

Supplementary materials for:

Ronald Grossarth-Maticcek, Renatus Ziegler: Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). *Forsch Komplementärmed* 2007;14:140–147.

Patients and Methods

Background

The three studies presented here are part of an encompassing long-term prospective epidemiological program to explore the influence and interaction of physiologic, psycho-social, individual and therapeutic factors on the survival of cancer patients [11, 14, 15]. Quality of life was assessed in these studies as the degree of psychosomatic «self-regulation», i.e. the capacity for autonomous regulation of emotional, social and psychological factors [16–20].

The 'Heidelberg Prospective Intervention Study', which started in 1972/73, is a comprehensive project that includes (i) the 'Heidelberg Primary Prevention Study' relating to chronic diseases and (ii) the 'Heidelberg Secondary Prevention Study' relating to cancer patients. Several institutions and private donors funded this project (see below and [11]) so as to enable Grossarth-Maticcek to complete it independently of any single institution. His priority throughout was on the overall project. From 1973 onwards, the research studies were designed and implemented during different phases of his work in a range of institutions (see below).

The cancer patients for the 'Heidelberg Secondary Prevention Study' – of relevance to the studies reported here – were drawn from sources specified in [11]; for example, these patients were recruited from clinics, or were seeking help at the Institute of Preventive Medicine (see below), or were recruited from the 'Heidelberg Prospective Prevention Study'.

No comparative studies were made between cancer patients from different sources, such as the Institute of Preventive Medicine or the 'Heidelberg Prospective Prevention Study'. For this reason there is no information about possible different levels of self-regulation in these groups. However, we made strenuous efforts to ensure that partners for matching pairs in randomized and non-randomized studies were recruited from the same data source, for example within the group that sought help at the Institute of Preventive Medicine.

Study Setting and Data Sources

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

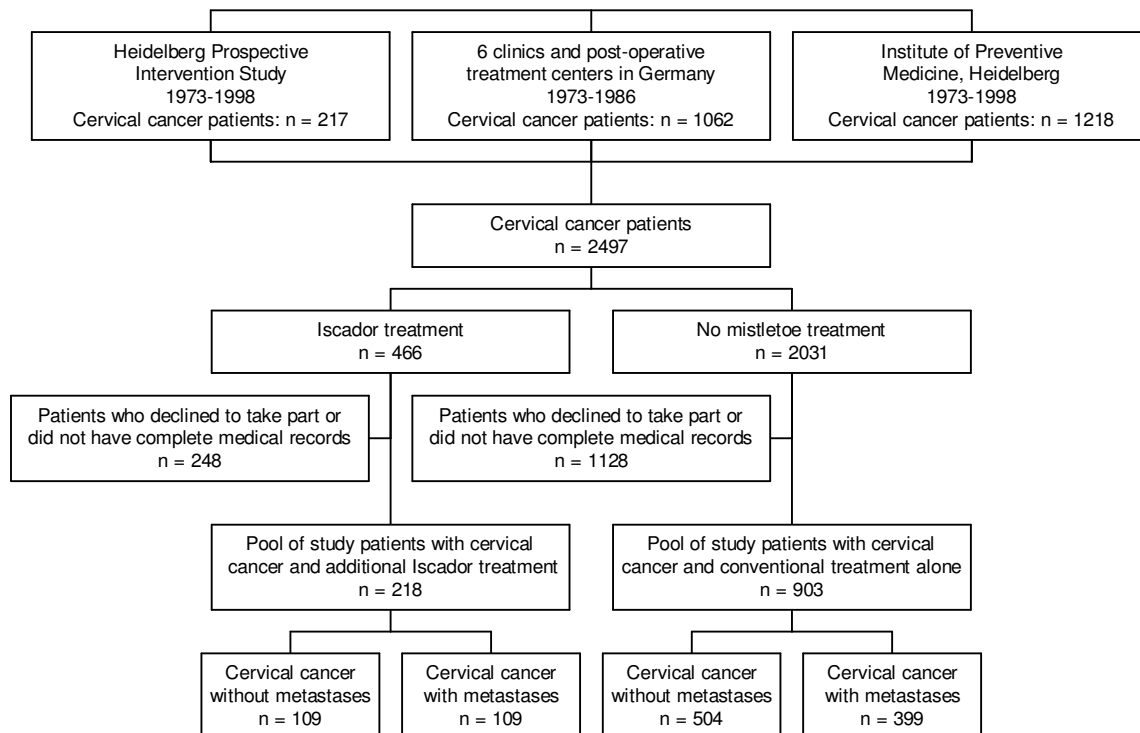


Figure 1: Flow chart for the pool of sources of study patients with cervical cancer for randomized and non-randomized matched-pair studies.

Institutional Setting

While carrying out the 'Heidelberg Prospective Intervention Study', largely completed by 1998, Grossarth-Maticcek was affiliated with diverse institutions. From 1973 to 1976 he was research scientist at the Institute for Social Medicine at the University of Heidelberg. Between 1976 and 1981 he was director of an international social science oncology research project in Heidelberg, which was funded by the Stuttgarter Stiftung für Bildung und Behindertenförderung, the Deutsche Forschungsgemeinschaft and the Deutsche Krebshilfe. From 1981 to 1989 he was co-director with the psychologist H.-J. Eysenck (University of London's

Institute of Psychiatry) of another international research program on prospective epidemiology and preventive behavioural medicine.

Between 1989 and 2003 he was director of the Institute of Preventive Medicine, Political, Economic and Health-related Psychology at the European Centre for Freedom and Development (ECPD) in Heidelberg. The ECPD is the regional department of the UN-founded University of Freedom. Since 2003 he has been director of the Centre for Multidisciplinary Research and Development of Preventive Strategies in Heidelberg. This centre is involved in multidisciplinary basic research and cooperates with many university institutes and research institutions. The centre focuses on investigating complex social phenomena via interactions between social structures and cognitive-emotional behaviour regulation. In addition, interventions at the behavioural level are devised in order to positively influence developments, i.e. in the field of preventive medicine. (For more information, see www.grossarth-maticek.de.)

Sources of funding

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Beginning in 1999, the final determination of time and cause of death of the study patients was partially financed by the Verein für Krebsforschung, 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 these studies as well as for the quality, reliability and documentation of the raw data; he contributed substantially to this paper by either drafts or comments; he gave final approval to the version to be published. Rénatus Ziegler started working on this project in 2001. He proposed, executed, documented and presented the statistical analysis for this paper; he wrote the several drafts of this paper and gave final approval to the version to be published.

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Survival Curves

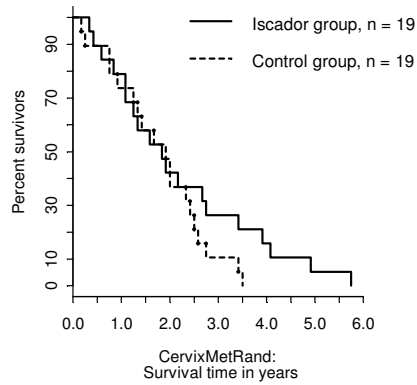


Figure 2: *CervixRand* (19 randomized matched pairs): Kaplan-Meier survival curves for the full set showing the two groups with and without Iscador.

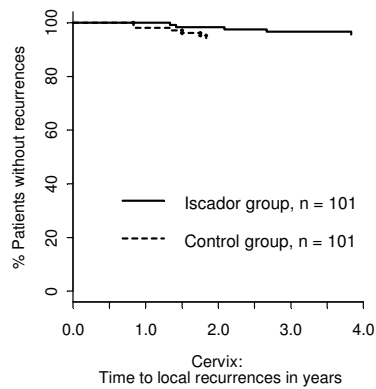


Figure 4: *Cervix* (102 non-randomized matched pairs, 1 pair with missing values in SR): Adjusted time to event curves for time to local recurrences showing the two groups with and without Iscador, based on the model in table 6 (type of analysis: III).

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CHARACTERISTICS OF DATA FLOW	N		N	
Candidates for the two non-randomized matched-pairs studies (fig. 1)	Primary cervical cancer without metastases 613		Primary cervical cancer with distant metastases 508	
Available for matching	Iscador 109	No Iscador 504	Iscador 109	No Iscador 399
Study	<i>Cervix</i>		<i>CervixMet</i>	
	<i>Iscador</i>	<i>Control</i>	<i>Iscador</i>	<i>Control</i>
Resulting matched pairs	106	106	70	70
Declined participation, not received therapy or drop-out before start of therapy in Iscador group	3 pairs		1 pair	
Discontinued therapy, drop-out after start of therapy	0 pairs		0 pairs	
Lost to follow-up	1 pair		0 pairs	
Raw data for analysis	102	102	69	69
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	102	102	66	66
Excluded from primary analysis	0	0	0	0
Survival analysis (Cox model)	102	102	66	66
Censored	0	0	0	0
Excluded (missing values)	1	0	2	26
Reduced data sets				
Balanced set	92	92	62	62
Strict matching	73	73	45	45

SR Self-regulation
Balanced set Subgroup of full set of matched-pairs *not* favoring patients with Iscador therapy
Strict matching Subgroup of full set of matched-pairs of patients exactly fulfilling all matching criteria

Table 2
Patient characteristics (matching variables and other variables) in the non-randomized matched-pair studies *Cervix* and *CervixMet*

		Study		Test p	CervixMet		Test p
		<i>Cervix</i>	Control		<i>CervixMet</i>	Control	
Prognostic variables		<i>Iscador</i>	Control		<i>Iscador</i>	Control	
		102	102		66	66	
Matching variables	FIGO			<0.01 ²			0.13 ²
	IB	37	37				
	IIA	28	27				
	IIB	20	12				
	IIIA	1	10				
	IIIB	7	7				
	IVA	9	9		28	24	
	IVB				27	31	
	IV				11	11	
	Age at first diagnosis			0.49 ¹			0.67 ¹
	mean	51.04	51.02		51.14	51.05	
	SD	8.36	8.31		6.81	7.05	
	range	34–66	35–67		38–67	35–66	
Grading			0.55 ²				
1	19	18					
2	11	13					
3	17	17					
NA	55	54		66	66		
Conventional therapy							
Operation	70	70	1.00 ³	29	27	0.84 ³	
Chemotherapy	0	0	1.00 ³	39	39	0.76 ³	
Radiotherapy	71	71	1.00 ³	31	33	1.00 ³	
Hormone therapy	3	2	0.68 ³	0	0	1.00 ³	
Baseline variables	Co-therapy						
	Non-Iscador CAM therapy	0	2	0.21 ³	0	0	1.00 ³
	Psychotherapy	14	17	0.58 ³	NA	NA	
	Self-regulation			0.33 ¹			<0.01 ¹
	mean / median	3.64 / 3.70	3.79 / 3.80		3.63 / 3.60	3.20 / 3.20	
	SD	0.65	0.60		0.82	0.70	
	range	1.8–5.1	2.3–5.3		1.9–5.7	1.8–5.3	
	Patient judgement*						
	Trust in physician	NA	NA				0.23 ²
	1				25	9	
	2				25	26	
	3				15	5	
	Iscador Therapy	NA	NA				
	1				28	0	
	2				32	0	
	3				6	0	
	Conventional Therapy	NA	NA				1.00 ²
1				11	11		
2				38	38		
3				17	16		
Physician judgement*							
Iscador therapy	NA	NA					
1				24	0		
2				26	0		
3				16	0		
Conventional therapy	NA	NA				0.61 ²	
1				20	27		
2				40	31		
3				6	8		
Therapy variable	Iscador use (years)	n = 102	n = 0		n = 66	n = 0	
	mean / median	5.31 / 5.08			1.82 / 1.46		
	SD	3.36			1.56		
	range	0.67–13.5			0.04–7.25		

SD

Standard deviation

NA

Not available

¹

Wilcoxon paired sample test (WPS)

²

Marginal homogeneity test (MH)

³

McNemar test (MN).

Categories of judgement

1 = strong, 2 = moderate, 3 = weak

Table 3		
Flow chart of primary cervical cancer patients with distant metastases from the randomized matched-pair study CervixMetRand.		
DATA SOURCES	N	
Pool of cervical cancer patients with no mistletoe therapy (fig. 1)	903	
CHARACTERISTICS OF DATA FLOW		
Primary cervical cancer patients with distant metastases and with no mistletoe therapy (table 1)	399	
Patients used as controls in parallel non-randomized studies (table 1)	-70	
Pool of patients for building randomized matched-pairs	329	
Study	CervixMetRand	
	<i>Iscador</i>	<i>Control</i>
Resulting matched patients	19	19
Declined participation, not received therapy or drop-out before start of therapy in Iscador group	0 pairs	
Discontinued therapy, drop-out after start of therapy	0 pairs	
Lost to follow-up	0 pairs	
Raw data for analysis	19	19
Pairs with 0 deviation from the specified matching criteria	13 pairs	
Pairs with 1 deviation from the specified matching criteria	6 pairs	
Survival analysis (Cox model)	19	19
Censored	0	0
Excluded	0	0

Table 4
Patient characteristics (matching variables and other variables) in the randomized matched-pair study *CervixMetRand*

	Study	CervixMetRand		Test p
		Iscador n = 19	Control n = 19	
Prognostic variables				
Matching variables	FIGO			
	IVA	4	5	
	IVB	15	14	
	Age at first diagnosis			
	mean	47.68	47.58	
	SD	6.44	6.16	
	range	36–58	37–59	
	Conventional therapy			
	Operation	5	4	
	Chemotherapy	9	9	
Radiotherapy	17	19		
Hormone therapy	0	0		
Baseline variables				
	Co-therapy			
	Non-Iscador CAM therapy	0	0	
	Psychotherapy	NA	NA	
	Self-regulation			
	mean / median	2.98 / 3.00	3.36 / 3.40	0.14 ¹
	SD	0.68	0.57	
	range	1.80–4.10	2.20–4.40	
	Patient judgement*			
	Trust in physician			0.10 ²
	1	7	5	
	2	9	5	
	3	3	9	
	Iscador Therapy			
	1	9	0	
	2	3	0	
	3	7	0	
	Conventional Therapy			1.00 ²
	1	5	5	
	2	9	6	
	3	5	7	
Physician judgement*				
Iscador therapy				
1	6	0		
2	8	0		
3	5	0		
Conventional therapy			0.53 ²	
1	5	8		
2	11	9		
3	3	2		
Therapy variable				
Iscador use (years)				
mean / median	n = 19	n = 0		
SD	1.70 / 1.33			
range	1.73			
	0.08–5.58			

SD

Standard deviation

NA

Not available

¹

Wilcoxon paired sample test (WPS)

²

Marginal homogeneity test (MH)

Categories of judgement

1 = strong, 2 = moderate, 3 = weak

Patient characteristics of non-randomized study *Cervix*: Building balanced pairs

Concerning the patient characteristics (table 2), the difference in the stages between the two groups is significant (MH test, $p = 0.004$). For 10 pairs, the stage is worse for the control patient. In the cases where the grading is known, the difference is not significant ($p = 0.55$); we ignored the minor differences, which were on average in favor of the control group anyway. Concerning therapies, there are only minor differences; the co-therapies are in favor of the control group. Concerning age at first diagnosis, the difference is not significant (WPS test, $p = 0.49$). The pairwise difference in the year of first diagnosis is less or equal ± 3 (data not shown). Hence, for building a «balanced set», 10 pairs where the Iscador patient had stages of lower risk were eliminated, yielding a balanced set of 92 pairs. «Strict matching», i.e. with no exceptions in all matching variables produced 73 pairs. – Self-regulation at baseline was not matched; the difference between the therapy groups is not significant (WPS test, $p = 0.33$).

Patient characteristics of non-randomized study *CervixMet*: Building balanced pairs

Concerning the patient characteristics (table 2), the differences in the stages between the two groups is not significant (MH test, $p = 0.13$). However, for 4 pairs, the stage is worse for the control patient. Concerning therapies, there are only minor differences which were judged as not relevant. The difference for age at first diagnosis is not significant (WPS test, $p = 0.67$). The pairwise differences in the year of first diagnosis are evenly distributed among the pairs and are not significant either (WPS test, $p = 0.37$). It turned out, that two pairs had a difference greater than ± 3 years (5 or 6 years respectively); however, this was judged as not relevant. Hence, for building a «balanced set», 4 pairs where the Iscador patient had stages of lower risk were eliminated, yielding a balanced set of 62 pairs. «Strict matching», i.e. with no exceptions in all matching variables produced 45 pairs. – Self-regulation at baseline was not matched; the difference between the two groups is not significant (WPS test, $p = 0.14$). The differences in trust towards the attending physician in the two groups is not significant (MH test, $p = 0.10$), as is the judgment towards the effectiveness of the conventional therapy by the patient (MH test, $p = 1.00$) and by the physician (MH test, $p = 0.53$).

Statistics

The analysis and presentation of the data sets reported here is made as close as possible to the suggestions made in the CONSORT statement for randomized studies [28] and its adaptation to non-randomized studies [29].

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, since there are no censored survival times. This yields generally a conservative result with respect to the Iscador group. The estimate of the median difference and the 95% confidence intervals are calculated according to Hodges-Lehmann [30]. All p -values are two-sided. In order to explore the sensitivity of the matching criteria, the full data sets are compared with the balanced sets and with the data sets according to strict matching.

In the baseline comparisons of Iscador and 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 [31].

In the second stage of the analysis of overall survival, a Cox proportional hazard regression model is fitted to the three full data sets separately. The therapy with Iscador is introduced using a binary variable: either therapy or no therapy. An indicator variable for the matched-pairs is introduced and a stratified analysis based on the pairs is performed taking into account all available prognostic factors and paired interactions of the significant factors. This stratification according to matched-pairs generally results in a conservative estimate in comparison to the unmatched analysis [32, § 7.1]. The model development and the assessment of model adequacy are performed according to the recommendations in [33, 34]. No automatic variable selection procedure was used. No adjustment of prognostic factors is performed in the randomized study. According to the recommendations in [34], the assumption of proportional hazards (PH) is checked 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».

The comparison of the time to the event of recurrences, lymphatic metastases, distant metastases and death by cancer between the groups with or without Iscador therapy is based on an analysis of multiple events per subject [35]. In order to compare the results of different statistical models, two options are analysed: (i) for the case of non-ordered events it is assumed that the multiple events can happen in any order of time, which is consistent with general clinical experience; (ii) for the case of ordered events, we assumed that recurrences occur first, then lymphatic metastases and finally distant metastases before death, since this sequence of events happens in most cases.

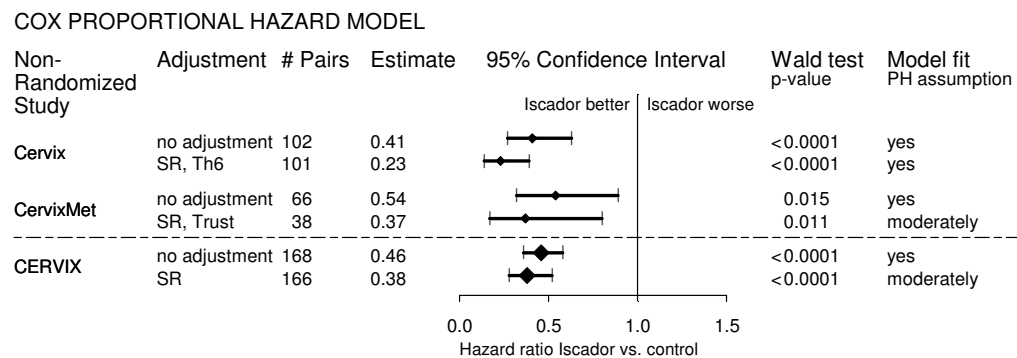
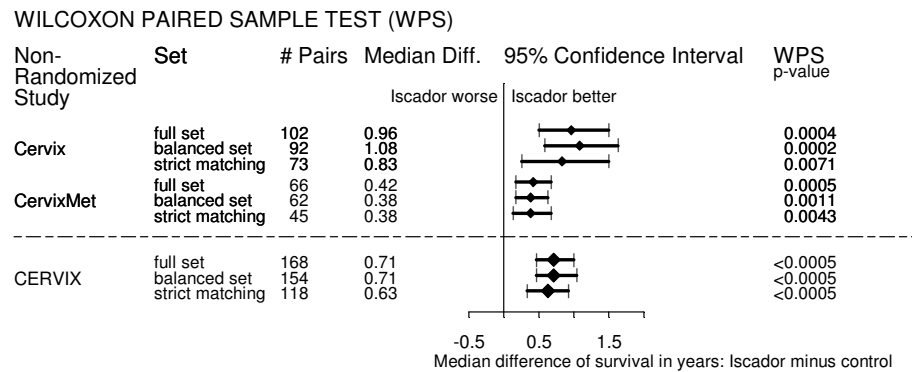
All statistical tests and confidence intervals are calculated on the basis of matched-pairs, i.e. we always used tests for two paired samples or tests with stratification according to the pairs, respectively. Confidence intervals (CI) are always 95%. CI and test results are regarded as significant if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

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 $n < 100$ with the exact procedures in StatXact 7 (Cytel Software Corporation 2005, Cambridge, Massachusetts).

Table 5

Overall survival for the data sets with non-randomized matched pairs: *Cervix* and *CervixMet* and their combination into *CERVIX*

Since all patients died within each study (no censored data), a Wilcoxon paired sample test (WPS) was performed on all data sets. – 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. There were no significant interactions. In each of the sets *Cervix* and *CervixMet* there is 1 pair with missing values from SR; the variable «Trust» in *CervixMet* has missing values in 27 pairs.



- Balanced set Subgroup of full set of matched-pairs *not* favoring the patients with Iscador therapy
- Strict matching Subgroup of full set of matched-pairs of patients fulfilling exactly all matching criteria
- WPS Wilcoxon paired sample test
- PH Proportional hazard
- ISC Iscador therapy
- SR Self-regulation at baseline
- Th6 Psychotherapy
- Trust Trust in attending physician

The hazard ratio estimate measures the Iscador vs. the control group and the p-value from the Wald test measures the significance of the estimated variable ISC. 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'.

Table 6											
Cervix: Numbers of events and time to the event of local recurrences, lymphatic metastases and distant metastases											
Type of analysis	Set of pairs	Statistics	Fitted variables	Indicator	Local recurrences		Lymphatic metastases		Distant metastases		
I	full set 2 × 102	count	–	number	Iscador 5	Control 6	Iscador 0	Control 0	Iscador 1	Control 0	
	balanced set 2 × 92	count		number	5	6	0	0	1	0	
	strict matching 2 × 73	count		number	2	2	0	0	1	0	
II	full set 2 × 102	WPS	–	Estimate and CI for median difference in survival in years	0.92	–	–	–	0.96	–	
					0.42, 1.50	–	–	0.42, 1.46	–		
		SLR	p-value	0.0014	–	–	0.0009				
			p-value	0.48	–	–	0.331				
		balanced set 2 × 92	WPS	–	Estimate and CI for median difference in survival in years	1.04	–	–	–	1.04	–
						0.50, 1.63	–	–	0.50, 1.58	–	
	SLR		p-value	0.0007	–	–	0.0004				
			p-value	0.48	–	–	0.317				
	strict matching 2 × 73		WPS	–	Estimate and CI for median difference in survival in years	0.83	–	–	–	0.79	–
						0.25, 1.46	–	–	0.17, 1.50	–	
		SLR	p-value	0.0078	–	–	0.0137				
			p-value	0.157	–	–	0.317				
III	2 × 101	Cox model	SR, Age	Estimate and CI for hazard ratio of ISC	1.42	–	–	–	–	–	
					0.37, 5.39	–	–	–	–		
					p-value	0.61	–	–	–		
					model adequacy	PH assumption	–	–	model does not converge		
					interactions	fulfilled	–	–	–		
					missing values	not significant	–	–	–		
					1 from self- regulation in Iscador group	1 from self- regulation in Iscador group	–	–	–		
Type of analysis	Set of pairs	Statistics	Fitted variables	Indicator	All events (including death)						
IV	2 × 101	Extended Cox model for unordered events	SR, Age	Estimate and CI for hazard ratio of ISC	0.29 0.18, 0.44						
				p-value model adequacy	< 0.0001 PH assumption fulfilled, no significant interactions; 1 missing value from self-regulation in Iscador group						
V	2 × 101	Extended Cox model for ordered events (An- dersen-Gill)	SR, Age	Estimate and CI for hazard ratio of ISC	0.32 0.22, 0.48						
				p-value model adequacy	< 0.0001 PH assumption fulfilled, no significant interactions; 1 missing value from self-regulation in Iscador group						

WPS Wilcoxon paired sample test

SLR Stratified log-rank test

CI 95 %-Confidence interval

PH Proportional hazard

ISC Iscador therapy

SR Self-regulation at baseline

Th2 Chemotherapy

Th3 Radio therapy

§ Model used in adjusted survival curve in fig. 4

Balanced set Subgroup of full set of matched-pairs *not* favoring the patients with Iscador therapy

Strict matching Subgroup of full set of matched-pairs of patients fulfilling exactly all matching criteria

The hazard ratio estimate measures the Iscador vs. the control group and the p-value from the Wald test measures the significance of the estimated variable ISC.

Type of analysis: (I) descriptive analysis; (II) WPS tests on the assumption that all patients had their events and SLR tests taking account of censored event times and matched pairs; (III) traditional Cox proportional hazards model with assessment of model adequacy, (IV) on the clinical plausible assumption that the time to the event of local recurrences, lymphatic or distant metastases do not necessarily happen in an ordered fashion, an extended Cox model with unordered events is set up according to [35, section 8.4]. (V) For reasons of comparison, a model according to Anderson and Gill for ordered events (first recurrence, then lymphatic and distant metastases before death) that are independent within subjects is constructed as outlined in [35, section 8.5].

All variables other than ISC with a significant influence on the outcome were included in the Cox model and are listed in the column 'Fitted variables'.