Conclusions:** Climatotherapy at the Dead Sea area can improve the condition of patients suffering from long-standing ankylosing spondylitis.

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Different modalities of spa therapy at the Dead Sea area of Israel are beneficial for patients with inflammatory arthritides such as rheumatoid arthritis [1–4] and psoriatic arthritis [5–7], as well as for patients with non-inflammatory arthritides such as osteoarthritis [8,9] and fibromyalgia [10,11].

Ankylosing spondylitis is a chronic inflammatory disease that predominantly affects the spine and may lead to significant functional disability. Physical therapy is one of the most important modalities of treatment to slow the progression of the spinal disease. Unfortunately, patients' long-time adherence to home exercises, as prescribed by physical therapists, is low.

Only a few clinical trials have been conducted in health resort areas to assess the efficacy of spa therapy, primarily balneotherapy, in AS. Surprisingly, no clinical trials have been

carried out at the Dead Sea area, the main health resort in Israel. We present the findings of a single-blind, randomized, controlled study to assess the efficacy of the unique climatic conditions at the Dead Sea area, with and without the addition of balneotherapy.

### Patients and Methods

Twenty-eight patients were recruited for the study from two sources: the Rheumatology Clinic of the Soroka University Medical Center and through an advertisement in an Israeli newspaper published in Russian. Patients were eligible for inclusion in the study if they fulfilled the modified New York criteria for AS [12] and had suffered from back pain during the 3 months prior to enrollment. Exclusion criteria included concomitant psoriasis or any other seronegative spondyloarthropathy (except AS), malignancies, equilibrium disturbances, mental disorders, or any active non-inflammatory spinal disease. These exclusion criteria also reflect concern regarding the ability of the participants to commit to a 2 week stay at the Dead Sea area and to the 3 month follow-up period. The Helsinki committee of the Soroka University Medical Center approved the study.

All 28 participants spent 14 days at a Dead Sea health resort spa hotel. They were randomly allocated by a coordinator study nurse to two groups of 14 patients each. The first group received balneotherapy in addition to exposure to the climatic conditions of the Dead Sea area (combined treatment group). The second group was allowed access to the fresh water pool (26–28°C) for an unlimited amount of time, in addition to exposure to the same climatic conditions, but did not receive balneotherapy (climatotherapy group).

The combined treatment group received daily treatments consisting of each of the following: 20 minute applications of mud packs heated to 39–40°C to the entire body, 20 minute sessions in a sulfur (mineral) pool at 36–37°C, and bathing in Dead Sea water (in the sea itself or in an indoor pool). These treatments were administered daily except Saturday, i.e., for 12 of the 14 days. Participants in the climatotherapy group had similar exposure to climatic conditions as the combined treatment group, but were prohibited from receiving any form of balneotherapy.

All patients in both groups were assessed four times by the same physician. The first assessment was performed immediately prior to their arrival at the Dead Sea, the second on the last day of stay at the Dead Sea, and the third and fourth 1 and

AS = ankylosing spondylitis  
VAS = Visual Analog Scale

3 months after the end of the treatment period, respectively. A physical examination was performed at each assessment. The following parameters were assessed each time: disease-related well-being, disease activity by means of the Bath AS Disease Activity Index (BASDAI) [13], and subjective quantification of disease severity by visual analog scales (from 0 to 100 mm), one for pain and the other for limitation of movement. Quality of life was assessed by the SF-36 questionnaire [14] at the first and last assessment. This questionnaire is designed to evaluate changes over a long period and was therefore not administered at the interim assessments.

The SF-36 measures physical and mental health, with four scores for each of these components. Physical health has scores for limitation in physical activities due to health problems, limitations in everyday activities due to physical problems, bodily pain and general health perception. Mental health is scored for mental health, social functioning, emotional state, and vitality.

All data were analyzed with the SPSS statistical package. Continuous variables were compared with the unpaired two-tailed Student *t*-test. Categorical variables were compared using the chi-square test. Two-way repeated measurement analysis of variance (ANOVA) was used to compare repeated measurements in the two groups and within each group, and the Bonferroni procedure was applied in post-hoc analyses. Results were considered significant at  $P < 0.05$ .

## Results

The baseline characteristics of the study participants are presented, by group, in Table 1. There were no statistically significant differences between the two groups, although there was a trend toward lower BASDAI scores in the combined treatment group. Table 2 presents the BASDAI scores, by study group, for each of the four assessments. Post-treatment BASDAI scores were lower than baseline values. BASDAI scores were significantly changed during the four assessment periods ( $P = 0.002$ ), but this change was not affected by treatment group ( $P = 0.5$ ). Post-hoc analyses revealed that this significant improvement in BASDAI scores stemmed from a significant improvement between the first two assessments (immediately preceding and immediately following the Dead Sea stay).

Table 3 shows the VAS scores for pain and limitation in movement. Both types of VAS evaluation show improvement. The results of the ANOVA analyses, taking into account the effect of time and the treatment group, mirror those found for the BASDAI scores. There was a significant effect of time within the four assessment periods (pain VAS,  $P = 0.002$ ; limitation of movement VAS,  $P = 0.011$ ), but no significant effect of the treatment group on either of the VAS scores ( $P = 0.77$ ).

BASDAI = Bath AS Disease Activity Index

**Table 1.** Baseline characteristics of study participants

	Combined (n=14)	Climatotherapy (n=14)	<i>P</i>
<b>Gender</b>			
Male	12	14	0.48
Female	2	0	
Age (yrs, mean $\pm$ SD)	49.7 $\pm$ 12.0	46.1 $\pm$ 13.4	0.46
Disease duration (yrs, mean $\pm$ SD)	17.1 $\pm$ 13.3	18.6 $\pm$ 12.2	0.77
<b>Medication use</b>			
Pain killers	7 (50%)	4 (28.6%)	0.22
Narcotics	0	1 (7.1%)	0.50
Non-steroidal anti-inflammatory drugs	9 (64.3%)	8 (57.1%)	0.50
Routine physical therapy	1 (7.1%)	0	0.50
<b>Baseline characteristics (mean <math>\pm</math> SD)</b>			
BASDAI	4.9 $\pm$ 2.0	6.1 $\pm$ 1.5	0.07
Pain VAS	6.7 $\pm$ 2.2	6.4 $\pm$ 2.4	0.75
Limitation of movement VAS	6.3 $\pm$ 2.4	7.1 $\pm$ 1.6	0.28
Morning stiffness (minutes)	46.3 $\pm$ 32.9	74.3 $\pm$ 48.6	0.10

**Table 2.** BASDAI scores at the four assessment points, by treatment group (mean  $\pm$  SD)

	Combined (n=14)	Climatotherapy (n=14)
Baseline	4.86 $\pm$ 1.98	6.10 $\pm$ 1.47
End of treatment at Dead Sea	3.96 $\pm$ 1.58	4.16 $\pm$ 2.18
1 month follow-up	4.83 $\pm$ 1.59	4.67 $\pm$ 1.56
3 month follow-up	4.77 $\pm$ 1.67	4.86 $\pm$ 1.96

$P = 0.002$  for the difference between the various assessment periods (within groups effect), and  $P = 0.5$  for differences between the two treatment groups (between groups effect) in two-way repeated measurement ANOVA.

**Table 3.** VAS scores for pain and movement limitation at the four assessment points, by treatment group (mean  $\pm$  SD)

	Combined (n=14)		Climatotherapy (n=14)	
	Pain	Movement	Pain	Movement
Baseline	6.7 $\pm$ 2.2	6.3 $\pm$ 2.4	6.4 $\pm$ 2.4	7.1 $\pm$ 1.6
End of treatment at Dead Sea	4.4 $\pm$ 2.2	5.9 $\pm$ 2.2	4.4 $\pm$ 2.5	5.1 $\pm$ 2.3
1 month follow-up	5.2 $\pm$ 2.5	5.9 $\pm$ 1.8	5.1 $\pm$ 2.1	5.4 $\pm$ 2.1
3 month follow-up	5.1 $\pm$ 2.7	6.1 $\pm$ 2.0	4.9 $\pm$ 2.5	5.6 $\pm$ 2.2

For pain VAS:  $P = 0.002$  for the difference between the various assessment periods (within groups effect) and  $P = 0.77$  for the difference between the two treatment groups (between groups effect).

For limitation of movement VAS:  $P = 0.011$  for the difference between the various assessment periods (within groups effect) and  $P = 0.7$  for the difference between the two treatment groups (between groups effect). Both were assessed by two-way repeated-measurement ANOVA

At each of the four assessment periods a pertinent physical examination was conducted that included the following measures commonly checked in AS patients: wall to occiput distance, chest expansion, distance between the tip of the third finger and the floor when bending as far as possible with the knees locked, and Schober's test. There were no significant changes in any of these values between patient assessment

**Table 4.** Selected physical examination tests for all 28 participants together

Test	Assessment period				P
	1	2	3	4	
Wall-occiput distance	10.5 ± 8.7	10.2 ± 8.7	10.5 ± 8.8	11.1 ± 9.0	0.67
Chest expansion	3.5 ± 4.7	3.3 ± 1.5	3.3 ± 1.2	3.6 ± 2.4	0.86
Finger 3 to floor distance	35.2 ± 11.4	31.5 ± 11.5	34.0 ± 13.5	33.8 ± 12.3	0.20
Schober's test	2.0 ± 1.3	3.1 ± 2.4	2.6 ± 1.2	2.4 ± 1.3	0.048

All values are in centimeters (mean ± SD)

Assessment period 1: immediately prior to departure for the Dead Sea area.

Assessment period 2: immediately before departure from the Dead Sea area.

Assessment period 3: one month follow-up.

Assessment period 4: three months follow-up.

P values reflect one-way repeated measures ANOVA results.

periods or between the treatment groups (results not shown). Physical examination changes were then assessed for the entire study population (n=28). The results are shown in Table 4.

Both groups reported values compatible with an overall low quality of life. None of the measures had improved significantly 3 months after completion of the treatment except for the measure of bodily pain, which was significantly improved only in the combined treatment group (results not shown).

## Discussion

Physical therapy plays an important role in the treatment of AS. Its aim is to improve mobility, fitness and strength, and to slow down the development of deformities [15,16]. Spa treatment has served as a treatment modality for AS since ancient times [17]. Nowadays, spa therapy consists of a broad range of different treatments including balneotherapy (bathing in mineral water), hydrotherapy (immersion of the entire body, or part of it, in heated fresh water), massages, mud packs, relaxation, and physical therapy. The exact mechanisms of action of spa therapy are only partially understood. Putative non-specific factors that may contribute to the success of spa therapy include change of environment, a non-competitive atmosphere with fellow patients, and distance from work and other stressful circumstances [18].

Very few clinical trials have been reported on the effect of spa therapy on AS. The results of the largest randomized controlled trial were recently published [19]. In that study 120 AS patients were randomly allocated to three treatment groups of 40 patients each. One group received 3 weeks of spa therapy at a spa in Austria, the second group received 3 weeks of spa therapy at a spa in the Netherlands, and the third group, which served as a control group, remained at home and continued standard treatment for the same 3 week period as the spa therapy in the other two groups. After the intervention period all patients continued weekly group physical therapy for another 37 weeks. The main conclusion of this study was that significant improvement was seen in the two groups treated at spa resort areas compared to the control group, and the improvement was maintained for at least 40 weeks. The same investigators, in another publication based on the same study population, concluded that combined spa-exercise therapy is more effective and

has favorable cost-effectiveness and cost-utility ratios compared with standard treatment alone [20].

The first study on the effectiveness of spa therapy in AS in Israel was published in 1995. Tishler et al. [21] conducted an uncontrolled study at a spa in Tiberias, and found that the combination of hot mineral water baths and mud packs significantly improved the range of movement and overall well-being of 16 AS patients, as assessed by both the patient and the physician. In another study, Hashkes [22] reported on 53 AS patients who underwent 4 weeks of climatotherapy at a spa in Tiberias. This was also an uncontrolled study and no details are provided as to the exact modalities of treatment administered during the 4 week treatment period. Thirty-two patients (60%) were considered responders, with males responding better and more often than females. Hafstrom and Hallengren [23] conducted a prospective study in which they compared the effectiveness of physical therapy in a subtropical climate at Tenerife, Spain with that at a spa in Tiberias, Israel. This study was based only on data obtained from two questionnaires — the Swedish version of the Stanford Health Assessment Questionnaire (HAQ) and a quality of life questionnaire (Nottingham Health Profile). The investigators' conclusion was that physical therapy and spa therapy at both sites led to improved functional capacity and health-related quality of life, as well as reduced pain.

The present study is the first to be conducted at the Dead Sea area, which is the main health resort area in Israel. We had originally planned to recruit a larger number of AS patients and to conduct the study over a longer treatment period. However, due to the prevailing state of the Israeli economy and a very high unemployment rate, many patients refused to participate in the study out of fear of losing their jobs. The fact that spa therapy is not yet recognized as acceptable therapy for AS and is not covered by the health management organizations also hindered the recruitment process.

The population in our study had relatively high baseline BASDAI scores, advanced disease and lower quality of life than previously reported for AS patients [24]. The poor baseline characteristics combined with the higher BASDAI scores in the combined treatment group and the low overall number of participants might account for the lack of statistical difference between the two groups. Despite the advanced disease and low quality of life characterizing participants in this study, we observed significant improvement in both treatment groups throughout the study duration. It seems, therefore, that the unique climate conditions at the Dead Sea area, primarily the high barometric pressure, low relative humidity, high constant temperatures, and sunny days associated with the non-specific factors previously mentioned are as important as balneotherapy itself. Future studies with larger study populations and for longer duration are necessary to assess the relative efficacy of climatotherapy versus balneotherapy at the Dead Sea.

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