Eur J Med Res (2008) 13: 107-120

Randomized and Non-randomized Prospective Controlled Cohort Studies in Matched Pair Design for the Long-term Therapy of Corpus uteri Cancer Patients with a Mistletoe Preparation (Iscador)

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Abstract
Background: Mistletoe preparations such as Iscador are in common use as complementary/anthroposophic medications for many cancer indications, particularly for solid cancers. Efficacy of this complementary therapy is still discussed controversially.
Objective: Does the long-term therapy with Iscador show any effect on survival or psychosomatic self-regulation of patients with corpus uteri cancer?
Patients and Methods: Prospective recruitment and long-term follow-up in the following 4 controlled cohort studies. (1) Two randomized matched-pairs studies: corpus uteri cancer patients without (30 pairs) and with distant metastases (26 pairs) that never used any kind of mistletoe therapy were matched for prognostic factors. By pairwise random allocation, one of the patients was suggested mistletoe therapy to be applied by the attending physician. (2) Two non-randomized matched-pairs studies: corpus uteri cancer patients without (103 pairs) and with distant metastases (95 pairs) that already received mistletoe (Iscador) therapy were matched by the same criteria to control patients without Iscador therapy.
Results: Concerning overall survival in the randomized studies, a significant effect in favour of Iscador therapy was present only in the first study, the second showed no evidence for an effect: estimate of the hazard ratio and 95% confidence interval: 0.36 (0.16, 0.82) and 1.00 (0.46, 2.16) respectively. In the non-randomized studies, the results that adjusted for relevant prognostic variables were: 0.41 (0.26, 0.63), and 0.61 (0.39, 0.93). The effect of therapy with Iscador within 12 months on psychosomatic self-regulation as a measure of autonomous coping with the disease shows a significant rise in the Iscador group against the control group in the randomized as well as in the non-randomized study on patients with corpus uteri cancer without metastases: estimate of the median difference and 95% confidence interval: 0.40 (0.15, 0.70) and 0.70 (0.25, 1.15) respectively.
Conclusion: The mistletoe preparation Iscador in these studies has the effect of prolonging overall survival of corpus uteri cancer patients. Psychosomatic self-regulation as a measure of autonomous coping with the disease, rises significantly more under Iscador therapy than under conventional therapy alone.

Key words: Corpus uteri cancer, metastases, overall survival, quality of life, self-regulation, mistletoe, Iscador, complementary/anthroposophic therapies

Introduction

In Europe, many women with gynaecological cancer take up complementary therapies, however, evidence of its efficacy on survival is still a topic of controversial discussion [1]. Among the complementary therapies used by cancer patients, the aqueous extracts of European mistletoe (*Viscum album* L.), developed on the basis of anthroposophic medicine, are the most frequently used medications, particularly in German speaking countries [2]. The 16 published prospective controlled studies up to June 2006 with the mistletoe extract Iscador show significant results in 10 cases in favour of Iscador [3, 4]. The only published prospective controlled study concerning the treatment of corpus uteri cancer with mistletoe extracts, particularly Iscador, did not show conclusive results [5].

This paper reports on four new data sets concerning the long-term therapy with the mistletoe preparation Iscador: two randomized matched pairs study with corpus uteri cancer patients with (26 pairs) and without distant metastases (30 pairs) and two non-randomized matched-pair studies with corpus uteri cancer patients with (95 pairs) and without distant metastases (103 pairs).

The two special design features of these cohort studies were the long-term follow-up and the integration of prospective controlled cohort studies with randomized trials [6, 7].

Both the non-randomized studies and the randomized study rely on matching pairs of patients according to important prognostic factors: in the first case, at the initiation of the study, the available mistletoe treated patients were matched with control patients and for any further incoming patient an additional control patient was sought in the available data base; in the second case, within the same cohort of control patients (but without intersection with the group of already «used» controls) matched-pairs were constructed and, after randomisation, to one of the patients of the pair a mistletoe therapy was suggested.

This design allows to compare results of randomized and non-randomized matched-pair studies. Thus better internal validity of the randomized studies (given comparable results) can be enriched by better generalizability of the non-randomized studies [8].

Patients and Methods

We give only a very short description of the study design and the matching methods since they were structurally the same as in earlier studies. For further information please refer to [6, 7, 9, 10].

Background

The four studies to be reported below were part of an encompassing long-term prospective epidemiological program to explore the influence of physiological, psycho-social, individual and therapeutic factors on the survival of cancer patients [11, 12]. In the following studies, which began in the early seventies, quality of life was assessed as the degree of psychosomatic «self-regulation». This concept encompasses the capacity for autonomous regulation of emotional, social and psychological factors [13–17].

Study Objectives

The primary question is: Does long-term therapy with Iscador in addition to conventional oncological treatment influence overall survival in patients with primary corpus uteri cancer of different stages in comparison to standard conventional treatment alone?

The secondary question is: Does therapy with Iscador in addition to standard conventional oncological treatment improve psychosomatic self-regulation in patients with corpus uteri cancer in comparison to standard treatment alone?

Study Setting and Data Sources

The study patients with corpus uteri cancer were recruited from a pool of three different sources of corpus uteri cancer patients (Fig. 1; further details in [7, 11, 12]).

Study Design

All four studies reported here were controlled cohort studies and prospective by design. All corpus uteri cancer patients included in these studies were recruited from the beginning of 1973, assessed, matched according to previously specified relevant prognostic factors and followed up during the life-time of all patients included. The only intended difference remaining between the matched-pairs was the presence or absence of therapy with the mistletoe preparation Iscador.

For the record: there was no written study protocol and no initial sample size calculation since the onset of these studies in 1973 was before the mandatory requirements of Good Clinical Practice. However, the study objectives, the structure of the initial and follow-up data assessments, the parameters to measure (survival, self-regulation), the data to retrieve (medical parameters) and the matching criteria were specified prior to the start of both studies in 1973.

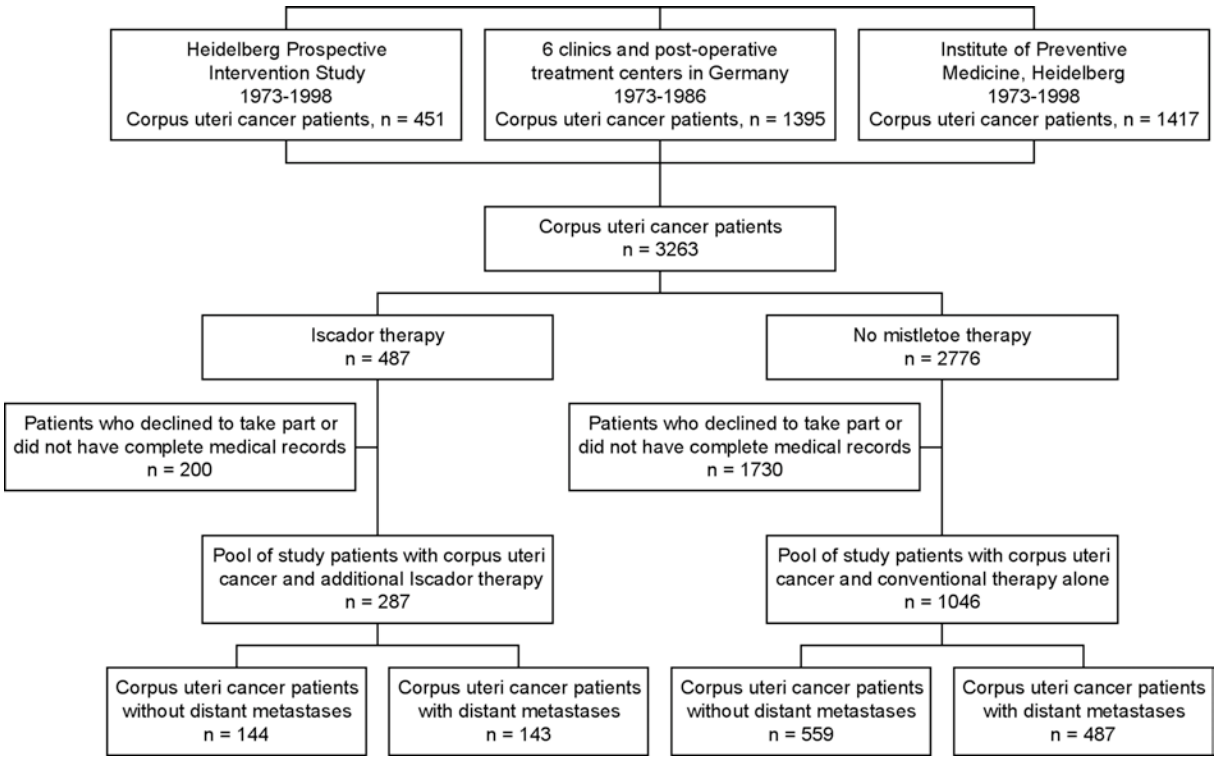


Fig. 1. Flow chart for the pool of sources of study patients with corpus uteri cancer for randomized and non-randomized matched-pair studies.

Patients

Only patients with sufficiently complete medical records for the purpose of these studies were included, as well as those who were not participating in any other clinical studies. All patients in the control and therapy groups received conventional oncological therapies, including, as necessary, surgery and radiotherapy. As the matching process included the year of the first diagnosis as a mandatory criteria, it was assured that matched patients received their first diagnosis and baseline treatment in similar times, thus it is very unlikely that different diagnostic procedures or different modes of conventional therapy due to advances in the medical sciences were used between matched pairs.

Recruitment and Initial Data Assessment

The patients' personal data were supplied by the patients themselves or their relatives; the medical data were supplied by the attending physicians and/or were retrieved from data records in clinics. They were collected during structured interviews with standardized checklists and later recorded on cards in patient files. There was no electronic data base for these raw data.

In most cases, the recruitment and initial data assessment of the patient was performed within 36 months of the first diagnosis with primary corpus uteri cancer. The zero point, or baseline, for all survival data was the year of first diagnosis. The medical data were then checked and complemented by the way of contact with the attending physician.

Quality of life was assessed by the level of psychosomatic self-regulation using a questionnaire with 16 items [11, 12, 14, 15, 18]. Self-regulation entered our studies as a prognostic factor, and if it is assessed more than once, also as an endpoint. In the former case, self-regulation indicates the status of autonomy at the beginning of the study and in the second it reveals how this status changed after 12 months of diverse therapies [11, 12].

Observed Therapy and Intervention

In the non-randomized studies, the investigators did not interfere with the treatment decisions (Iscador therapy or not) made by the patients or the attending physicians, they only observed the applied therapy. In the randomized matched-pairs studies, one of the partners was allocated to receive the suggestion of a therapy with Iscador (see below).

In both randomized studies and non-randomized studies, Iscador therapy was administered by the doctors the patients themselves had selected («attending physician») and not by special study physicians. The complementary therapy with Iscador applied in these studies, in addition to conventional oncological treatments, was an aqueous extract of the European mistletoe (*Viscum album* L.) that was first used for cancer therapy in 1918 by Rudolf Steiner and Ita Wegman on the basis of anthroposophy [19]. It is the most commonly used complementary cancer therapy in Germany and Switzerland today [2]. The pharmacological and toxicological properties of mistletoe extracts were documented in various publications on pre-clinical studies and on immunological and anticancer effects in vitro and in vivo (see the overviews in [2, 20–23]).

Iscador was (and is) generally administered subcutaneously 2 to 3 times a week. There were different doses, different sorts of Iscador depending on the host tree, and different schemes of application [21, 24]. However, in order to keep these studies as simple as possible, only the mere fact of Iscador therapy and its duration in months was documented. No information concerning dosage, variations in dose, breaks in therapy, host trees, etc. exists.

Matching Process for the two Prospective Non-Randomized Studies

The basis for building matched-pairs for the non-randomized prospective studies was the group of corpus uteri cancer patients with or without distant metastases at the time of first diagnosis already receiving Iscador therapy (Table 2). The difference between the year of first diagnosis, which coincides with the year of the first operation, and the year of recruitment and initial data assessment was 36 months or less (data not shown). As the patients were consecutively recruited into the data pool from 1973 to 1998 (Fig. 1) and met all inclusion criteria, a control patient was taken form the pool of already available patients in the data files who had not received mistletoe therapy. The matching process was performed within 12 months after a patient with Iscador therapy entered the study and had been visited for the initial data assessment. For the purpose of matching it was checked whether the control patient was still alive at the particular time of matching, if she was still willing to participate in a controlled cohort study and which further therapies she had received since the last contact. If no living matching partner could be found, then the Iscador patient was excluded from all of the studies. Control patients were only used once in the mistletoe studies and were never used in different studies. Control patients were not excluded if they received mistletoe treatments during the follow-up.

The matching criteria included (Table 4): tumour stage at first diagnosis, year of first diagnosis of corpus uteri cancer with or without distant metastases with up to ± 3 years difference (data not shown), age at first diagnosis with up to ± 3 years difference and type of conventional therapy. In order not to lose too many patients, deviations from the matching criteria were allowed in up to two criteria (Table 2), except for deviations in the year of first diagnosis (for exceptions to this rule, see below). If there was more than one control patient available, the pair with the smallest age difference was included in the study.

A patient group with pairs with «strict matching» is a subgroup of all matched-pairs of patients that meet all matching criteria. A patient group with a «balanced set» is a subgroup of all matched-pairs of patients, where pairs with prognostic factors favouring patients with Iscador therapy were eliminated; this set lies in between the complete data set and the set with strict matching.

Matching and Randomisation for the two Prospective Randomized Matched-Pair Studies

From 1978 to 1993 matched pairs were built successively from an already existing pool of corpus uteri cancer patients with distant metastases and new patients as they came into the study pool (Table 1).

The matching criteria included (Table 3): tumour stage at first diagnosis, year of first diagnosis of corpus uteri cancer with or without distant metastases with up to ±3 years difference (data not shown), age at first diagnosis with up to ±3 years difference and type of conventional therapy. In order not to lose too many patients, with the exception of the year of first diagnosis, deviations from the matching criteria were allowed in one criterion at most within each data set (Table 1).

The difference between the year of the first diagnosis and the year of recruitment and initial data assessment was 36 months or less (data not shown). The matching process was performed during the first 12 months after the initial data assessment. At the time of matching, it was checked whether both patients of the pair in question were still alive and both willing to participate in a controlled cohort study. Immediately after this was confirmed, the suggestion of an intervention was randomly allocated to one of these patients by the following process: Two slips of paper with the names of the two matched partners were put into a hat by the main investigator (G.-M.), and a masked assistant drew one of the slips of paper. Beforehand, it was determined, that the patient selected first, had to be asked if she was willing to ask her attending doctor for a complementary therapy with Iscador. It must be noted that the intervention consisted not of giving a therapy with Iscador, but of suggesting that the patient should ask her doctor for an Iscador therapy.

Control patients were used only once in the mistletoe studies, they were never used again in different studies with a similar background. Consent for study participation in this case was one-sided, only the patient who was allocated to receive the suggestion of a therapy with Iscador was informed of this process.

Exclusion of Pairs

If for any reason, a single patient had to be excluded from a study, the whole matched-pair including this patient was excluded. Such excluded pairs have not been followed up any more and particularly not used for any other purpose in any other mistletoe study.

Particularly, this exclusion of pairs guarantees that in the randomized matched-pair studies the random treatment allocation was not disturbed. Concerning the non-randomized matched-pair studies, this process does not explicitly favour one of the two therapy groups.

Outcome Parameters

The primary outcome parameter was overall survival, i.e. the time from the first diagnosis until death for any reason (except certified non-tumour-related accidents and suicides). The secondary outcome parameter was psychosomatic self-regulation at the second assessment, 12 months after the initial data assessment.

Follow-up

Patients were checked by a team of scientific researchers working for the Institute of Preventive Medicine (Heidelberg). Up to 1998, they made standardised telephone interviews or home visits periodically from 1 to several months, performing structured interviews using predefined case report forms in each case. The patients were asked about their well-being, progression of disease, further diseases, continuation of conventional treatment, continuation of complementary therapy, particularly therapy with Iscador if applicable, and the start of new therapies.

In the final follow-up from 1999–2002 any dates and causes of death not yet registered were determined from the local residents' registration offices («Einwohnermeldeamt») and from the local boards of health («Gesundheitsamt»).

Statistics

The analysis and presentation of the data sets reported here were made as closely as possible in accordance with the suggestions made in the CONSORT statement for randomized studies [25] and its adaptation to non-randomized studies [26].

In the first stage of the analysis of overall survival, the median of the differences in survival was estimated by the nonparametric Wilcoxon paired sample test, ignoring the censoring of the survival times (if there were any). Since there were at least as many censored survival times (if any) in the group with Iscador therapy as in the control group, this generally yields a conservative result with respect to the Iscador group. The estimate of the median difference and the 95% confidence intervals were calculated according to Hodges-Lehmann [27]. In addition, given censored survival times, the log-rank statistic was used, including stratification according to the matched-pairs. All p-values are two-sided. In order to explore the sensitivity of the matching criteria, the complete data sets were compared with the balanced sets and with the strictly matched set.

In the baseline comparisons of the Iscador and the control groups in the non-randomized matched-pairs studies, the Wilcoxon paired sample test (WPS) was used for continuous variables, the marginal homogeneity test (MH) for counted data with ordered categories in paired samples and the McNemar test (MN) for binomial data in paired samples [28].

In the second stage of the analysis of overall survival, a Cox proportional hazard regression model was fitted to the four complete data sets individually. The therapy with Iscador was introduced using a binary variable: either therapy or no therapy. An indicator variable for the matched-pairs was introduced and a stratified analysis based on the pairs was performed taking into account all available prognostic factors. For the randomized studies, no adjustment of prognostic factors was performed. According to the recommendations in [29], the assumption of proportional hazards

(PH) was assessed statistically and graphically; if any one but not both of these methods fail to show a positive result, we describe the PH assumption as «moderately» fulfilled.

All statistical tests and confidence intervals were calculated on the basis of the matched-pairs, i.e. we always used tests for two paired samples or tests with stratification according to the pairs, respectively. Confidence intervals (CI) are always 95% CI and test results are regarded as significant if $p < 0.05$.

The statistical analyses were performed using S-Plus 7.0 for Windows Professional Edition (Insightful Corp. 2005, Seattle, Washington). The Wilcoxon paired sample tests, the Hodges-Lehmann estimate and confidence intervals, as well as the marginal homogeneity tests were calculated for $n < 100$ using the exact procedures in StatXact 7 (Cytel Software Corporation 2005, Cambridge, Massachusetts).

Results

Data Sets and Patient Characteristics

Randomized matched-pair study ***CorpusRand****:* 2 × 30 patients with corpus uteri cancer without distant metastases (Tables 1 and 3). The recruitment and initial data assessment was performed between 1978 and 1993. From the available 418 primary corpus uteri cancer patients without distant metastases that had no mistletoe therapy, 38 randomized matched-pairs could be formed during this period. Eight pairs had to be excluded due to declined participation or drop-out before the start of therapy with Iscador, resulting in 30 pairs. No patients were alive at the time of the last assessment in 2002. The matching was close to perfect in all variables including stage (Table 3). The difference in self-regulation was not significant ($p = 0.90$).

Randomized matched-pair study ***CorpusMetRand****:* 2 × 26 patients with primary corpus uteri cancer with distant metastases (Tables 1 and 3). The recruitment and initial data assessment was performed between 1978 and 1993. From the available 387 primary corpus uteri cancer patients with distant metastases that had no mistletoe therapy, 26 randomized matched-pairs could be formed during this period. No pair had to be excluded. All patients had died by the time of the last assessment in 2002. The matching was close to perfect in all variables including stage (Table 3). The difference in self-regulation was not significant ($p = 0.72$). The differences in trust towards the attending physician in the two groups was not significant (MH test, $p = 0.99$), as was the judgment towards the effectiveness of the conventional therapy by the patient (MH test, $p = 0.64$) and by the attending physician (MH test, $p = 0.99$).

Table 1. Flow chart of primary corpus uteri cancer patients from the randomized matched-pair study *CorpusRand* and *CorpusMetRand*.

DATA SOURCES	N	
Pool of corpus uteri cancer patients without mistletoe therapy (see Figure 1)	1046	
CHARACTERISTICS OF DATA FLOW		
Primary corpus uteri cancer patients without mistletoe therapy (see Table 2)	Primary corpus uteri cancer without distant metastases 559	Primary corpus uteri cancer with distant metastases 487
Patients used as controls in parallel non-randomized studies (see Table 2)	−141	−100
Pool of patients for building randomized matched pairs	418	387
Matched pairs	38	26
Study	***CorpusRand***	***CorpusMetRand***
	Iscador [N] / *Control [N]*	*Iscador [N]* / *Control [N]*
Allocation to therapy with Iscador or control	38 / 38	26 / 26
Declined participation, did not receive therapy or drop-out before start of therapy in the Iscador group	7 pairs	0 pairs
Discontinued therapy, drop-out after start of therapy	1 pair	0 pairs
Lost to follow-up	0 pairs	0 pairs
Raw data for analysis	30 pairs	26 pairs
Pairs with 1 deviation from the specified matching criteria	5 pairs	0 pairs
Pairs with 0 deviation from the specified matching criteria	25 pairs	26 pairs
Survival analysis (Cox model)	30 / 30	26 / 26
Censored	0 / 0	0 / 0
Excluded	0 / 0	0 / 0

Table 2. Flow chart of primary corpus uteri cancer patients from the non-randomized matched-pair studies *Corpus* and *Corpus-Met* (SR = self-regulation). «Balanced set»: subgroup of complete set of matched-pairs not favouring the patients with Iscador therapy. «Strict matching»: subgroup of complete set of matched-pairs of patients fulfilling exactly all matching criteria.

CHARACTERISTICS OF DATA FLOW	N		N	
Candidates for the two non-randomized matched-pairs studies (see Figure 1)	Primary corpus uteri cancer without distant metastases 703		Primary corpus uteri cancer with distant metastases 630	
Treated with Iscador	Iscador	No Iscador	Iscador	No Iscador
	144	559	143	487
Study	***Corpus***		***CorpusMet***	
	Iscador	*Control*	*Iscador*	*Control*
Matched pairs	141	141	100	100
Declined participation, did not receive therapy or drop-out before start of therapy in the Iscador group	24 pairs		3 pairs	
Discontinued therapy, drop-out after start of therapy	10 pairs		0 pairs	
Lost to follow-up	2 pairs		2 pairs	
Raw data for analysis	105 pairs		95 pairs	
Excluded from analysis: incomplete matching with more than 2 deviations from the specified criteria	2 pairs		0 pairs	
Matching with 2 deviations at most from the specified criteria	103	103	95	95
Survival analysis (Cox model)	103	103	95	95
Censored	12	9	0	0
Excluded (missing SR)	0	0	1	1
Reduced data sets				
Balanced set	100	100	93	93
Strict matching	34	34	63	63

Non-Randomized matched-pair study ***Corpus:*** 2 × 103 primary corpus uteri cancer patients without distant metastases (Tables 2 and 4). The recruitment and initial data assessment was performed between 1973 and 1998. From the available 144 primary corpus uteri cancer patients without distant metastases that had already received mistletoe therapy (Iscador), 141 non-randomized matched-pairs could be formed during the same period. 103 matched-pairs were included in the final analysis after the exclusion of 36 pairs (for details, see Table 2). Twelve patients from the Iscador group and nine from the control group were still alive at the time of the last assessment in 2002.

Concerning the patient characteristics (Table 4), there were no relevant differences in the stages between the two groups. For conventional therapies, there were no significant differences. However, in the critical stage IC, where radiotherapy might be effective [30, 31], there were 3 Iscador patients who received radiotherapy, whereas their matched partners did not. The difference in age at first diagnosis was not significant (WPS test, $p = 0.55$). Hence we excluded the 3 pairs with differences in radiotherapy, yielding 100 pairs in the «balanced set». «Strict matching», i.e. with no exceptions in all matching variables produced 34 pairs. Five patients in the control group used Iscador, which might work in favour of the control group. Self-regulation at baseline was not matched; the difference between the two groups was significant (WPS test, $p < 0.0005$).

Non-Randomized matched-pair study ***CorpusMet:*** 2 × 95 primary corpus uteri cancer patients with distant metastases (Tables 2 and 4). The recruitment and initial data assessment was performed between 1973 and 1998. From the available 143 primary corpus uteri cancer patients with distant metastases that had already received mistletoe therapy (Iscador), 100 non-randomized matched-pairs could be formed during the same period. 95 matched-pairs were included in the final analysis after the exclusion of 5 pairs (for details, see Table 2). All patients had died by the time of the last assessment in 2002.

Concerning the patient characteristics (Table 4), there were no differences in the stages between the two groups. For conventional therapies, there were only minor differences which were judged as not relevant. The difference in age at first diagnosis was not significant (WPS test, $p = 0.22$). The difference in the years of first diagnosis were evenly distributed among the pairs and were not significant either (WPS test, $p = 0.65$, data not shown). However, there were two pairs with a difference of more than 10 years which works in favour of the Iscador group. Hence they were eliminated from building a «balanced set» with 93 pairs. «Strict matching», i.e. with no exceptions in

Table 3. Patient characteristics (matching variables and other variables) in the randomized matched-pair studies *CorpusRand* and *CorpusMetRand* (SD = standard deviation, NA = not available). Tests: [1]Wilcoxon paired sample test (WPS), [2]Marginal homogeneity test (MH), [3]McNemar test (MN). Categories of judgement: 1 = strong, 2 = moderate, 3 = weak.

	Study	*CorpusRand*		Test	*CorpusMetRand*		Test
		Iscador	*Control*	P	*Iscador*	*Control*	P
Prognostic variables		n = 30	n = 30		n = 26	n = 26	
Matching variables	**FIGO**						
	IA	11	11				
	IB	9	9				
	IC	10	10				
	IVA				17	17	
	IVB				9	9	
	Age at first diagnosis						
	mean	55.07	55.10		61.50	61.46	
	SD	5.53	5.54		3.81	3.97	
	range	45–63	45–64		55–68	55–67	
	Conventional therapy						
	Operation	30	30		26	26	
	Chemotherapy	0	0		0	0	
	Radiotherapy	28	27		26	26	
	Hormone therapy	0	0		0	0	
Baseline variables	**Co-therapy**						
	Non-Iscador CAM therapy	0	0	0.99[3]	0	0	0.99[3]
	Psychotherapy	2	2	0.99[3]	0	0	0.99[3]
	Self-regulation			0.90[1]			0.72[1]
	mean / median	3.42 / 3.50	3.42 / 3.45		3.05 / 3.10	3.15 / 3.19	
	SD	0.58	0.59		0.97	0.86	
	range	2.1–4.6	2.1–4.7		1.2–5.7	1.5–5.6	
	Patient judgement						0.99[2]
	Trust in physician	NA	NA				
	1				10	11	
	2				10	8	
	3				6	7	
	Iscador Therapy	NA	NA				
	1				10		
	2				13		
	3				3		
	Conventional Therapy	NA	NA				0.64[2]
	1				8	7	
	2				14	13	
	3				4	6	
	Physician judgement						
	Iscador therapy	NA	NA				
	1				10		
	2				7		
	3				9		
	Conventional therapy	NA	NA				0.99[2]
	1				6	6	
	2				14	14	
	3				6	6	
Therapy variable	**Iscador use (years)**	n = 30	n = 0		n = 26	n = 0	
	mean / median	6.59 / 4.92			2.21 / 0.83		
	SD	4.78			2.52		
	range	0.83–16.67			0.08–7.92		

all matching variables produced 63 pairs. Self-regulation at baseline was not matched; the difference between the two groups was significant (WPS test, p = 0.009). The differences in trust towards the attending physician in the two groups was significant (MH test, p = 0.02), the remaining differences in the judgment towards the effectiveness of the conventional therapy by the patient (MH test, p = 0.58) and by the attending physician (p = 0.83) were not significant.

The data set *CORPUSRAND* combines the data sets *CorpusRand* and *CorpusMetRand* into one data set with 56 randomized matched-pairs. The data set *CORPUS* combines the data sets *Corpus* and *Corpus-*

Table 4. Patient characteristics (matching variables and other variables) in the non-randomized matched-pair studies *Corpus* and *CorpusMet* (SD = standard deviation, NA = not available). Tests: [1]Wilcoxon paired sample test (WPS), [2]Marginal homogeneity test (MH), [3]McNemar test (MN). Categories of judgement: 1 = strong, 2 = moderate, 3 = weak.

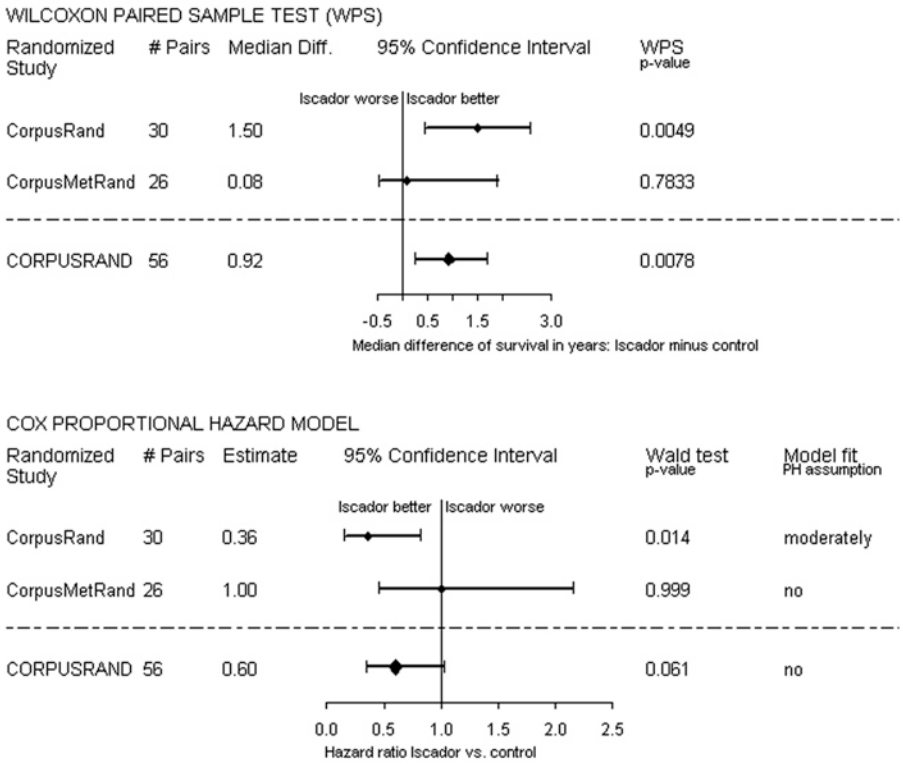
	Study	*Corpus*		Test	*CorpusMet*		Test
		Iscador	*Control*	P	*Iscador*	*Control*	P
Prognostic variables		n = 103	n = 103		n = 95	n = 95	
Matching variables	**FIGO**			0.99[2]			0.99[2]
	IA	46	46				
	IB	48	48				
	IC	9	9				
	IIIA				22	22	
	IIIB				22	22	
	IVA				25	25	
	IVB				26	26	
	Age at first diagnosis			0.55[1]			0.22[1]
	mean	58.52	59.05		63.78	63.55	
	SD	5.11	4.66		5.42	5.51	
	range	47–67	47–67		50–74	48–73	
	Conventional therapy						
	Operation	102	102	0.99[3]	95	94	0.53[3]
	Chemotherapy	0	0	0.99[3]	0	0	0.99[3]
	Radiotherapy	91	95	0.53[3]	95	95	0.99[3]
	Hormone therapy	0	0	0.99[3]	0	0	0.99[3]
Baseline variables	**Co-therapy**						
	Non-Iscador CAM therapy	5	5	0.99[3]	1	1	0.99[3]
	Psychotherapy	9	7	0.68[3]	0	0	0.99[3]
	Self-regulation			< 0.01[1]			< 0.01[1]
	mean / median	2.89 / 3.00	3.34 / 3.40		3.67 / 3.60	3.21 / 3.00	
	SD	0.62	0.53		1.17	1.31	
	range	1.1–5.1	1.9–4.7		1.2–5.9	1.0–5.8	
	Patient judgement						
	Trust in physician	NA	NA				0.02[2]
	1				41	28	
	2				39	39	
	3				14	27	
	Iscador Therapy	NA	NA				
	1				36		
	2				45		
	3				14		
	Conventional Therapy	NA	NA				0.58[2]
	1				15	27	
	2				57	39	
	3				21	28	
	Physician judgement						
	Iscador therapy	NA	NA				
	1				33		
	2				39		
	3				23		
	Conventional therapy	NA	NA				0.83[2]
	1				16	31	
	2				64	37	
	3				14	26	
Therapy variable	**Iscador use (years)**	n = 103	n = 5		n = 95	n = 0	
	mean / median	6.80 / 5.17	6.90 / 6.58		2.37 / 1.42		
	SD	5.52	2.64		2.28		
	range	0.83–23.33	3.25–9.58		0.08–8.50		

Met into one data set with 198 non-randomized matched-pairs. The combined set of the balanced sets has 193 pairs, and the combined set of the sets with strict matching has 97 pairs.

Overall Survival

For the randomized studies *CorpusRand* and *CorpusMetRand*, the effect estimate with the Cox model

Table 5. Overall survival for the data sets with randomized matched-pairs: *CorpusRand* and *CorpusMetRand* with their combination into *CORPUSRAND*. – A Wilcoxon paired sample test (WPS) was performed on all data sets; a stratified log-rank test was only calculated for the data sets with censored survival data. «Balanced set»: subgroup of complete set of matched-pairs not favouring the patients with Iscador therapy. «Strict matching»: subgroup of complete set of matched-pairs of patients exactly fulfilling all matching criteria. – The estimate of the hazard ratio measures the Iscador vs. the control group and the p-value from the Wald test measures the significance of the estimated variable ISC = Iscador therapy (PH = proportional hazards).



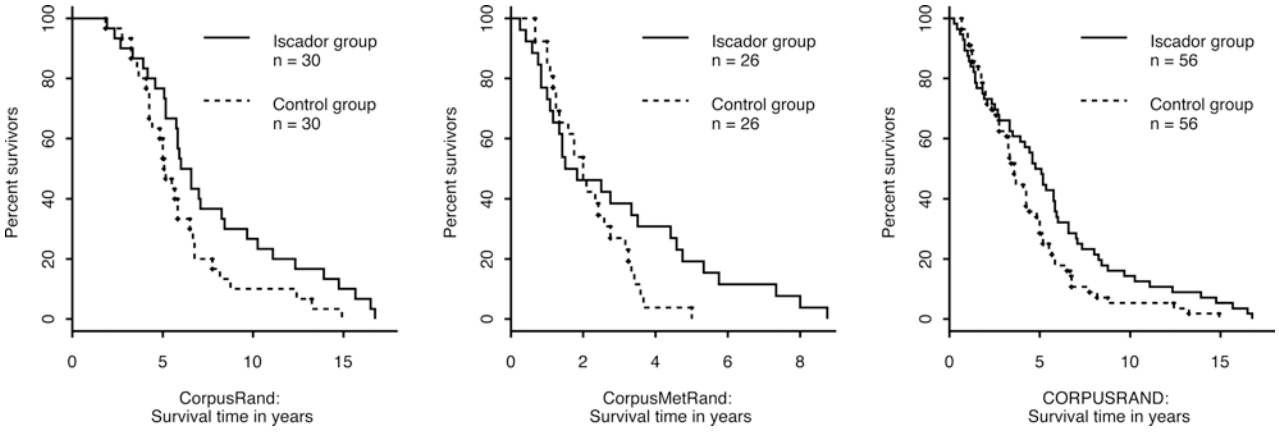


Fig. 2. *CorpusRand*, *CorpusMetRand* and *CORPUSRAND*: Kaplan-Meier survival curves for the complete sets (30, 26 and 56 randomized matched pairs respectively), showing the two groups with and without Iscador.

shows a significant effect in the first case and no effect in favour of the Iscador therapy in the second (*CorpusRand*: estimate of the hazard ratio and 95% confidence interval: 0.36 (0.16, 0.82), p = 0.014; *CorpusMetRand*: 1.0 (0.46, 2.16), p = 0.99). However, for *CorpusMetRand* the model was not adequate: the proportional hazards assumption was not fulfilled. Since there were no censored survival times in both studies, the therapy effect can be adequately represented by the estimate of the median difference of survival time according to the WPS test, that nevertheless supports the above estimates: 1.50 (0.46, 2.58), p = 0.005 and 0.08 (–0.46, 1.92), p = 0.78 (Table 5). The combined study *CORPUSRAND* showed a significant effect of Iscador therapy according to the WPS test: 0.92 (0.25, 1.71), p = 0.0078; the Cox model was not adequate and showed only a strong trend (Table 5). These results can also be inferred from the Kaplan-Meier curves for these data sets (Fig. 2) where one sees that the possible Iscador effect manifested itself only after 2 to 3 years. On the average, the possible gain for survival in the Iscador group was less than one year.

The results of the non-randomized studies *Corpus* and *CorpusMet* were significant in favour of Iscador therapy for all but one individual study and one of its subsets (*Corpus* with strict matching); the adjusted and unadjusted estimates with the Cox model were all significant in favour of Iscador therapy, and all models were adequate. In particular, we have an estimate of the adjusted hazard ratio of 0.41 (0.26, 0.63) with p < 0.0001 for *Corpus* and for *CorpusMet* of 0.61 (0.39, 0.93) with p = 0.023. For the combined set *CORPUS*,

Table 6. Overall survival for the data sets with non-randomized matched-pairs: *CorpusRand* and *CorpusMetRand* and their combination into *CORPUSRAND*. – A Wilcoxon paired sample test (WPS) was performed on all data sets; a stratified log-rank test was only calculated for the data sets with censored survival data. «Balanced set»: subgroup of complete set of matched-pairs not favouring the patients with Iscador therapy. «Strict matching»: subgroup of complete set of matched-pairs of patients fulfilling exactly all matching criteria. – The estimate of the hazard ratio measures the Iscador vs. the control group and the p-value from the Wald test measures the significance of the estimated variable ISC = Iscador therapy (PH = proportional hazards). Adjusted variables: SR = Self-regulation, Th5 = Non-Iscador CAM therapy, Th6 = Psychotherapy, Trust = Trust in physician. In *CorpusMet* and *CORPUS* there was 1 missing value from SR in 1 pair. One more pair with missing values in *CorpusMet* came from the variable Trust. All variables other than ISC with a significant influence on the outcome were included in the Cox model and are listed in the column 'Adjustment'.

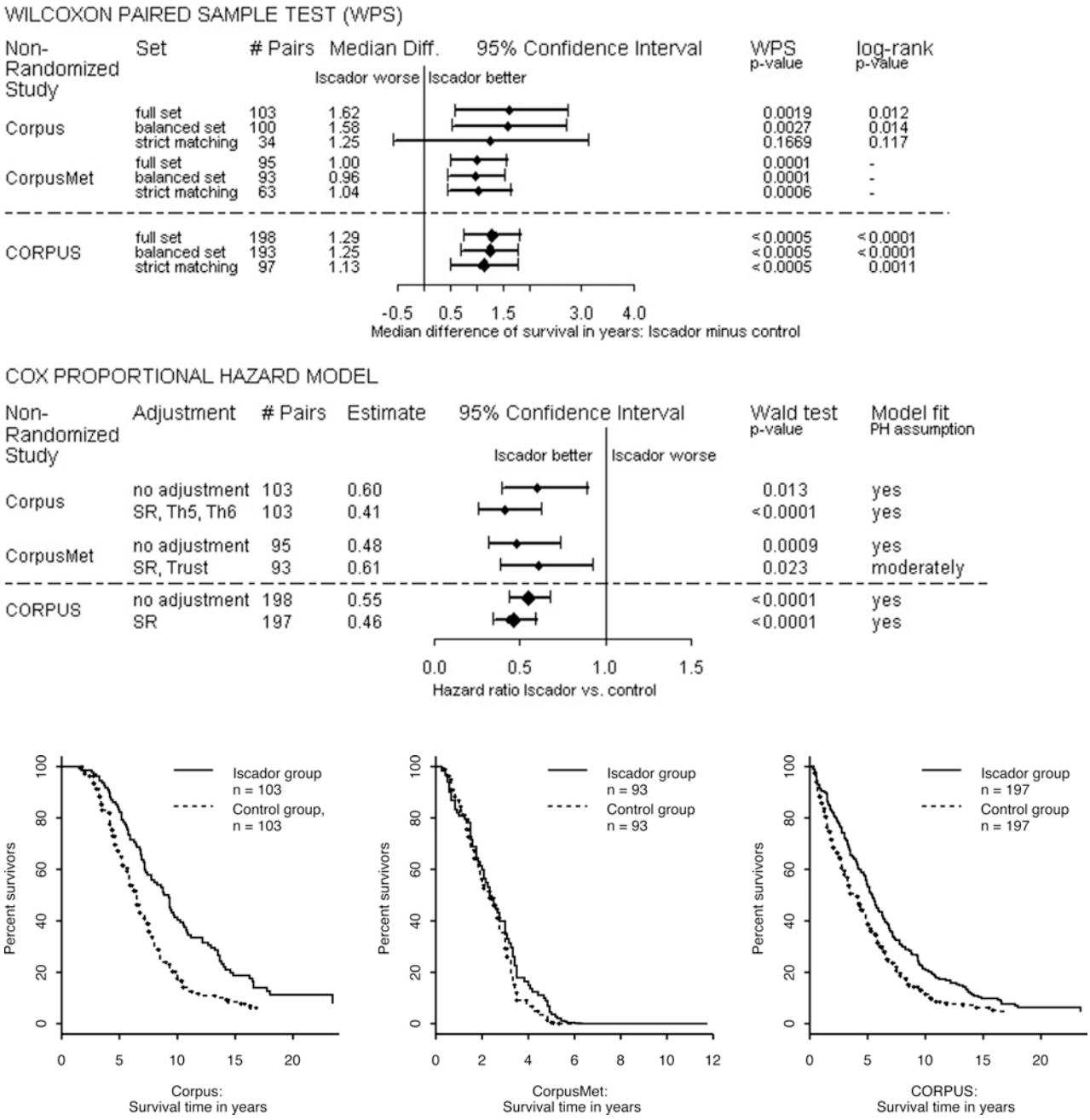


Fig. 3. Corpus (103 non-randomized matched-pairs), *CorpusMet* (95 non-randomized matched-pairs, 2 pairs with missing values) and *CORPUS* (198 non-randomized matched-pairs, 1 pair with missing value): Adjusted survival curves, showing the two groups with and without Iscador, based on the models that were adjusted for self-regulation and other variables (see Table 6).

the results were highly significant in all types of analysis (Table 6). On the average, the possible gain for survival in the Iscador group was more than one year. The adjusted survival curves for *Corpus*, *CorpusMet* and *CORPUS* according to the models with the adjusted variables indicated in Table 6 are shown in Fig. 3.

Self-Regulation

Psychosomatic self-regulation was assessed twice for both data sets, *CorpusRand* and *Corpus*. The second assessment was performed 12 months after the initial data assessment. For *CorpusRand*, the effect estimate (median difference and 95 % confidence interval) was 0.40 (0.15, 0.70) with $p = 0.0012$. For *Corpus*, the Wilcoxon paired sample test was applied to the complete set, the balanced set and the set with strict matching; the effect estimate was highly significant in all cases. Complete set: 0.65 (0.40, 0.95), $p < 0.0005$; strict matching: 0.70 (0.25, 1.15), $p = 0.0037$.

Adverse Events

The systematic registration of all kinds of adverse events of either therapy with mistletoe extracts Iscador or conventional treatment was not part of the study design. Patients were informed about mild and moderate adverse events that might occur during therapy with mistletoe extracts Iscador, such as local reactions at the injection site and fever. They were advised only to report severe events which make more than one consultation with their attending physician necessary, such as severe allergies, anaphylactic reactions. However, there were no reports of such events.

Discussion

The design and analysis features of these studies, the general limitations (bias) of our approach, as well as the properties of the evaluation of psychosomatic self-regulation have already been discussed in [7, 32] and will not be repeated here.

For overall survival, the randomized matched-pairs study *CorpusRand* (30 pairs) shows a significant effect in favour of Iscador therapy; *CorpusMetRand* shows no effect (Table 5). In the first study, the margin of improvement of psychosomatic self-regulation after 12 months was also significant in favour of the long-term complementary Iscador therapy vs. conventional treatment alone.

Overall survival in the two non-randomized studies *Corpus* and *CorpusMet* was significant in favour of Iscador therapy in most cases of analysis (Table 6). This was particularly notable in the study *Corpus*, where 5 patients from the control group opted for Iscador therapy after recruitment and initial assessment. In addition, the improvement of psychosomatic self-regulation in the study *Corpus* after 12 months was significant in favour of the long-term complementary Iscador therapy vs. conventional treatment alone.

Paired matching was used to reduce selection bias in the non-randomized studies for some known prognostic factors. However, the matching process could not be performed without exceptions in order to recruit a relevant number of patients (see Tables 2 and 4). In order to deal with the biases occurring by loose matching, with two deviations at most from the strict matching, several analytic approaches were used as a kind of sensitivity analysis: within non-adjusted analyses, balanced sets and sets with strict matching (see Methods section) were formed and analysed separately in order to compare results. In addition, Cox proportional hazards models were built with and without adjustments for factors other than therapy. In summary, the unadjusted analyses show comparable results for the different subsets (Table 6), proving that the original sets were fairly well balanced, at least with respect to the prognostic factors used in the matching process. This was supported by the fact that the results of the Cox proportional hazards model do not differ very much between adjusted and unadjusted analyses (Table 6).

The most important sources of bias in non-randomized studies are selection bias and confounding [33]. Particularly, residual bias might stem (i) from non-perfect matching, (ii) from non-matched prognostic factors and (iii) from not measured (un)known prognostic factors. The first case has already been dealt with. The second and third cases are more severe. According to the study design, several important medical prognostic factors have not been recorded in all cases, or not recorded at all (i.e. histopathological type and histopathological grading). In addition, other factors were not deemed as relevant for the study objectives at the outset of the studies in 1973 and are therefore not available for analysis (i.e. exact dates of first diagnosis, operation, initial and follow-up data assessments and matching; socio-economic status; social support; spirituality). The source of recruitment and the hospital were not included for reasons of anonymity. This leaves the problem of unknown factors open for speculation.

With this study design, attrition bias was a minor problem, since with the drop-out of any study patient, the matching partner has also been excluded and hence the balance of the groups was not severely affected. There was no evidence that the reason for drop-out was related to the outcome.

The (internal) validity of the results was, first of all, limited by selection bias and confounding as discussed above. Further limitations of the validity might come from the fact that there was no written protocol and hence no pre-specified formulation of statistical hypotheses; the sample size was small and there was no sample-size calculations in advance as well as no adjustments for multiple testing. However, in the combined data sets the estimated effects were very strong and hence not severely affected by these limitations.

As in the case of randomized studies, the generalisability (external validity) of the non-randomized studies might be limited by the fact that the inclusion and exclusion criteria were not very precise and not all of them were explicitly formulated in advance. In addition, there were, apart from the matching criteria, no explicit procedures for building pairs. Only the best matching partner was looked for. If there were deviations from the main matching criteria, no rule was reported as to how one had to proceed in these cases. In these studies there might be a preference for patients with a good prognosis, since patients from both groups who died shortly after the diagnoses could not take part in the study.

Concerning the improvement of psychosomatic self-regulation in the *Corpus* study, estimated by the median of the pair-wise differences from the second

to the first evaluation of self-regulation, the analyses of the original set and the subsets all show significant improvements. The estimate of the median of improvement was well above 0.5, and hence could be of clinical relevance [14]. However, this strong improvement might also be due to the fact that the Iscador group started with a significantly lower level of self-regulation in comparison with the control group (Table 4), thus regressing to the mean.

Consistency and Generalisability

The matched baseline values of the randomized matched-pair study *CorpusRand* and the non-randomized matched-pair study *Corpus* were comparable (Tables 3 and 4), as were the results (Tables 5 and 6). That is, the results of the randomized study *CorpusRand* were consistent with the results of the non-randomized study *Corpus*: they point in the same direction. Together, both studies gain from each other: The first has the stronger internal validity and the latter the stronger generalisability. The same was more or less true for the other two studies: The matched baseline values of the randomized matched-pair study *CorpusMetRand* and the non-randomized matched-pair study *CorpusMet* were comparable (Tables 3 and 4), as were the results with respect to the WPS test (Tables 5 and 6). Again, the results of the randomized study *CorpusMetRand* were consistent with the results of CorpusMet: they point in the same direction.

There is only one other published prospective controlled study concerning the treatment of corpus uteri cancer with Iscador [5]. However, this study is of low quality [3, 34], has too few patients (n = 17) and does not report sufficient data for conclusive results. References for case series can be found in [2].

Two recently published non-randomized controlled studies concerning gynaecological cancers show a tendency for improvement in overall quality of life and the side effects of chemotherapy in patients treated with Iscador in addition to conventional therapy vs. patients receiving only conventional therapy [35, 36].

Tolerability and Safety

The documentation of unintended adverse drug reactions of a therapy with Iscador has not been part of the design of these studies. However, there is no evidence of severe adverse effects that can plausibly be related to this therapy (see the overviews in [2, 37]). This was also supported by newer data on the tolerability and safety of a complementary therapy with Iscador [38–42]. In addition, apart from its effects on prolonging overall survival, mistletoe therapy with Iscador seems to reduce the side effects of conventional chemotherapy [35, 36, 38, 43], that is, this type of complementary therapy helps patients to achieve a better quality of life despite the impairments of chemotherapy.

Conclusion

The consistency of the results across randomized and non-randomized studies, as well as across different types of analyses, gives some evidence that a long-term therapy with mistletoe preparations, particularly Iscador, might have a clinically relevant positive effect on overall survival in these studies with corpus uteri cancer patients of all stages. In the short term, psychosomatic self-regulation as a measure of autonomous coping with the disease, increases significantly more under Iscador therapy than under conventional therapy alone for corpus uteri cancer patients without metastases. Overall, therapy with Iscador seems to prolong survival and improve the well-being of corpus uteri cancer patients in a clinically relevant manner.

Sources of funding:
Deutsche Forschungsgemeinschaft e. V., Bonn; Deutsche Krebshilfe e. V., Bonn; Stiftung für Bildung und Behindertenförderung GmbH, Stuttgart; Eduard Aeberhardt-Stiftung zur Förderung der Gesundheit, Zürich; Institute of Psychiatry (H.-J. Eysenck), University of London; Institut für Sozialmedizin, Universität Heidelberg; Rosemarie Schäfer, Florida, USA.

Beginning in 1999, the final determination of time and cause of death of the study patients were partially financed by the Society for Cancer Research, Arlesheim. The analysis of the data and the preparation of this paper were partially financed by the same institution.

Contributors:
R. Grossarth-Maticek was responsible for the design and implementation of this study as well as for the quality, reliability and documentation of the raw data. He contributed substantially to this paper with preliminary drafts and comments and gave final approval to the version to be published. Renatus Ziegler started working on this project in 2001. He proposed, executed, documented and presented the statistical analysis for this paper; wrote several drafts of this paper and gave final approval to the version to be published.

Acknowledgements: For advice concerning gynaecological matters we thank Clifford Kunz (Arlesheim) and Uwe Semmelroggen (Basel).

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Received: January 15, 2007 / Accepted: January 9, 2008

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