USE OF ISCADOR, AN EXTRACT OF EUROPEAN MISTLETOE *(VISCUM ALBUM)*, IN CANCER TREATMENT: PROSPECTIVE NONRANDOMIZED AND RANDOMIZED MATCHED-PAIR STUDIES NESTED WITHIN A COHORT STUDY

Ronald Grossarth-Maticek, Prof Dr med, Dr phil, Helmut Kiene, Dr med, Stephan M. Baumgartner, Dr sc nat, and Renatus Ziegler, Dr rer nat

Ronald Grossarth-Maticek is director of the Institute for Preventive Medicine, European Center for Peace and Development, United Nations, in Heidelberg, Germany. **Helmut Kiene** is director of the Institute for Applied Epistemology and Medical Methodology in Bad Krozingen, Germany. **Stephan M. Baumgartner** is a researcher at the Institute for Complementary Medicine (KIKOM), University of Bern, Switzerland. **Renatus Ziegler** is a researcher in the Department of Mathematical Statistics and Actuarial Sciences at the University of Bern, Switzerland.

Context • *In anthroposophical medicine, total extracts of* Viscum album *(mistletoe) have been developed to treat cancer patients. The oldest such product is Iscador. Although Iscador is regarded as a complementary cancer therapy, it is the most commonly used oncological drug in Germany.*

Objective • *To determine whether Iscador treatment prolongs survival time of patients with carcinoma of the colon, rectum, or stomach; breast carcinoma with or without axillary or remote metastases; or small cell or non–small-cell bronchogenic carcinoma; and to explore synergies between Iscador treatment and psychosomatic self-regulation.*

Design • *Prospective nonrandomized and randomized matched-pair studies nested within a cohort study.*

Setting • *General community in Germany.*

Participants • *10226 cancer patients involved in a prospective long-term epidemiological cohort study, including 1668 patients treated with Iscador and 8475 who had taken neither Iscador nor any other mistletoe product (control patients).*

Intervention • *Iscador.*

Main Outcome Measure • *Survival time.*

Results • *In the nonrandomized matched-pair study, survival time of patients treated with Iscador was longer for all types of cancer studied. In the pool of 396 matched pairs, mean survival time in the Iscador groups (4.23 years) was roughly 40% longer than in the control groups (3.05 years;* P < *.001). Synergies between Iscador treatment and self-regulation manifested in a longer survival advantage for Iscador patients with good self-regulation (56% relative to control group;* P = *.03) than for patients with poor self-regulation. Results of the 2 randomized matched-pair studies largely confirmed the results of the nonrandomized studies.*

Conclusion • *Iscador treatment can achieve a clinically relevant prolongation of survival time of cancer patients and appears to stimulate self-regulation. (Altern Ther Health Med. 2001;7(3):57-78)*

Reprint requests: InnoVision Communications, 169 Saxony Rd, Suite 104, Encinitas, CA 92024; phone, (760) 633-3910 or (866) 828-2962; fax, (760) 633-3918; e-mail, alternative.therapies@innerdoorway.com.

Cancer treatment with Iscador, an extract of *Viscum album* (European mistletoe), was studied as part of a large epidemiological cohort study on 10226 cancer patients.[1] This study was conducted to investigate the influence of psychosomatic self-regulation on the survival of cancer patients and the interactions of psychosomatic self-regulation with therapeutic factors such as surgery, radiotherapy, chemotherapy, and unconventional therapies (eg, Iscador).

The term *self-regulation* applies to intrinsic activities of a human being through which he or she achieves well-being, inner equilibrium, appropriate stimulation, a feeling of competence, and a sense of being able to control stressful situations.[2] Self-regulation influences the incidence and course of cancer. Studies covering a 27-year period and involving 35 814 participants[3] showed a higher incidence of cancer in those with poor self-regulation, revealing detrimental synergies between low self-regulation and other cancerigenic risk factors.[1,3] In patients with manifest cancer, higher self-regulation correlated with longer survival.[1,3] In randomized controlled trials,[4,5] patients with breast cancer and axillary metastases achieved longer survival through

autonomy training[6] that improved self-regulation,[4] or through similar psychostimulation.[5]

To investigate interactions between self-regulation and other therapeutic factors, a multitude of prospective nonrandomized and randomized matched-pair studies were nested into a cohort study on 10226 cancer patients; 1 of the nonrandomized studies and 2 of the randomized studies were related to Iscador treatment; these studies are described here.

Iscador is a total extract of European mistletoe (*Viscum album*) that was first used for cancer therapy in 1922 by Rudolf Steiner and Ita Wegman on the basis of anthroposophy.[7] Even though Iscador is regarded as a complementary cancer treatment, it is the most commonly used oncological medicine in Germany today.[8]

Mistletoe extracts are generally administered subcutaneously and sometimes intravenously or peritumorally. They contain a multitude of substances that have immunostimulatory and cytotoxic or—as illustrated by animal studies—antitumorigenic and antimetastatic effects, including viscotoxins, lectins (ML-I, ML-II, ML-III, VisalbCBA), polysaccharides (eg, rhamnogalacturonane), oligosaccharides, Vester proteins, Kuttan peptides, alkaloids, and vesicles.[9,10] Important effects of mistletoe extracts include immunostimulation, triggering of programmed tumor cell death (apoptosis), and DNA protection.[10]

According to a 1989 review article, 6 evaluable case series and 35 evaluable clinical studies, most of which included historical control groups, had been published.[11] In 34 of these studies, the results (survival times, remission rates, quality of life) of the patients treated with mistletoe were superior to those of the control patients[11]; the methodological rigor of these studies, however, was disputed.[12] The authors of a 1994 review[13] did not find sufficient evidence to recommend the use of mistletoe products for the treatment of cancer.

The primary purpose of the total systemic epidemiology study program, of which the Iscador studies reported here were part, was to investigate psychosomatic self-regulation and its interactions with other therapeutic factors. This explains why only the mere fact of Iscador treatment has been documented; the types of Iscador, dosages, variations in dose, and breaks in treatments were not recorded. Nevertheless, the nonrandomized and randomized studies related to Iscador offer interesting insights into the use of Iscador. A structural overview of these studies is given in Figure 1.

OBJECTIVES

The purpose of this study was to clarify interactions between Iscador treatment and psychosomatic self-regulation. The primary question was as follows: Does Iscador treatment influence the survival time of cancer patients? Secondary questions were as follows: Does Iscador treatment influence self-regulation? Does self-regulation influence the results of Iscador treatment?

Tertiary questions were as follows: Does the influence (if any) of Iscador treatment on the survival time of cancer patients depend on the duration of treatment? (Mistletoe therapy in anthroposophical medicine is often applied as long-term treatment. Is long-term application justified?) Does the influence (if any) of Iscador treatment on the survival time of cancer patients depend on the patients' willingness or unwillingness to participate in a double-blind study? (The concept of psychosomatic self-regulation suggests that participation in a double-blind study, in the German healthcare system, presupposes low self-regulation on behalf of the patient.)

METHODS

Recruitment of Patients

The total epidemiological study program (the cohort study and the nested nonrandomized and randomized studies) was based on a pool of 11009 cancer patients with carcinoma of the breast, rectum, colon, or stomach, or bronchogenic carcinoma, who were recruited as follows:

- 5809 patients from the Heidelberg prospective intervention study.[1,3] In this study, 35814 persons were questioned on their degree of self-regulation to examine the link between self-regulation and the prevalence of chronic diseases. At the time of the initial questioning between 1971 and 1978, 2293 of the respondents already had a diagnosis of cancer. Up to 1988, an additional 3516 respondents had cancer diagnosed, yielding 5809 cancer patients total.
- 1117 patients from the oncological aftercare register of the University Surgery Clinic of Heidelberg, Germany, between 1973 and 1978.
- 918 patients from files of 12 other clinics in the Federal Republic of Germany between 1971 and 1978.
- 3165 patients who consulted the Institute for Preventive Medicine, Heidelberg, between 1971 and 1988, with various practical questions on diet, psychology, and so on.

These 11009 cancer patients were invited by letter or telephone to participate in a study seeking to identify factors that promote a favorable course of disease. A total of 783 patients declined to participate for various reasons (eg, because they were unwilling to disclose any information). A total of 10226 patients (92.9%) agreed to participate and were visited by interviewers. A total of 150 interviewers were employed between 1973 and 1988.

Of the 10226 patients who were willing to participate in the study, 1668 (16%) had received Iscador treatment, 83 (1%) had been treated with other mistletoe products, and 8475 (83%) had not received any form of mistletoe treatment.

Information Collected About Patients

Data on the patients, supplied by the patients, their relatives, the attending physicians, and available at the clinics, were collected using an interviewer-based standardized checklist that included the following questions (because computerized data management systems were still in their infancy at the beginning of the 1970s, data were recorded on cards in patients' files):

1. Personal data including date of birth, sex, and date of first cancer diagnosis.

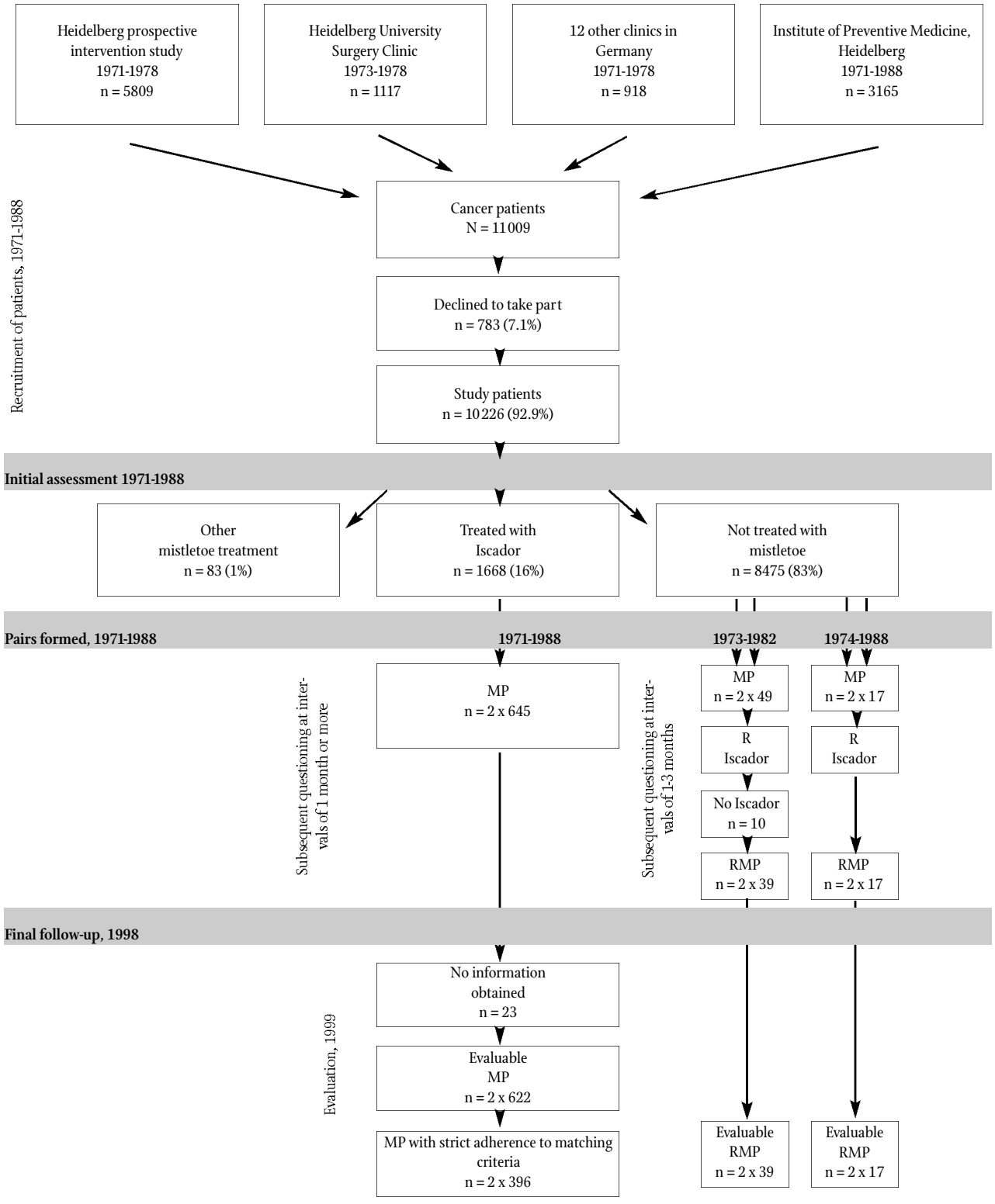

FIGURE 1 Flow chart: prospective nonrandomized and randomized matched-pair studies on Iscador treatment. MP indicates matched pairs; R, randomization; RMP, randomized matched pairs.

2. Information about the tumor, such as tumor type and stage at the date of the first cancer diagnosis, plus histologic findings in the case of bronchogenic carcinoma.

3. Conventional treatment: Had the patient undergone surgery, chemotherapy, radiotherapy, or hormone treatment? If so, which ones, when, and how often?

4. Alternative therapies: Had the patient been treated with Iscador, other mistletoe products, enzyme products, thymus products, multivitamin or mineral products, bacterial (active) pyrotherapy, physical (passive) pyrotherapy, or psychotherapy? If so, did the treatment last for 1 to 3 months, 4 to 6 months, 7 to 9 months, 10 to 12 months, or longer?

5. Self-regulation: A questionnaire[3] with 16 items and scaled response options was used to rate patients' self-regulation (scores from 1 to 6). The test-retest reliability of this questionnaire is 0.80 and the Cronbach α is 0.82.[6]

6. Willingness to take part in a double-blind study: patients were asked whether they would be willing to take part in a clinical double-blind study for the purposes of scientific research into treatments with unknown efficacies.

Inclusion and Allocation of Patients

Nonrandomized, Prospective, Matched-pair Study on Iscador Treatment. During the continuous recruitment of patients from 1973 to 1988, for every newly recruited patient who had been treated with Iscador, a matching patient was chosen from the pool of file cards on patients who had not received mistletoe treatment. In each case it was verified by telephone or through a home visit that this matched patient was still alive at the time of pairing; what further therapies the patient had received since the last contact were also checked. The matching criteria are listed in Table 1. Therefore, to be included in this prospective matched-pair study, a patient had to have the information available to be matched; patients who did not have a match were excluded.

In an effort to generate a large number of matched pairs, up to 2 minor deviations from the matching criteria (Table 1) were tolerated in each case. This method yielded 645 pairs of patients. Follow-up of all patients in 1998 revealed that most of these 645 pairs of patients had died; their dates of death were ascertained from the local resident's registration office (*Einwohnermeldeamt*). Twenty-three of the patients treated with Iscador were still alive, but none of the control patients had survived. In 23 cases, final information was not available; thus 622 (645 – 23) matched pairs of patients remained.

At the final evaluation, the authors divided these 622 pairs into 2 subgroups: (1) 226 pairs of patients with up to 2 minor deviations from the matching criteria (Table 1), and (2) 396 pairs of patients with complete adherence to the matching criteria (Table 1). The results for these 2 groups were essentially equivalent. In this article, we report only about the subgroup of 396 pairs of patients who were strictly matched; the results for the other subgroup will be published elsewhere.

Among the study population of 396 strictly matched pairs, the Iscador group and the control group did not differ significantly in patients' age and year of first diagnosis (Mann-Whitney test). Only small differences were apparent: the patients in the Iscador group were on average 0.05 years (SD, 1.81 years) older than the patients in the control group, and the date of first diagnosis was on average 0.18 years (SD, 1.19 years) earlier than in the control group. (See Table 2 for the distribution of patients according to tumor type.)

Randomized, Prospective, Matched-pair Studies on Iscador Treatment. From 1973 to 1982, a total of 49 matched pairs were formed among the 8475 patients who had not been treated with mistletoe. Again, the matching criteria in Table 1 were used, although deviations in sex, birth year, and year of first diagnosis were tolerated. Still, on average, the 2 groups did not differ significantly in sex distribution (χ^2 test), patients' age, and year of first diagnosis (Mann-Whitney test).

One patient from each of the 49 matched pairs was randomly selected as a candidate for Iscador treatment: the principal investigator put 2 slips of paper (each with the name of 1 of the patients in the pair) in a hat, and a masked assistant selected 1. The 49 candidates selected were asked if they would be willing to ask their doctors for treatment with Iscador.

Similarly, from 1974 and 1988, out of the same pool of 8475 patients, another 17 matched pairs were formed. All 34 patients had breast cancer with axillary metastases; they were not only in strict adherence with all the matching criteria listed in Table 1, but they had matching self-regulation scores. Seventeen candidates were randomly selected from each pair and advised to ask their doctor for Iscador treatment. Once again, to be included in these 2 study populations (49 pairs and 17 pairs) patients had to have sufficient data available to fulfill the matching criteria (Table 1), and patients for whom no match could be found were excluded.

Of the 49 candidates for Iscador treatment in the first study, 9 patients either did not ask their doctor or were not given the treatment, 1 died before commencing treatment, and 39 ultimately received Iscador treatment. Because the random allocation had referred to every single matched pair, any potential bias from these 10 patients who dropped out could be fully neutralized by removing the matching patient from further data assessment and evaluation. No such dropping out occurred among the 17 candidates for Iscador treatment in the second study; all 17 received treatment with Iscador. The types and stages of the tumors in the 2 groups of matched pairs are listed in Table 3. The dates of death were ascertained from the local resident's registration office during the final follow-up of all patients in 1998.

Additional Data Assessment in the Randomized Studies

For each of the 56 patients (39 + 17) randomized to receive Iscador treatment, the degree of self-regulation was assessed shortly before the Iscador treatment was started and 3 months afterwards. For the corresponding control patient, data were assessed in the same week (in the following week in 2 cases).

Intervention

The nonrandomized matched-pair study did not interfere

TABLE 1 Pairing criteria

General matching criteria

- **Same sex**
- **Maximum difference in the birth year of the patient: ± 3 years**
- **Maximum difference in the year of initial diagnosis: ± 3 years**

Tumor-specific matching criteria	
Rectum carcinoma	
Stage	I (T1-T2 N0 M0), II (T3-T4 N0 M0), III (N>0 M0), IV (M1)
Surgery	Yes/no
Chemotherapy	Yes/no
Radiotherapy	Yes/no
Colon carcinoma	
Stage	I (T1-T2 N0 M0), II (T3-T4 N0 M0), III (N>0 M0), IV (M1)
Surgery	Yes/no
Chemotherapy	Yes/no
Breast carcinoma without metastases (N = 0, M = 0)	
T stage	1, 2, 3, or 4
Menopause/chemotherapy, hormone therapy	(i) Premenopausal with chemotherapy, (ii) premenopausal without chemotherapy, (iii) postmenopausal with hormone therapy, (iv) postmenopausal without hormone therapy
Radiotherapy	Yes/no
Breast carcinoma with axillary metastases (N > 1, M = 0)	
Stage	IIA (T1 N1 M0), IIB (T2 N1 M0), IIIA (T1-T2 N2 M0 or T3 N1-N2 M0), IIIB (T4 N1-N4 M0 or T1-T3 N3 M0)
Menopause/chemotherapy, hormone therapy	(i) Premenopausal with chemotherapy, (ii) premenopausal without chemotherapy, (iii) postmenopausal with hormone therapy, (iv) postmenopausal with chemotherapy
Radiotherapy	Yes/no
Breast carcinoma with remote metastases (M = 1)	
Ubiquitous remote metastases with hormone therapy	Yes/no
Ubiquitous remote metastases with chemotherapy	Yes/no
Skeletal metastases with hormone therapy (sequential)	Yes/no
Skeletal metastases with chemotherapy	Yes/no
Skeletal metastases with radiotherapy	Yes/no
Lung metastases including pleura with hormone therapy	Yes/no
Lung metastases including pleura with chemotherapy	Yes/no
Liver metastases with hormone therapy	Yes/no
Liver metastases with chemotherapy	Yes/no
Brain metastases with hormone therapy	Yes/no
Brain metastases with chemotherapy	Yes/no
Other visceral metastases with hormone therapy	Yes/no
Other visceral metastases with chemotherapy	Yes/no
Soft tissue metastases (skin, lymph nodes, abdominal) with hormone therapy	Yes/no
Soft tissue metastases (skin, lymph nodes, abdominal) with chemotherapy	Yes/no
Locoregional recurrence (thorax wall, scar, etc) with radiotherapy	Yes/no
Radiotherapy	Yes/no
Other combinations	Yes/no
Stomach carcinoma	
T stage	1, 2, 3, or 4
N stage	0, 1, 2
M stage	0, 1
Surgery	Yes/no
Chemotherapy	Yes/no
Radiotherapy	Yes/no
Non–small-cell bronchogenic carcinoma	
Stage	I (T1-T2 N0 M0), II (T1-T2 N1 M0), IIIA (T1-T2 N2 M0 or T3 N0-N2 M0), IIIB (T1-T4 N3 M0 or T4 N0-N3 M0), IV (M1)
Surgery	(i) Surgery with the aim of cure (radical in stages I or II), (ii) other surgery, (iii) no surgery
Radiotherapy	Yes/no
Chemotherapy	Yes/no/palliative
Small-cell bronchogenic carcinoma (M = 0, only "limited disease" [tumor confined to 1 hemithorax])	
T stage	1, 2, 3, or 4
N stage	0, 1, 2
Surgery	Yes/no
Radiotherapy	Yes/no
Chemotherapy	Yes/no

with the patients' treatments; in that study, only therapies that were administered anyway were assessed. The randomized matched-pair studies induced therapeutic interventions, though only in an indirect manner, because the patients were advised to ask their doctor for Iscador treatment. In both the nonrandomized and randomized matched-pair studies, Iscador treatments were not applied by special study physicians, but by the doctors the patients themselves had selected.

Follow-up

Every patient in the nonrandomized and randomized matched-pair studies was repeatedly contacted (by telephone or home visit) and questioned about well-being, progression of disease, further diseases, continuation of treatment, and new therapies commenced. The time intervals between the inquiries were 1 to several months. Matched patients in the randomized studies were always contacted in the same week.

In the nonrandomized study and the randomized studies, only the basic fact of an Iscador treatment and its global duration were documented. The type of Iscador that was used (eg, Iscador Mali, called apple tree mistletoe; Iscador Pini, pine tree mistletoe; or Iscador Quercus, oak tree mistletoe), the dosage, and temporary interruptions of treatment were not documented.

At the final follow-up in 1998, any dates of death and causes of death not yet registered were determined from the local resident's registration offices (*Einwohnermeldeamt*) and from the local boards of health (*Gesundheitsamt*).

Evaluation and Statistics

The statistical evaluations were done at the Institute for Complementary Medicine (*Kollegiale Instanz für Komplementärmedizin*) of the University of Bern, Switzerland. All calculations were performed with the software Statistica 4.1 for Macintosh (StatSoft, Inc, Tulsa, Okla). The entire evaluation was cross-checked at the Institute for Mathematical Statistics of the University of Bern, using "S-Plus 2000" (Insightful Corp, Seattle, Wash).

The same tests were used to analyze both the nonrandomized and the randomized matched-pair studies: Statistics for categorical data (eg, sex) was calculated with the χ^2 test. Variables on an ordinal scale (eg, self-regulation, except for survival time) were examined with the Mann-Whitney test or with the Wilcoxon matched-pairs test in cases of repeated measures of the same subject. Statistical analysis of survival time was done with the log-rank test. This test rather underestimates the statistical significance of treatment effects because it does not explicitly address the matched pair allocation; however, a conservative evaluation seemed justified.

The authors did not perform analyses according to "intention to treat." Impairments of internal validity due to patients who dropped out were neutralized by excluding the corresponding matched patients.

RESULTS

Nonrandomized, Prospective, Matched-pair Study

Survival Time: Iscador vs Control. Mean survival time was longer in patients treated with Iscador than it was in control patients of the nonrandomized study, both overall and when broken down according to tumor type (carcinoma of the rectum, carcinoma of the colon, carcinoma of the stomach, breast carcinoma with or without axillary metastases or remote metastases, small cell and non–small-cell bronchogenic carcinoma). In 6 of the 8 subgroups, the difference in survival time was significant ($P<.05$), and in 4 of these 6 and in the group overall, the difference was highly significant ($P<.01$) (Table 2). The Kaplan-Meier

TABLE 2 Survival time: Iscador group vs control group

Type of cancer	No. of pairs of patients	Mean survival time, years		Difference		*P* (log-rank test)
		Iscador group	Control group	Years	%	
Rectum carcinoma	69	4.68	3.04	1.64	54	.002
Colon carcinoma	90	6.18	4.46	1.72	39	<.001
Breast carcinoma without metastases	29	6.08	4.44	1.64	37	.01
Breast carcinoma with axillary metastases	38	3.86	2.97	0.89	30	<.001
Breast carcinoma with remote metastases	53	3.42	2.38	1.04	44	<.001
Stomach carcinoma	44	2.06	1.41	0.65	46	.06
Non–small-cell bronchogenic carcinoma	52	3.08	2.60	0.48	18	.05
Small-cell bronchogenic carcinoma	21	1.99	1.44	0.55	38	.02
All	396	4.23	3.05	1.18	39	<.001

TABLE 3 Characterization of pairs of patients in the randomized matched-pair studies according to the criteria of TABLE 1

Type and stage of tumor	No. of pairs of patients Group 1	Group 2
Rectum carcinoma		
Stage I, surgery	1	
Stage III, surgery	2	
Stage III, surgery, chemotherapy	1	
Stage IV, surgery, chemotherapy	3	
Colon carcinoma		
Stage II, surgery	1	
Stage III, surgery, chemotherapy	2	
Stomach carcinoma		
T1N0M0, surgery	3	
T1N1M0, surgery	2	
T1N0M1, surgery, radiotherapy, chemotherapy	1	
T2N0M0, surgery	1	
T2N1M0, surgery, chemotherapy	1	
T2N1M1, surgery, chemotherapy	1	
Non–small-cell bronchogenic carcinoma		
Stage I, surgery (curative aim)	2	
Stage I, surgery (curative aim), radiotherapy, chemotherapy (palliative)	1	
Stage I, surgery (curative aim), chemotherapy (palliative)	1	
Stage IV, surgery (other aim), chemotherapy (palliative)	1	
Stage IV, surgery (other aim), radiotherapy	1	
Small cell bronchogenic carcinoma (M = 0, only "limited disease" [tumor confined to 1 hemithorax])		
T1 N0 M0, surgery	3	
T1 N0 M0, surgery, chemotherapy	1	
T1 N1 M0, chemotherapy, radiotherapy	1	
T2 N0 M0, surgery, chemotherapy	1	
Breast carconoma without metastases (N = 0, M = 0)		
T2, premenopausal, no chemotherapy	1	
T4, premenopausal, no chemotherapy	1	
Breast carcinoma with axillary metastases (N > 1, M = 0)		
Stage IIA, premenopausal, chemotherapy	1	
Stage IIA, postmenopausal, hormone therapy	2	
Stage IIIA, premenopausal, no chemotherapy		1
Stage IIIA, premenopausal, chemotherapy, radiotherapy		2
Stage IIIA, premenopausal, radiotherapy, no chemotherapy		1
Stage IIIA, postmenopausal, hormone therapy		1
Stage IIIA, postmenopausal, hormone therapy, radiotherapy		1
Stage IIIB, premenopausal, no chemotherapy		5
Stage IIIB, premenopausal, chemotherapy	1	1
Stage IIIB, premenopausal, chemotherapy, radiotherapy		2
Stage IIIB, postmenopausal, hormone therapy		1
Stage IIIB, postmenopausal, hormone therapy, radiotherapy		1
Stage IIIB, postmenopausal, chemotherapy, radiotherapy		1
Breast carcinoma with remote metastases (M = 1)		
Ubiquitous remote metastases, chemotherapy	1	
Skeletal metastases, chemotherapy	1	
Total number of randomized pairs of patients	**39**	**17**

cumulative survival times are shown in Figures 2 through 10.

Survival Times of Iscador-treated and Control Patients With Poor vs Good Self-regulation. The patients' initial assessment of the self-regulation (scores, 1-6) revealed a positive correlation between self-regulation and survival time, both for the Iscador group and the control group. High self-regulation scores on the questionnaire administered when data on the patient were collected initially were associated with long survival times (Table 4).

The distribution of self-regulation scores was significantly heterogeneous in the Iscador and control groups (χ^2 test, $P<.001$). More Iscador-treated patients than control patients exhibited high self-regulation scores on the initial questionnaire (Table 4). One might wonder, therefore, whether patients with better self-regulation tend to use Iscador, and whether the higher survival time in the Iscador-treated group (Table 2) is due to the fact that Iscador treatment is an indicator rather than a cause of longer survival. The following investigation helped to clarify this issue.

Survival Times in Pairs With Identical Self-regulation Scores: Iscador vs Control. In 121 of the 396 matched pairs, both patients had identical self-regulation scores on the initial questionnaire. Among the Iscador-treated patients in this subgroup, the mean survival time was 3.82 years, compared to 2.98 years in the corresponding control patients. The difference of 0.84 years in favor of the Iscador-treated group is significant ($P=.01$; log-rank test, Table 5). This difference cannot be due to better self-regulation in the patients treated with Iscador, because the initial self-regulation scores were identical in these 121 Iscador-treated patients and the matched control patients. The result suggests that Iscador treatment can indeed increase the survival time of cancer patients.

Among these 121 matched pairs with matching initial self-regulation values, we found that the higher the degree of self-regulation, the longer the mean survival advantage with Iscador treatment: 0.00 years for scores 1 to 2; 0.44 years for score 3; 1.06 years for score 4; and 2.90 years for scores 5 to 6 (Table 5). This finding suggests that self-regulation influences the effects of Iscador treatment on survival time.

Survival Time as a Function of the Relative Duration of Iscador Treatment: Iscador vs Control. It needed to be clarified whether the success of Iscador treatment was dependent on the duration of administration. However, reference to the absolute length of treatment would introduce a selection bias, because patients who live longer have more time to take the Iscador. Therefore, the relative duration of treatment was determined for every Iscador-treated patient in the 396 matched pairs; that is, whether Iscador treatment lasted 0% to 20%, 20% to 40%, 40% to 60%, 60% to 80%, or 80% to 100% of the survival time. Only when relative treatment duration was greater than 20% did Iscador-treated patients have a survival advantage over control patients, and that advantage increased with longer durations of treatment (Table 6).

Survival Time as a Function of the Relative Duration of Iscador Treatment in Patients With Initially Identical Self-regulation: Iscador vs Control. Whether the survival advantage afforded by long-term treatment with Iscador (see preceding sections) was due merely to an initially higher self-regulation had to be clarified. It is conceivable that patients with better self-regulation might show a greater tendency to long-term use of Iscador, in which case their longer survival times could simply be a consequence of self-regulation rather than a result of their relatively longer Iscador treatment. To rule out this possibility, those 121 matched pairs with initially

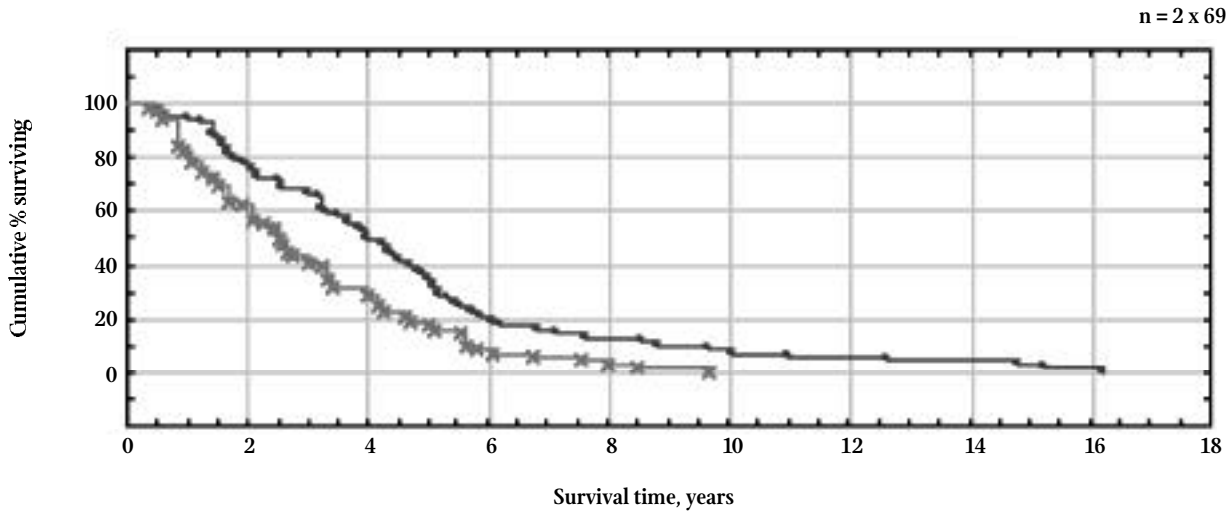

FIGURE 2 Rectum carcinoma: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

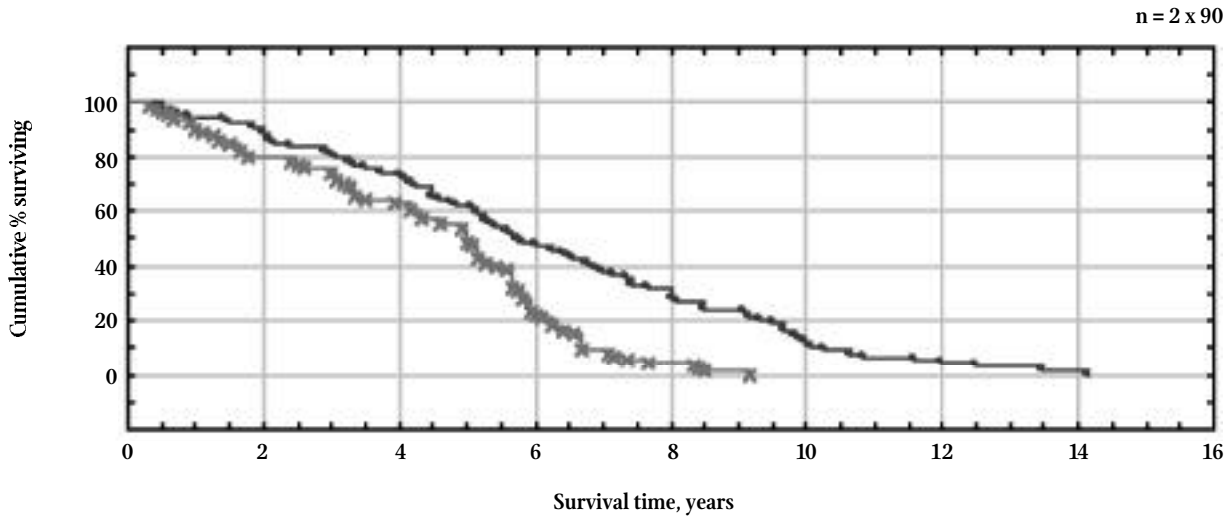

FIGURE 3 Colon carcinoma: Cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

identical self-regulation scores (preceding sections) were checked. Their survival time was examined as a function of the relative durations of Iscador treatment (0-20%, 20-40%, 40-60%, 60-80%, and 80-100% of survival time). Again, there was a positive correlation between the survival advantage and the relative duration of administration (Table 7). In view of the initially identical self-regulation scores of these 121 matched pairs, it is unlikely that this positive correlation would be a consequence of primarily different levels of self-regulation.

Self-regulation and Survival Time in Patients Willing and Unwilling to Participate in a Double-blind Study: Iscador vs Control. To clarify whether willingness to participate in a double-blind study expresses reduced self-regulation, thereby leading to shorter survival time, the following procedure was adopted. All patients were asked whether they would be willing to take part in a double-blind clinical study for the purposes of scientific research into new treatments. Among the 396 matched pairs (n=792 patients), a total of 732 responses were obtained.

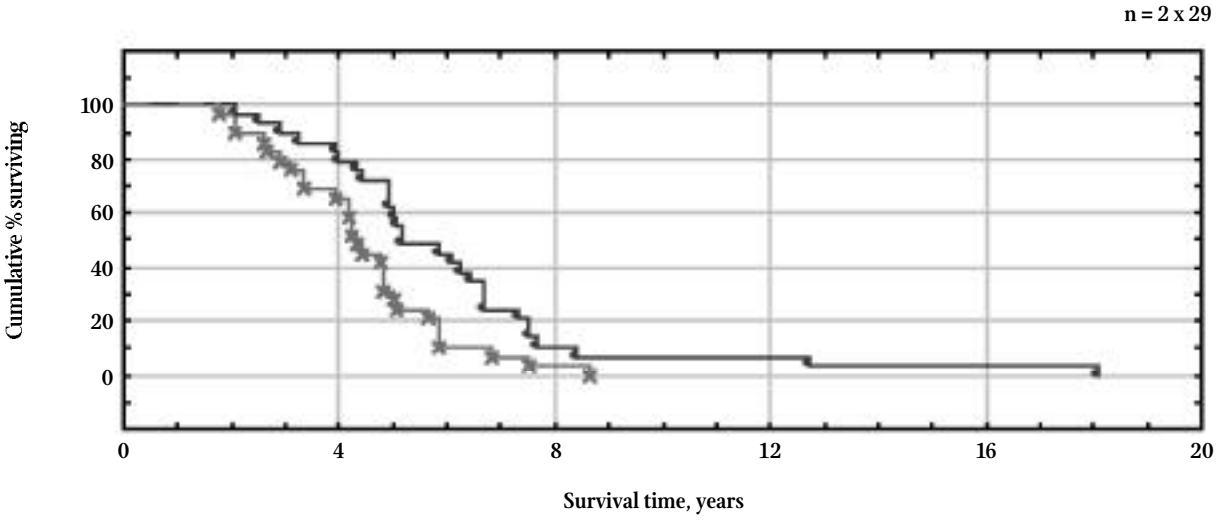

FIGURE 4 Breast carcinoma without metastases: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

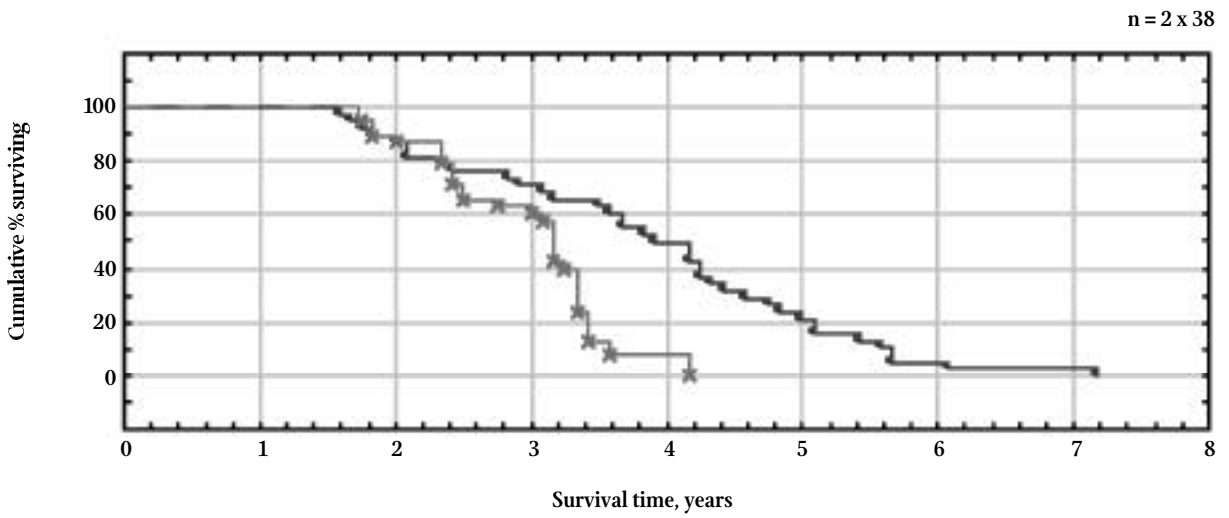

FIGURE 5 Breast carcinoma with axillary metastases : cumulative survival timewith Iscador (upper curve) and without Iscador (lower curve).

Patients unwilling to participate in a double-blind study (n=546) were found to exhibit superior results compared to patients who were willing to participate (n=186), with higher mean self-regulation (3.69 vs 2.81) and a longer mean survival time (3.87 vs 2.46 years).

In 26 of the 396 pairs, both patients were willing to participate, whereas in 205 pairs neither patient was willing. Among the 26 pairs in which both members were willing to participate, the mean self-regulation values (2.69 vs 2.65) and mean survival times (2.41 vs 2.42 years) did not differ between the Iscador-treated and control patients. By contrast, in the 205 pairs in which both members were unwilling to participate, the mean values in the Iscador-treated group were better than those in the control group (self-regulation, 3.92 vs 3.45; survival time, 4.55 vs 3.25 years; Table 8). Apparently, willingness to take part in a double-blind study had an influence on the outcome of Iscador

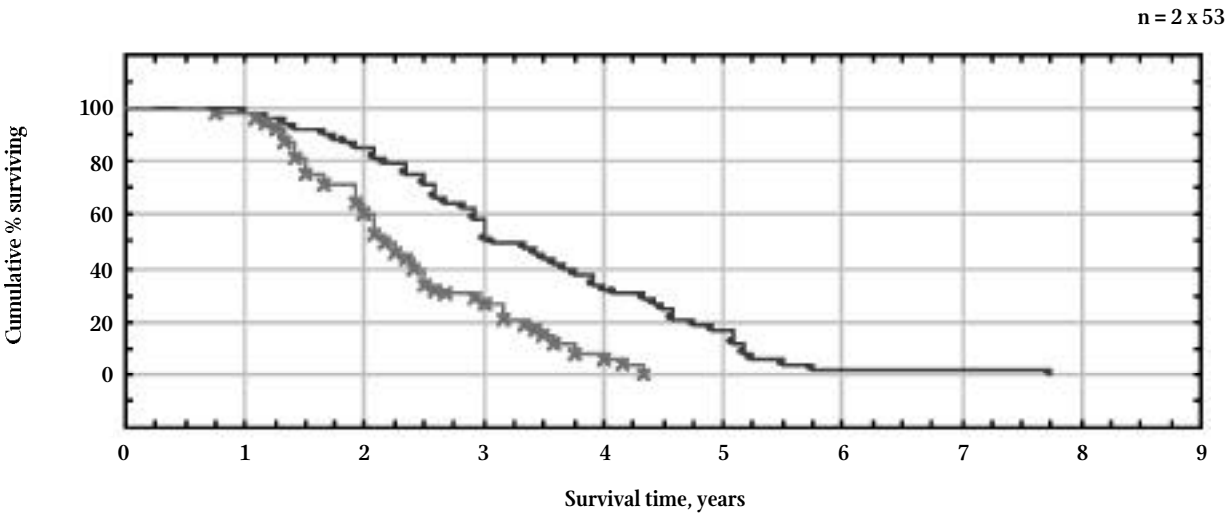

FIGURE 6 Breast carcinoma with remote metastases: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

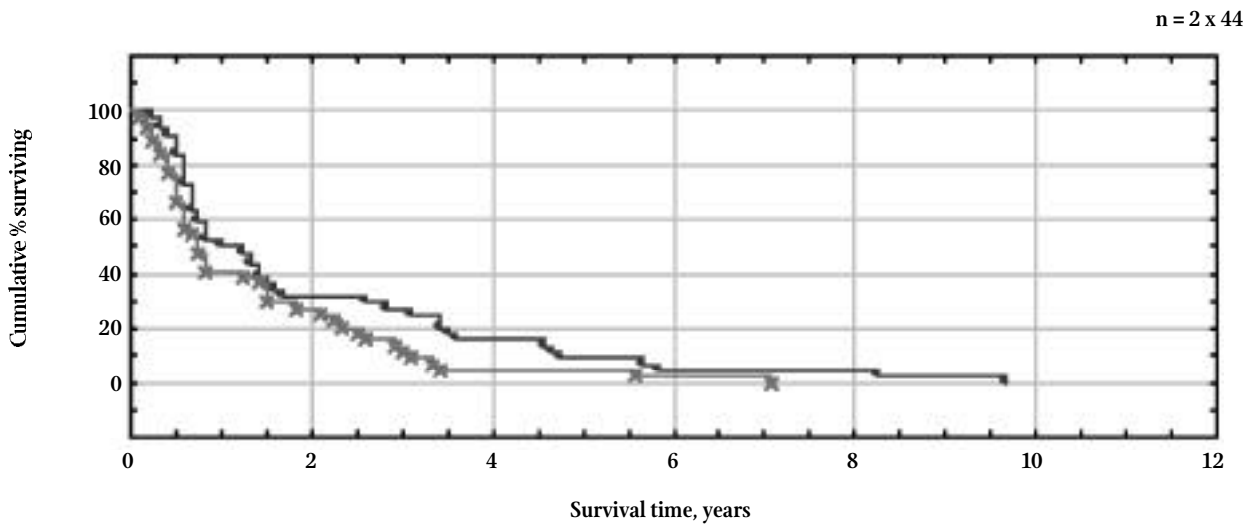

FIGURE 7 Stomach carcinoma: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

treatment (possibly via self-regulation); survival advantage with Iscador treatment was seen only in the patients unwilling to participate in a double-blind study.

Randomized, Prospective, Matched-pair Studies

Self-regulation: Iscador vs Control. In both randomized matched-pair studies (39 pairs and 17 pairs), the mean self-regulation values increased distinctly after 3 months of treatment with Iscador, from 3.41 to 3.87 (+0.46) in the first study and from 2.92 to 3.70 (+0.78) in the second study. In the control patients, self-regulation ratings decreased slightly or increased only marginally from 3.85 to 3.62 (–0.23) and from 2.87 to 2.99 (+0.12) (Figure 11).

The difference in the change in self-regulation values was statistically significant in the first study, but not in the second study (Mann-Whitney test, $P=.022$ and $P=.13$). For the entire

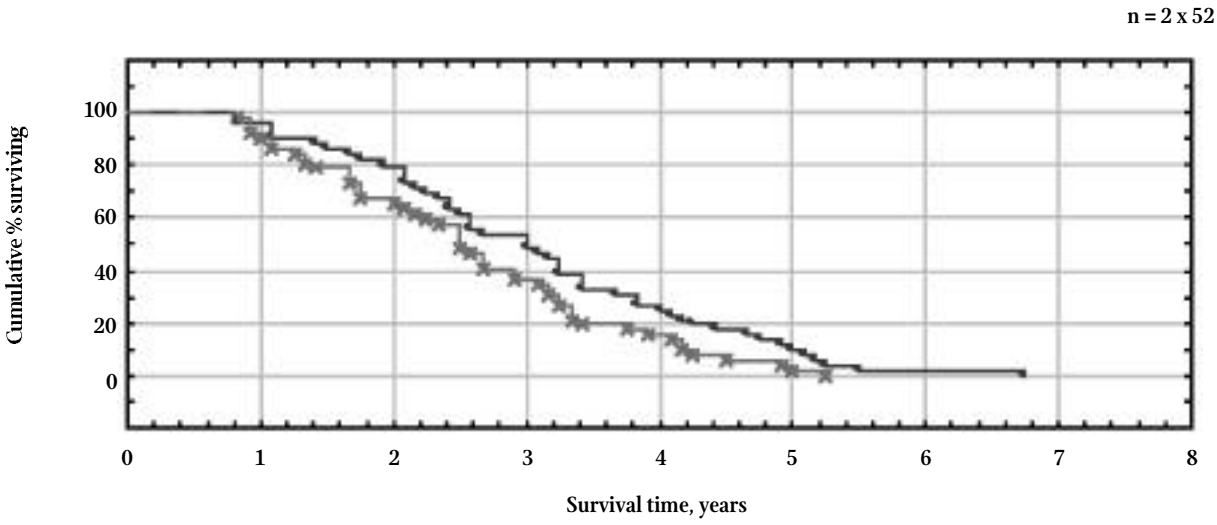

FIGURE 8 Non–small-cell bronchogenic carcinoma: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

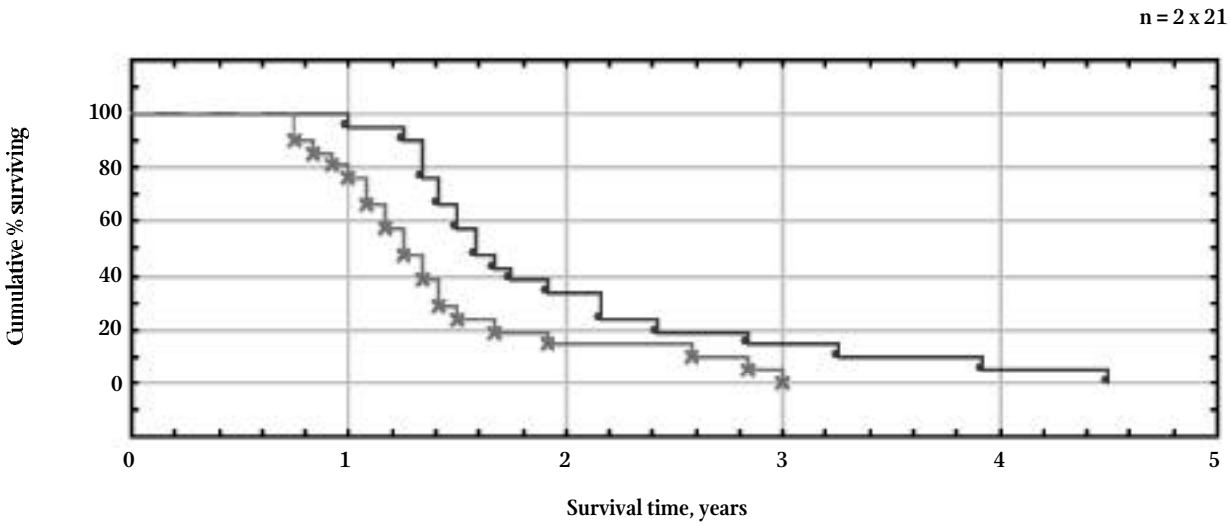

FIGURE 9 Small-cell bronchogenic carcinoma: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

pool of 56 pairs of patients in the 2 studies, the change in self-regulation in the Iscador group (+0.56) differed significantly (P= .005) from that in the control group (–0.13).

Survival Time: Iscador vs Control. In the first matched-pair study with randomized assignment to treatment group (39 pairs), the mean survival time in patients treated with Iscador was 3.49 years, compared to 2.45 years in the control group. In the second randomized study (17 pairs), the mean survival time was 4.79 years in the group treated with Iscador versus 2.41 years in the control group.

The differences of 1.04 years in the first study and 2.38 years in the second study correspond to longer mean survival times with Iscador treatment of 42% and 99%, respectively (statistically significant P= .04 and P= .02; log-rank test). The Kaplan-Meier cumulative survival times are shown in Figures 12 and 13.

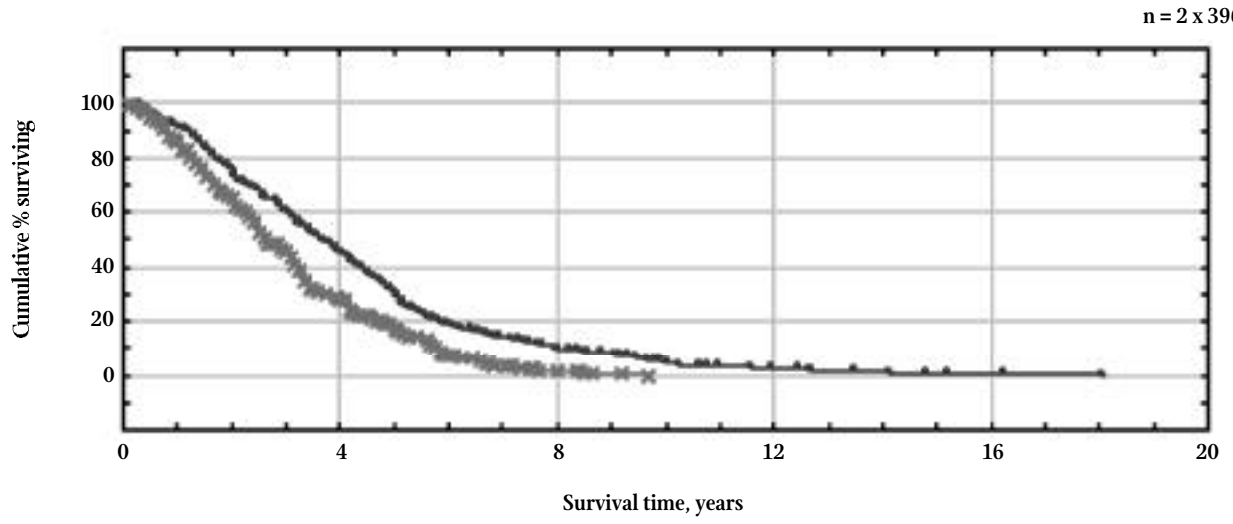

FIGURE 10 Entire data set for all 8 tumor types studied: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

TABLE 4 Survival time of patients in the Iscador and control groups with high vs low self-regulation

Self-regulation score at time of first assessment	Iscador group			Control group		
	No. (%) of pairs of patients	Mean survival time, years		No. (%) of pairs of patients	Mean survival time, years	
1	16 (4)	2.07		16 (4)	1.33	
2	46 (12)	2.09	↓ Increase	78 (20)	1.82	↓ Increase
3	126 (32)	3.13	in	159 (40)	2.88	in
4	103 (26)	4.36	↓ survival	96 (24)	3.64	↓ survival
5	49 (12)	5.95	time	31 (8)	4.44	time
6	56 (14)	7.38		16 (4)	6.13	
Total	396(100)	4.23		396 (100)	3.05	

Survival Time in Pairs Showing the Same Change in Self-regulation: Iscador vs Control. The 2 randomized studies included 28 pairs in which self-regulation after 3 months of treatment had either increased, remained unchanged, or decreased in both patients. When self-regulation increased, the Iscador-treated patients had a mean survival advantage of 3.83 years over the control patients; however, when self-regulation decreased or remained constant, the mean survival advantage under Iscador was only 0.51 and 0.28 years, respectively (Table 9).

DISCUSSION

The results described in the preceding sections were obtained from a prospective long-term epidemiological study of 10226 cancer patients conducted to identify factors that promote a favorable clinical course, particularly in relation to psychosomatic self-regulation. This program included nonrandomized and randomized prospective matched-pair studies related to Iscador treatment and its interactions with self-regulation. Iscador is one of the mistletoe (*Viscum album*) extracts developed in anthroposophical medicine[14]; it is the most widely used complementary cancer treatment in Germany.[15]

Prospective matched-pair studies, even when they are not randomized, have high internal validity (based on prospective pair matching and neutralization of dropouts by excluding the corresponding matched patients). It has been claimed that nonrandomized studies routinely lead to false-positive conclusions about efficacy,[16] but empirically this claim has been shown to be wrong.[17-19] Many methodologists advocate well-done nonrandomized studies,[20] warn against their "dogmatic rejection,"[21] or even consider them to be the "future of clinical research."[22] Beyond this, our systemic epidemiology program also included exemplary randomized studies that further strengthen the internal validity. On the other hand, our nonrandomized matched-pair studies had a high level of external validity because they assessed the reality of everyday therapy quite authentically. Even the 2 randomized matched-pair studies avoided the artificial experiment situation, because the patients were treated by their own physicians. Therefore, these results arrive at an integration of high internal *and* external validity that neither the randomized nor the nonrandomized studies alone could afford.

The results of our studies favor Iscador treatment. In the nonrandomized matched-pair study, the mean survival time was longer in patients treated with Iscador than in control groups for all cancer diagnoses considered, including rectum carcinoma, colon carcinoma, stomach carcinoma, small cell and non–small-cell bronchogenic carcinoma, and breast carcinoma without metastases, with axillary metastases, and with distant metastases. For 6 of these 8 diagnoses, the difference in favor of

TABLE 5 Survival time in pairs of patients with identical self-regulation scores: Iscador group vs control group

Self-regulation score	No. of pairs of patients	Mean survival time, years		Difference		*P* (log-rank test)
		Iscador group	Control group	Years	%	
1, 2	17	1.23	1.23	0.00	0	.79
3	58	2.97	2.53	0.44	17	.12
4	31	4.79	3.73	1.06	28	.06
5, 6	15	8.09	5.19	2.90	56	.03
1-6	121	3.82	2.98	0.84	28	.01

TABLE 6 Survival time as a function of the relative duration of treatment with Iscador: Iscador group vs control group

Duration of treatment relative to survival time, %	No. of pairs of patients	Mean survival time, years		Difference		*P* (log-rank test)
		Iscador group	Control group	Years	%	
0-20	41	3.44	3.42	0.02	1	.94
20-40	117	3.89	3.16	0.73	23	.02
40-60	108	3.44	2.70	0.74	27	.02
60-80	78	4.39	2.88	1.51	52	<.001
80-100	52	7.08	3.48	3.60	103	<.001
0-100	396	4.23	3.05	1.18	39	<.001

Iscador was statistically significant ($P<.05$), and it was highly significant in 4 of them ($P<.01$). For the whole group of 396 pairs, the difference was highly significant ($P<.001$; Table 2 and Figures 2-10).

These results were confirmed by the 2 randomized studies (Figures 12 and 13). The numerical value (99%) for survival advantage of the Iscador-treated group in the second of these 2 studies has a large statistical variation, owing to the small number of patients (17 pairs), meaning that statistical differentiation from the results of the prospective studies was not possible. One criticism of the first of the 2 randomized studies might be that deviations from the matching criteria were tolerated in sex, birth year, and year of first diagnosis. However, no statistically significant differences were found between Iscador-treated patients and the control group with respect to these criteria, and tumor-specific criteria (Table 1) were firmly matched. Above all, matching was followed by randomization.

At the first interview, more Iscador-treated patients than control patients exhibited high self-regulation values (Table 4). This raises the question of whether in the nonrandomized study the survival advantage of patients treated with Iscador was not merely a consequence of initially better self-regulation in these patients. However, Iscador-treated patients with initial self-regulation values equal to those of matched control patients still exhibited a mean survival advantage of 28% over the control patients (3.82 vs 2.98 years; Table 5); therefore, this 28% survival advantage cannot be a consequence of better primary self-regulation among the Iscador-treated patients. Contrarily, selecting patients with equal self-regulation can induce a bias *against* the group of Iscador patients, because they already had been treated with Iscador before the first interview. However, any positive effects on self-regulation (and survival) of this previous Iscador treatment is leveled out in these 121 pairs.

Another bias against Iscador treatment—not only in the nonrandomized study, but also in the randomized studies—could arise as a consequence of the evaluation not taking into account the causes of death. All deaths not directly caused by a malignant illness would tend to conceal the specific life-prolonging anticancer effect of the treatment when compared with the control group.

The patients treated with Iscador for short periods (0-20% of the survival time) had no mean survival advantage over the control patients (Table 6). This suggests that a minimum period of treatment is necessary for Iscador to exert any appreciable survival-prolonging effect. It is also possible that the groups with shorter treatment periods contained many patients who had experienced inconstant or erratic treatment with Iscador. No information on this topic can be gleaned from the recorded data. On the other hand, the longer the period of treatment with Iscador, the clearer the survival advantage (Table 6).

TABLE 7 Survival time as a function of the relative duration of Iscador treatment in patients with initially identical self-regulation: Iscador group vs control group

Duration of treatment relative to survival time, %	No. of pairs of patients	Mean survival time, years		Difference		*P* (log-rank test)
		Iscador group	Control group	Years	%	
0-20	13	2.32	2.28	0.04	2	>.99
20-40	39	3.38	3.06	0.32	10	.63
40-60	39	4.11	3.08	1.03	33	.11
60-80	22	4.27	2.92	1.35	46	.09
80-100	8	5.85	3.44	2.41	70	.03
0-100	121	3.82	2.98	0.84	28	.01

TABLE 8 Self-regulation and survival time in patients willing and unwilling to participate in a double-blind study: Iscador group vs control group

Willing to take part in double-blind study	No. of pairs of patients	Self-regulation score		*P* (*U* test)	Mean survival time, years		*P* (log-rank test)
		Iscador group	Control group		Iscador group	Control group	
Yes	26	2.69	2.65	.73	2.41	2.42	.88
No	205	3.92	3.45	<.001	4.55	3.25	<.001

Because the pairing of patients was done by hand, and the study workers responsible were not blinded as to which patient was treated with Iscador, we must consider whether the pair-matching was subject to a subtle selection bias. This appears unlikely, however, for the following reasons: (1) the study personnel involved had no preference for Iscador, and (2) the patients in the Iscador group were on average only 0.05 years older and their initial diagnosis had on average been made only 0.18 years earlier, indicating that overall matching was very precise. Above all, the argument of a subtle selection bias is ruled out in the case of the randomized studies, when matching was followed by randomization.

There might be criticism against the 2 randomized studies because of their relatively small number of patients (2 x 39 = 78; 2 x 17 = 34). Such criticism, however, is not justified. Large randomized studies are only necessary when treatment effects are small.[23] In the case of our randomized studies, both displayed statistically significant results; therefore, effects were obviously large enough and the number of patients was sufficient.

Because the patients have not been blinded to Iscador treatment, the question of a possible placebo effect remains. In light of our findings on self-regulation, the placebo question takes on a new dimension. Self-regulation means the precise opposite of a passive placebo effect stemming from simple belief in the effec-

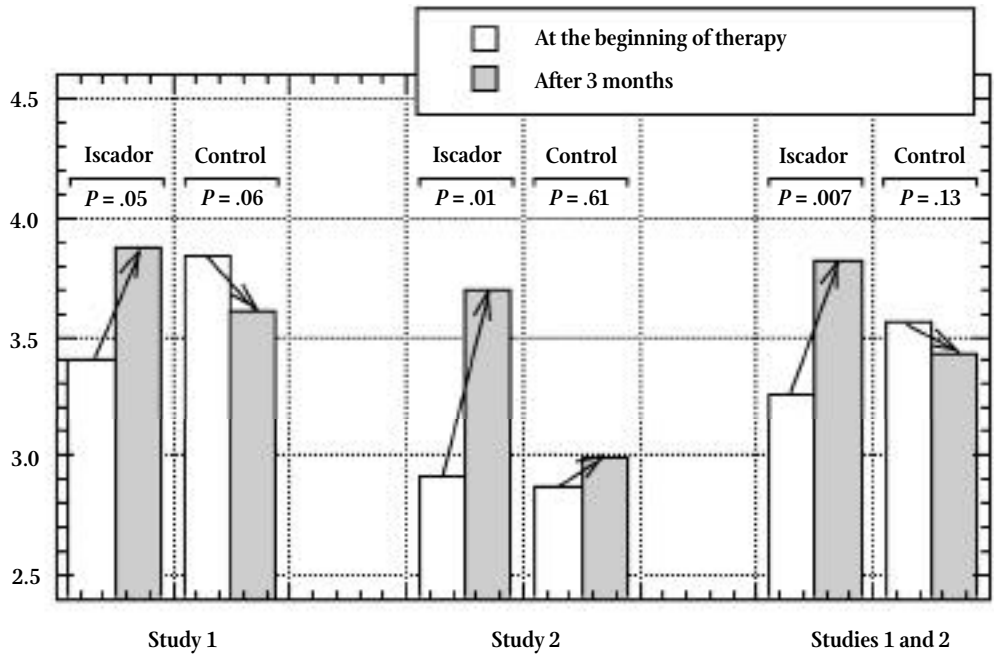

FIGURE 11 Change in self-regulation in Iscador and control groups in the course of the randomized matched-pair studies (studies 1 and 2). The *P* values given for the change in self-regulation within groups were determined by the Wilcoxon matched pairs test.

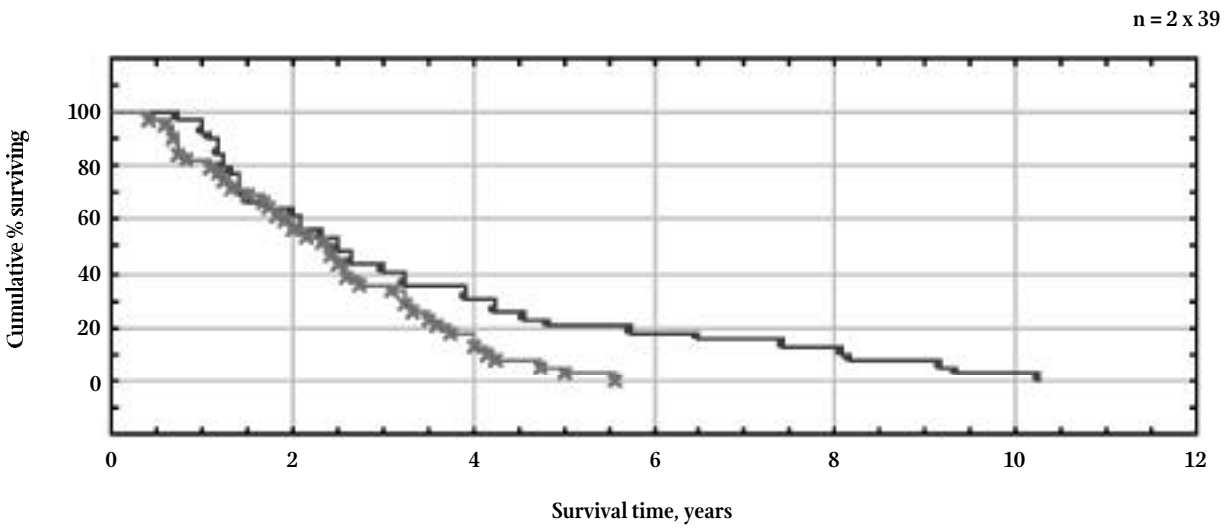

FIGURE 12 First randomized matched-pair study: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

tiveness of the treatment. Self-regulation is the ability actively to achieve well-being, inner equilibrium, appropriate stimulation, a feeling of competence, and a sense of being able to control stressful situations; thus, it includes also compliance with therapies that are deemed effective in the eyes of the patient. Indeed, higher self-regulation values were not only associated with longer survival times (Table 4); the Iscador groups included relatively more patients with high self-regulation values (Table 4).

However, these high self-regulation values could themselves be caused or induced by Iscador treatment already under way at the time of the initial assessment. The likeliness of this assumption is illustrated by the results of the 2 randomized studies, in which the increase in self-regulation values in patients treated with Iscador is significantly greater than that seen in the control groups (Figure 11). There seems to be a synergistic effect between Iscador treatment and self-regulation. In the 121 matched pairs with

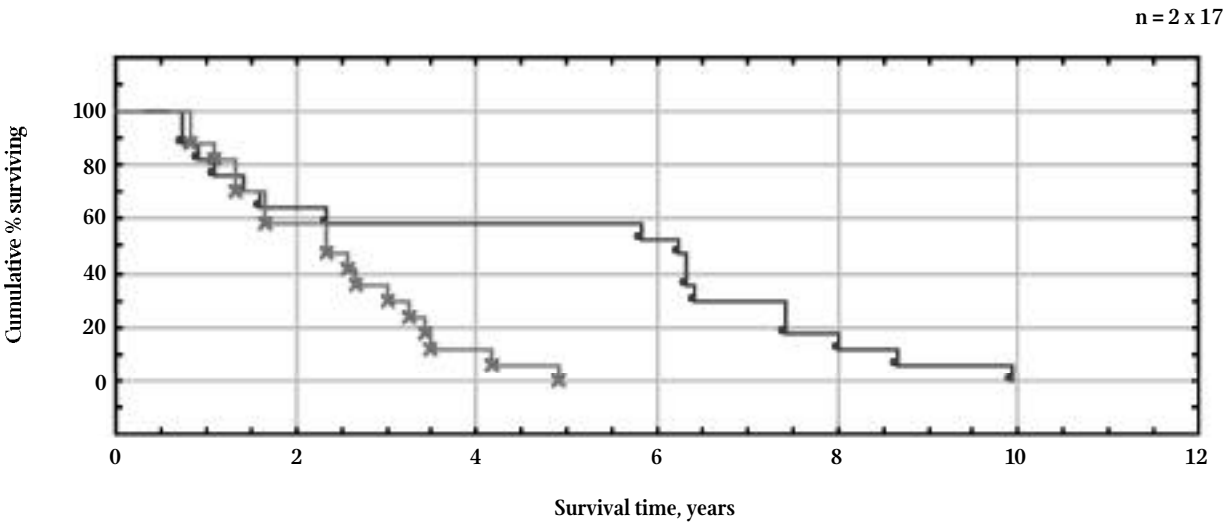

FIGURE 13 Second randomized matched-pair study: cumulative survival time with Iscador (upper curve) and without Iscador (lower curve).

TABLE 9 Survival time in pairs showing the same change in self-regulation: Iscador group vs control group

Change in self-regulation	No. of pairs of patients	Mean survival time, years		Difference, years	*P* (log-rank test)
		Iscador group	Control group		
Deteriorated	4	1.14	0.63	0.51	.04
No change	17	2.65	2.37	0.28	.45
Improved	7	8.07	4.18	3.89	.006

identical self-regulation values, the higher the self-regulation of the pair, the greater the survival advantage of patients treated with Iscador (Table 5). Likewise, in the 2 randomized studies there were stronger effects of Iscador treatment when it was accompanied by a rise in self-regulation values (Table 9).

Whether there is a passive placebo effect (whose existence is questioned by recent research[24,25]) apart from the synergy between Iscador treatment and self-regulation is not ascertainable for methodological reasons. In potential participants in a double-blind study, both the self-regulation values and the survival advantage in patients treated with Iscador were smaller than those in patients unwilling to participate (Table 8). This result is consistent with the concept of self-regulation (because participation in a double-blind study, at least under conditions of healthcare in Germany, seems to ask for reduced activity levels, feelings of competence, and control of the situation). This result not only means that a double-blind study is not appropriate for evidencing the efficacy of Iscador, but also that a possible placebo effect cannot be subtracted. Yet for the successfully treated patient, this issue is purely academic and irrelevant; for him or her, the outcome within the real treatment situation in everyday clinical practice counts, and this result can be optimally assessed—validly and reliably—by integrating pair-matching and randomization in a prospective cohort study.

The described results of mistletoe treatment confirm the results obtained in earlier clinical studies on mistletoe; in most of these studies, the survival time of mistletoe-treated patients was superior to that in (usually historical) control groups.[11] A recently published randomized study[26] on head and neck cancer patients did not show superior survival for mistletoe-treated patients. However, a mistletoe preparation was used that was standardized to a very low dose of ML-I, neglecting the other antitumoral active ingredients of mistletoe extracts and processed differently from mistletoe products in anthroposophical medicine. On the other hand, our results shed light on the outcomes of another trial that was supposed not to have shown survival advantage either.[13] It was the most methodologically rigorous Iscador study carried out to date: a placebo-controlled randomized trial of patients with non–small-cell brochogenic carcinoma.[27] However, Iscador patients in that trial had a 20% longer mean survival time than did control patients, similar to our results for non–small-cell bronchogenic cancer (18%) (Table 2). Statistical significance may have been missed in that trial, because the originally intended number of participants was not reached.

CONCLUSION

Mistletoe extracts, which contain a complex of oncologically relevant active substances and exert a variety of anticancer effects, appear to prolong survival times in patients with various tumor types. In the studies described here, efficacy was observed in patients with rectum carcinoma, colon carcinoma, stomach carcinoma, breast carcinoma (with or without axillary metastases or remote metastases), and small cell and non–small-cell bronchogenic carcinoma. The study findings support the claim of anthroposophical medicine that mistletoe therapy is generally effective for treating cancer, irrespective of tumor type.[28] Iscador treatment seems to exert general oncological effects that are not confined to specific tumor cells. An important effect of Iscador, according to our findings, is that it can enhance patients' self-regulation.

Acknowledgments

We are grateful for support of this work by Deutsche Forschungsgemeinschaft, Bonn, Germany; Deutsche Krebshilfe, Bonn, Germany; Eduard Aeberhardt Stiftung, Zürich, Switzerland; Institute of Psychiatry, University of London, England; Institute of Social Medicine, University of Heidelberg, Germany; University Association, Heidelberg, Germany; and the Society for Cancer Research, Arlesheim, Switzerland.

References

1. Stierlin H, Grossarth-Maticek R. *Krebsrisiken—Überlebenschancen: Wie Körper, Seele und soziale Umwelt zusammenwirken.* Heidelberg, Germany: Carl-Auer-Systeme Verlag; 1999.
2. Grossarth-Maticek R, Eysenck HJ. Self-regulation and mortality from cancer, coronary heart disease, and other causes: a prospective study. *Pers Indiv Diff.* 1995;19:781-795.
3. Grossarth-Maticek R. *Systemische Epidemiologie und präventive Verhaltensmedizin chronischer Erkrankungen: Strategien zur Aufrechterhaltung der Gesundheit.* Berlin, Germany: Walter de Gruyter; 1999.
4. Grossarth-Maticek R, Schmidt P, Vetter H, et al. Psychotherapy research in oncology. In: Steptoe A, Mathews A, eds. *Health Care and Human Behavior.* New York, NY: Academic Press; 1984:325-341.
5. Spiegel D, Bloom JR, Kraemer H, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet.* 1989;2:888-891.
6. Grossarth-Maticek R. Das *Autonomietraining: Gesundheit und Problemlösung durch Anregung der Selbstregulation.* 1st ed. Berlin, Germany: Walter de Gruyter; 2000.
7. Steiner R. *Geisteswissenschaft und Medizin.* 6th ed. Dornach, Switzerland: Rudolf Steiner Verlag; 1985.
8. Schwabe U, Paffrath D. *Arzneiverordnungsreport 1998.* Heidelberg, Germany: Springer Verlag; 1998.
9. Scheer R, Becker H, Berg PA, et al. *Grundlagen der Mistletherapie.* Stuttgart, Germany: Hippokrates Verlag; 1996.
10. Büssing A. Apoptose-Induction und DNA-Stabilisierung durch Viscum album L. *Fortsch Komplementärmed.* 1998;5:164-171.

11. Kiene H. Klinische Studien zur Misteltherapie karzinomatöser Erkrankungen: Eine Übersicht. *Therapeutikon.* 1989;3:347-353.
12. Hauser SP. Unproven methods in cancer treatment. *Curr Opin Oncol.* 1993;5:646-654.
13. Kleijnen J, Knipschild P. Mistletoe treatment for cancer: review of controlled trials in humans. *Phytomedicine.* 1994;1:255-260.
14. Evans M, Rodger I. *Anthroposophical Medicine: Healing for Body, Soul and Spirit.* London, England: Harper Collins; 1992.
15. Schwabe U, Paffrath D. *Arzneiverordnungsreport 1998.* Heidelberg, Germany: Springer Verlag; 1998.
16. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ.* 1996;312:71-72.
17. Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. Choosing between randomised and non-randomised studies: a systematic review. *Health Technol Assess.* 1998;2(13):1-124.
18. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med.* 2000;342:1878-1886.
19. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342:1887-1892.
20. Feinstein AR. Clinical biostatistics. 24. The role of randomization in sampling, testing, allocation, and credulous idolatry (conclusion). *Clin Pharmacol Ther a p.* 1983;14:1035-1051.
21. Abel U, Koch A, eds. *Nonrandomized Comparative Clinical Studies.* 1st ed. Düsseldorf, Germany: Symposion Publishing; 1998.
22. Porzsolt F, Pöppel E. Kommentar: Zur Diskussion über das drohende Ende der randomisierten kontrollierten Studien—es geht ans Eingemachte. *Dtsch Med Wochenschr.* 2000;125(45):A-14.
23. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med.* 1984;3:409-420.
24. Kienle GS, Kiene H. Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Altern Ther Health Med.* 1996;2(6):39-54.
25. Kienle GS, Kiene H. The powerful placebo effect. Fact or fiction? *J Clin Epidemiol.* 1997;50:1311-1318.
26. Steuer-Vogt MK, Bonkowsky V, Ambrosch P. The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. *Eur J Cancer.* 2001;37:23-31.
27. Dold U, Edler L, Mäurer HCh, et al. *Krebszusatztherapie beim fortgeschrittenen nichtkleinzelligen Bronchialkarzinom.* Stuttgart,Germany: Georg Thieme Verlag; 1991.
28. Leroi R. *Misteltherapie: Eine Antwort auf die Herausforderung Krebs.* Stuttgart, Germany: Verlag Freies Geistesleben; 1987.