Prospective Controlled Cohort Studies on Long-term Therapy of Ovarian Cancer Patients with Mistletoe (*Viscum album* L.) Extracts Iscador

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Abstract

Background: **Mistletoe extracts such as Iscador® are commonly used as complementary/anthroposophic medications for many cancer indications, particularly for solid cancers. The efficacy of this complementary therapy is still controversial.**
Objective: **Does long-term therapy with mistletoe extracts Iscador show any effect on survival and psychosomatic self-regulation of patients with ovarian cancer?**
Patients and methods: **Prospective recruitment and long-term follow-up in controlled cohort studies. (1) Two randomized matched-pair studies: *OvarRand* (ovarian cancer patients without distant metastases; 21 pairs) and *OvarMetRand* (ovarian cancer patients with distant metastases; 20 pairs); patients having no mistletoe therapy were matched for prognostic factors. By paired random allocation, one of the patients of each pair was suggested therapy with mistletoe extracts Iscador to be applied by her attending physician. (2) Two non-randomized matched-pair studies: *Ovar* (ovarian cancer patients without distant metastases; 75 pairs) and *OvarRand* (ovarian cancer patients with distant metastases; 62 pairs); patients that already received therapy with mistletoe extracts Iscador were matched by the same criteria to control patients without therapy with mistletoe extracts Iscador.**
Results: **For overall survival in the randomized studies, the effect in favor of therapy with mistletoe extracts Iscador was significant in *OvarMetRand* but not in *OvarRand;* hazard ratio estimate and 95 % confidence interval: 0.40 (0.15, 1.03) and 0.33 (0.12, 0.92), respectively. In the non-randomized studies *Ovar* and *OvarMet,* the results adjusted for relevant prognostic variables were 0.47 (0.31, 0.69) and 0.62 (0.37, 1.05). Psychosomatic self-regulation in the Iscador group increases significantly within 12 months on a scale from 1 to 6 compared with the control group in the randomized study *OvarRand* as well as in the non-randomized study *Ovar* on patients with ovarian cancer without distant metastases; estimate of the median difference and 95 % confidence interval: 0.58 (0.30, 0.90) and 0.30 (0.05, 0.65), respectively.**
Conclusion: **Mistletoe extracts Iscador might have the effect of prolonging overall survival of ovarian cancer patients. In the short term, psychosomatic self-regulation increases more markedly under Iscador therapy than under conventional therapy alone.**

Key words

- **Alternative medicine**
- **Complementary medicine**
- **Iscador®**
- **Mistletoe extracts Iscador**
- **Ovarian cancer, overall survival, quality of life**
- ***Viscum album* L.**

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1. Introduction

In Europe, many women with gynaecological cancer use 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]. From the 16 prospective controlled studies published up to June 2006 with the mistletoe extracts Iscador®, 10 show significant results in favor of Iscador [3]. The only published prospective controlled study concerning the treatment of ovarian cancer with mistletoe extracts, particularly Iscador, did not show conclusive results [4].

This paper reports on four new data sets concerning the long-term therapy with the mistletoe extracts Iscador: two randomized matched pairs studies, *OvarRand* (ovarian cancer patients without distant metastases; 21 pairs) and *OvarMetRand* (ovarian cancer patients with distant metastases; 20 pairs), and two non-randomized matched-pairs studies, *Ovar* (ovarian cancer patients without distant metastases; 75 pairs) and *OvarRand* (ovarian cancer patients with distant metastases; 62 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 [5, 6].

Both the non-randomized studies *Ovar*, *OvarMet* and the randomized studies *OvarRand*, *OvarMetRand* rely on matched pairs of patients according to important prognostic factors. In the first case: patients already being treated with mistletoe extracts Iscador were matched with control patients at the beginning of the study, and an additional control patient was sought for within the available data base for each of the following incoming patients. In the second case, matched pairs were built from within the same cohort of control patients (but without intersection with the group of already «used» controls) and, after randomization, a therapy with mistletoe extracts Iscador was suggested to one of the patients of each pair.

This design allows to compare the results of randomized and non-randomized matched-pairs studies. Thus better internal validity of randomized studies (given comparable results) can be enriched by the better generalizability of non-randomized studies [7].

2. Patients and methods

We only provide 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 [5–8].

2.1. Background

The four studies *Ovar*, *OvarMet*, *OvarRand* and *OvarMetRand* presented here are part of a comprehensive long-term prospective epidemiological program to explore the influence and interaction of physiological, psycho-social, individual and therapeutic factors on the survival of cancer patients [9–10]. All patients were asked if they want to participate in the epidemiologic study program and were only included if the answer was affirmative.

Quality of life was assessed in these studies as the degree of psychosomatic "self-regulation". This term 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 [5, 11–15]. Self-regulation influences the incidence and course of cancer. Studies covering a 27-year period and involving 35 814 participants [9] showed a higher incidence of cancer in those with poor self-regulation, revealing detrimental synergies between low self-regulation and other cancer risk factors [9, 10]. In patients with manifest cancer, higher self-regulation correlated with longer survival [9, 10].

2.2. Study objectives

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

The secondary question is: Does therapy with mistletoe extracts Iscador in addition to conventional oncological treatment influence psychosomatic self-regulation in patients with ovarian cancer in comparison to standard treatment alone?

2.3. Study setting and data sources

The study patients with ovarian cancer were recruited from a pool of three different sources of ovarian cancer patients (Fig. 1).

2.4. Study design

All four studies *Ovar*, *OvarMet*, *OvarRand* and *OvarMetRand* to be reported are controlled cohort studies and overall have been prospective by design, that is, ovarian cancer patients were recruited beginning in 1973, assessed, matched according to prespecified relevant prognostic factors and followed up during the life-time of all patients included. The only intended difference between the matched pairs was the presence or absence of therapy with the mistletoe extracts Iscador.

There was no written study protocol and no initial sample size calculation since these studies started in 1973, i.e. before the mandatory requirements of Good Clinical Practice were issued. Nonetheless, the structure of the initial and follow-up data assessments, the parameters to measure (self-regulation), the data to retrieve (medical parameters) and the matching criteria were specified prior to the start of all studies.

2.5. Patients

Only patients with sufficiently complete medical records were included in the studies, given that they did not participate in any other clinical study. Each patient of the control and of the therapy group received conventional oncological therapies, including surgery and chemotherapy. Since the matching process included the year of the first diagnosis as a mandatory criteria,

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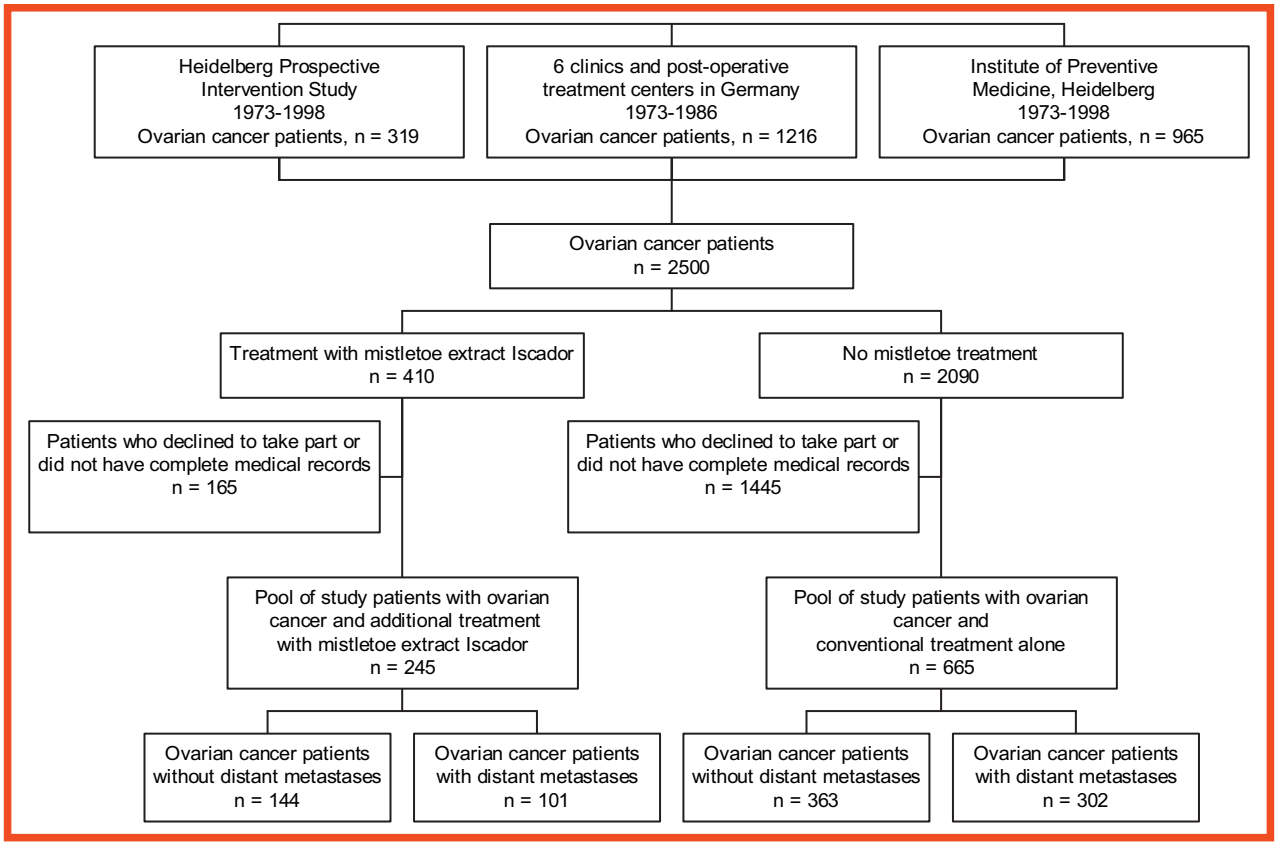

Fig. 1: Flow chart for the pool of sources of study patients with primary ovarian cancer for randomized and non-randomized matched-pair studies.

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 scientific progress were used between matched pairs.

2.6. Initial data assessment

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

In most cases, initial data were assessed within 3 years of the first diagnosis with primary ovarian cancer after the patients gave their consent to participate in the epidemiological study program. The zero point, or baseline, for all survival data was the year of first diagnosis. The medical data were then checked and complemented through personal contact with the attending physician.

Quality of life was assessed by the level of psychosomatic self-regulation using a questionnaire with 16 items [9, 10, 12, 16]. Self-regulation was included in our studies as a prognostic factor, and in two studies was also used as an endpoint, where it was measured twice. In the former case, self-regulation indicates the status of autonomy at the beginning of the study, in the latter case it reveals how this status changed during various therapeutic performances [12, 14].

2.7. Observed therapy and intervention

In the non-randomized studies *Ovar* and *OvarMet*, the investigators did not interfere with the treatment decisions (therapy with mistletoe extracts Iscador or no such therapy) of the patients or the attending physicians, but only observed the applied treatment. In the randomized matched-pair studies *OvarMet* and *OvarMetRand*, one partner of each pair was allocated to receive the Iscador treatment suggestion. In all four studies, Iscador therapy was not administered by study physicians but by the attending physicians the patients had chosen themselves. The complementary therapy with Iscador applied in these studies, in addition to conventional oncological treatments, was aqueous extracts 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 [17]. Pharmacological and toxicological properties of mistletoe extracts Iscador are documented in various publications on preclinical studies and on immunological and anti-cancer effects *in vitro* and *in vivo* [2, 18–24]. Mistletoe extracts Iscador is generally administered subcutaneously 2–3 times a week. There were different doses, different sorts of Iscador depending on the host tree, and different application schemes [19, 25]. Yet, to keep the studies as simple as possible, only the mere fact of Iscador therapy and its duration in months was documented. There is no information available concerning dosages, variations in dose, breaks in therapy, host trees, etc.

2.8. Matching process for the two prospective non-randomized studies *Ovar* and *OvarMet*

The basis for building matched pairs for the observational non-randomized prospective studies *Ovar* and *OvarMet* was the group of ovarian cancer patients without or with distant metastases at the time of first diagnosis already receiving therapy with mistletoe extracts Iscador (Table 2). The difference between the year of first diagnosis, which coincides with the year of first operation, and the year of initial data assessment was up to 3 years (data not shown). As the patients were consecutively recruited into the data pool from 1973 to 1998 (Fig. 1) and met inclusion criteria, control patients were taken from the pool of already available patients from the data files with no mistletoe therapy and within the same data source. The matching process was performed within 12 months after a patient with Iscador therapy had entered the study and was visited for initial data assessment. For the purpose of matching it was checked if the respective control patient was still alive, willing to participate in a controlled cohort study, and what kind of therapies she had received since the last contact. If no matching partner could be found, the Iscador patient in question was excluded. Every control patient participated only once in all studies with mistletoe extracts Iscador and never in different studies. Control patients were not excluded it they received mistletoe extracts during follow-up.

The matching criteria for *Ovar* and *OvarMet* included (Table 4): tumor stage at first diagnosis, year of first diagnosis of ovarian cancer with or without distant metastases (±3 years) (data not shown), age at first diagnosis (±3 years) and type of conventional therapy. In order not to lose too many patients, deviations in matching criteria were allowed in up to two criteria (Table 2). If more than one control patient was available, the pair with the smallest age difference was included in the study.

Patient groups 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, out of which pairs with prognostic factors in favor of patients with therapy with mistletoe extracts Iscador were eliminated; they lie in between the full data set and the set with strict matching.

2.9. Matching and randomization for the two prospective randomized matched-pair studies *OvarRand* and *OvarMetRand*

From 1978 to 1993 matched pairs were built successively from an already existing pool of ovarian cancer patients without and with distant metastases and new patients as they came into the study pool (Table 1). Matching criteria (Table 3) for the studies *OvarRand* and *OvarMetRand* included tumor stage at first diagnosis, year of first diagnosis of ovarian cancer with or without distant metastases (±3 years) (data not shown), age at first diagnosis (±3 years) and type of conventional therapy. In order not to lose too many patients, deviations in matching criteria were allowed in up to one criterium, except for deviations in the year of first diagnosis (Table 1).

The difference between the year of first diagnosis and the year of initial data assessment was up to 3 years (data not shown). The matching process was performed within 12 months after initial data assessment. At the time of matching, it was checked if both patients of the pair in question were still alive and willing to participate in a controlled cohort study. If yes, a treatment suggestion was randomly allocated to one of these patients without delay according to 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. The patient selected first was suggested to ask her attending physician for a complementary therapy with mistletoe extracts Iscador. The intervention was not to administer Iscador, but to suggest the patient ask her doctor for Iscador therapy.

Every control patient participated only once in all studies with mistletoe extracts Iscador and never in different such studies. Consent for study participation in this case was one-sided, only the patient who was suggested Iscador therapy was informed about this process [5, 6]. Since the therapy suggestion was implemented by the attending physician, it was paid for by the regular health insurance of the patient.

2.10. Exclusion of pairs

If a patient had to be excluded from a study, her matched partner was excluded, too. Excluded pairs were not followed up any more and not used for any other purpose in any study with mistletoe extracts Iscador. The exclusion of pairs guarantees that the random treatment allocation in *OvarRand* and *OvarMetRand* is not disturbed. Concerning the non-randomized matched-pair studies *Ovar* and *OvarMet*, this process does not favor one of the two therapy groups.

2.11. Outcome parameters

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

2.12. Follow-up

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

In the final follow-up during1999–2002 any dates and causes of death that had not been registered before were determined by the local residents' registration offices (Einwohnermeldeamt) and the local boards of health (Gesundheitsamt).

2.13. 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 [26] and its adaptation to non-randomized studies [27].

In the first stage of the analysis of overall survival, the median of the differences in survival was estimated by the non-parametric Wilcoxon paired-sample test, ignoring the censoring of the survival times (if there was any). As there were at least as many censored survival times (if any) in the group with therapy with mistletoe extracts Iscador 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-Leh-

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Table 1: Flow chart of primary ovarian cancer patients from the randomized matched-pairs studies *OvarRand* and *OvarMetRand*.

Data sources	N			
Pool of ovarian cancer patients with no mistletoe therapy (Fig. 1)	665			
Characteristics of data flow				
Primary ovarian cancer patients with no mistletoe therapy (Table 2)	Primary ovarian cancer without metastases		Primary ovarian cancer with distant metastases	
	363		302	
Patients used as controls in parallel non-randomized studies (Table 2)	–99		–66	
Pool of patients for building randomized matched pairs	264		236	
Study	*OvarRand*		*OvarMetRand*	
	Iscador	*Control*	*Iscador*	*Control*
Resulting matched patients	25	25	24	24
Declined participation, not received therapy with mistletoe extracts Iscador or drop-out before start of therapy in Iscador group	4 pairs		4 pairs	
Discontinued therapy, drop-out after start of therapy	0 pairs		0 pairs	
Lost to follow-up	0 pairs		0 pairs	
Raw data for analysis	21	21	20	20
Pairs with 1 deviation at most from the specified matching criteria	3 pairs		0 pairs	
Pairs with 0 deviation from the specified matching criteria	18 pairs		20 pairs	
Survival analysis (Cox model)	21	21	20	20
Censored	1	0	0	0
Excluded	0	0	0	0

Table 2: Flow chart of primary ovarian cancer patients from the non-randomized matched-pair studies *Ovar* and *OvarMet*. A "balanced set" is a subgroup of a full set of matched pairs *not* favoring patients with therapy with mistletoe extracts Iscador; a set with "strict matching" is a subgroup of a full set of matched pairs of patients exactly fulfilling all matching criteria.

Characteristics of data flow	N		N	
Candidates for the two non-randomized matched-pairs studies (Fig. 1)	Primary ovarian cancer without distant metastases 507		Primary ovarian cancer with distant metastases 403	
Treated/not treated with mistletoe extracts Iscador	Iscador 144	No Iscador 363	Iscador 101	No Iscador 302
Study	*Ovar*		*OvarMet*	
	Iscador	*Control*	*Iscador*	*Control*
Resulting matched pairs	99	99	66	66
Declined participation, not received therapy with mistletoe extracts Iscador or drop-out before start of therapy in Iscador group	19 pairs		1 pair	
Discontinued therapy, drop-out after start of therapy	4 pairs		0 pairs	
Lost to follow-up	1 pair		0 pairs	
Raw data for analysis	75	75	65	65
Excluded from analysis: incomplete matching with more than 2 deviations from the specified criteria	0 pairs		3 pairs	
Matching with at most 2 deviations from the specified criteria	75	75	62	62
Survival analysis (Cox model)	75	75	62	62
Censored	7	2	0	0
Excluded (missing self-regulation)	1	0	0	0
Reduced data sets				
Balanced set	63	63	60	60
Strict matching	29	29	11	11

mann [28]. 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 full 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 the 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 [29].

Table 3: Patient characteristics (matching variables and other variables) in the randomized matched-pair studies *OvarRand* and *OvarMetRand*.

	Study	*OvarRand*		Test P	*OvarMetRand*		Test P
	Prognostic variables	*Iscador* n = 21	*Control* n = 21		*Iscador* n = 20	*Control* n = 20	
Matching variables	FIGO						
	IA	5	4				
	IB	5	5				
	IC	11	12				
	IV				20	20	
	Age at first diagnosis						
	mean	45.38	45.48		57.35	57.20	
	SD	5.47	5.08		4.83	4.25	
	range	37–55	37–55		48–66	50–64	
	Conventional therapy						
	Operation	21	21		20	20	
	Chemotherapy	20	20		20	20	
	Radiotherapy	0	0		0	0	
	Hormone therapy	0	0		0	0	
Baseline variables	Self-regulation			0.53[1]			0.32[1]
	mean / median	3.29 / 3.30	3.34 / 3.40		3.45 / 3.12	3.30 / 3.24	
	SD	0.36	0.40		0.83	0.80	
	range	2.4–3.8	2.3–3.9		1.3–4.2	1.80–4.60	
	Patient judgement						
	Trust in physician	NA	NA				0.99[2]
	1				5	5	
	2				10	11	
	3				5	4	
	Iscador Therapy	NA	NA				
	1				8		
	2				8		
	3				4		
	Conventional Therapy	NA	NA				0.19[2]
	1				3	6	
	2				10	11	
	3				7	3	
	Physician judgement						
	Iscador therapy	NA	NA				
	1				7		
	2				12		
	3				1		
	Conventional therapy	NA	NA				0.99[2]
	1				6	6	
	2				9	10	
	3				5	4	

SD = standard deviation, NA = not available. Test: [1] Wilcoxon paired-sample test (WPS), [2] Marginal homogeneity test (MH), [3] McNemar test (MN). Categories of judgement: 1 = strong, 2 = moderate, 3 = weak.

In the second stage of the analysis of overall survival, a Cox proportional hazard regression model was fitted to the four full data sets individually. The therapy with mistletoe extracts 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 and paired interactions of the significant factors. This stratification according to matched pairs generally produced a conservative estimate in comparison with the unmatched analysis ([30], § 7.1). The model development and the assessment of model adequacy were performed according to the recommendations in [31, 32]. An automatic variable selection procedure was not used. No adjustment of prognostic factors was performed in the randomized studies. According to recommendations in [32], the assumption of proportional hazards (PH) was assessed statistically *and* graphically; if any one but not both of these methods failed to show a positive result, we described the PH assumption as "moderately" fulfilled.

All statistical tests and confidence intervals were calculated on the basis of 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 were 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).

3. Results

3.1. Data sets and patient characteristics

Randomized matched-pair study OvarRand: 2 × 21 patients with primary ovarian cancer without distant me-

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Table 4: Patient characteristics (matching variables and other variables) in the non-randomized matched-pairs studies *Ovar* and *OvarMet*.

	Study	*Ovar*		Test P	*OvarMet*		Test P
	Prognostic variables	*Iscador* n = 75	*Control* n = 75		*Iscador* n = 62	*Control* n = 62	
Matching variables	FIGO			0.25[2]			0.99[2]
	IA	31	28				
	IB	17	19				
	IC	27	28				
	IV				62	62	
	Age at first diagnosis			0.05[1]			0.98[1]
	mean	43.01	45.08		55.66	55.98	
	SD	8.12	8.24		8.04	8.10	
	range	23–62	23–61		38–68	39–68	
	Conventional therapy						
	Operation	75	75	0.99[3]	55	55	0.99[3]
	Chemotherapy	68	67	0.84[3]	61	62	0.53[3]
	Radiotherapy	0	0	0.99[3]	0	0	0.99[3]
	Hormone therapy	0	0	0.99[3]	0	0	0.99[3]
Baseline variables	Co-therapy						
	Non-Iscador CAM therapy	1	1	0.99[3]	6	8	0.53[3]
	Psychotherapy	1	1	0.99[3]	NA	NA	
	Self-regulation			0.07[1]			< 0.01[1]
	mean / median	3.10 / 3.20	3.33 / 3.50		3.65 / 3.56	2.80 / 2.85	
	SD	0.69	0.52		1.23	1.02	
	range	1.1–4.5	1.8–4.2		1.2–5.8	1.2–5.9	
	Patient judgement						
	Trust in physician	NA	NA				
	1				33	24	0.07[2]
	2				21	22	
	3				8	16	
	Iscador Therapy	NA	NA				
	1				26		
	2				23		
	3				13		
	Conventional Therapy	NA	NA				0.08[2]
	1				19	27	
	2				27	27	
	3				16	8	
	Physician judgement						
	Iscador therapy	NA	NA				
	1				32		
	2				11		
	3				19		
	Conventional therapy	NA	NA				0.54[2]
	1				23	18	
	2				25	29	
	3				14	15	

SD = standard deviation, NA = not available. Test: [1] Wilcoxon paired-sample test (WPS), [2] Marginal homogeneity test (MH), [3] McNemar test (MN). Categories of judgement: 1 = strong, 2 = moderate, 3 = weak.

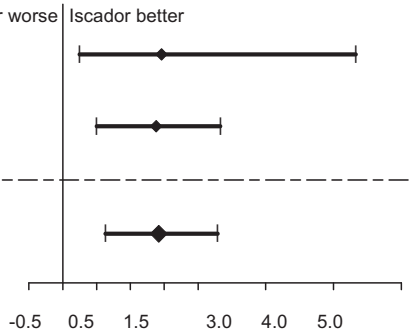
tastases (Tables 1, 3). Initial data assessment was performed between 1973 and 1993. Of the available 264 primary ovarian cancer patients without distant metastases that received no mistletoe therapy, 25 randomized matched pairs could be formed. Four pairs had to be excluded due to declined participation or drop-out before the start of therapy with mistletoe extracts Iscador, resulting in 21 pairs. Only one patient from the Iscador group was 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 at baseline was not significant (p = 0.53).

Randomized matched-pair study OvarMetRand: 2 × 20 patients with primary ovarian cancer with distant metastases (Tables 1, 3). Initial data assessment was performed between 1973 and 1993. Of the available 236 primary ovarian cancer patients with distant metastases that received no mistletoe therapy, 24 randomized matched pairs could be formed. Four pairs had to be excluded due to declined participation or drop-out before the start of therapy with mistletoe extracts Iscador, resulting in 20 pairs. 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 at baseline was not significant (p = 0.32). The differences in trust towards the attending physician in the two groups was not significant (MH

Table 5: Overall survival for the data sets with randomized matched pairs: *OvarRand* and *OvarMetRand* with their combination into *OVARRAND*. – 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 full set of matched pairs *not* favoring the patients with therapy with mistletoe extracts Iscador. "Strict matching": subgroup of full 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.

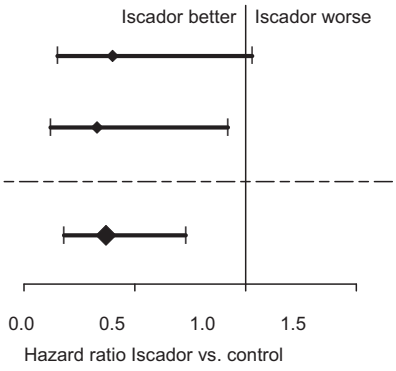
WILCOXON PAIRED SAMPLE TEST (WPS)

Randomized Study	# Pairs	Median Diff.	95% Confidence Interval	WPS p-value	log-rank p-value
OvarRand	21	1.46		0.0117	0.0495
OvarMetRand	20	1.38		0.0010	-
OVARRAND	41	1.42		< 0.0005	0.0030



COX PROPORTIONAL HAZARD MODEL

Randomized Study	# Pairs	Estimate	95% Confidence Interval	Wald test p-value	Model fit PH assumption
OvarRand	21	0.4		0.058	moderately
OvarMetRand	20	0.33		0.033	moderately
OVARRAND	41	0.37		0.004	yes



PH = proportional hazard.

test, p = 0.99), as was the judgment towards the effectiveness of the conventional therapy by the patient (MH test, p = 0.19) and by the attending physician (MH test, p = 0.99).

Non-randomized matched-pairs study Ovar: 2 × 75 primary ovarian cancer patients without distant metastases (Tables 2, 4). Initial data assessment was performed between 1973 and 1998. Of the available 144 primary ovarian cancer patients without distant metastases that already received therapy with mistletoe extracts Iscador, 99 non-randomized matched pairs could be formed. 75 matched pairs entered into the final analysis after the exclusion of 24 pairs (Table 2). Seven patients from the Iscador group and two from the control group were still alive at the time of the last assessment in 2002.

Concerning the patient characteristics (Table 4), the difference in the stages between the two groups was not significant (MH test, p = 0.25). However, for 3 pairs, the stage was worse for the control patient (IB instead of IA). There was no significant difference in the conventional therapies and in the critical case of stage IC, where chemotherapy might be highly effective [33, 34] the therapeutic situation was balanced as well. The pair-wise difference in the year of first diagnosis was less or equal ±3 years (data not shown). The difference in age at first diagnosis was significant (WPS test, p = 0.05) with more advanced ages in the control group. For

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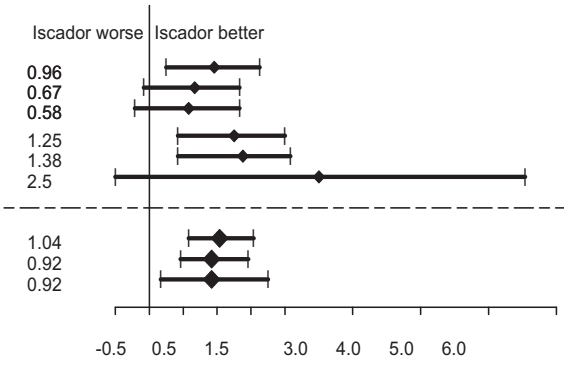
Table 6: Overall survival for the data sets with non-randomized matched pairs: *Ovar* and *OvarMet* and their combination into *OVAR*. – A Wilcoxon paired sample test (WPS) was performed on all data sets; a stratified log-rank test was only calculated for the data sets with censored survival data. "Balanced set": subgroup of full set of matched pairs *not* favoring the patients with therapy with mistletoe extracts Iscador. "Strict matching": subgroup of full 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. There were no significant interactions between adjusted variables in any model. In *Ovar* and *OVAR* there was one pair with missing values from selt-regulation. All variables other than "mistletoe extracts therapy" with a significant influence on the outcome were included in the Cox model and are listed in the column 'Adjustment'.

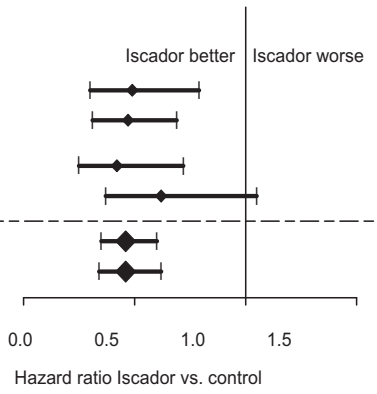
WILCOXON PAIRED SAMPLE TEST (WPS)

Non-Randomized Study	Set	# Pairs	Median Diff.	95% Confidence Interval	WPS p-value	log-rank p-value
Ovar	full set	75	0.96		0.0140	0.0025
	balanced set	63	0.67		0.0799	0.0223
	strict matching	29	0.58		0.1387	0.0411
OvarMet	full set	62	1.25		0.0001	-
	balanced set	60	1.38		0.0001	-
	strict matching	11	2.5		0.0830	-
OVAR	full set	137	1.04		< 0.0005	< 0.0001
	balanced set	123	0.92		< 0.0005	< 0.0001
	strict matching	40	0.92		0.0221	0.0114



COX PROPORTIONAL HAZARD MODEL

Non-Randomized Study	Adjustment	# Pairs	Estimate	95% Confidence Interval	Wald test p-value	Model fit PH assumption
Ovar	no adjustment	75	0.49		0.0035	no
	SR	74	0.47		0.0002	no
OvarMet	no adjustment	62	0.42		0.0016	moderately
	SR	62	0.62		0.0770	moderately
OVAR	no adjustment	137	0.46		< 0.0001	yes
	SR	136	0.46		< 0.0001	moderately



WPS = Wilcoxon paired sample test; SR = self-regulation; PH = proportional hazard.

this reason we excluded the 3 pairs with stage differences mentioned above and the 9 pairs with age differences of 10 or more years. Hence, in order to build a "balanced set", 12 pairs were eliminated, yielding 63 pairs. "Strict matching", i.e. with no exceptions in all matching variables, produced 29 pairs. Self-regulation at baseline was not matched; the difference between the two groups was not significant (WPS test, p = 0.07).

Non-Randomized matched-pair study OvarMet: 2 × 62 primary ovarian cancer patients with distant metastases (Tables 2, 4). Initial data assessment was performed between 1973 and 1998. Of the available 101 primary ovarian cancer patients with distant metastases that had already received therapy with mistletoe extracts Iscador, 66 non-randomized matched pairs could be formed. 62 matched pairs entered into the final analysis after the exclusion of 4 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. There were only minor differences in therapies, which were judged as not relevant. The difference in age at first diagnosis was not significant (WPS test, p = 0.98). The differences in the years of first diagnosis were evenly distributed among the pairs and were not significant either (WPS test, p = 0.58). It turned out, however, that there were two pairs with a difference of more than 10

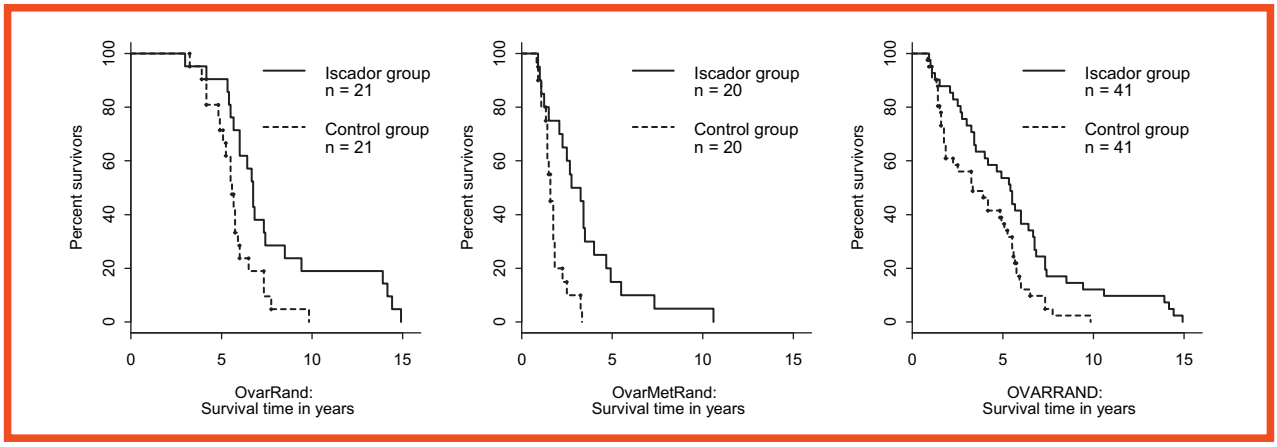


Fig. 2: *OvarRand, OvarMetRand* and *OVARRAND:* Kaplan-Meier survival curves for the full sets (21, 20 and 41 randomized matched pairs, respectively), showing the two groups with and without mistletoe extracts Iscador.

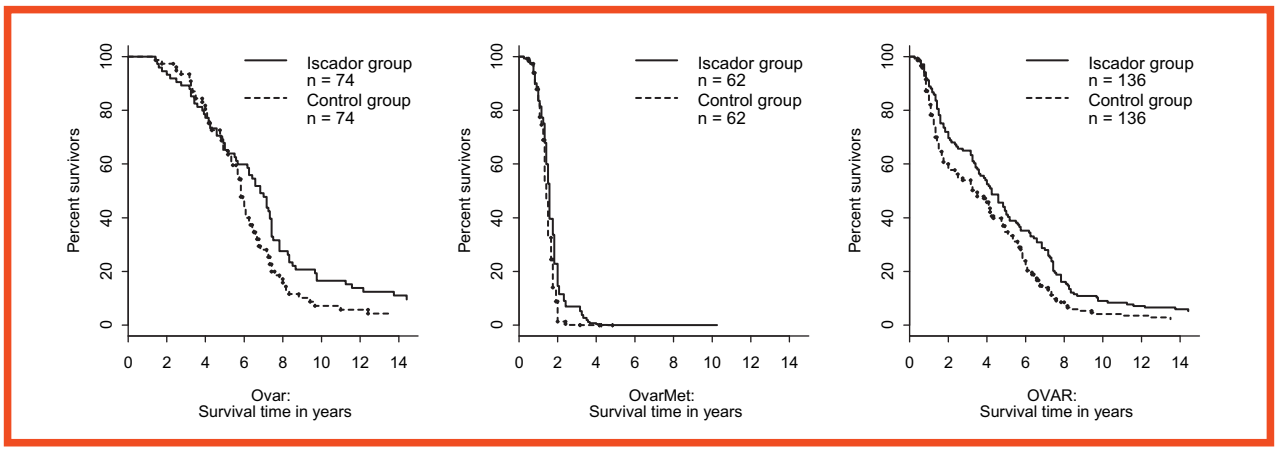


Fig. 3: *Ovar* (75 non-randomized matched-pairs, 1 pair with missing value), *OvarMet* (62 non-randomized matched pairs) and *OVAR* (137 non-randomized matched pairs, 1 pair with missing value): Adjusted survival curves, showing the two groups with and without mistletoe extracts Iscador, based on the models that were adjusted for self-regulation (see Table 6).

years. Hence they were eliminated from building a "balanced set" with 60 pairs. "Strict matching", i.e. with no exceptions in all matching variables produced 11 pairs. Self-regulation at baseline was not matched; the difference between the two groups was significant (WPS test, p = 0.0006). The differences in trust towards the attending physician in the two groups was not significant (MH test, p = 0.07), as was the judgment towards the effectiveness of the conventional therapy by the patient (MH test, p = 0.08) and by the attending physician (MH test, p = 0.54).

The data set *OVARRAND* combines the data sets *OvarRand* and *OvarMetRand* into one data set with 41 randomized matched pairs (Table 5). The data set *OVAR* combines the data sets *Ovar* and *OvarMet* into one data set with 137 non-randomized matched pairs. The combined set of the balanced sets has 123 pairs, and the combined set of the sets with strict matching has 40 pairs (Table 6).

3.2. Overall survival

Concerning the randomized studies *OvarRand* and *OvarMetRand*, the effect estimate with the Cox model showed a trend in the first case and a significant effect in favor of the therapy with mistletoe extracts Iscador in the second (*OvarRand*: hazard ratio estimate and 95 % confidence interval: 0.40 (0.15, 1.03), p = 0.058; *OvarMetRand*: 0.33 (0.12, 0.92), p = 0.033). Since there was only one censored survival time, these effects were supported by the estimates of the median differences of survival time according to the Wilcoxon paired-sample (WPS) test which were both significant (Table 5). The combined study *OVARRAND* shows a highly significant effect of Iscador therapy (Table 5). These results can also be inferred from the Kaplan-Meier curves for these data sets (Fig. 2). On the average, the possible gain for survival in the Iscador group was more than one year.

The results for the non-randomized studies *Ovar* and *OvarMet* were, for nearly all individual studies, their subsets, the adjusted and unadjusted estimates, significant in favor of therapy with mistletoe extracts Iscador.

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In particular, we had an estimate of the adjusted hazard ratio of 0.47 (0.31, 0.69) with p = 0.0002 for *Ovar* and for *OvarMet* of 0.62 (0.37, 1.05) with p = 0.077; there were no significant interactions. However, the model for *Ovar* was not adequate; the proportional hazards assumption was not fulfilled. For the combined set *OVAR* the results were even highly significant in most types of analysis (Table 6) and the Cox model was adequate with no significant interactions. On the average, the possible gain for survival in the Iscador group was more than half a year. The adjusted survival curves for *Ovar*, *OvarMet* and *OVAR* according to the models with the adjusted variable self-regulation (SR) from Table 6 are shown in Fig. 3.

3.3. Self-regulation

Psychosomatic self-regulation was assessed on a scale from 1 (low) to 6 (high) twice for both data sets *OvarRand* and *Ovar*. The second assessment was 12 months after the initial one. For *OvarRand*, the effect estimate (median difference and 95 % confidence intervall) was 0.58 (0.30, 0.90) with p = 0.0002. For *Ovar*, the Wilcoxon paired sample test was applied to the full set, the balanced set and the set with strict matching; the effect estimate was the same in all cases: 0.30 and the confidence intervals were (0.10, 0.60), (0.05, 0.55) and (0.05, 0.65), respectively, with p < 0.026 in all cases. Both studies show significant improvements, hence Iscador therapy may help in improving the clinical well-being of ovarian cancer patients without metastases.

3.4. 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 shocks. However, there were no reports of such events.

4. Discussion

4.1. Validity and generalizability

For overall survival *OvarMetRand* (20 pairs) and *OvarRand* (21 pairs) show a significant effect and a strong positive trend, respectively, in favor of long-term complementary therapy with mistletoe extracts Iscador as compared to conventional treatment alone. In the first case, the margin of improvement of psychosomatic self-regulation after 12 months was highly relevant and significant in favor Iscador group.

Overall survival in the two non-randomized studies *Ovar* and *OvarMet* was significant in favor of the long-term complementary Iscador therapy *vs.* conventional treatment alone in most cases of analysis. The improvement of psychosomatic self-regulation in *Ovar* after 12 months was significant in favor of the Iscador group.

Paired matching was used to reduce selection bias in the non-randomized studies for several known prognostic factors. However, to recruit a relevant number of patients, the matching process could not be performed without some exceptions. In order to deal with the biases due to lose matching, with up to two deviations from strict matching, several analytic approaches are applied as a kind of sensitivity analysis: within non-adjusted analyses, balanced sets and sets with strict matching were formed and analyzed separately to compare results. In addition, Cox proportional hazards models were built with and without adjustments of other factors than therapy (including interactions of the first kind, if significant).

In summary, the unadjusted analyses show comparable results for the different subsets, proving that the original sets were fairly well balanced, at least with respect to the prognostic factors used in the matching process. This is supported by the fact that the results of the Cox proportional hazards model do not differ very much between adjusted and unadjusted analyses. The only exception was the set *OvarMet*, where the set with strict matching comprises of only 11 pairs, making the confidence interval for the median difference of survival time rather large, including 0; this was mirrored by the adjusted analysis with the Cox model, where the confidence interval for the hazard ratio estimate includes 1.

The most important sources of bias in non-randomized studies are selection and confounding [35]. More specifically, residual bias might stem from (i) non-perfect matching, (ii) non-matched prognostic factors and (iii) not measured (un)known prognostic factors. The first case has already been dealt with. The second and third cases are more serious. According to the study design, several important medical prognostic factors were either not recorded throughout all cases, or not recorded at all (i.e. steroid receptor; 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 hence are not available for analysis (i.e. exact dates of first diagnosis, operation, initial and follow-up data assessments and matching; socioeconomic status; social support; spirituality). The source of recruitment and the hospital were dropped for reasons of anonymity. This leaves the case of unknown factors open for speculation. Attrition bias was a minor problem, since with the drop-out of any study patient, her matching partner was excluded as well 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 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 were neither sample-size calculations in advance nor adjustments for multiple testing. Still, in the combined data sets *OVARRAND* and *OVAR* the estimated effects were very strong and thus not affected by these limitations.

As in the case of the randomized studies, the generalizability (external validity) of the non-randomized studies might be limited by the fact that the inclusion and exclusion criteria were not very precise. Furthermore, apart from the matching criteria, there were no explicit procedures for building pairs. It was simply looking for the best matching partner. In the case of deviations from the main matching criteria, there was no rule how to proceed. In these studies there might have been a preference for patients with a good prognosis, as patients from either group who died shortly after diagnosis could not take part in the study.

Concerning the short-term improvement of psychosomatic self-regulation in *Ovar*, estimated by the median of the pair-wise differences of self-regulation between second and first evaluation, the analyses of the original set and the subsets all show significant improvements. However, the estimate of the median of improvement was well below 0.5, but may still be clinically relevant [12].

4.2. Consistency and generalizability

The baseline values of *OvarRand* and *Ovar* were comparable, and so were the results. That is, although not in all cases significant, the results of *OvarRand* were consistent with those of *Ovar*: they point in the same direction. Together, both studies gain from each other: The first has better internal validity and the latter has better generalizability. The same was true for the other two studies. The baseline values of the randomized matched-pair study *OvarMetRand* and the non-randomized matched-pair study *OvarMet* were comparable as were the results. Again, the results of the randomized study *OvarMetRand* were consistent with the results of *OvarMet*: they point in the same direction.

A randomized study performed in China [36] with a total of 233 patients included 71 ovarian cancer patients and showed a significant improvement in quality of life and much fewer adverse events under the treatment of mistletoe extracts Helixor in comparison with Lentinan, both in addition to conventional oncological therapy. However, the results for this subgroup of ovarian cancer patients were not reported. There is only one published prospective controlled study particularly concerning the treatment of ovarian cancer with mistletoe extracts Iscador [4]. However, this study is of low quality [37, 38], has too few patients (n = 19) and does not report sufficient data for conclusive results. There are reports in two controlled retrospective studies, one with a concurrent control from another clinic [39] and one with a historical control from the literature [40, 41]. The first is of a fairly good quality [2, 42, 43] and shows a significant prolonging effect on survival in favor of therapy with mistletoe extracts Iscador. The second one is of low quality [2, 42, 43]; the groups were definitely not comparable and hence the results were not relevant. References for case series can be found in [2, 42].

4.3. Tolerability and safety

A documentation of unintended adverse drug reactions to therapy with mistletoe extracts Iscador was not part of the design of these studies. However, there is no evidence of severe adverse effects that can plausibly be related to this therapy [2, 23, 24, 44–47]. This has also been supported by more recent data on the tolerability and safety of a complementary therapy with Iscador [48, 49]. In addition, apart from its effects on prolonging of overall survival, therapy with mistletoe extracts Iscador seems to reduce the side effects of conventional chemotherapy [36, 48] i.e. help patients to live better through the impairments of chemotherapy.

5. Conclusion

The consistency of 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 extracts Iscador might have clinically relevant therapeutic effects on overall survival in these studies with ovarian cancer patients. In the short run, psychosomatic self-regulation, as a measure of autonomous coping with the disease, improves significantly more under Iscador therapy than under conventional therapy alone for ovarian cancer patients with and without metastases. Overall, therapy with mistletoe extracts Iscador seems to prolong survival and improve well-being of ovarian cancer patients to a clinically relevant extent.

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Contributors

Ronald Grossarth-Maticek was responsible for the design and implementation of these studies, as well as for the quality, reliability and documentation of the raw data; he contributed substantially to this paper by earlier drafts and comments; he 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; he wrote the first draft of this paper and gave final approval to the version to be published.

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