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Retrospektive Untersuchung der Wirksamkeit von Misteltherapie bei Mamma-Ca-Patienten

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Retrospektive Untersuchung der Wirksamkeit von Misteltherapie bei Mamma-Ca-Patienten

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1. AIM OF THE STUDY

The influence of mistletoe therapy on state of health, disease progression and survival of patients with breast cancer will be investigated in the underlying study. Tolerance of mistletoe therapy in patients with preceding surgery of breast cancer will be evaluated as well as the importance of extend and application rate of mistletoe medication. Further, analysis of local relapse and appearance of distant metastasis, as marker of tumour progression will be performed. Main objective, however, will be the survival rate of patients under mistletoe therapy.

2. STUDY DESIGN

The study represents a retrospective, monocentric survey with 3022 patients. On contrary to classical retrospective studies, inspection record and hypothesis were formulated before data collection.

2.1. Study Design and Population Selection

The study was realised in collaboration with the tumour ambulance of the Gemeinschaftskrankenhaus Herdecke (GKH-Herdecke). The survey consisted of a mail questionnaire sent to every patient diagnosed with breast cancer and introduced at GKH-Herdecke since opening of the tumour ambulance in 1981. Patients were retrospectively asked for information about extend, tolerance and side effects of mistletoe therapy. Further questions concerned post-operative therapies (chemotherapy, hormone therapy and radiation therapy) and occurrence of local relapse and distant metastasis. The first questionnaire was sent during the second half of the year 1999 and a second questionnaire in the year 2000 to patients not responding the first request.

Additional diagnostic information was obtained from clinical records including information of type of surgery, TNM-classification, histopathological grading, oestrogen-/ progesterone receptor status, lymph node status and family history of disease.

The GKH-Herdecke follows anthroposophical guidelines and attracts most likely patients not representative for the general population. This selection bias cannot be avoided.

In general, retrospective studies are susceptible to various sources of errors as for example selection bias due to pre-selection of patients with favourable disease outcome. To prevent this phenomenon all patients with breast cancer who applied at the tumour ambulance

were surveyed without exception, also patients who visited GKH-Herdecke only once were included. Still one has to keep in mind that the proportion of deceased patients in the trial population will most likely not represent reality and possibly causing an overestimation of survival rates. Furthermore retrospective data are always prone to recall bias concerning the general inaccuracy of recalling information from the past resulting in incomplete data sets. Missing data are depicted in the following analysis as Missing, NMISS or similar.

2.2. Objectives

Principal object of the study will be the survival analysis of patients under mistletoe therapy. Furthermore frequency of local relapse and occurrence of distant metastasis will be assessed. The tolerance of mistletoe preparation will be described and incidence of side effects will be reported as secondary objectives. Similar, the extend of mistletoe medication will be evaluated.

2.3. Statistical Methods to analyse the Trial Population

The statistical analysis will be performed using SAS Version 8.01. Demographic characteristics of the study group will be summarized. Characteristics of condition, disease history and extend of malignancy will be shown by frequency tables. Details of the progression of malignancy will be listed in details.

2.4. Statistical Methods to analyse Tolerance of Mistletoe Therapy

Tolerance of mistletoe therapy will be presented merely by description. Frequency tables will present state of health and side effects under mistletoe therapy.

2.5. Statistical Methods to analyse Survival Rates

Survival rates were analyzed and visualized by Kaplan-Meier plots. The stratified log rank trend test was used to test for equality over strata. Missing values and categories with less than 5 events were not considered in this test.

2.6. Definition of event times and censoring

Event times were determined for patients which answered the questionnaire personally, for patients with lifetime information given by relatives, or for patients with relevant lifetime

information from other sources (code on CRF 2,3 and 4). The detailed algorithm to define event times and censoring is given in the Appendix (8.1)

3. ANALYSIS OF TRIAL POPULATION

The study comprises 3022 patients (N=3022) with assured breast cancer who applied at the tumour ambulance of GKH-Herdecke through the years 1981 to 2000. These patients include 15 male patients who generally develop mamma-carcinomas very different in prognosis and progression to tumours in female patients and were excluded from analyses (female patients N=3007).

Since TNM-classification of tumours is an important prognostic factor for survival of patients, only patients with enlisted TNM-classification and respective staging according to UICC guide lines in the clinical record are considered in the analysis. With this restriction 834 non-TNM classified patients have to be excluded from the final patient group analyzed (female, UICC staged patients N=2173).

Subtracting patients for whom information about mistletoe therapy was missing leaves 1279 patients treated explicitly with mistletoe-therapy in the trial population. However, not all of these patients answered the questionnaire by themselves, for several patients information was obtained from relatives or the examining medical doctor and have to be regarded with reservation, especially with respect to issues concerning tolerance of mistletoe therapy, condition and side effects of therapy. Source of information is presented as frequency table in **Table 1.**

Table 1. Information about mistletoe therapy.

	Trial population	N=1246	%
Information about mistletoe therapy	1st Q answered by patient	588	47.2
	1st Q answered by relative	99	7.9
	2nd Q answered by patient	98	7.9
	2nd Q answered by relative	46	3.7
	Information by medical doctor	409	32.8
	No Information	6	0.5

Q: questionnaire.

From the population of 1279 mistletoe treated patients, 33 female patients diagnosed with metachronous bilateral malignancy were finally excluded. From the remaining 1246 patients, 1223 patients are unilateral diseased and 23 patients synchronous bilateral diseased.

Since bilateral patients are recorded twice and have to be considered as dependent data in statistical analysis, we considered for analysis only the record with worse prognosis. One has to keep in mind that in case of bilateral diseased patients, monochronous as well as synchronous, analysis of survival time, one of the main objectives of the study, might vary from unilateral patients. Several studies suggest that bilateral breast cancer patients have worse prognosis of survival compared to unilateral patients (Eur. J. Surg. Oncol. 2002 Jun;28(4); World J. Surg. 2001Sep;25(9)).

In fact, 1246 patients are analysed in the final analysis with details of trial population are shown in **Figure 1**. Of this population (N=1246), 520 patients were treated with mistletoe preparation from Helixor. The remaining 726 patients obtained mistletoe preparation from Iscador, Abnoba, Eurixor, Lektinol, Plenosol, Vysorel or even a mixture of different preparations.

3.1. Demography of the Population

The selected patient population (N=1246) considered in the following analysis consists of female patients unilateral or synchronous bilateral diseased, with known TNM classification and explicitly treated with mistletoe. The demography of the population was described by explorative analysis of age and origin of patients whereby the latter was encoded by the first two digits of the postcode. Analysis of age is shown in **Table 2.**

Table 2. Age at diagnosis (N=1246).

	GROUP	NOBS	NMISS	MEAN	SDEV	MIN	Q1	MED.	Q3	MAX
Age	Mistletoe_yes	1221	25	49.2	10.3	21.0	42.0	49.0	56.0	80.0

Patient's postal code was further used to extract regional provenance. The majority of surveyed population is domiciled in Germany, except 15 patients who resident abroad. A frequency plot of postcodes from Germany is shown in **Figure 2.** In the analysis, the first two digits of the postal code were applied. An accumulation of local patients from the area around the GKH-Herdecke (post code: **58** for Herdecke) is revealed. Furthermore, many patients come from the close-by urban centers of Bochum, Dortmund and Essen (post code: **44-45**).

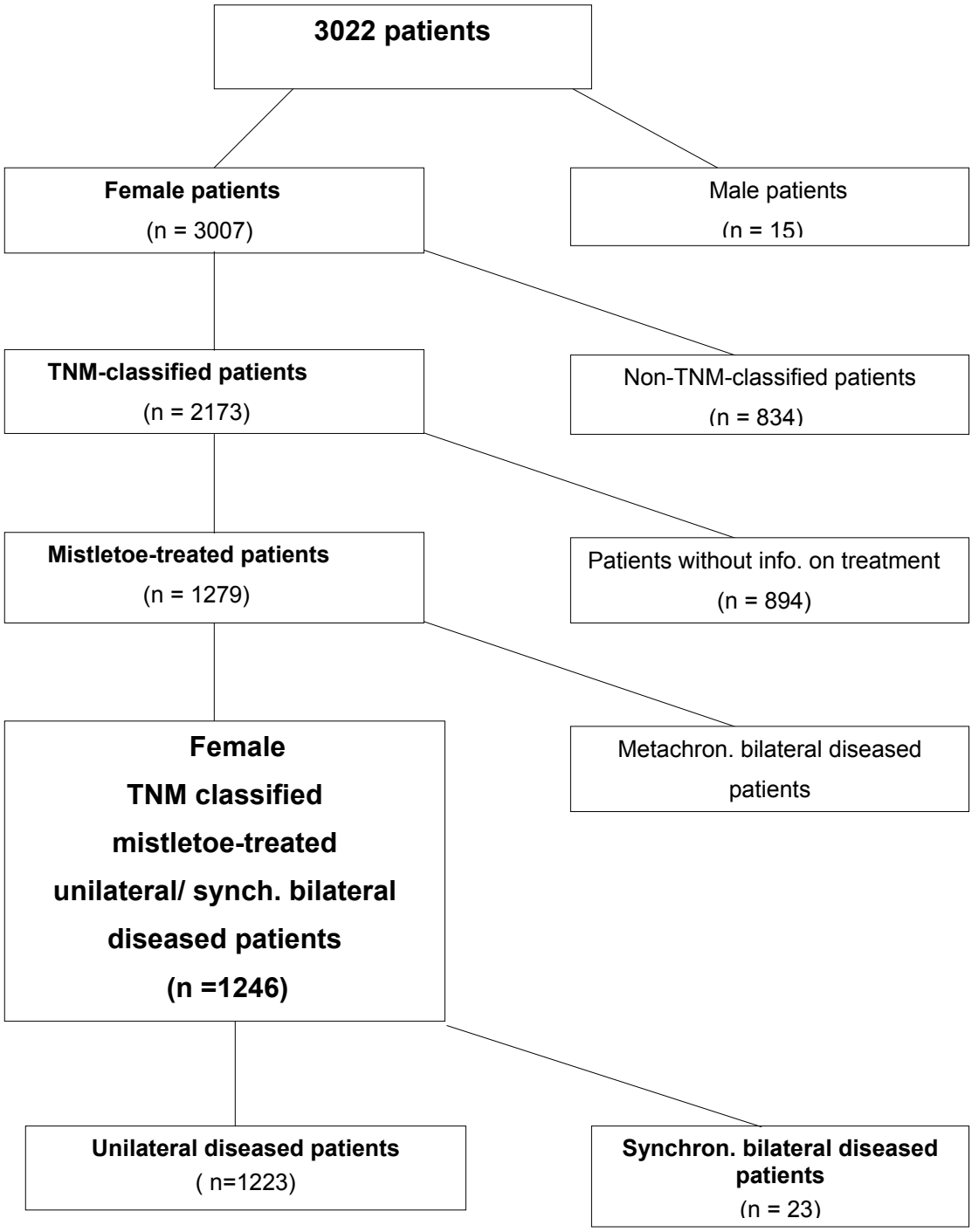

Figure 1. Subgroup of patient's analysis in the following study.

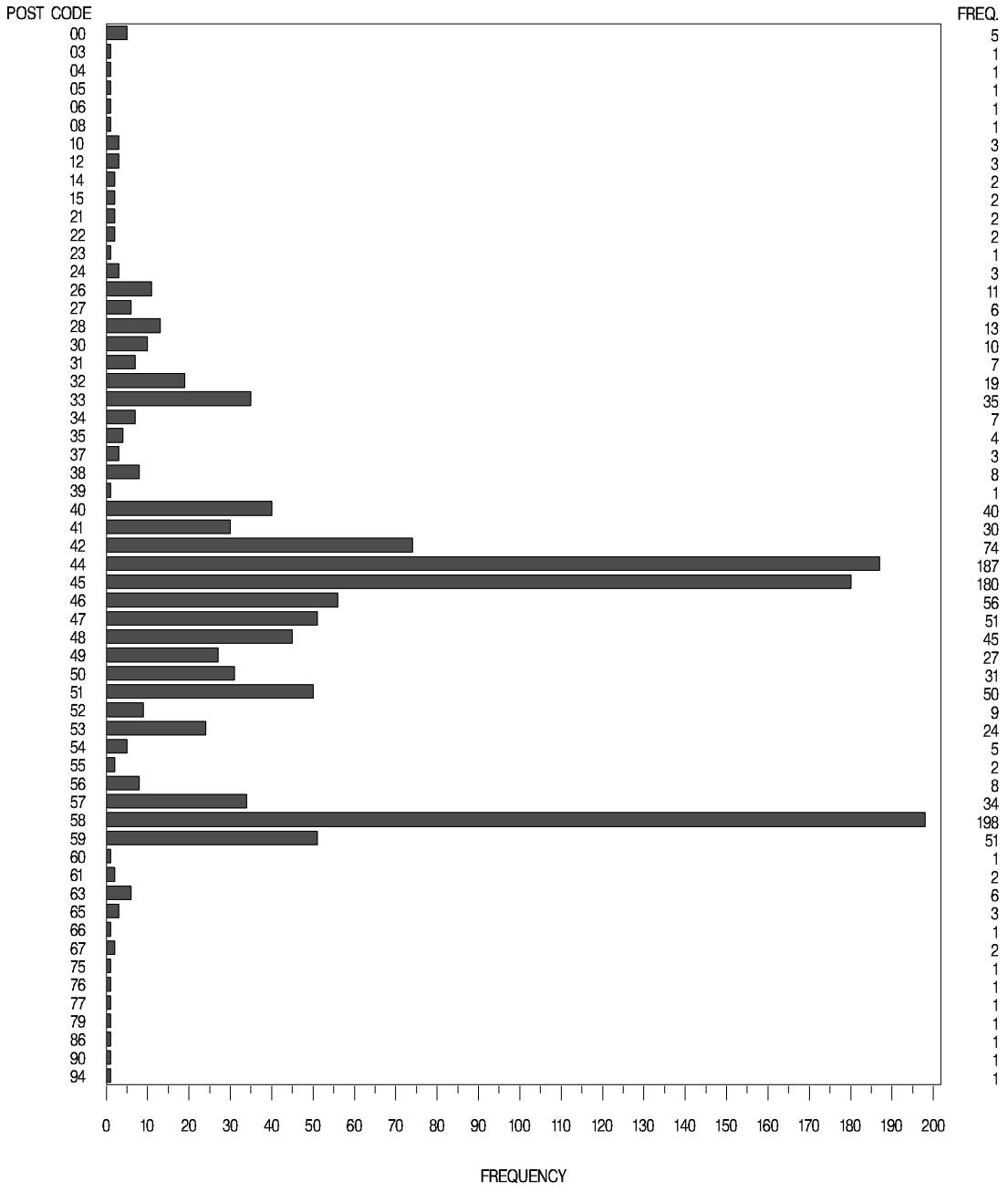

Figure 2. Post code of patients visiting GKH-Herdecke.

3.2. Extend of Disease and Tumour Classification

Breast tumours are characterized by the UICC-tumour classification system, differentiation status and expression of hormone receptors for estrogen and progesterone. Categories of TNM_T, TNM_N and TNM_M classification reporting primary tumour characteristics, lymph node status and the existence of distant metastasis, respectively, are combined to a "stage" variable according UICC guidelines and depicted in **Table 3** and **Table**

4 indicating that 60% of the trial population is assigned to stage II, while stage 0 and IV is hardly represented.

Table 3. Disease characteristics I. – TNM classification.

		Mistletoe_treated N=1246	
		N	%
TNM_T	Tis	6	0.5
	T1	482	38.7
	T2	588	47.2
	T3	99	7.9
	T4	65	5.2
	Missing	6	0.5
TNM_N	N0	570	45.7
	N1	590	47.4
	N2	72	5.8
	N3	7	0.6
	NX	2	0.2
	Missing	5	0.4
TNM_M	M0	1212	97.3
	M1	34	2.7

Table 4. Disease characteristics II. – UICC classification for tumour stage.

		Mistletoe_treated N=1246	
		N	%
Stage	0	6	0.5
	I	289	23.2
	II	747	60.0
	III	170	13.6
	IV	34	2.7

In addition, information of histopathological grading determining the differentiation status and expression of the estrogen and progesterone hormone receptors are enlisted in **Table 5** and **Table 6**, respectively. Differentiation status of the primary tumour is categorized

in well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3) and non-differentiated (G4) tumours.

Table 5. Disease characteristics III. Histopathological Grading defining the differentiation status.

		Mistletoe_treated N=1246	
		N	%
Histopath. Differentiation Status	Missing	355	28.5
	G1	60	4.8
	G2	436	35.0
	G3	394	31.6
	G4	1	0.1

Table 6. Disease characteristics IV. Receptor status.

		Mistletoe_treated N=1246	
		N	%
Estrogen receptor	Missing/ unknown	307	24.6
	yes	608	48.8
	no	331	26.6
Progesterone receptor	Missing/ unknown	311	25.0
	yes	588	47.2
	no	347	27.8

Occurrence of metastasis at time of diagnosis and post OP is depicted in **Table 7** and **Table 8**. At time of diagnosis lymph node metastasis are found in about half of the trial population, distant metastasis are found only in a small portion (2.7%). 80% of patients with distant metastasis at time of diagnosis develop further distant metastasis post OP.

Table 7. Metastasis at time of diagnosis. (N=1246)

	Mistletoe_treated patients N=1246	
	N	%
Lymph node metastasis at time of diagnosis	669	53.7
No lymph node metastasis at time of diagnosis	570	45.7
Missing	7	0.6
Distant metastasis at time of OP	34	2.7
No distant metastasis at time of OP	1212	97.3

Table 8. Distant metastasis at time of diagnosis and occurrence of metastasis post OP. (N=1246).

	Distant metastasis at time of OP N=34		No distant metastasis at time of OP N=1212	
	N	%	N	%
Metastasis post OP	27	79.4	309	25.5
No metastasis post OP	0	0.0	513	42.3
Missing	7	20.6	390	32.2

Lymph node metastasis and distant metastasis post OP were observed 518 times and localisation of these cases is enlisted as frequency table in **Table 9**.

Table 9. Localisation of metastasis occurring post OP. (N=518* metastasis in N=1246 patients)

	Metastasis occurring post OP		
	N=518*	%	% of total population (N=1246)
Lymphnodes	98	18.9	7.9
Bones	163	31.5	13.1
Brain	33	6.4	2.6
Liver	80	15.4	6.4
Lung	93	18.0	7.5
Skin	24	4.6	1.9
Other Location	27	5.2	2.2

* Multiple statements possibly

3.3. Description of Family History, Surgery and after Treatment

Additional to information on primary tumour diagnosis, clinical records give information about family history, type of surgery and primary tumour localization, which are enlisted as frequency table in **Table 10**. Furthermore, type of post OP therapy is presented in **Table 11**.

Table 10. Description of family history, type of surgery and primary tumour localization.

		N=1246	%
Family history	Missing	27	2.2
	Yes	30	2.4
	No	7	0.6
	Unknown	1182	94.9
Type of surgery	Unknown	26	2.1
	Biopsy	1	0.1
	Partial resection	428	34.3
	Total resection	748	60.0
	Total resection and reconstruction	43	3.5
Localization	Unknown	28	2.2
	Right	584	46.9
	Left	611	49.0
	Bilateral (right)	11	0.9
	Bilateral (left)	12	1.0
ICD-10 Code.C50	Nipple / areola	14	1.1
	Central	21	1.7
	Upper inner quadr.	62	5.0
	Lower inner quadr.	35	2.8
	Upper outer quadr.	181	14.5
	Lower outer quadr.	42	3.4
	Axillary tail	3	0.2
	Overlapping	14	1.1
	Unspecified	874	70.1

Table 11. Disease characteristics II; (therapy following surgery)

	N=1246	%
Missing	269	21.6
Chemotherapy	203	16.3
Radiotherapy	263	21.1
Hormone therapy	88	7.1
Chemo- and radiotherapy	236	18.9
Chemo- and hormone therapy	44	3.5
Radio- and hormone therapy	79	6.3
Radio- and hormone and chemotherapy	64	5.1

3.4. Description of Mistletoe Therapy

Application of different mistletoe preparations and therapy characteristics – recommendation to mistletoe therapy, reason for end of mistletoe therapy and interruption of mistletoe therapy - are in **Table 12** for all patients treated with mistletoe preparation. Similar, information of patients receiving explicitly Helixor preparation is summarized in **Table 13**.

Table 12. Frequency table of mistletoe preparation and mistletoe therapy characteristics.

		N=1246	%
Mistletoe preparation	Missing	99	7.9
	Helixor	520	41.7
	Iscador	447	35.9
	Abnoba	25	2.0
	Eurixor	6	0.5
	Lektinol	9	0.7
	Plenosol	1	0.1
	Vysorel	1	0.1
	Other preparation	6	0.5
	Combination	132	10.5
Recommendation for therapy	Missing	516	41.4
	Medical doctor	373	29.9
	Pharmacy	16	1.3
	No medical practitioner	37	3.0
	Relative/ acquaintance	220	17.7
	Media	84	6.7
Reason for therapy end	Missing	916	73.5
	Cured	110	8.8
	Strong reaction	69	5.5
	Progression of disease	44	3.5
	Dissuaded from therapy	12	1.0
	Don’ t remember	14	1.1
	Other	81	6.5
Interruption of therapy	Missing	540	43.3
	Yes	111	8.9
	No	572	45.9
	Don't remember	23	1.8

Table 13. Frequency table of mistletoe preparation and therapy characteristics of Helixor patients.

		N=520	%
Recommendation for therapy	Missing	185	35.6
	Medical doctor	213	41.0
	Pharmacy	7	1.3
	No medical practitioner	14	2.7
	Relative/ acquaintance	101	19.4
	Media	0	0
Reason for therapy end	Missing	392	75.4
	Cured	37	7.1
	Strong reaction	31	6.0
	Progression of disease	11	2.1
	Dissuaded from therapy	8	1.5
	Don´t remember	6	1.2
	Other	35	6.7
Interruption of therapy	Missing	189	36.3
	Yes	38	7.3
	No	288	55.4
	Don't remember	5	1.0

In addition, duration of mistletoe therapy in month in the overall population treated with mistletoe and the group of Helixor patients is shown in **Table 14**. The mean extend of therapy is about 31 months for the overall population and 29 months for Helixor–treated patients.

Table 14. Duration of mistletoe therapy in months (Total N=1246, Helixor patients N=520).

	GROUP	NOBS	NMISS	MEAN	SDEV	MIN	Q1	MED	Q3	MAX
Therapy length	Mistletoe_treated	645	601	31.3	31.9	0.0	8.0	21.0	44.0	217.0
	Helixor	252	268	29.0	28.5	1.0	9.0	20.5	41.0	217.0

Doses of mistletoe preparation given per injection of mistletoe preparation is enlisted in **Table 15**. While the mean doses of Helixor preparation contains about 49mg/ injection of mistletoe, the total population of mistletoe-treated patients obtains about 36mg/ injection of mistletoe preparation.

Table 15. Doses of mistletoe preparation in mg/ injection (Total N=1246, Helixor patients N=520).

	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MED	Q3	MAX
Doses	Mistletoe_treated	743	503	36.2	44.2	0.0	10.0	20.0	50.0	400.0
	Helixor	399	121	48.9	52.4	0.1	20.0	50.0	50.0	400.0

4. ANALYSIS OF TOLERANCE OF MISTLETOE THERAPY

Tolerance of mistletoe therapy is inferred from information of condition and side effects under mistletoe therapy. Frequency tables of the mistletoe-treated population and Helixor-treated population in particular are depicted in **Table 16** and **Table 17**.

Table 16. Frequency table of condition under mistletoe therapy (N=1246).

		N=1246	%	N=652*	%
Condition	Missing	637	48.4	-	-
	Better	314	23.8	314	48.2
	Same	307	23.3	307	47.1
	Worse	31	2.4	31	4.7
	Don't remember	28	2.1	-	-

*** missing values excluded**

Table 17. Frequency table of condition under Helixor therapy (N=520).

		N=520	%	N=309*	%
Condition	Missing	204	39.2	-	-
	Better	140	26.9	140	45.3
	Same	158	30.4	158	51.1
	Worse	11	2.1	11	3.6
	Don't remember	7	1.3	-	-

*** missing values excluded**

The variables describing side effects – redness, pain, swelling, itching – were summarized to the new variable - local reaction which is presented with the variable - fever in **Table 18** and **Table 19**. The high number of missing values in the side effects and state of health might be explained by the retrospective inquiry that makes it especially difficult to answer questions of condition dating back several years in an accurate manner.

Table 18. Frequency table of side effects under mistletoe therapy (N=1246).

		N=1246	%	N=657*	%
Local reaction	Missing	589	47.3	-	-
	Yes	510	40.9	510	77.6
	No	147	11.8	147	22.4
		N=1246	%	N=536*	%
Fever	Missing	634	50.9	-	-
	Yes	45	3.6	45	8.4
	No	491	39.4	491	91.2
	Don't remember	76	6.1	-	-

*** missing values excluded**

Table 19. Frequency table of side effects under Helixor therapy (N=520).

		N=520	%	N=315*	%
Local reaction	Missing	205	39.4	-	-
	Yes	246	47.3	246	78.1
	No	69	13.3	69	21.9
		N=520	%	N=271*	%
Fever	Missing	231	44.4	-	-
	Yes	18	3.5	18	6.6
	No	253	48.6	253	93.4
	Don't remember	18	3.5	-	-

*** missing values excluded**

Table 20. Frequency table of side effects under mistletoe therapy with preparations other than Helixor (N=726).

		N=726	%	N=342*	%
Local reaction	Missing	384	52.9	-	-
	Yes	264	36.4	264	77.2
	No	78	10.7	78	22.8
		N=726	%	N=265*	%
Fever	Missing	403	55.5	-	-
	Yes	27	3.7	27	10.2
	No	238	32.8	238	89.8
	Don't remember	58	8.0	-	-

*** missing values excluded**

5. ANALYSIS OF SURVIVAL RATES

Kaplan-Meier plots of survival, tumour free survival, relapse free survival and metastasis free survival of mistletoe-treated patients are shown in **Figure 3**, **Figure 4**, **Figure 5** and **Figure 6.** Similar Kaplan-Meier plots of survival, tumour free survival, relapse free survival and metastasis free survival were generated for different UICC classified tumour stages with the respective stratified log rank tests as shown in **Figure 7**, **Figure 8**, **Figure 9** and **Figure 10** and also for different lymphnode status as shown in **Figure 11**, **Figure 12, Figure 13** and **Figure 14.** Median survival times cannot always be determined since the event of death, local relapse or distant metastasis occurred in less than 50% of the considered population. Due to the fact that only very few patients were classified with stage 0 (n=4, no events) and the fact that in stage IV (n=10, 5 events) all events took place not later than 3.5 years after diagnosis, rates and confidence intervals for 5 and 10 years survival could not be calculated.

Significant differences in survival and metastasis free survival rates are observed between UICC classified tumour stages, stratified p-values are in both cases <0.001. On the contrary, tumour free survival and relapse free survival are not distinguishable in different tumour stages. Similar, stratification for lymph node status revealed significant differences between survival time and metastasis free survival time ($p<0.001$ in both cases).

There were no significant differences in survival rate between Helixor, Iscador and other mistletoe preparations (data not shown).

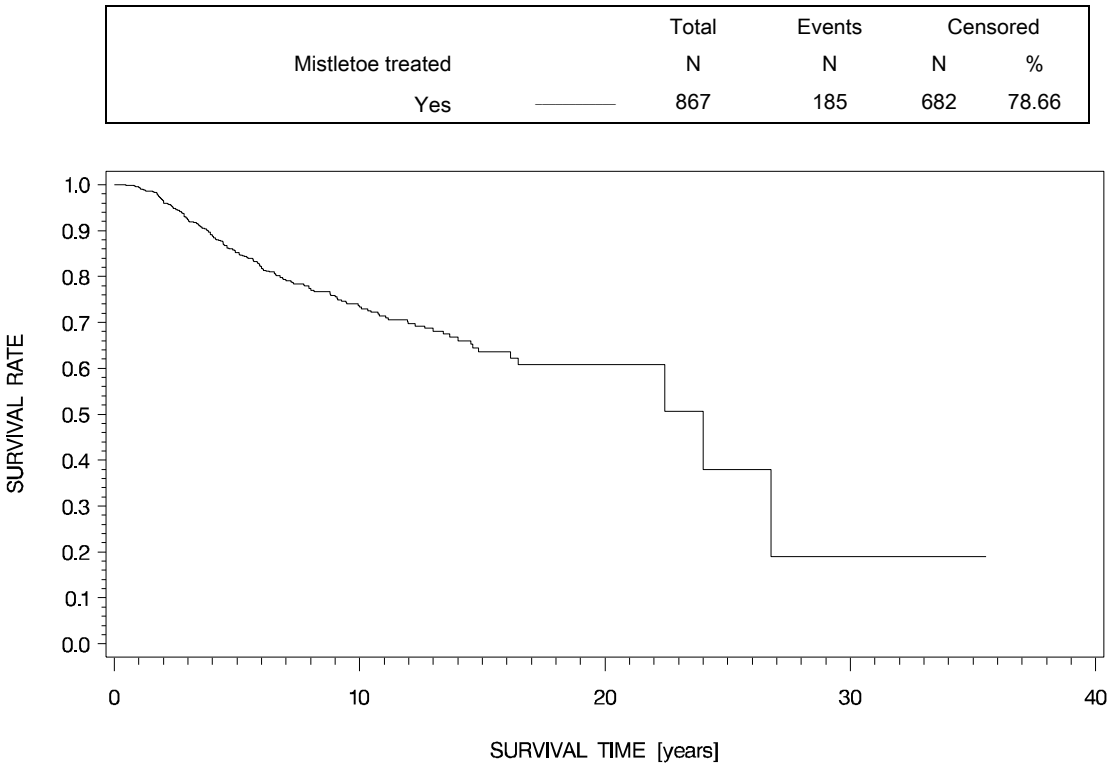

Figure 3. Kaplan-Meier plot of survival time of mistletoe-treated patients.
($N_{missing,\ surv}$=62)

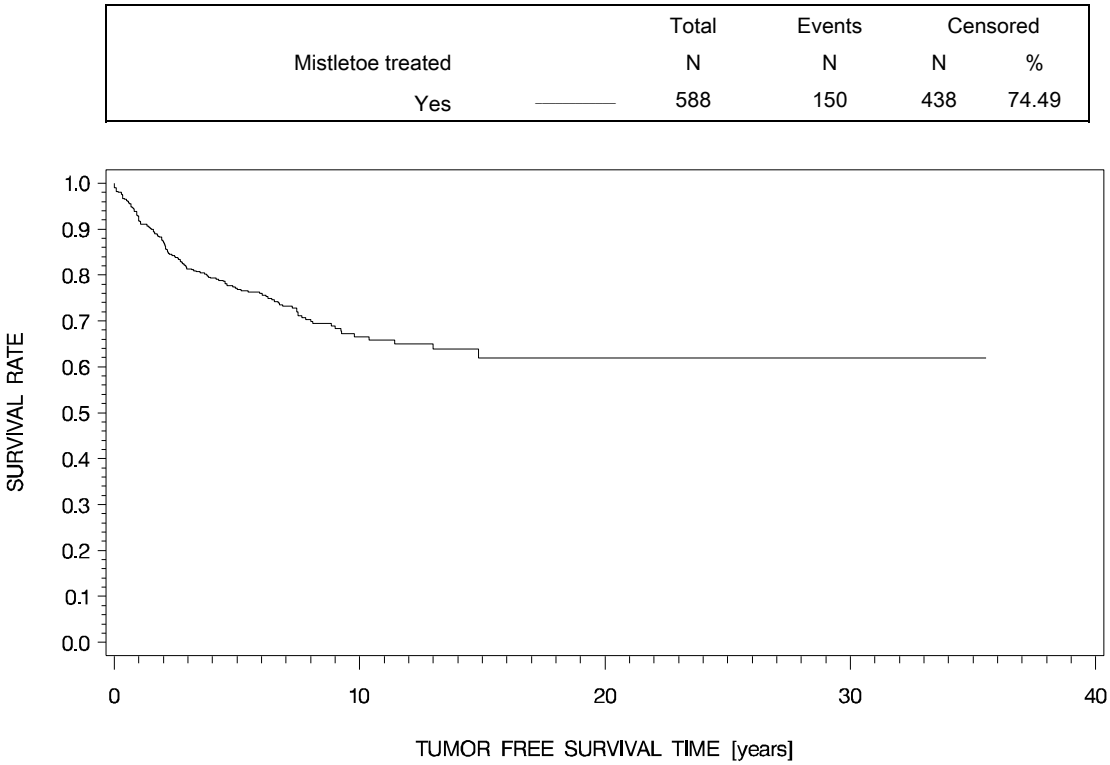

Figure 4. Kaplan-Meier plot of tumour free survival time of mistletoe-treated patients.
($N_{missing,\ surv\_tumourfree}$=341)

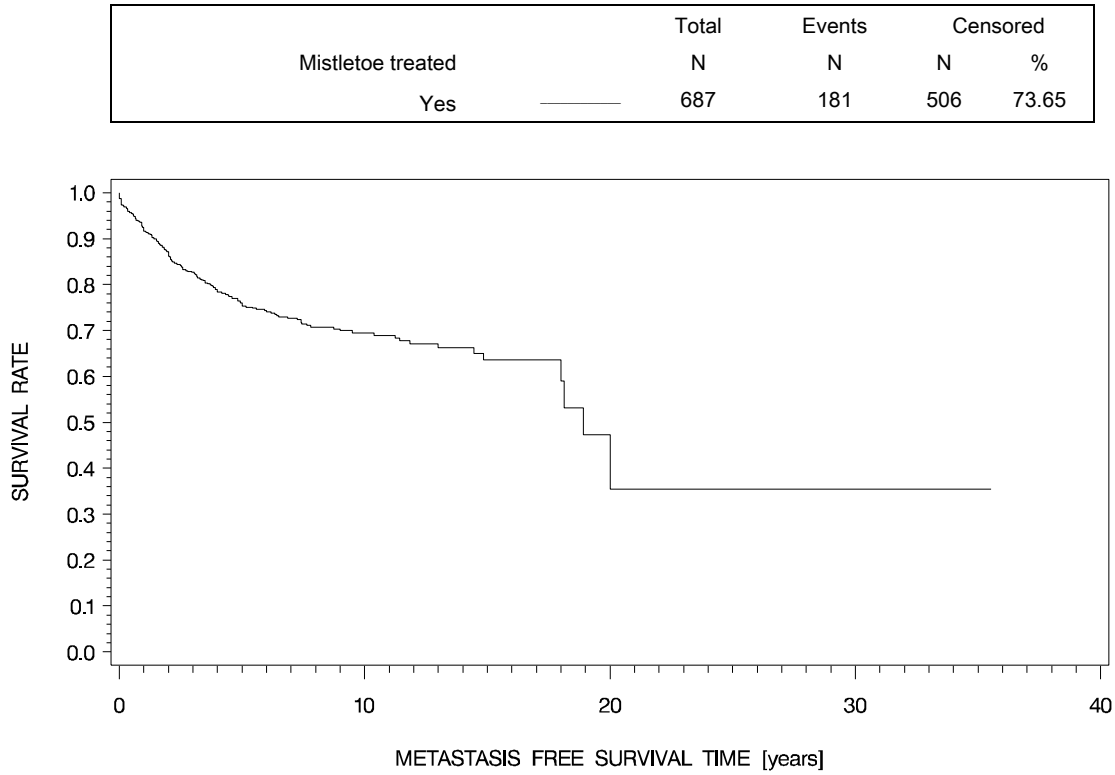

Figure 5. Kaplan-Meier plot of metastasis free survival time of mistletoe-treated patients. ($N_{missing,\ surv\_metfree}$=242)

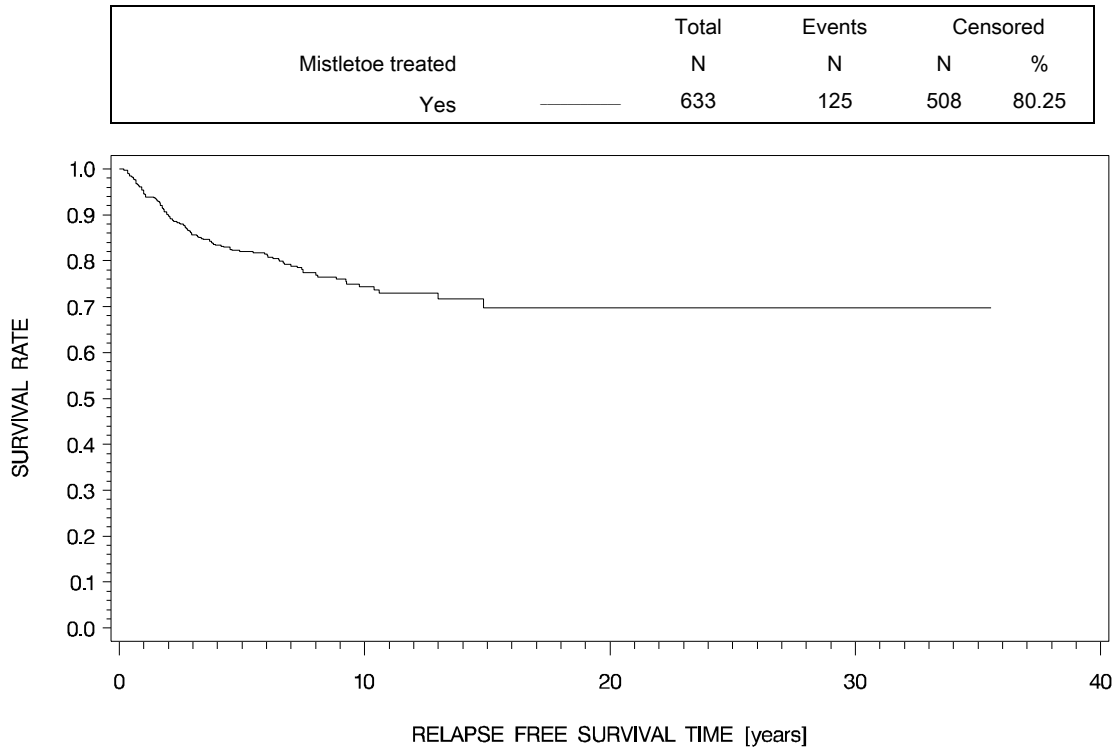

Figure 6. Kaplan-Meier plot of local relapse free survival time of mistletoe-treated patients. ($N_{missing,\ surv\_relapsefree}$=296)

UICC tumour classification		Total N	Events N	Censored N	Censored %	P-value
Stage I	———	219	21	198	90.41	<.0001
Stage II	- - - - - - - - -	531	121	410	77.21	
Stage III	———	103	38	65	63.11	
Total		853	180	673	78.90	

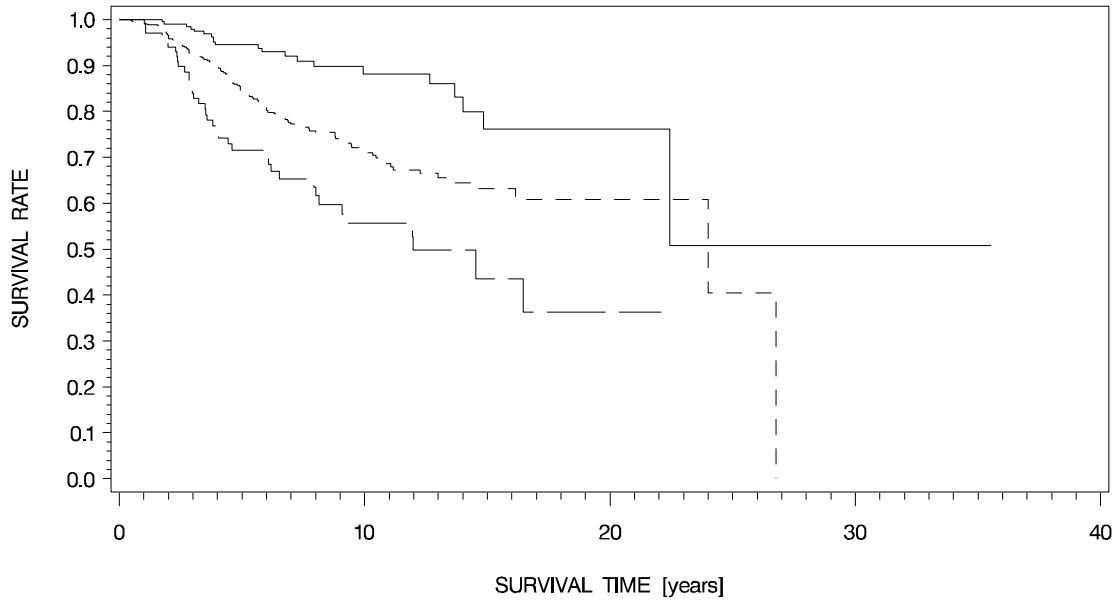

Figure 7. Kaplan-Meier plot of survival time by UICC-tumour classification. P-value: testing equality over strata by log rank trend test. ($N_{missing, surv}$=54)

UICC tumour classification		Total N	Events N	Censored N	Censored %	P-value
Stage I	———	172	36	136	79.07	0.2455
Stage II	- - - - - - - - -	356	94	262	73.60	
Stage III	———	55	17	38	69.09	
Total		583	147	436	74.79	

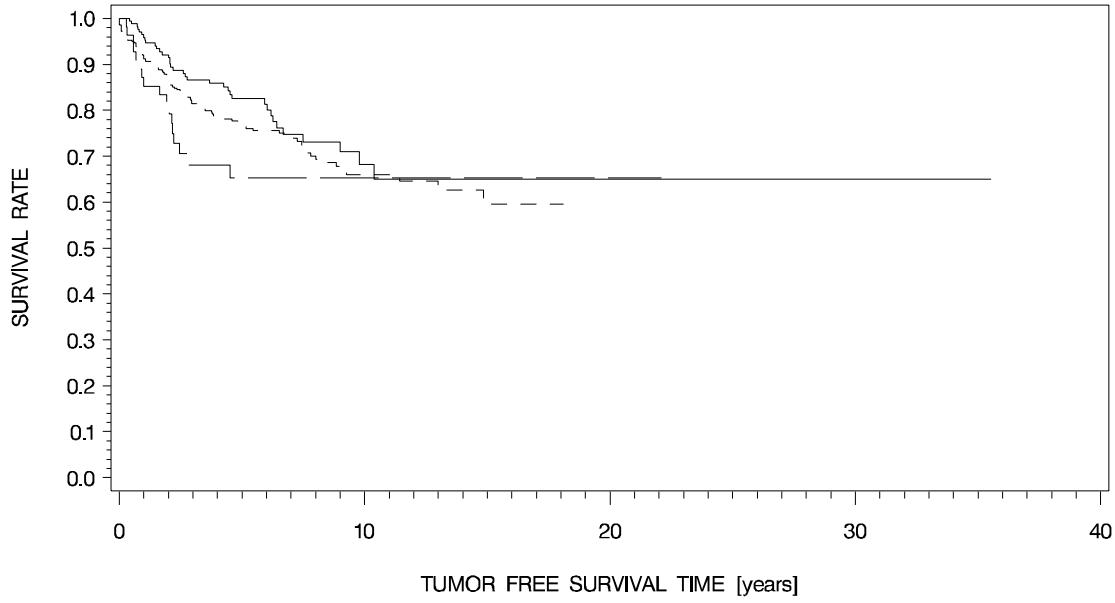

Figure 8. Kaplan-Meier plot of tumour free survival time by UICC-tumour class. P -value: testing equality over strata by log rank trend test. ($N_{missing, surv\_tumourfree}$=324)

UICC tumour classification		Total N	Events N	Censored N	Censored %	P-value
Stage I	————	190	24	166	87.37	<.0001
Stage II	- - - - - - - - -	412	117	295	71.60	
Stage III	— — —	68	26	42	61.76	
Total		670	167	503	75.07	

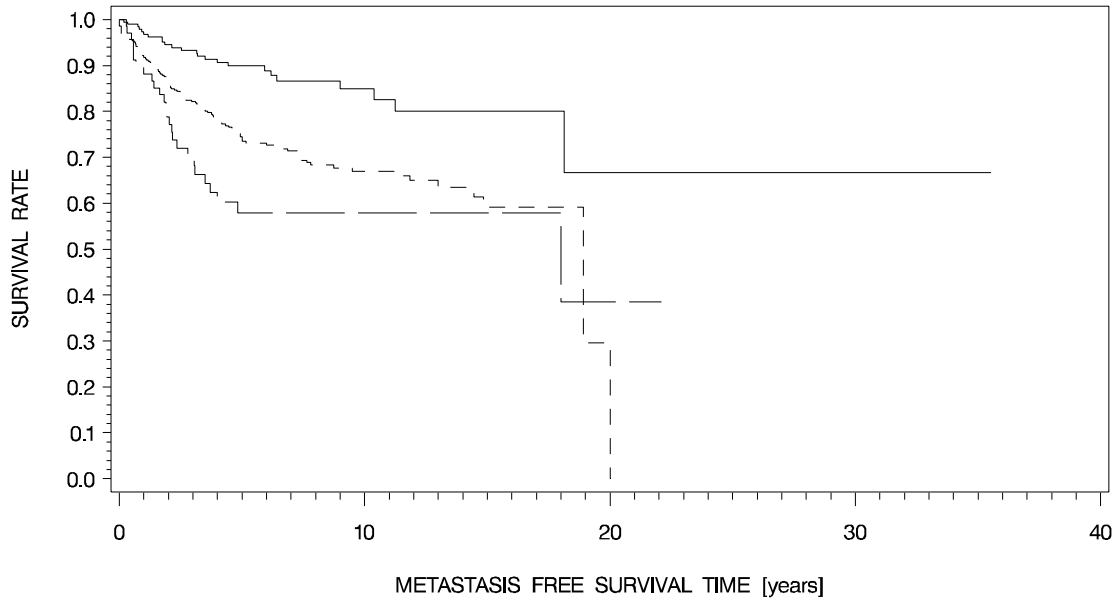

Figure 9. Kaplan-Meier plot of metastasis free surv. time by UICC-tumour class. P-value: testing equality over strata by log rank trend test. ($N_{missing,\ surv\_metfree}$=237)

UICC tumour classification		Total N	Events N	Censored N	Censored %	P-value
Stage I	————	179	32	147	82.12	0.6183
Stage II	- - - - - - - - -	389	78	311	79.95	
Stage III	— — —	60	14	46	76.67	
Total		628	124	504	80.25	

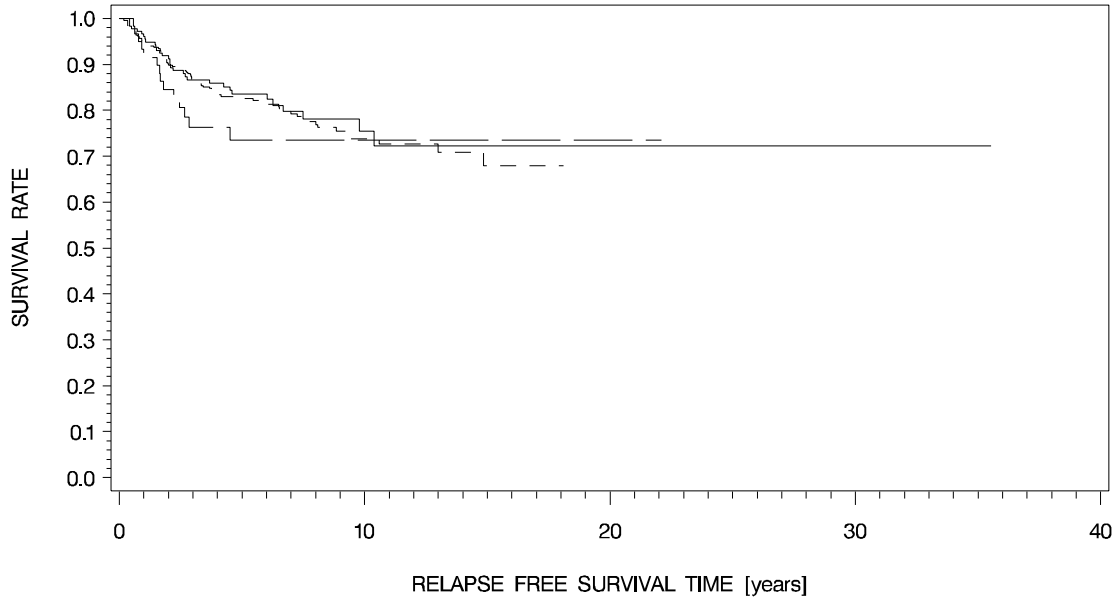

Figure 10. Kaplan-Meier plot of local relapse free surv. time by UICC-tumour classif. P value: testing equality over strata by log rank trend test. ($N_{missing,\ surv\_relapsefree}$=279)

		Total	Events	Censored		P-value
LN Status		N	N	N	%	
LN neg.	———	416	54	362	87.02	<.0001
LN pos.	- - - - - - - - -	447	129	318	71.14	
Total		863	183	680	78.79	

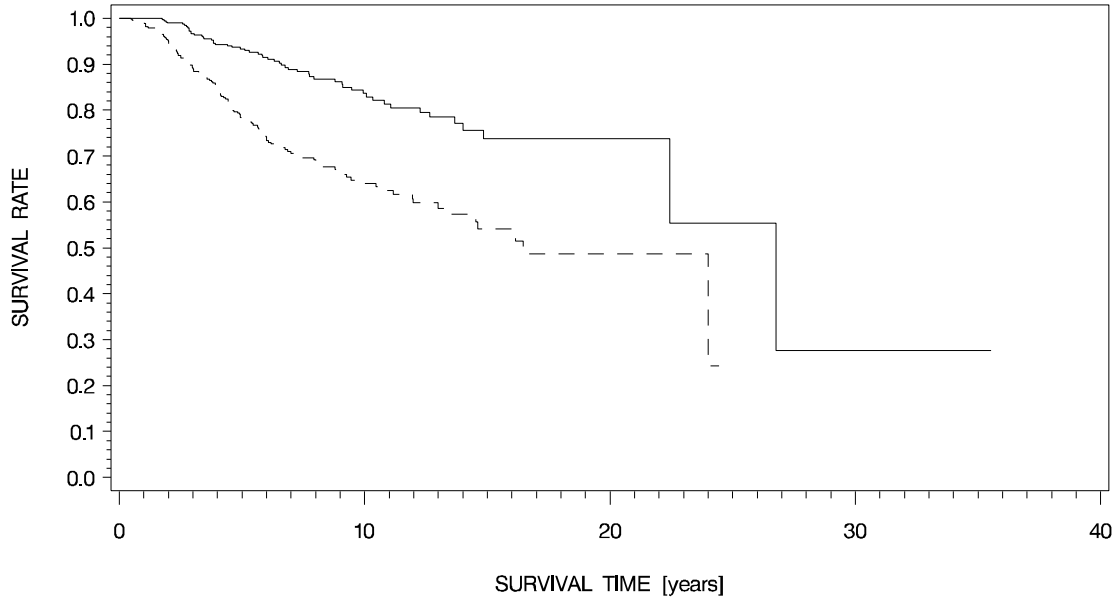

Figure 11. Kaplan-Meier plot of survival time by LN status. P-value: testing equality over strata by log rank trend test. ($N_{missing, surv}$=66)

		Total	Events	Censored		P-value
LN Status		N	N	N	%	
LN neg.	———	318	76	242	76.10	0.2518
LN pos.	- - - - - - - - -	268	72	196	73.13	
Total		586	148	438	74.74	

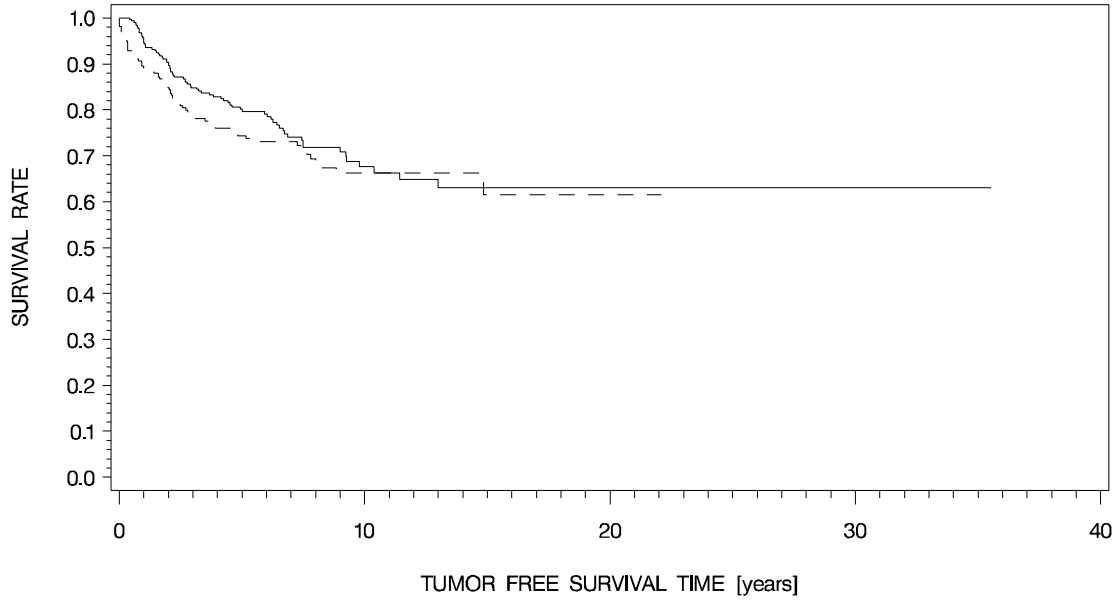

Figure 12. Kaplan-Meier plot of tumour free survival time by LN status. P-value: testing equality over strata by log rank trend test. ($N_{missing, tumour\ free\ surv}$=343)

LN Status		Total N	Events N	Censored N	Censored %	P-value
LN neg.	———	351	60	291	82.91	<.0001
LN pos.	- - - - - - - - -	332	117	215	64.76	
Total		683	177	506	74.08	

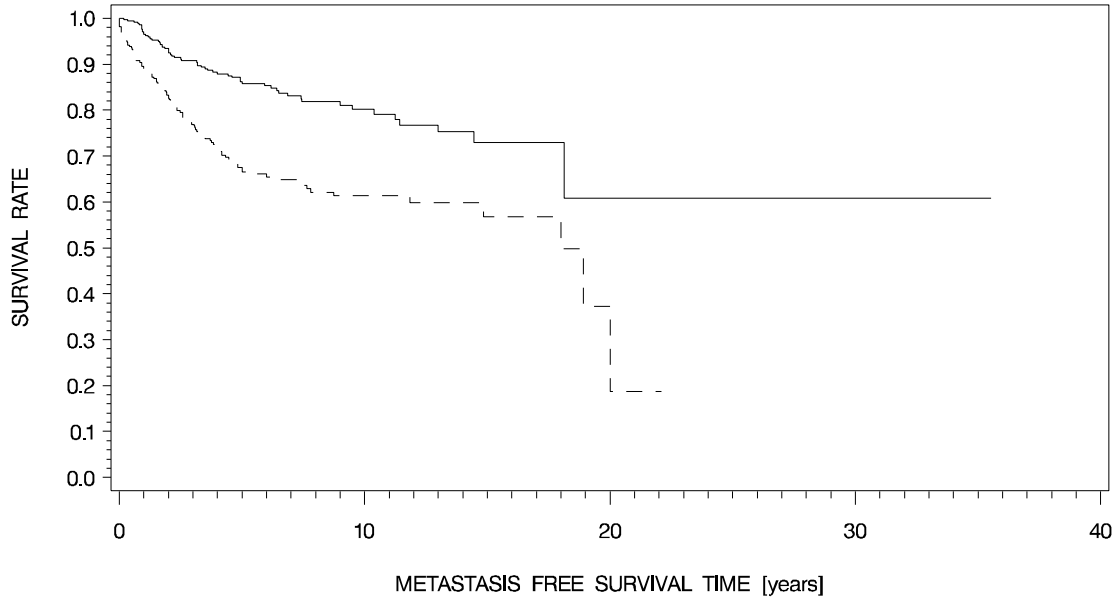

Figure 13. Kaplan-Meier plot of metastasis free survival time by LN status. P-value: testing equality over strata by log rank trend test. ($N_{missing,\ surv\_metfree}$=246)

LN Status		Total N	Events N	Censored N	Censored %	P-value
LN neg.	———	335	66	269	80.30	0.7813
LN pos.	- - - - - - - - -	296	59	237	80.07	
Total		631	125	506	80.19	

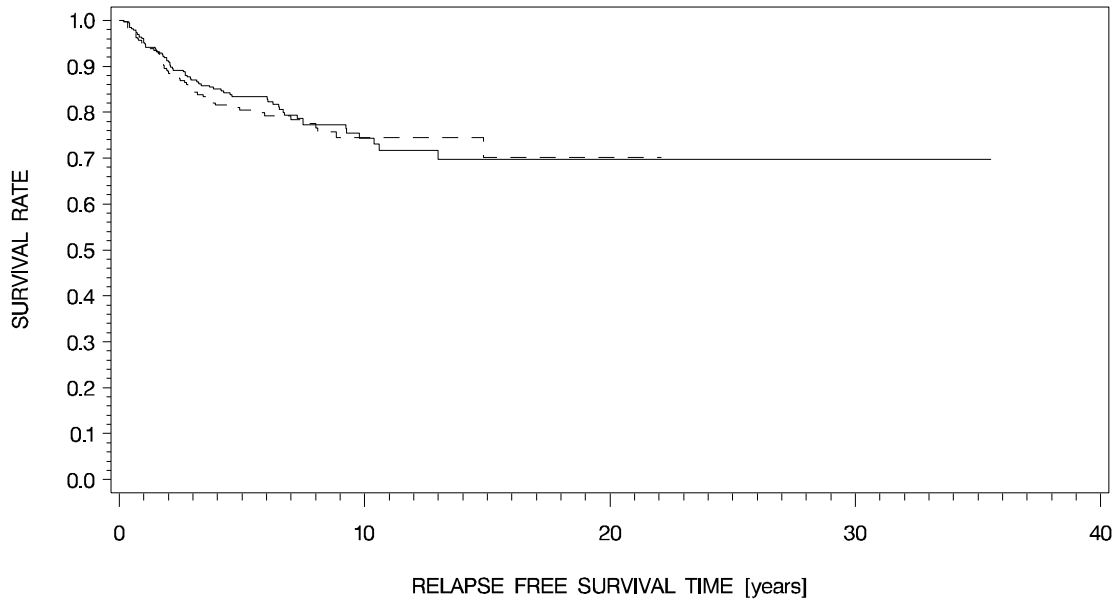

Figure 14. Kaplan-Meier plot of local relapse free survival time by LN status. P-value: testing equality over strata by log rank trend test. ($N_{missing,\ surv\_metfree}$=298)

Survival rate of mistletoe treated patients after 5 and 10 years are depicted in **Table 21**. To show that this is indeed the case the actual life status of a small pool of randomly chosen patients who did not answer the questionnaires was inquired post analysis. See Appendix for details.

Table 21. 5 and 10yrs survival rate of mistletoe-treated patients (N=929)

			Survival Time	
	N	NMISS	5 years	10 years
Mistletoe-treated patients	867	62	85.2%	73.3%
Mistletoe-treated patients stratified for tumour stages				
Stage I	219	8	94.6%	88.1%
Stage II	531	37	84.7%	71.6%
Stage III	103	9	71.5%	55.6%
Mistletoe-treated patients stratified for LN status				
LN pos. patients	416	24	77.9%	63.8%
LN neg. patients	447	37	93.4%	83.7%

Table 22. Median survival times of mistletoe-treated patients (N=929)

			Median Survival Time in years	
	N	NMISS	overall	metastases free
Mistletoe-treated patients	867	62	24.0	18.9
Mistletoe-treated patients stratified for tumour stages				
Stage I	219	8	> 22.4	> 18.1
Stage II	531	37	24.0	18.9
Stage III	103	9	12.0	18.0
Mistletoe-treated patients stratified for LN status				
LN pos. patients	416	24	16.5	18.0
LN neg. patients	447	37	26.8	> 18.1

For the purpose of comparing the information about survival time with the Münchner Tumour Register, stages II and III have been evaluated additionally, divided into II a and b as well as III a and b.

Table 23. 10yrs survival rate of mistletoe-treated patients with stage II a, II b, III a, III b

Stage	Total	Events	Censored	Percent Censored	10 years survival time	95% Confidence Interval
IIA	313	55	258	82.43	78.5%	[72.8%; 84.2%]
IIB	218	66	152	69.72	61.2%	[52.6%; 69.8%]
IIIA	66	27	39	59.09	45.7%	[30.5%; 60.9%]
IIIB	37	11	26	70.27	72.2%	[54.1%; 90.3%]

6. CONCLUSION

This retrospective study was designed to describe a breast cancer patient population treated with mistletoe therapy adjuvant to conventional post-operative treatment in respect to the objectives survival time and condition under therapy.

A collective of 3022 breast cancer patients applied in the antroposophical institution of GKH Herdecke - Gemeinschaftskrankenhaus Herdecke (GKH) - during the time of 1980 to 2000. For analysis, a trial population of N=1246 patients was extracted from the overall population (N=3022), these 1246 patients meet the following criteria: female, known tumour stage according to UICC guidelines, explicit mistletoe treatment, unilateral or synchronous bilateral diseased.

Demography of the population revealed an average patient's age of 49 yrs. Extend of the disease was mainly characterized by TNM classification and respective tumour staging, 60% of the trial population were diagnosed with stage II tumours, while only 23% of patients were found with stage I and 14% with stage III tumours. Stage 0 and stage IV were found only marginally. The histopathological differentiation status revealed about one third of patients with moderate differentiated tumours and another third of patients with poorly differentiated tumours. The categories well differentiated tumours as well as non differentiated tumours were only poorly occupied.

Concerning metastasis at time of diagnosis, in about 50% of patients lymph node metastasis were found, while distant metastasis were diagnosed in only 3% of patients. Metastasis post OP were found most prominent in bones (32% of all metastasis occurring post OP), lymphnodes (19%), lung (18%) and liver (15%).

Parameters such as family history, surgery and postoperative treatment revealed the following: The family history of the majority of patients was unknown. More than 60% of patients obtained total resection of the breast and one third of patients partial resection. Localisation of the tumour is well balanced between left and right breast cancer patients. About 2% of patients were diseased bilateral. Therapy following surgery was divided in 16%

chemotherapy, 22% radiotherapy, 7% hormone therapy and several combinations of the above, most prominent a combination of chemo- and radiotherapy (19%).

Patients received various mistletoe preparations, however, Helixor (42%) and Iscador (36%) preparations comprised the largest groups. Other preparations such as Abnoba, Eurixor, Lektinol, Plenosol and Vysorel were used less than 3% each. Several patients (about 10%) received a combination of different preparations. Mistletoe medication was given in average over a period of 31 months, explicit Helixor preparation for 29 months. The average doses of all mistletoe preparations was 36 mg/ injection, while Helixor treatment was given in 49 mg/ injection on average. 48% of patients under mistletoe therapy feel in better condition and 47% of patients feel the same under mistletoe treatment, less than 5% of patients feel worse. Similar results were obtained for the group of patients explicit under Helixor treatment. Local reactions to mistletoe medication were declared by almost 80% of patients who answered this question. Fever, however, was observed only in a small part of the trial population (8%). Again, similar results were obtained from patients under Helixor treatment.

Finally, analysis of survival rates was performed, indicating a 10 yrs survival rate for 73.3% of mistletoe-treated breast cancer patients. Stratification for tumour stages revealed a 10yrs survival rate for 88.1% (stage I), 71.6% (stage II), 55.6% (stage III) of breast cancer patients. Separation of patients by lymph node status revealed a 10 yrs survival rate for 63.8% of lymph node positive and 83.7% of lymph node negative patients. There were no significant differences in survival between Helixor, Iscador and other preparations (data not shown).

Comparing these data with survival rates of breast cancer patients in Germany published by the Münchner Tumour Register (2001; overall 10yrs survival rate of 55%, stage I 90%, stageII 65% (stage II a 78.5%, stage II b 61.2%), stage III < 30% (stage III a 45.7 %, stage III b 72.2%) indicates a clear difference of survival rates in stage III and alerts for possible weakness of retrospective surveys, especially concerning the objective survival time. Regarding the high rate of excluded subgroups in comparison to the investigated population, survival rates for mistletoe treated breast cancer patients may be interpreted with reservation.

7. SURVIVAL IN EXCLUDED POPULATIONS

7.1. Patients without TNM staging

As almost 60 % of all patients have been excluded due to missing data, it was important to determine their survival rate as well, in order to exclude a possible bias for the total population to the greatest extent.

This analysis studies patients without TNM staging. There are 834 patients within this group of whom 86 suffer on a second tumour. Only 315 patients out of the 834 had a documented survival time. There are 224 patients with additional information on treatment, one of them did not know wether she had mistletoe therapy or not.

There are 18 patients without *treatment.* The 5-years and 10-years survival probability (with 95% confidence interval) are given by 81.6% (95% CI [56.9%; 99.6%]) and 53.2% (95% CI [32.8%; 86.5%]).

A total of 205 patients were treated. The 5-years and 10-years survival probability (with 95% confidence interval) are given by 92.7% (95% CI [88.9%; 96.6%]) and 77.5% (95% CI [71.0%; 84.6%]).

The log-rank test does not confirme a significant difference between both groups (p=0.26) (Figure 15).

7.2. Patients with TNM staging without documented treatment

There are 894 patients with TNM staging but without documented treatment. The group survival and UICC-stage specific survival (5-years and 10-years survival probability with 95% confidence interval) is given in Table 24. Survival was documented for 150 patients. No patient had a carcinoma in situ (UICC 0).

Table 24. Survival rate in patients with UICC staging and no documented treatment (see fig. 15; group III)

	5-years (survival, 95% CI)	10-years (survival, 95% CI)
Total group N=150	42.0% [34.8%; 51.1%]	14.4% [9.6%; 21.8%]
UICC I N=24	67.2% [49.9%; 90.5%]	28.8% [14.7%; 56.5%]
UICC II N=87	42.6% [33.2%; 54.6%]	13.7% [7.8%; 23.9%]
UICC III N=27	33.3% [19.6%; 56.8%]	7.4% [1.9%; 28.1%]
UICC IV N=12	12.5% [2.3%; 68.2%]	-

The clinical and epidemiological relevance of the given survival rates has to be considered with care.

7.3. Combined Analysis

Combining the populations from sections 7.1 and 7.2, a total of 465 patients with documented survival time can be found. The group survival (5-years and 10-years survival probability with 95% confidence interval) is given by 68.6% [64.4%; 73.1%] (5 years survival) and 42.3% [37.7%; 47.6%] (10 years survival).

Figure 15: 5/10y survival in selected patient groups

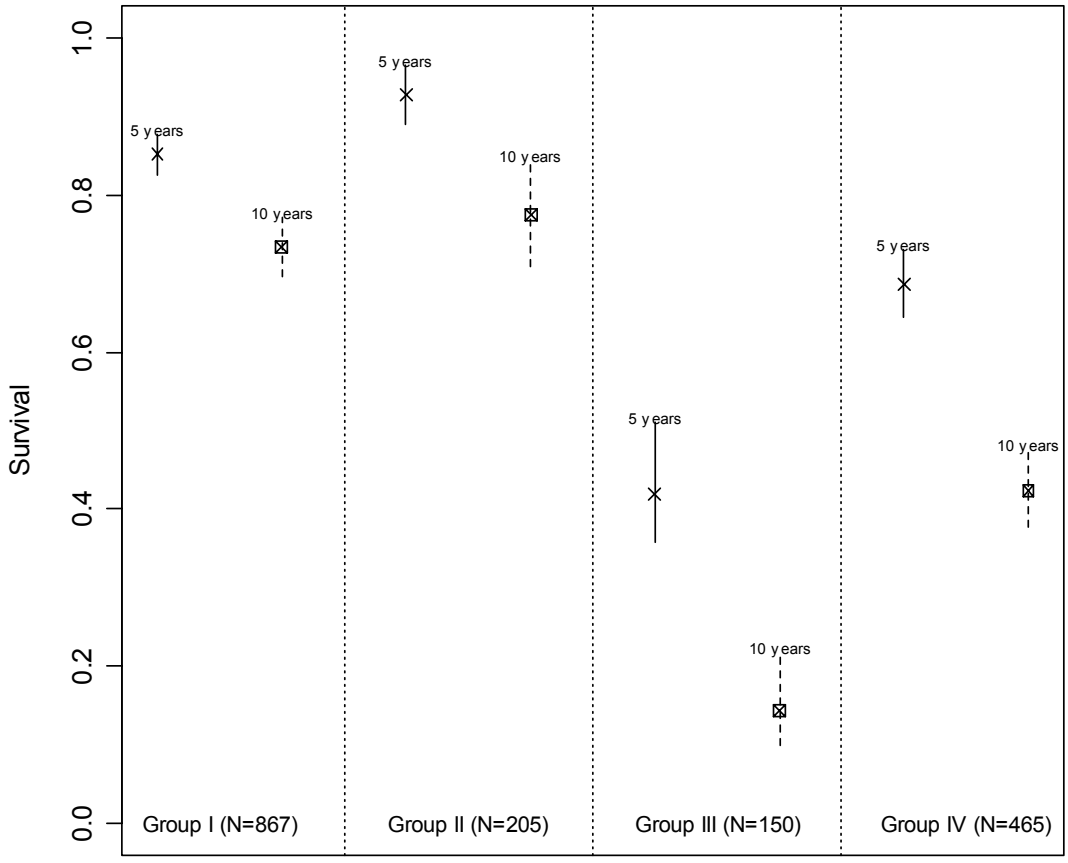

Figure 15 shows 5 and 10 years survival rate together with 95% confidence intervals for selected patient groups.

Group I:	Patients treated with mistletoe and documented tumour staging
Group II	Patients treated with mistletoe without documented tumour staging
Group III	Patients with documented tumour staging but missing treatment information
Group IV	All patients with documented survival but missing of tumour staging or missing treatment information

7.4. Randomly chosen patients

To have an idea of the difference of the portion of deceased patients in the study and the portion of deceased patients in the group which was excluded from investigation, a inquiry about survival of 50 randomly chosen patients who did not answer the questionnaire was evaluated and revealed that the rate of deceased in the non answering patient population is about 67% (~ 33 % survival). In contrast, the study population under analysis, mainly based on patients with data obtained during the survey, reveals a rate of deceased of only 22% (185 of patients 929).

8. APPENDIX

8.1. Algorithm to define event time and censoring.

The following code was used to transform the information given in the CRFs to relevant data on event time and censoring.

```
if geb_jahr<1923 then fb1date=mdy(8,15,2000);
if geb_jahr<1923 then fb2date=mdy(10,15,2000);

if geb_jahr>=1923 then fb1date=mdy(11,15,1999);
if geb_jahr>=1923 then fb2date=mdy(12,15,1999);

fbdate=fb1date;
if fb2 in(3,4) then fbdate=fb2date;

if tod_jahr<0 then survz=0;
if tod_jahr>0 then survz=1;

last_date=tod;
if tod<0 then last_date=fbdate;

surv=round(((last_date-diag)/365.25),.01);


/* lt. Fragebogen: Pat. verstorben, alle Pat. werden auf survz=1 (tot)
gesetzt,
   bei fehlendem Todesdatum wird surv=. (Ueberlebenszeit=missing)
*/
if fb1=2 or fb2=2 then do;
   if survz=0 then survz=1;
   if tod_jahr<0 then surv=.;
end;

/* Status und Ueberlebenszeit auf missing, wenn keine Frageboegen
zurueckkamen, bzw.
   nicht verschickt wurden
*/
if (fb1=0 and fb2=0) or (fb1=0 and fb2=1) or (fb1=1 and fb2=0) or (fb1=5 and
fb2=0) then do;
survz=.;
surv=.;
end;


if survz=0 and rezidive=2 and metast=2 then survz_tf=0;
if survz=1 or rezidive=1 or metast=1 then survz_tf=1;

if survz=0 and metast=2 then survz_mf=0;
if survz=1 or metast=1 then survz_mf=1;

if survz=0 and rezidive=2 then survz_rf=0;
if survz=1 or rezidive=1 then survz_rf=1;


if survz_rf=1 then surv_rf=round(((rez1-diag)/365.25),.01);
if survz_rf=0 then surv_rf=surv;

if survz_mf=1 then surv_mf=round(((met_1-diag)/365.25),.01);
if survz_mf=0 then surv_mf=surv;
```

```
if survz_tf=1 then do;
if (surv_rf>=0 and surv_mf>=0) then surv_tf=min(surv_mf,surv_rf);

if metast=1 and met_1>=0 and rezidive ne 1 then surv_tf=surv_mf;

if rezidive=1 and rez1>=0 and metast ne 1 then surv_tf=surv_rf;

if rezidive=1 and rez1=. then surv_tf=.;
if metast=1 and met_1=. then surv_tf=.;

if metast not in(1,2) or rezidive not in(1,2) then surv_tf=.;
end;

if survz_tf=0 then surv_tf=surv;
```

8.2. Bias due to Missing Answers

Considering the extremely high survival rates one suspects a bias due to missing answers a common disadvantage of retrospective studies. For this reason a random sample of 50 patients was chosen from the population of patients who did not answer any of the two questionnaires to estimate the portion of actual survivors. The list of randomly chosen patients is shown in Table 25.

Table 25. Pool of 50 randomly chosen patients to estimate the bias due to missing answers.

Obs	ID	Letter	Alive/ deceased
1	2856	Practitioner/ patient unknown	-
2	2878	Practitioner/ patient unknown	-
3	3088	Practitioner	No answer
4	3104	Practitioner/ patient unknown	-
5	3321	Practitioner/ patient unknown	-
6	1550	Practitioner	22.1.1985
7	1055	Practitioner/ patient unknown	-
8	1179	Practitioner unknown	-
9	1931	Practitioner/ patient unknown	-
10	2425	Practitioner	No answer
11	964	Practitioner/ patient unknown	-
12	1337	Practitioner	No answer
13	2533	Practitioner unknown	-
14	191	Practitioner/ patient unknown	-
15	865	Practitioner	1985
16	1511	Practitioner	1998
17	1636	Practitioner unknown	-
18	2179	Practitioner unknown	-
19	2639	Practitioner	12.1992
20	715	Practitioner	No answer
21	1552	Practitioner	alive
22	2266	Practitioner unknown	-
23	580	Practitioner unknown	-
24	1403	Practitioner unknown	-
25	105	Practitioner	7.2001

26	2516	Practitioner	No answer
27	547	Practitioner	deceased (DOD missing)
28	1768	Practitioner	1996
29	2409	Practitioner	1995
30	2553	Practitioner unknown	-
31	2288	Practitioner	No answer
32	2627	Practitioner	1997
33	1252	Practitioner unknown	-
34	642	Practitioner unknown	-
35	1080	Practitioner	deceased (DOD missing)
36	136	Practitioner unknown	-
37	1547	Practitioner	alive
38	1577	Practitioner	alive
39	1332	Practitioner	8.2001
40	1828	Practitioner	3.1996
41	1886	Practitioner unknown	-
42	1979	Practitioner	1996
43	1477	Practitioner	1995
44	1659	Practitioner unknown	-
45	1558	Practitioner unknown	-
46	762	Practitioner unknown	-
47	1041	Practitioner unknown	-
48	2312	Practitioner	No answer
49	2282	Practitioner unknown	-
50	2002	Practitioner unknown	-

50 patients were randomly chosen from the population of not-answering patients and life status of these patients was inquired from the general practitioner. For 18 patients the general practitioner could not be traced. From the remaining 32 patients, 8 patients were not known by the practitioner, 7 practitioners did not answer within 8weeks, 10 patients died until the year 2000 (year of the second questionnaire), 5 patients are still alive or died after the year 2000 and 2 patients died without specified date of death (as seen in **Table 26**).

Table 26. Scheme of inquiry to estimate the actual portion of survivors.

50 randomly chosen patients	
18x general practitioner unknown	32x inquiries sent to practitioner
	8 x patients are unknown to practitioner 10x patients died until 2000 5 x patients are alive or died after 2000 2 x patients missing date of death 7 x patients no answer from practitioner

The information from the inquiry of 50 randomly chosen patients suggests that within the population that did not answer the questionnaire the rate of deceased is about 67% (10 of 15 patients). In comparison, the study population under analysis, mainly based on patients who answered the questionnaire themselves, reveals a rate of deceased of 16% (194 of patients 1246). We conclude that survival rates of the analysis are systematically over-estimated. A systematic error, however, in over-estimating survival rates of retrospective data cannot be circumvented.

LISTINGS

Listings of demography (Listing 1.), listings of information about mistletoe therapy and disease progression mainly provided by patients (Listing 2.) and listings of primary tumour characteristics (Listing 3.) are supplied electronically due to extend. Every listing is separated in 3 parts representing the population of male patients, bilateral patients and unilateral female patients, the latter of which were used for the analyses.

An example of each listing will be given in the following (**Listing 1.; Listing 2.; Listing 3.** for the male population).

Listing 1. Demography of male patients. N=15.

ID	Sex	Date of birth	Date of death	Age	Postcode	Country
97	m	04/04/40		55	45884	D-
231	m	15/01/47		43	45481	D-
420	m	09/02/37	10/10/96	58		D-
552	m	28/02/27	17/07/84	56	51381	D-
657	m	12/03/34		44	42719	D-
1206	m	22/05/26		61	50996	D-
1509	m	05/07/29		59	40878	D-
1871	m	21/08/28	07/11/92	57	55758	D-
1956	m	03/09/41	26/08/95	52	42651	D-
2283	m	11/10/54		45	51467	D-
2652	m	05/12/29		51	32547	D-
2727	m	16/12/28		60	45136	D-
2760	m	20/12/54		44	33189	D-
3045	m	05/09/21		64	53175	D-
3079	m	18/10/19	03/01/86	66	58509	D-

Listing 2. Information about mistletoe therapy and disease progression of male patients. N=15.

ID	Questionaire	Date of diagnosis	Chemo-therapy	Radiation therapy	Hormone therapy	Mistletoe therapy	Recommendation	Duration (months)	Inter-ruption	End of therapy	Relapse	Metastasis	Relapse and/or metastasis	Tumourfree
97	patient	03/03/95			yes	yes	Medical doctor		no		no	no	Rez/Met neg	Tumourfree
231	patient	15/01/90				yes	Medical doctor	60	no	cured	no	no	Rez/Met neg	Tumourfree
420	clinician	15/05/95				yes		15						
552	relative	27/01/83	yes		yes	yes	Relative					yes		
657	no info	15/06/78		yes										
1206	patient	15/03/87		yes		yes	Medical doctor	32	no	discouraged	no	no	Rez/Met neg	Tumourfree
1509	clinician	15/02/88				yes			yes					
1871	clinician	15/01/85	yes	yes		yes		31				yes		
1956	relative	15/05/93		yes		yes	Medical doctor		no	progression	yes	yes	Rez/Met_pos	Rez and/or Met
2283	patient	15/01/99				yes	Medical doctor		no		no	no	Rez/Met neg	Tumourfree
2652	no info	15/06/80	yes	yes	yes							yes		
2727	no info	15/10/88										yes		
2760	no info	15/07/98	yes									yes		
3045	clinician	15/06/85		yes		yes		28						
3079	relative	15/02/85				yes		6						

ID	Preparation	Dose (mg/day)	Preparation 1	Condition 1	Preparation 2	Condition 2	Preparation 3	Condition 3	Redness	Pain	Swelling	Itching	Fever
97	Helixor	30	Helixor M	better					no	no	no	no	no
231	Helixor	30	Helixor A	same					no	no	no	no	no
420	Helixor	20	Helixor P										
552													
657													
1206	Iscador		Iscador	same					yes	no			no
1509	Helixor		Helixor A										
1871	Iscador	30	Iscador										
1956	Helixor		Helixor	don't remember							yes		don't remember
2283	Helixor	5	Helixor A	same					yes	no	yes	yes	no
2652													
2727													
2760													
3045	Iscador		Iscador										
3079	Iscador	20	Iscador										

Listing 3. Primary tumour characteristics of male patients. N=15.

ID	Family history	Type of operation	ICD-10 Code C50	TNM Tumour	TNM Node	TNM Metastasis	Stage	Primary tumour	Positive nodes	Resected nodes	Differentiation grade	Estrogen receptor	Progesterone receptor
97		unknown	9			M0						unknown	unknown
231	unknown	total resection	9	Tis	N0	M0	0	intraductal	0	8	G1	unknown	unknown
420	unknown	total resection	9	T2	N1	M0	IIB	ductal invasive	2	14	G2	yes	yes
552	unknown	total resection	9	T1	N1	M0	IIA		2	7	G3	unknown	unknown
657	unknown	total resection	9									unknown	unknown
1206	unknown	total resection	9		N0	M0		ductal invasive	0	17		unknown	unknown
1509	unknown	partial resection	9	T1	N0						G2	unknown	unknown
1871	unknown	total resection	0	T1	N1	M0	IIA	ductal invasive	5	9	G3	unknown	unknown
1956	unknown	total resection	9	T4	N1	M0	IIIB		12	19	G2	yes	no
2283	unknown	total resection	9	T1	N0	M0	I	ductal invasive	0	10	G2	yes	yes
2652	unknown	total resection	9	T1	N1	M0	IIA					unknown	unknown
2727	unknown	total resection	9	T2	N1	M0	IIB	ductal invasive	1	10		yes	yes
2760	unknown	unknown	9			M1						yes	yes
3045	unknown	total resection	9	T2	N2	M0	IIIA		9			yes	yes
3079	unknown	total resection	9	T4	N0	M0	IIIB				G3	unknown	unknown