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Influence of a complementary treatment with oral enzymes on patients with colorectal cancers – an epidemiological retrolective cohort study

Abstract *Purpose*: To evaluate the impact of postoperative treatment with an oral enzyme (OE) preparation given complementary to an antineoplastic therapy in patients with all stages of colorectal cancer. *Methods*: The design of this epidemiological study was a retrolective cohort analysis with parallel groups. Design and conduct of the study were performed to current standards for prospective, controlled clinical trials. Of a cohort of 1242 patients with colorectal cancer (documented in 213 centres), 616 had received complementary treatment with OE (182 OE only, 405 other complementary drugs, 29 protocol violators) and 626 had not received OE (368 control only, 229 other complementary drugs, 29 protocol violators). Of 1162 patients who had undergone primary surgery, 526 received adjuvant chemotherapy and 218 radiotherapy. The median follow-up time for the OE group was 9.2 months and for the control group 6.1 months. The primary test criterion of efficacy for OE treatment was the multivariate effect size of the changes from baseline of the disease- and therapy-associated signs and symptoms (nausea, vomiting, changes in appetite, stomach pain or stomach disorder, tiredness, depression, memory or concentration disorder, sleep disturbance, dizziness, irritability, dyspnoea at rest, dyspnoea during activity, headache, tumour pain, cachexia, skin disorders and infections). Tumour-related events, e.g. death, were evaluated by the number of events observed and time to event. Safety of treatment with OE was analysed in terms of number and severity of adverse events, their duration, treatment and outcome. *Results*: A significant reduction in disease-associated signs and symptoms was observed in patients treated with OE alone, but not in those receiving OE in addition to other complementary treatments. Adverse reactions to chemo- and radiotherapy were diminished in all patients receiving OE. Analysis of survival did not demonstrate a reduced number of deaths in the OE group. However, a trend to prolongation of survival was demonstrated, particularly in the patients with disease stage Dukes' D, in the subgroup receiving OE in addition to other complementary treatments. Similar but less-pronounced trends were observed for disease stages Dukes' B and C. In the OE group, 21 of 616 patients (3.4%) experienced OE-associated adverse reactions, all of them mild to moderate gastrointestinal symptoms. *Conclusion*: Complementary treatment of colorectal cancer patients with OE improves their quality of life by reducing both the signs and symptoms of the disease and the adverse reactions associated with adjuvant antineoplastic therapies. This epidemiological retrolective cohort analysis provides evidence that patients may also benefit by a prolongation of survival time. OE were generally well tolerated.

Key words Epidemiological cohort study · Colorectal cancer · Proteolytic enzymes · Complementary therapy · Adverse drug reactions · Cancer symptoms · Survival · Oral enzyme preparation

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Introduction

Colorectal cancer is the third most common tumour in industrialized countries and shows an increasing incidence. Cancer of the colon is a highly treatable and often curable disease when localized. Surgery is the primary form of treatment and results in cure in approximately 50% of patients. Adjuvant chemo- and radiotherapy regimens complete the standard antineoplastic treatment of colorectal cancer. However, recurrence of the disease

remains a major problem and often is the ultimate cause of death [1, 4, 7, 17, 18, 32].

Complementary therapeutic approaches have an important role to play alongside standard antineoplastic treatment programmes and include, for example, phytoextracts and organoextracts, antioxidant vitamins, trace elements and oral enzyme (OE) preparations. While these complementary treatments are not an alternative to the established antineoplastic approaches, they may provide valuable tools in the optimization of these therapies [3].

OE preparations have long been available on the German market, but their mechanism of action in complementary cancer therapy is not fully understood. There are a variety of mechanisms by which they are thought to contribute to antineoplastic efficacy. Orally administered proteases are known to bind irreversibly to antiproteinases such as α_2-macroglobulin and α_1-antitrypsin leading to synthesis of antiproteinases. Increased levels of antiproteinases inactivate other proteinases, e.g. cathepsins, which are thought to play a role in tumour development and metastasis. Cysteine proteinases of plant origin (papain) are known to influence the balance between proteinase and antiproteinase and as a consequence may also influence tumour metastasis [12, 14]. Furthermore, enzymes are known to interact with the cytokine network. The binding of proteinases to α_2-macroglobulins leads to the formation of α_2-macroglobulin-proteinase complexes with a high capacity for binding and clearing cytokines, e.g. IL-1β, IL-6, IFN-γ and TGF-β. TGF-β promotes immunosuppression in the host and tumour immune escape thus modulating tumour growth [31].

Also enzymes reduce TGF-β overproduction at the levels of mRNA and protein synthesis [8, 20]. Enzymes also interact with adhesion molecules which play an important role in tumour development and metastasis. The modulation or downregulation of adhesion molecules by enzymes has been shown, amongst others, for B7-1, CD4, CD29, CD44, CD49, CD51, CD54 and CD58 and this may contribute to their antitumour efficacy [24, 37]. Finally, enzymes influence the levels of antioxidant enzymes and reactive oxygen molecules. An increase in the synthesis of antioxidative protective mechanisms as shown by a small chronic oxidative stress has been shown in patients with burn injuries [21, 36]. Recently a novel role for extracellular proteases as inhibitors of intracellular signal transduction pathways has been described [23].

These results obtained in both experimental and preclinical settings support the use of enzymes in rational complementary tumour therapy. However, convincing clinical evidence of their efficacy is still limited. The use of epidemiological methods in collecting and analysing existing data provides the means not only to evaluate the safety and efficacy of a particular treatment, but also to generate hypotheses for the development of well-designed prospective clinical trials [10, 26]. It is the goal of the scientific complementary oncology community to subject all cancer treatments to critical evaluation through appropriately designed and conducted clinical trials. In this paper the use of today's methodology for epidemiological studies to assess the efficacy of complementary oral enzyme medication in patients with colorectal cancer is described.

Methods

Study subjects

A total of 213 study centres were identified in Germany (hospitals, hospital units with beds at physician's disposal, specialist practices) and supplied data on 1242 patients with colorectal cancer, of whom 616 received complementary treatment with an oral enzyme (OE) preparation (Wobe-Mugos E, MUCOS Pharma, Geretsried, Germany) and 626 were not receiving OE. The criteria for inclusion in the study cohort were: colorectal cancers of all stages, age 18–80 years, treatment 1991 to 1997 with OE (OE group) or without OE (control group) in addition to antineoplastic therapy (primary surgical treatment; adjuvant systemic chemotherapy, radiotherapy). Patients could have received other complementary medications, e.g. physical therapy, phytoextracts or organic extracts, trace elements or vitamins. For the purpose of the analysis presented here, they were excluded if they had received another additive enzyme therapy, or if a secondary malignancy was present.

Data collection

Prior to data collection the data elements required for the study were identified and defined in the trial protocol and a case report form. Data were retrieved by the investigators from the patients' medical records at the study centres and transferred to standardized case report forms. Data collected included patients demographic details, characteristics of the tumour disease, treatments, signs, symptoms and side effects experienced by the patient, and the course of the disease. Staging of the tumours was reported using the TNM classification, but, for the purpose of analysis, the stages were converted to the Dukes' classification scheme [11]. A clinical quality assurance audit was carried out by an independent institution which confirmed that the data were acceptable for the purpose of a clinical trial.

Study end-points/statistical methods

The study design was a retrolective cohort analysis with parallel groups [9, 10, 15, 16]. Design and conduct of the study were performed to current standards for prospective, controlled clinical trials [13, 35]. The primary test criterion of efficacy for OE was the multivariate effect size of the changes from baseline of the disease- and therapy-associated signs and symptoms during the period of observation [19, 33]. The signs and symptoms that were prespecified as reflecting the quality of life of patients during and after the adjuvant antineoplastic therapy (radio- or chemotherapy) were: nausea, vomiting, changes in appetite, stomach pain or stomach disorder, tiredness, depression, memory or concentration disorder, sleep disturbance, dizziness, irritability, dyspnoea at rest, dyspnoea during activity, headache, tumour pain, cachexia, skin disorders and infections.

Secondary target criteria for evaluation of the efficacy of OE treatment were the changes in the individual disease- and therapy-associated signs and symptoms, the final rating of the patients by the physician as "free of symptoms", the number of patients with adverse reactions caused by the adjuvant antineoplastic therapy, the severity of these events, the changes in the performance and Karnofsky indexes, body weight, body temperature, tumour-free status and overall survival time.

The primary end-point relating to drug safety was based upon the physician's assessment of tolerability, using a five-point ordinal scale, after OE treatment. The secondary end-point criterion for safety was the frequency of adverse drug reactions associated with OE treatment. The evaluation included the type, number and severity of the adverse drug reactions.

With respect to statistical analyses the primary end-point (test criterion) of efficacy was provided by the multivariate Mann-Whitney statistic (MWS) which was calculated as the effect size of the symptom change from baseline [19, 22, 33]. The MWS specifies the probability that a randomly selected patient from the test group is more free from the signs and symptoms of disease than a randomly selected patient from the control group. The hypothesis test was performed on the MWS with the multivariate directional simultaneous Wilcoxon-Mann-Whitney (WMW) test. Statistical significance was based on two-sided confidence intervals calculated for $\alpha = 0.05$. The base for descriptive and inferential procedures was the percent change from baseline. The measure of relevance for defining superiority was the MWS value and the change in percent. The established MWS benchmarks were: 0.71 "large superiority", 0.64 "medium-sized (relevant) superiority", 0.56 "small superiority", 0.50 "no difference", 0.44 "small inferiority", 0.36 "medium-sized inferiority" and 0.39 "large inferiority" [5].

Secondary end-points were described by the MWS. For conclusions based on individual symptom results, the Bonferroni correction for multiple end-points was applied. Time-until-occurrence of cancer events was calculated using univariate survival analysis with the Kaplan-Meier estimator and comparisons were done using the log-rank test. Safety was determined using logistic regression for the main criterion and by descriptive analysis for the secondary criteria.

To further evaluate the reliability of the results a separate sensitivity analysis of the data based on propensity score matched pairs was performed [27, 28, 29, 30]. For construction of the propensity scores the following covariates were used: OE treatment, tumour stage, postoperative response, Karnofsky index at baseline, time of treatment/observation, age and sex, nature of the antineoplastic therapy and type of study centre. The propensity score is a so-called balancing score representing the probability of allocating a patient to the test drug as a function of his or her individual characteristics, prognostic factors and the characteristics of the treating centre. The propensity score can be calculated from the study data by the multivariate logistic regression and is used for adjusting the results on primary end-points to all relevant confounding factors by matching, stratification, or regression techniques. Thus, under optimal circumstances, the adjustment of the results by propensity score might yield an unbiased estimate of the treatment effect in nonrandomized observational cohort studies.

Results

Patients

The original cohort consisted of 1242 patients with colorectal cancer (total sample for safety evaluation according to the "intent-to-treat" principle). Of the 1242 patients, 616 were additionally treated with OE, while 626 patients did not receive OE. Excluded from the efficacy analysis were 58 patients (29 OE group, 29 control group) who did not comply with the inclusion criteria (Fig. 1). Of the 1242 patients, 1162 underwent primary surgery for colorectal cancer, 243 of whom underwent further surgery, mainly for progressive disease, and 526 received standard adjuvant chemotherapy and 218 received radiotherapy. The OE group consisted of 587 patients, of whom 182 received exclusively OE as the only complementary treatment (OE-monotherapy subgroup) and 405 received OE together with other concurrent aftercare measures, such as physical therapy, phytoextracts or organic extracts, trace elements or vitamins (OE-complementary therapy subgroup). The control group consisted of 597 patients without OE therapy, 368 with no complementary treatment (control-monotherapy subgroup), and 229 who received complementary treatment (control-complementary subgroup). The demographic data, disease characteristics and treatment modalities for the monotherapy and complementary therapy subgroups are displayed in Table 1. For the monotherapy subgroup, significant and potentially clinically relevant differences between the treatment groups were found at baseline for the type of tumour, some symptoms, residual tumour and study centres. For the complementary therapy subgroup, significant and potentially clinically relevant baseline differences were found for T-stage, tumour localization and adjuvant chemotherapy.

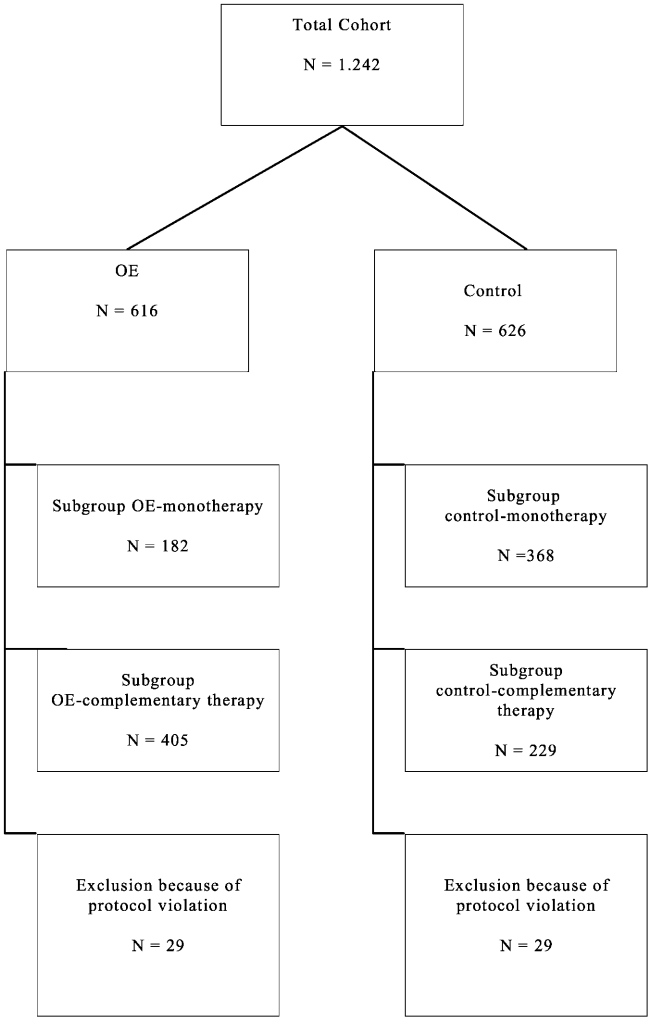

Fig. 1 Description of study patients

Analyses for efficacy were performed separately for the monotherapy subgroup (550 patients) and the

Table 1 Baseline demographic data, disease characteristics, and treatment modalities

	Total group		Monotherapy group		Complementary therapy group	
	OE	Control	OE	Control	OE	Control
Number of patients	616	626	182	368	405	229
Age (years)						
Mean	64.3	67.2	67.4	67.9	62.7	65.2
Range	11.7	11.1	11.3	10.9	11.6	11.1
Weight (kg)						
Mean	73.0	72.9	75.7	74.0	72.0	71.3
Range	13.4	12.5	12.3	12.3	13.6	12.7
Height (cm)						
Mean	171.4	179.8	172.0	170.1	171.4	169.7
Range	8.6	8.7	8.2	9.0	8.6	8.4
Males (*n*)	326	324	112	196	204	116
Dukes' stage (*n*)						
A	113	170	57	100	57	61
B	117	117	50	92	73	32
C	115	114	34	119	143	66
D	125	105	26	40	89	61
Missing	135	100	15	17	43	9
Karnofsky index (%)						
Mean	81.1	82.2	81.5	83.6	81.6	81.3
Range	15.1	15.9	16.4	15.5	13.9	15.3
Surgery (*n*)						
Standard	570	592	1	3	353	207
Anus praeter	124	145	34	92	83	45
Anastomosis	74	70	24	33	42	32
Other (unknown)	418	411	124	243	280	152
Median observation time (days)	275	184	259[a]	153	337[b]	229
Tumor status after surgery (*n*)						
Complete/partial remission	495	494	149	277	328	198
Minimal response	81	65	24	33	50	26
Other/missing	40	66	9	57	27	5
Standard adjuvant therapy (*n*)						
Chemotherapy	275	251	60	160	210	90
Radiotherapy	91	127	29	90	59	35
Other	420	349	57	184	349	159
Concomitant disease (*n*)	298	335	69	195	217	123

[a] OE starting 31 days (mean) after surgery for 184 days (mean)
[b] OE starting 153 days (mean) after surgery for 181 days (mean)

complementary therapy subgroup (634 patients). In the monotherapy subgroup 182 OE patients were compared with 368 control patients and for the complementary therapy subgroup 405 OE patients were compared with 229 control patients. The propensity score matched pairs sensitivity analysis was performed for both subgroups separately. For this analysis, the monotherapy subgroup and complementary therapy subgroup consisted of 137 and 161 evaluable matched pairs, respectively. Safety of the OE treatment was analysed for the total cohort.

Efficacy

The primary end-point and test criterion of efficacy was the multivariate effect size (MWS) calculated from the disease- and therapy-associated signs and symptoms expressed as severity scores. Comparison was made over the observation period using the start-points and end-points. The median follow-up time (surgery to end of observation) was 275 days in the OE group and 184 days in the control group.

In the monotherapy subgroup, the comparison of efficacy (effect size of the symptom change from baseline) between the treatment and control groups resulted in a MWS of 0.6077 (95% CI 0.5535–0.6619, $P < 0.0001$). This result can be interpreted as a small superiority of OE (Table 2), e.g. a positive influence of OE on the patients' quality of life. Analysis of the secondary end-points revealed similar beneficial effects of OE in terms of the mean score of symptom change (MWS 0.6478, 95% CI 0.5898–0.7058, $P < 0.0001$; medium-sized superiority of OE; Table 2). In the OE group, significantly fewer patients suffered from adverse reactions due to chemo- or radiotherapy (MWS 0.6721, 95% CI 0.6080–0.7363, $P < 0.0001$; medium-sized superiority of OE). Neither the performance index nor the Karnofsky index showed significant differences between the treatments. Among the individual symptoms, OE favourably influenced the following: nausea, vomiting, changes in appetite, diarrhoea, tiredness, depression, memory or concentration disorders, sleep disturbances and irritability. These results confirm a beneficial effect of OE monotherapy on disease- and treatment-associated symptoms.

Table 2 Efficacy and safety, overview of statistical analysis results (*MWS* Mann-Whitney statistic)

	Monotherapy group					Complementary therapy group				
	Mean difference, OE/control	MWS	95% CI of MWS	*P*-value	MWS results[a]	Mean difference, OE/control	MWS	95% CI of MWS	*P*-value	MWS results[a]
Primary end-point of efficacy										
Signs and symptoms	–	0.6077	0.5535–0.6619	< 0.0001	Small superiority of OE	–	0.5224	0.4756–0.5692	0.3486	No difference
Secondary end-points of efficacy (see text)										
Mean score of symptom change	3.05/3.86 (−0.80%)	0.6478	0.5898–0.7058	< 0.0001	Medium-sized superiority of OE	3.69/3.71 (−0.026%)	0.5040	0.4548– 0.5532	0.8727	No difference
Global result "patient free of complaints" (%)	52.8/44.4 (+8.4%)	0.5440	0.4950–0.5929	0.0798	No difference	37.2/33.0 (+4.2%)	0.5570	0.5120–0.6020	0.0138	No difference
Relevant reduction of adverse events due to chemo- or radio therapy	63.7/34.2 (+29.5%)	0.6721	0.6080–0.7363	< 0.0001	Medium-sized superiority of OE	65.1/53.2 (+11.9%)	0.5880	0.5246–0.6514	0.0062	Small superiority of OE
Performance index	−0.03/0.11 (−0.14%)	0.5645	0.5166–0.6124	0.0071	No difference	0.38/0.54 (−0.16%)	0.4718	0.4284–0.5151	0.1930	No difference
Karnofsky's index (%)	−1.6/−1.48 (−0.13%)	0.4947	0.4411–0.5483	0.0846	No difference	−0.41/−3.06 (+2.65%)	0.5202	0.4725–0.5679	0.4003	No difference
Primary end-point of safety	78.2/32.8 (+45.4%)	0.7471	0.7054–0.7889	< 0.0001	Large superiority of OE	66.8/53.4 (+13.4%)	0.5865	0.5455–0.6275	< 0.0001	Small superiority of OE
Global result "tolerability very good" (%)										
Secondary end-points of safety	7.2/34.0	0.6339	0.6020–0.6659	< 0.0001	Small superiority	12.2/15.5	0.5171	0.4882–0.5459	0.2679	No difference
Number of adverse events	(−26.8%)				of OE	(−3.4%)				

[a] 0.36 medium-sized inferiority, 0.44 small inferiority, 0.50 no difference, 0.56 small superiority, 0.64 medium-sized superiority, 0.71 large superiority

The complementary therapy subgroup showed no differences between treatments for the primary end-point, the mean score of the symptom change, nor the physician's judgement of patients as being "free of complaints". Similarly, neither the performance index nor the Karnofsky index showed significant differences (Table 2). In the OE group, as compared with the control group, however, significantly fewer patients suffered from adverse reactions due to chemo- or radiotherapy (MWS 0.5880, 95% CI 0.5246–0.6514, $P = 0.0062$; small superiority of OE). These results indicate a lack of efficacy in terms of disease symptoms, but a clinically relevant efficacy in terms of the treatment-associated symptoms in the complementary therapy group.

Sensitivity analyses for efficacy

After multivariate adjustment of the test results for possible influences of the oncological basic therapy (chemo- or radiotherapy), disease stage, postsurgical tumour status and patients' age, the results remained comparable with the nonadjusted data. Consequently, in the present analysis the efficacy results were not significantly influenced by the potential confounding criteria (covariates) and therefore can be interpreted as consistent and unbiased by confounding (data not shown).

OE therapy

Long-term treatment with OE was found to be more efficient than an interval or acute therapy (data not shown). The dose used most frequently was the recommended dosage of two tablets three times per day. Patients were also treated with higher doses (up to 40 tablets per day) which were tolerated without problems. Measurable effects of the therapy such as alleviation of the signs and symptoms of disease and a reduction in the adverse reactions to the radio- and chemotherapy were observed within weeks (data not shown).

Sensitivity analyses with propensity score matched pairs

The multivariate matching by propensity scores led to a considerably smaller evaluable sample size than the total sample. Nevertheless, a good correlation between the results of the primary analysis and the propensity score matched pairs analysis on efficacy was found (Table 3). For the monotherapy subgroup a significant and clinically relevant difference in favour of OE could be confirmed particularly for the symptoms nausea, tiredness, depression and sleep disturbances.

Survival analysis

The median follow-up time was 9.2 months for the OE group and 6.1 months for the control group. The total number of tumour events was not significantly different between the treatment groups. A comparative analysis between the monotherapy subgroup and complementary therapy subgroup based on Kaplan-Meier estimate and Cox regression analyses indicated a trend to prolongation of survival as a result of OE treatment in the complementary therapy subgroup, particularly with disease stage Dukes' D. The median survival time for patients in the OE group was 34.1 months, as compared with 14.5 months in the control group patients ($P_{\text{log-rank}} = 0.0025$; Fig. 2A). Similar but less-pronounced trends were observed for disease stages Dukes' B and C. Sensitivity analysis of survival by Kaplan-Meier estimate and Cox regression analyses based on the propensity score matched pairs confirmed this finding (Fig. 2B).

Safety

Antineoplastic therapy was significantly better tolerated in patients receiving OE, either alone or in combination with other complementary therapies, than in those receiving control therapy without OE (Table 2). For the monotherapy group a medium-sized superiority of OE was found (MWS 0.6721, 95% CI 0.6080–0.7363, $P < 0.0001$) and for the complementary therapy group the superiority of OE was small (MWS 0.5880, 95% CI 0.5246–0.6514, $P = 0.0062$).

The primary end-point of OE safety was the physician's judgement on overall tolerance and treatment with OE was rated "very good". As the secondary end-point, the total number of OE-associated adverse reactions was analysed (Table 2). Table 4 shows a list of all adverse reactions reported. In the OE group, 108 adverse reactions were reported overall. Of these, 51 were associated with chemotherapy, 20 with radiotherapy, 16 with other reasons and 21 with the OE treatment. In the control group, a total of 296 adverse reactions were reported. Of these, 104 were associated with chemotherapy, 101 with radiotherapy, 19 with surgery and 72 with other unclear reasons. Thus, in the OE group, 21 of 616 patients (3.4%) experienced OE-associated adverse reactions, all of them reported as mild to moderate gastrointestinal symptoms. In two patients the dose of OE had to be reduced and in one patient OE were discontinued because of intolerance. Consequently, in colorectal cancer patients OE was generally well tolerated.

Discussion

This epidemiological cohort study provides evidence that patients with colorectal cancer benefit from receiving OE therapy complementary to the standard antineoplastic therapy. The general condition of the patients receiving OE as the only complementary

Table 3 Result of end-point criteria: comparison of the total sample analysis with the sensitivity analysis using propensity score matched pairs

	Total sample analysis				Propensity score matched pairs			
	Valid, OE/control (*n*)	Results (OE/control)	Mean difference	P-value (two-sided)[a]	Valid pairs (*n*)	Results (OE/control)	Mean difference	P-value (two-sided)[a]
Monotherapy group								
Efficacy criteria								
Efficacy (% all symptoms relieved)	176/338	52.8/44.4	8.40	0.0798	125	54.4/48.0	6.60	0.080
Mean symptom score change	166/327	3.05/3.86	−0.81	< 0.0001	113	2.88/3.87	−0.99	0.000
Adverse reaction reduction "very large" (%)	91/184	63.7/34.2	29.50	< 0.0001	38	63.2/26.3	36.90	0.001
Performance index (mean change)	182/368	−0.03/+0.11	−0.14	0.0071	118	−0.21/+0.4	−0.61	0.001
Karnofsky index (mean change)	149/297	−1.6/−1.48	0.12	0.0845	93	+0.59/−3.3	−3.89	0.239
Safety criteria								
Safety rated "excellent" (%)	179/296	78.2/32.8	45.40	< 0.0001	112	75.9/25.0	50.90	0.000
Frequency of adverse reactions (%)	166/341	7.2/34.0	−26.80	< 0.0001	114	7.9/32.5	−24.60	0.000
Complementary group								
Efficacy criteria								
Efficacy (% all symptoms relieved)	398/227	37.2/33.0	4.20	0.0138	156	36.0/34.2	1.80	0.002
Mean symptom score change	357/208	3.69/3.71	−0.02	0.8727	128	3.64/3.74	−0.10	0.412
Adverse reaction reduction "very large" (%)	175/94	65.1/53.2	11.90	0.0062	32	29.8/24.8	5.00	0.936
Performance index (mean change)	302/167	+0.38/+0.54	−0.16	0.1938	149	+0.05/+0.25	−0.20	0.142
Karnofsky index (mean change)	383/201	−0.41/−3.06	2.65	0.4003	128	−1.11/−3.44	2.33	0.288
Safety criteria								
Safety rated "excellent" (%)	397/221	66.8/53.4	13.40	< 0.0001	156	67.1/52.8	14.30	0.001
Frequency of adverse reactions (%)	385/224	12.2/15.6	−3.40	0.2679	153	11.8/13.0	−1.20	0.862

[a] Wilcoxon-Mann-Whitney

treatment was improved as determined by a reduction in the signs and symptoms of the disease and its treatment. In addition, a statistically significant and clinically relevant reduction in typical disease- and therapy-associated signs and symptoms was observed. In particular, the frequency and severity of the adverse reactions caused by radiotherapy and chemotherapy were significantly reduced. Such a reduction in adverse events associated with the standard antineoplastic therapy is an accepted and important goal in the therapy of these patients. Thus, by the addition of OE to standard treatment regimens the quality of life of colorectal cancer patients could be substantially improved.

The present data collected on 1242 patients included a variety of different complementary care schemes including physical therapy, phytoextracts or organic extracts, trace elements or vitamins combined with OE. In the absence of a rationale in most cases, it is of interest to gain more information on the efficacy of individual drugs so as to eventually develop recommendations on which drugs should be used and how they should be used. The analysis of the large body of data by observational studies is a sensitive and valid approach to achieving this goal. It has been shown recently that the results of well-designed observational studies are neither consistently larger than nor qualitatively different from those obtained in randomized, controlled trials [2, 6]. Studies such as these can be used to generate hypotheses for the development of controlled prospective randomized clinical trials.

In this study, for the complementary therapy subgroup it was not possible to discriminate between the effects of OE and the effects of other complementary care drugs. In contrast, in the OE group as compared with the control group significantly fewer patients suffered from adverse reactions due to chemo- and radiotherapy. These results indicate a lack of efficacy in terms of disease symptoms, but a substantial efficacy in terms of the treatment-associated symptoms in the complementary therapy group. One possible explanation is that other complementary drugs do have a similar efficacy to that of OE and by adding OE no better efficacy can be achieved. Another explanation could be that by adding other complementary drugs to OE the efficacy of OE is compromised. Unfortunately, it was not possible to gain further insight as a descriptive analysis of the subgroups control-monotherapy vs control-complementary (data not shown) revealed that the two groups were not comparable at baseline (complementary group more severe). In addition, OE but not the other complementary drugs had an influence on tumour events. The results suggest that the recurrence- and metastasis-free survival as well as the overall survival time were prolonged in the OE group but the data did not achieve significance. These results, however, have to be verified further since the observation time (6 to 9 months) was short. Therefore, the present results can only be regarded as a trend.

The results of this retrolective cohort study are in good agreement with the results of a small placebo-controlled prospective pilot study with 60 patients suffering from colorectal cancer of stages Dukes' B and C [25]. Patients underwent surgery and received adjuvant

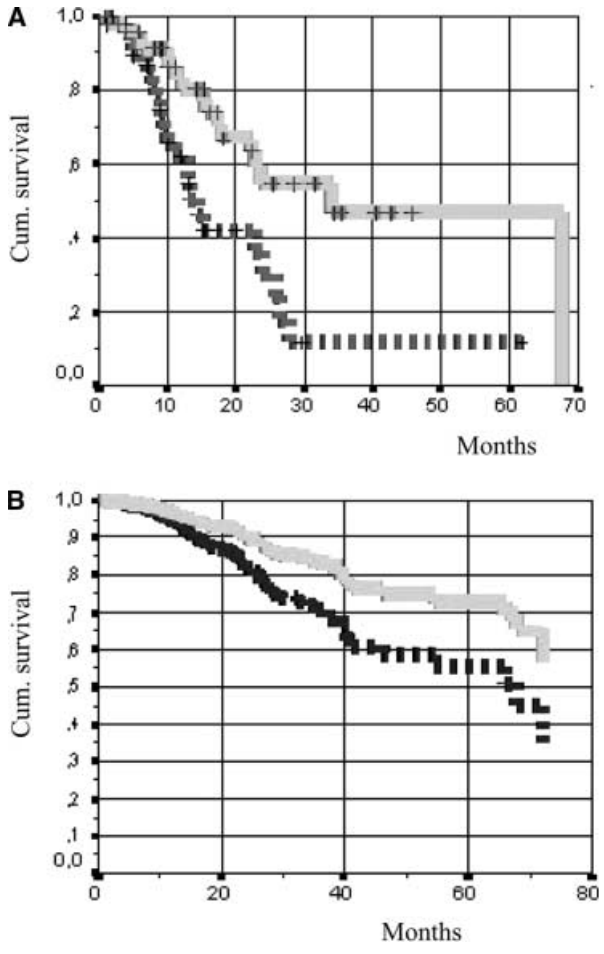

Fig. 2 **A** Survival curves for colorectal cancer patients receiving OE and complementary drugs and for controls. Kaplan-Meier analysis for Dukes' D, Log-rank statistic $P = 0.0025$, median survival time OE group 34.1 months (censored events 17/51 33.3%), control 14.5 months (censored events 23/49 46.9%). **B** Survival curves for colorectal cancer patients receiving OE and complementary drugs and for controls. Multivariate Cox proportional hazard regression for all Dukes' stages combined, adjusted for demographic and disease risk factors (confounders); OR adjusted 0.5483, 95% CI = 0.3259 – 0.9222, $P_{\text{Wald}} = 0.035$, *black bars* control; *shaded* OE

chemotherapy with 5-fluorouracil and levamisole. In addition, 30 patients were treated with OE and 30 patients received placebo. Quality of life was significantly improved in the OE group, which also showed fewer metastases. A Kaplan-Meier plot revealed a significantly higher number of relapse- and metastases-free survivors in the OE group after approximately 30 months of follow-up. The results of this pilot study as well as the results of the present epidemiological cohort study were considered for the design of a current ongoing larger controlled prospective study investigating the effect of OE in colorectal cancer patients of Dukes' stages B and C, undergoing surgery and receiving chemotherapy with 5-fluorouracil and levamisole.

The drugs used in the standard antineoplastic treatment of colorectal cancer produce a number of unpleasant side effects and additional treatments that improve the quality of life of the patients through alleviation of their discomfort may be a beneficial option if the treatment does not compromise the antineoplastic action of their chemotherapy. The results presented here suggest that treatment with OE not only improves patients' quality of life but also may lead to an improvement in their survival time. Tolerability of the complementary treatment with OE was excellent and only a low rate of mostly mild side effects were recorded. Thus treatment with OE can be evaluated as being safe. Therefore, OE represents a promising complementary therapy option for the treatment of colorectal cancer that has to be verified in prospective randomized trials.

Table 4 Number and type of adverse events in the total cohort (organ systems according to reference 34)

	Adverse events	
	OE group (n = 616)	Control group (n = 626)
Patients with adverse events		
Total	59 (9.5%)	151 (24.1%)
More than one event	20 (3.2%)	71 (11.3%)
Gastrointestinal system disorders	84	184
Skin and appendages disorders	3	57
CNS disorders	9	21
Respiratory disorders		2
Haematological toxicity		3
Cardiovascular disorders	4	1
Allergy		1
Pain	3	1
Coagulation disorders		3
General status reduced	1	4
Infections	1	4
Urogenital disorders	1	6
Immune status		1
Metabolic disorders		1
Others	2	7
Total	108	296

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References

1. Advanced Colorectal Cancer Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10(6): 896
2. Benson K, Hartz AJ (2000) A comparison of observational studies, and randomized, controlled trials. New Engl J Med 342(25): 1878
3. Beuth J, Moss RW (2000) Wissenschaftlich-begründete komplementäre Therapiemaßnahmen in der Onkologie. J Oncol 2: 45
4. Bleiberg H, de Gramont A (1998) Oxaliplatin plus 5-fluorouracil: clinical experience in patients with advanced colorectal cancer. Semin Oncol 25 [2 Suppl 5]: 32
5. Colditz GA, Miller JN, Mosteller F (1988) Measuring gain in the evaluation of medical technology: the probability of a better outcome. Int J Technol Assess Health Care 4: 637

6. Concato J, Shah N, Horwitz RI (2000) Randomized, controlled trials, observational studies, the hierarchy of research designs. New Engl J Med 342(25): 1887
7. de Gramont A, Vignoud J, Tournigand C, Louvet C, Andre T, Varette C, Raymond E, Moreau S, Le Bail N, Krulik M (1997) Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. Eur J Cancer 33(2): 214
8. Desser L, Sakalova A, Zavadova E, Holomanova D, Mohr T (1997) Concentrations of soluble tumor necrosis factor receptors, beta2-microglobulin, IL-6 and TNF in serum of multiple myeloma patients after chemotherapy and after combined enzyme-chemotherapy. Int J Immunother 13: 121
9. Feinstein AR (1984) The role of observational studies in the evaluation of therapy. Stat Med 3: 341
10. Feinstein AR (1985) Clinical epidemiology. Saunders, Philadelphia
11. Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP, O'Sullivan B, Sobin LH, Yarbro JW (eds) (1997) AJCC cancer staging manual, 5th edn. Lippincott Williams & Wilkins, Philadelphia, p 83
12. Gebauer F, Micheel B, Stauder G, Ransberger K, Kunze R (1997) Proteolytic enzymes modulate the adhesion molecule CD44 on malignant cells in vitro. Int J Immunother 13(3/4): 111
13. German Professional Society of Epidemiology (2000) Guidelines and recommendations for insuring good epidemiological practice (GEP). Gesundheitswesen 62(5): 295
14. Gettins P, Patston PA, Olson ST (1996) Serpins: structure, function and biology. Springer-Verlag, Heidelberg
15. Horwitz RI (1990) Developing improved observational methods for evaluation therapeutic effectiveness. Am J Med 89(5): 630
16. Horwitz RI, Feinstein AR (1981) Improved observational method for studying therapeutic efficacy. JAMA 246: 2455
17. IMPACT (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 345(8955): 939
18. Johnston PG, Allegra CJ (1995) Colorectal cancer biology: clinical implications. Semin Oncol 22(5): 418
19. Lachin JM (1992) Some large-sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. Stat Med 11(9): 1151
20. Lackovic V, Rovensky J, Horvahova M, Malis F (1997) Interferon production in whole blood cultures from volunteers and rheumatoid arthritis patients after medication with oral enzymes. Int J Immunother 13(3/4): 159
21. Latha B, Ramakrishnan M, Jayaraman V, Babu M (1998) The efficacy of trypsin/chymotrypsin preparation in the reduction of oxidative damage during burn injury. Burns 24: 532
22. Maurer W, Hothorn LA, Lehmacher W (1995) Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In: Vollmar J (ed) Biometrie in der chemisch-pharmazeutischen Industrie. Gustav Fischer Verlag, Jena, p 3
23. Mynott TL, Ladhams A, Scarmato P, Engwerda CR (1999) Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. J Immunol 163(5): 2568
24. Pemberton PA (1997) The role of serpin superfamily members in cancer. Cancer J 10: 24
25. Popiela T, Kulig J, Klek S, Bock PR, Hanisch J (2000) Enzyme therapy in patients with advanced colorectal cancer. Influence of an additive treatment with enzymes to standard therapy. Fourth Annual Meeting of the European Society of Surgery, Krakow, Poland
26. Rosenbaum PR (1995) Observational studies. Springer, Berlin Heidelberg New York
27. Rosenbaum PR, Rubin DB (1983) The central role of the propensity score in observational studies for causal effects. Biometrika 70: 41
28. Rosenbaum PR, Rubin DB (1984) Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 79: 516
29. Rosenbaum PR, Rubin DB (1985) Constructing a control group using multivariate matched sampling methods that incorporates the propensity score. Am Stat 39: 33
30. Rubin DB (1998) Estimation from nonrandomized treatment comparison using subclassification on propensity scores. In: Abel U, Koch A (eds) Non-randomized comparative clinical studies. Symposion Publishing, Düsseldorf, p 85
31. Staender M, Naumann U, Wick W, Weller M (1999) Transforming growth factor-beta and p-21: multiple molecular targets of decorin-mediated suppression of neoplastic growth. Cell Tissue Res 296(2): 221
32. Swedish Rectal Cancer Trial (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer [published erratum appears in N Engl J Med 1997 May 22; 336(21): 1539]. New Engl J Med 336(14): 980
33. Wei LJ, Lachin JM (1984) Two-sample asymptotically distribution-free tests for incomplete multivariate observations. J Am Stat Assoc 79: 653
34. WHO Collaborating Centre For International Drug Monitoring (1992) WHO adverse reaction dictionary. World Health Organization, Geneva
35. Wittenborg A, Bock PR, Hanisch J, Saller R, Schneider B (2000) Vergleichende epidemiologische Studie bei Erkrankungen des rheumatischen Formenkreises am Beispiel der Therapie mit nichtsteroidalen Antiphlogistika versus einem oralen Enzymkombinationspräparat (Comparative epidemiological study in patients with rheumatic diseases illustrated in an example of a treatment with non-steroidal anti-inflammatory drugs versus an oral enzyme combination). Arzneimittelforschung 50 (II)(8): 728
36. Zavadová E, Desser L, Mohr T (1995) Stimulation of reactive oxygen species production and cytotoxicity in human neutrophils in vitro and after oral administration of a polyenzyme preparation. Cancer Biother 10: 147
37. Zawadzki V, Perschl A, Rosel M, Hekele A, Zoller M (1998) Blockade of metastasis formation by CD44-receptor globulin. Int J Cancer 75(6): 919