Retrospective study of treatment with mistletoe extracts in patients with colorectal cancer

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Summary
A retrospective study looked at the survival times of all patients with colorectal cancer who were treated with mistletoe extracts at the Outpatient Oncology Clinic of Herdecke Communal Hospital between 1981 and 2001. The data were compared to corresponding patient data from the Saarland Epidemiological Cancer Registry for the same period. The median survival time of the patients treated with mistletoe extracts was 59 months, significantly longer than that of the patients in the Saarland Epidemiological Cancer Registry (38 months; p < 0.0001, log-rank test). The 5 to 10 year survival rates for the patients treated with mistletoe extracts were 48.9% and 42.7% respectively, considerably higher than those for the reference groups (40.3% and 27.2% respectively). Analysis of the prognostic factors for survival time showed that tumour stage had the greatest influence on survival, followed by age, inclusion in the mistletoe treatment group and sex. Patients with tumour stages III or IV and under 68 years of age who were treated with mistletoe were shown to have a clear advantage in an exploratory analysis. The patients reported that they tolerated the mistletoe extracts well. The results of this retrospective study are further evidence of the increased survival time of patients with colorectal cancer with adjuvant mistletoe therapy.

Key words: Colorectal cancer, mistletoe therapy, adjuvant therapy, retrospective analysis, survival time

Introduction
There have been many clinical studies (retrospective, prospective and randomised) on the treatment of different malignant disorders with mistletoe extracts in which tumour regression, increased survival times, immunomodulation and improved quality of life were reported [1, 3, 4, 7 - 9, 12 - 14, 16, 17, 20, 22, 24 - 26, 28]. These results have been the subject of some controversy on methodological grounds [2, 6, 10, 11, 15, 18, 19, 21, 23]. There are also publications on colorectal cancer which suggest that mistletoe therapy has a beneficial effect on the disease, although prognostic factors were not taken into account in many cases, so that a conclusive assessment is still not possible:

The first publications on the use of mistletoe extracts in the treatment of patients with colorectal cancer were by Günczler and Salzer in 1969 [14]. Although patients who were given mistletoe extract following surgery for rectal cancer had a longer survival time, no comparative analysis of prognostic factors was carried out, so that it is unclear whether the two cohorts were even comparable. Similar retrospective comparative studies with inoperable colorectal cancer were published by Leroi [20] and Hoffmann [17].
A retrospective study by Salzer [24] analysed the survival times of patients with colorectal cancer who underwent surgery between 1973 and 1990 at the Ludwig Boltzmann Institute in Vienna. In this study, both the mean and the median survival times were longer in the mistletoe treatment group, although the criteria for assignment to treatment groups were not given, making the evaluation more difficult. Data from the same institute and for a similar period (1975 - 1990) were studied by Hellan et al. [16]. With the exception of Stage II and Stage IV colon cancer and Stage IV rectal cancer, a clear trend towards increased survival time was observed in the mistletoe treatment group compared to the untreated control group. A clearly reduced recurrence rate in the mistletoe group was statistically significant for both Stage III colon cancer and Stage I and Stage II rectal cancer.

Boie and Gutsch [3, 4] published retrospective studies in 1978 and 1980 on patients with inoperable rectal cancer in which prognostic factors such as age, sex, histology, frequency and extent of liver metastases, frequency of distant metastases, stage of the disease when inoperability was diagnosed, type of palliative operation and previous recurrence-free interval in patients with previous radical surgery and subsequent inoperable recurrence were taken into account. Despite the poorer prognosis of patients in the mistletoe extract group, there was a clear difference in terms of median survival time, with 11 months in the mistletoe extract group compared to 5 months in the control group.

Two prospective matched-pair studies of colon and rectal cancer were carried out as part of a long-term epidemiological study by Grossarth-Maticek et al. [2, 13]. In a total of 130 colon cancer patient pairs and 93 rectal cancer patient pairs, a significantly longer mean survival time was described for the mistletoe treatment group.

In 1986, Douwes et al. [9] published a prospective randomised study of metastatic colorectal cancer in which 20 patients were assigned to each of 3 treatment arms (chemotherapy according to the Machover schedule, chemotherapy + organic extract and chemotherapy + mistletoe extract). The groups were comparable in terms of age, sex, previous cytostatic treatment and location of the primary tumour. The rate of remission was comparable in the 3 groups, the mean survival time in the groups with adjuvant mistletoe and organic extract therapy was distinctly longer than in the group with chemotherapy alone. In a further study of metastatic colorectal cancer by the same group, the median survival time was clearly higher in the group with adjuvant mistletoe therapy [8].

In 2002, Cazacu et al. [7] published a randomised study of 64 patients with colorectal cancer and 3 treatment arms (chemotherapy, chemotherapy + i.v. mistletoe extract, no other treatment). Median survival was longer in the group with adjuvant mistletoe therapy in patients with Duke’s C tumours (significant) and with Duke’s D tumours.

For a detailed summary evaluation of all clinical studies of mistletoe therapy published to date, please refer to the review studies by Kienle et al. [18] and Ernst et al. [10] and to the descriptions in Kienle and Kiene [19]. Kienle et al. assess the studies of mistletoe extracts positively, but point out the variety of methodological deficiencies in the studies reviewed.
As it had been in existence for twenty years, it was in the interests of the Outpatient Oncology Clinic of the Herdecke Communal Hospital to evaluate the clinical data of patients with colorectal cancer treated to date with mistletoe extracts. The hypothesis to be tested in this study was whether the frequency of local recurrence and metastases was reduced and the survival time extended in patients with colorectal cancer treated with mistletoe therapy (study population) compared to controls from a cancer registry (external reference group) and a reference group from the Herdecke Outpatient Oncology clinic not treated with mistletoe extract (internal reference group). The tolerability of mistletoe therapy was also studied.

**Patients and methods**

**Patients in the study population**

The study was designed as a single-centre, single-arm, retrospective questionnaire survey. In order to ensure the quality of the data and thus of the results, as far as was possible in a retrospective study, it was carried out in accordance with a study protocol based on ICH/GCP guidelines and the results analysed per protocol. All patients, without exception, who had had a consultation or been treated with mistletoe extract for colorectal cancer at the Outpatient Oncology Clinic in the Herdecke Communal Hospital since it was founded (1981) were sent a letter asking them to complete a questionnaire on the recommended treatment with mistletoe extracts and the clinical outcome. The following data were collected: personal data; start, duration, type and tolerability of the mistletoe therapy; date of first recurrence; data of first metastases; start, duration and type of other treatments carried out. The survey period covered the years 1981 - 2001. The survey was based on the Outpatient Oncology Clinic’s internal patient records which were available in their entirety. Patients who had not responded to the first request after 8 weeks were sent another survey to complete. If the patients had already died, their relatives often answered the questionnaire. The information received was supplemented and compared with data from patient records (e.g. histological classification) and from other sources (e.g. death notices, personal contacts, family doctor).

**Patients in the reference population**

Apart from the internal reference group (= patients from the Outpatient Oncology Clinic of the Herdecke Communal Hospital who, despite recommendations did not receive mistletoe therapy), a comparable external patient group was also recruited from the Saarland Epidemiological Cancer Registry, which kindly made available the data on all patients with colorectal cancer registered during the period from 1981 to 2001. The following data were recorded for these patients: sex, month and year of birth, diagnosis, month and year of diagnosis, dates of events (month and year of recurrence, metastases and death) and the TNM classification of the tumour.
Inclusion criteria

Inclusion criteria were defined for inclusion of the patients in the different populations for evaluation. The patients from the Herdecke Communal Hospital were included in the study population if they fulfilled the following inclusion criteria: response to the questionnaire, indication of a usable TNM classification, question concerning mistletoe therapy should not be answered with “Can’t remember” and the survival status had to be given. For inclusion of the data from the Epidemiological Cancer Registry in the external reference population, the following inclusion criteria applied: the indication of the TNM classification had to be valid and comparable with the data of the study population patients.

Parameters of the statistical analyses

The primary study objectives were comparisons between the two population groups of local recurrence-free time, metastasis-free time and survival time. The start of the survey period for each patient was the time of the first diagnosis. Apart from the comparison of the local recurrence-free time, metastasis-free time and survival time, in a further analysis the 5-year and 10-year survival rates were differentiated according to stages and compared between the “mistletoe therapy” and “external reference population” groups.

For the groups of patients who “definitely” received mistletoe therapy, the tolerability of the treatment and general condition of the patients during treatment were also analysed.

Data entry and method of analysis

The data were entered electronically in an MS Access database (MS Access 97) and the statistical analysis was carried out using the SPSS analysis system, version 12.01 and SAS®, version 8.01. The recurrence-free period, the metastasis-free period and the survival time of the patients were analysed using Kaplan-Meier models. The influence of prognostic factors on the survival times of patients was tested using univariate and multivariate Cox models.

Results

Study population

Letters were sent to a total of 1354 patients. All patients who failed to respond to the first questionnaire were sent a duplicate two months later. A response to the questionnaire was received from 53.2 % of patients (n = 720), either from the patients themselves or from their relatives. No response was received from 46.8 % (n = 634), or else they had moved to an unknown address. Information on patients who failed to reply or who were uncontactable and information on patients who had died was supplemented, where possible, by information from hospital records and/or the patient’s family doctor. Fulfillment of the inclusion criteria was tested for all 1354 patients. The formation of the study population can be seen in the flow chart in Fig. 1. Accordingly, 35.2 % of the patients with sufficient information on the tumour stage, mistletoe therapy and survival status (n = 476) were available for analysis as the study population.
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Fig. 1: Flow chart showing the formation of the study population from patients of the Herdecke Communal Hospital Outpatient Oncology Clinic

Mistletoe therapy

Of these 476 patients, 70.2% (n = 334) received one or more mistletoe extract preparations during the course of their illness. There was no useful information available concerning this for 25.6% (n = 122) of the patients. 4.2% (n = 20) had definitely not received any mistletoe extract preparation. Over half of the patients had received a Helixor® preparation and a quarter each had received either Iscador® or other mistletoe preparations. The average duration of treatment with mistletoe extracts was given for 68.8% of patients (n = 230) and was 22.8 ± 26.2 months.
Demographic characteristics of the patients

The age of the patients at diagnosis ranged from 25 to 85 years, with an average of $56.8 \pm 10.3$ years. Of the 476 patients, 47.7 % ($n = 227$) were female and 52.3 % ($n = 249$) were male. Analysis of the places of residence of the patients using post codes showed that most patients (84.5 %, $n = 402$) came to the Herdecke Communal Hospital for consultation/treatment from the immediate vicinity or neighbouring regions.

Distribution of tumour location

Cancers of the rectum (32.1 %, $n = 153$) and of the sigmoid colon (29.2 %, $n = 139$) were the most common. 11.6 % ($n = 55$) of the patients had cancer of the ascending colon, 8.4 % ($n = 40$) had cancer of the descending colon and 6.9 % ($n = 33$) cancer of the caecum. All other tumour locations were found in fewer than 5 % of the patients.

Type of first operation

Nearly all the 476 patients underwent surgery (97.3 %, $n = 463$). The most common type of operation was the sigmoid/rectal resection (47.3 %, $n = 225$). A further 12.8 % of patients ($n = 61$) also underwent this operation in conjunction with the creation of an artificial anus. A hemicolecction (right, left or bilateral) was carried out in 29.0 % ($n = 128$) and a transverse resection in 2.7 % ($n = 13$). The remaining operations were varying combinations of these surgical procedures.

Time from diagnosis to surgery

The time from diagnosis to the first operation could be calculated for 463 of the 476 patients. For the patients who received mistletoe therapy ($n = 332$) the median time to the first operation was 5 days, in the group which “definitely did not receive mistletoe therapy” ($n = 20$) it was 3.5 days and in the group of patients for whom there was no information on treatment ($n = 111$) it was 23 days. These differences are not statistically significant ($p < 0.5151$, Kruskal-Wallis test).

Distribution of tumour classification

Colorectal cancers are characterised by the UICC tumour stage classification (or TNM classification) and by histological tumour grading. The tumours of all 476 patients were classified according to the TNM classification. The T3N1M0 class was the most commonly represented with 10.5 % ($n = 50$). On the basis of the TNM classification, the tumour stage was determined using the UICC and/or AJCC classification. Stage III of the disease was the most common with 41.0 % ($n = 195$). The distribution of the tumour stages in the various groups (including the external reference group) can be seen in Table 1.
Table 1: Demographic data and distribution of tumour stages in the study population (n = 476) and in the external reference population (n = 8151)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Unknown treatment (n = 122)</th>
<th>Definitely no mistletoe (n = 20)</th>
<th>Mistletoe therapy (n = 334)</th>
<th>External reference population (n = 8151)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>Age (years)</td>
<td>Sex (f/m)</td>
<td>Tumour stages</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>56.8 (± 10.1)</td>
<td>41.8 %/58.2 %</td>
<td>Stage I</td>
<td>3.3 % (4)</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td>Stage II</td>
<td>10.7 % (13)</td>
</tr>
<tr>
<td>(n = 122)</td>
<td></td>
<td></td>
<td>Stage III</td>
<td>44.3 % (54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stage IV</td>
<td>41.8 % (51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No information</td>
<td>-</td>
</tr>
<tr>
<td>Definitely no</td>
<td>53.3 (± 12.0)</td>
<td>45 %/55 %</td>
<td>Stage I</td>
<td>10.0 % (2)</td>
</tr>
<tr>
<td>mistletoe</td>
<td></td>
<td></td>
<td>Stage II</td>
<td>20.0 % (4)</td>
</tr>
<tr>
<td>(n = 20)</td>
<td></td>
<td></td>
<td>Stage III</td>
<td>50.0 % (10)</td>
</tr>
<tr>
<td>Mistletoe</td>
<td>57.0 (± 10.2)</td>
<td>50 %/50 %</td>
<td>Stage IV</td>
<td>10.0 % (2)</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td>No information</td>
<td>-</td>
</tr>
<tr>
<td>(n = 334)</td>
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<tr>
<td>External</td>
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<tr>
<td>population</td>
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<tr>
<td>(n = 8151)</td>
<td></td>
<td></td>
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</tbody>
</table>

Histopathological diagnosis of the tumours

Histopathological diagnosis showed adenocarcinoma in 85.1 % of the patients (n = 405). For 14.5 % of the patients (n = 69) either no information was available or the histology was unknown. Two patients (0.4 %) had a different histopathological tumour type. Information on the degree of histopathological differentiation of the tumours was available for 82.8 % of the patients (n = 394). There was minor histopathological differentiation of the tumours for 61.6 % of the patients (n = 293) and moderate histopathological differentiation for 7.4 % (n = 35).

Adjuvant therapies

After the initial surgery, the patients were mainly treated with chemotherapy (35.1 %, n = 167). Post-operative radiotherapy was carried out in 7.6 % (n = 36), combined chemotherapy/radiotherapy in 4.0 % (n = 19) and other unspecified therapies in 3.8 % of the patients (n = 18). 19.1 % (n = 91) received no post-operative treatment.

Tolerability of mistletoe extract therapy and condition during treatment

In the questionnaire, the patients were asked about the tolerability of the mistletoe extract therapy and their condition during the treatment. Of the 70.2 % of patients (n = 334) in the study population who had definitely used a mistletoe extract preparation for the treatment of colorectal cancer, 22.8 % (n = 76) remembered that some kind of reaction had occurred at least once during the course of the treatment. 74 of these 76 patients (97 %) had experienced transient redness at the injection site and 53 (72 %) remembered a swelling at the injection site; 14 of these patients (18 %) developed a high temperature after the mistletoe extract injection and 4 (5 %) experienced pain. In our experience, these are dose-related reactions which occur in the initial phase of the treatment and quickly regress without treatment. 42.8 % of the patients (n = 143) who answered the questionnaire evaluated their condition during the mistletoe therapy retrospectively as positive. 47 % (n = 157) were unable to respond from memory.
Local recurrence

During the course of the disease, 17.2 % of the patients (n = 82) experienced a local recurrence, 38.2 % (n = 182) did not and 0.6 % (n = 3) could not remember. The remaining 43.9 % of the patients (n = 209) did not provide information on local recurrence in the questionnaire. The recurrence-free period could be calculated for 97.2 % (n = 463) of the patients in the total population (n = 476). In the group which definitely received mistletoe treatment, there were 57 local recurrences (17.2 %) during the course of the disease compared to 15 (13.5 %) in the group which did not provide any information on mistletoe therapy and 3 (15 %) in the group which definitely did not receive mistletoe therapy. No statistically significant difference in the local recurrence-free period could be determined between the three groups with different information on mistletoe therapy (mistletoe therapy, no mistletoe therapy and unknown) (p = 0.6372, log rank test).

Occurrence of metastases

The colorectal cancer metastasised during the course of the disease in over half of all patients (58.8 %, n = 280) (42.9 % liver, 13.2 % lung, 7.4 % lymph nodes, 4.2 % bones) and a quarter of the patients (25.2 %, n = 120) remained free of metastases. A total of 15.5 % (n = 74) did not answer the question about metastases and 2 patients (0.4 %) were unable to remember. The occurrence of metastases was most common in the group of patients which was unable to provide information on the treatment (73.8 %, n = 90).

Analysis of survival time

The survival time was calculated for 97.2 % of the patients (n = 463) in the total population (n = 476). The overall median survival time for all these patients was 42 months (range 1 - 260 months). The patients for whom there was no information on treatment had the shortest survival time of 21 months (median: range 1 - 128 months). The patients who definitely received mistletoe therapy had a median survival time of 59 months (range 2 - 260 months) and patients who definitely did not receive mistletoe therapy (n = 18) survived the longest with 61.5 months (median: range 6 - 244 months). These differences are statistically significant (p < 0.0001, log rank test).

Analysis of 5 and 10-year survival rates

The 5 and 10-year survival rates were only calculated for the patients for whom the tumour stage was given. No tumour stage could be determined for 6 patients in the study population (4 out of the mistletoe therapy group and 2 out of the group which definitely did not receive mistletoe therapy), despite information being provided on the TNM classification of the tumour. Of the study population who received mistletoe therapy (n = 328), a total of 48.9 % (95 % CI 43.4 - 54.5) of patients survived for more than 5 years and 42.7 % (95 % CI 37.0 - 48.4) for more than 10 years. The 5 and 10 year survival rates in the different treatment groups are shown in Table 2, in total and differentiated according to tumour stages.
Table 2: 5 and 10 year survival rates in the study population and the external reference population (total and according to staging)

<table>
<thead>
<tr>
<th></th>
<th>Unknown therapy (n = 111)</th>
<th>Definitely no mistletoe therapy (n = 18)</th>
<th>Mistletoe therapy (n = 328)</th>
<th>External reference population (n = 8151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year survival</td>
<td>10.8 %</td>
<td>68.7 %</td>
<td>48.9 %</td>
<td>40.3 %</td>
</tr>
<tr>
<td>rate</td>
<td>2.0 %</td>
<td>68.7 %</td>
<td>42.7 %</td>
<td>27.2 %</td>
</tr>
<tr>
<td>Stage I</td>
<td>n = 4</td>
<td>n = 2</td>
<td>n = 38</td>
<td>n = 1394</td>
</tr>
<tr>
<td>5-year survival</td>
<td>0 %</td>
<td>100 %</td>
<td>78.3 %</td>
<td>69.2 %</td>
</tr>
<tr>
<td>rate</td>
<td>0 %</td>
<td>100 %</td>
<td>66.2 %</td>
<td>50.4 %</td>
</tr>
<tr>
<td>Stage II</td>
<td>n = 11</td>
<td>n = 4</td>
<td>n = 78</td>
<td>n = 2220</td>
</tr>
<tr>
<td>5-year survival</td>
<td>36.4 %</td>
<td>75.0 %</td>
<td>66.5 %</td>
<td>55.8 %</td>
</tr>
<tr>
<td>rate</td>
<td>9.1 %</td>
<td>75.0 %</td>
<td>58.3 %</td>
<td>34.6 %</td>
</tr>
<tr>
<td>Stage III</td>
<td>n = 50</td>
<td>n = 10</td>
<td>n = 131</td>
<td>n = 2653</td>
</tr>
<tr>
<td>5-year survival</td>
<td>12.0 %</td>
<td>56.0 %</td>
<td>49.4 %</td>
<td>36.4 %</td>
</tr>
<tr>
<td>rate</td>
<td>5.0 %</td>
<td>56.0 %</td>
<td>42.9 %</td>
<td>24.3 %</td>
</tr>
<tr>
<td>Stage IV</td>
<td>n = 46</td>
<td>n = 2</td>
<td>n = 81</td>
<td>n = 1884</td>
</tr>
<tr>
<td>5-year survival</td>
<td>4.3 %</td>
<td>50.0 %</td>
<td>15.3 %</td>
<td>7.1 %</td>
</tr>
<tr>
<td>rate</td>
<td>2.2 %</td>
<td>50.0 %</td>
<td>13.7 %</td>
<td>5.1 %</td>
</tr>
</tbody>
</table>

External reference population

All the patients in the Saarland Epidemiological Cancer Registry with colorectal cancer who were registered during the period 1981-2001 were recruited (n = 16234). The tumour classification was given for 65 % of the patients (n = 10551) and this information was useable for 84.2 % (n = 8884). In order to be able to compare this population with the study population, all tumour entities which were not included in the study population (8.3 %, n = 733) were also excluded from the external reference population. The data on a total of 8151 patients (50.2 %) from the Saarland Epidemiological Cancer Registry were used (Fig. 2).

Demographic characteristics of the patients

The age of the 8151 patients at the time of diagnosis was known and was between 18 and 99 years, with an average of 68.3 ± 11.3 years. 51.2 % (n = 4171) of the patients were female and 48.8 % (n = 3980) were male (Table 1).
Fig. 2: Flow chart showing the formation of the study population from patients of the external reference population from the Saarland Epidemiological Cancer Registry (*The Registry does not contain information on treatment)

Distribution of tumour location

Here, too, the most common tumours were cancers of the rectum (31.9%, n = 2600) and of the sigmoid colon (23.7%, n = 1931). 9.9% of the patients (n = 804) had a cancer of the caecum and 8.4% (n = 681) in the ascending colon and 5.9% (n = 482) in the rectosigmoid junction. The frequency was below 5% in the transverse colon (4.7%, n = 382) and in the descending colon (2.9%, n = 235). The distribution of tumour location was very similar to that of the treatment group.

The proportion of patients with a cancer of an unknown or unspecified location within the colon was 10.0% (n = 814). A cancer overlapping in several parts was diagnosed in 2.7% (n = 222).
Distribution of tumour classification

The tumours of the 8151 patients were initially divided according to the TNM classification and then assigned to the relevant tumour stages using the UICC and/or AJCC classification. Stage III disease was the most common, accounting for 32.6 % (n = 2653) whilst 17.1 % (n = 1394) had Stage I tumours, 27.2 % (n = 2220) Stage II and 23.1 % (n = 1884) Stage IV (Table 1). The stage distribution in the external control group was slightly more favourable than in the treatment group.

Surgery and adjuvant therapy

No information was available in the Saarland Epidemiological Cancer Registry on either the type of surgery carried out or on adjuvant therapies.

Local recurrence

According to the registry data, 8.3 % of the 8151 patients (n = 678) experienced a local recurrence during the course of the disease. 91.7 % of the patients (n = 7473) either suffered no local recurrence or no information was recorded on this. Of the 687 patients who had a local recurrence, there was no information on the time of recurrence for 15 of these (2.2 %). Thus, the recurrence-free period could be calculated for only 663 patients (97.8 %). Of the patients with tumour Stage I (17.1 %, n = 1394), 7.7 % (n = 107) suffered a recurrence, of those with tumour Stage II (27.2 %, n = 2220) 8.0 % (n = 177), in the patient group with tumour Stage III (32.6 %, n = 2653), 285 (10.7 %) suffered a recurrence and in the group with tumour Stage IV (23.1 %, n = 1884), there were 109 recurrences (5.8 %).

Metastases

During the course of the disease, the colorectal cancer metastasised in a good half of all patients in the external reference population (57.2 %, n = 4665). In the remainder (42.8 %, n = 3486), there were either no metastases or no answer was given or the patient had already died when he or she was entered in the Saarland Epidemiological Cancer Registry. Of the 57.2 % of patients for whom metastases were reported, only 10.6 % (n = 496) gave information on the time of occurrence, so that the metastasis-free period could only be calculated for these patients. Of the patients with tumour Stage I (17.1 %, n = 1394), 7.6 % (n = 106) had developed metastases during the course of the disease, of those with tumour Stage II (27.2 %, n = 2220) 11.7 % (n = 259), in the group with tumour Stage III (32.6 %, n = 2653) 2514 patients (94.8 %) developed metastases and in the tumour Stage IV group (23.1 %, n = 1884) 1786 patients (94.8 %).

Analysis of survival time

The median survival time for the total external reference population included in the analysis (n = 8151) was 38 months (range 0 - 250 months).
Analysis of 5 and 10-year survival rates

The data on 5 and 10-year survival rates for the external reference population (Saarland Epidemiological Cancer Registry) are given in Table 2, both in total and differentiated according to tumour stages.

Primary target parameters of the study

The primary target parameters for the assessment of the efficacy of mistletoe therapy were recurrence-free period, metastasis-free period and survival time. In the confirmatory analysis, the patients who received mistletoe therapy were compared with the patients in the external reference group.

Comparison of recurrence-free period

In the sub-group of the study population which definitely received mistletoe therapy (n = 332), the proportion of patients who had a local recurrence was 17.2 % (n = 57). Of the patients in the external reference population, 8.3 % (n = 678) had a recurrence, with information available on the time of recurrence for 663 patients (8.1 %). There was a statistically significant difference in the local recurrence-free period between the two groups (log-rank test p = 0.0013), with patients in the external reference population remaining recurrence-free for longer. In order to provide a possible explanation for the higher local recurrence rate in the study population, in addition to the time at which the local recurrence developed, the time at which it developed in relation to the start of mistletoe therapy was also calculated. It was found that in 5.1 % of the patients (n = 17) who definitely received mistletoe therapy (n = 332), the recurrence had taken place before the start of this treatment, in 11.1 % of the patients (n = 37) after the start of mistletoe treatment and at the same time as the start of treatment in 0.9 % of the patients (n = 3).

Comparison of metastasis-free time

The proportion of patients with metastases in the subgroup of the study population who received mistletoe therapy compared to the patient group from the Saarland Cancer Registry was 46.7 % (n = 155) versus 57.2 % (n = 4665). Precise information on the time of occurrence of the metastases was only given for 10.6 % of the 4665 patients (n = 496). Consequently, because of the fact that 89.4 % of the patients in the external group (n = 4169) could not be taken into account, a comparison of the metastasis-free period of the external population with the mistletoe group would not be very informative. Because of the blurring of the distinction between recurrence, local recurrence and metastases in the external patient group, the events (event = recurrence and/or local recurrence and/or metastases) were analysed in a supplementary exploratory analysis. 43.7 % of the patients in the mistletoe group (n = 145) experienced no event, with 25.3 % of the patients (n = 84) experiencing an event before the start of mistletoe therapy (Table 3). In comparison, 40.7 % of the patients in the external group (n = 3317) experienced no event, with only 8.1 % of the patients (n = 663) having an event for which the date was shown (Table 3).
Comparison of survival time

The proportion of patients who died in the study population which received mistletoe therapy was 54.8 % (n = 182) compared to 59.1 % (n = 4815) in the external reference population. The median survival time was 59 compared to 38 months. Fig. 3 gives a graphic representation of the survival times of the mistletoe group and the external reference population, differentiated according to Stages I - IV (Kaplan-Meier model). When the two groups are compared in terms of survival time, the probability of a longer survival time in the mistletoe extract group is statistically significantly higher (p < 0.0001, log-rank test).

**Table 3: Time of start of treatment (Herdecke Communal Hospital) or indication of date (external reference group) of occurrence of an event**

<table>
<thead>
<tr>
<th>Event and time of start of treatment in the case of patients of the Herdecke Communal Hospital</th>
<th>Mistletoe therapy (n = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>43.7 % (145)</td>
</tr>
<tr>
<td>Event before the start of treatment</td>
<td>25.3 % (84)</td>
</tr>
<tr>
<td>Event after the start of treatment</td>
<td>25.9 % (86)</td>
</tr>
<tr>
<td>Event at the same time as the start of treatment</td>
<td>5.1 % (17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event and indication of date in the case of the external reference group</th>
<th>External reference population (n = 8151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No event</td>
<td>40.7 % (3317)</td>
</tr>
<tr>
<td>Event with indication of date</td>
<td>8.1 % (663)</td>
</tr>
<tr>
<td>Event with no indication of date</td>
<td>51.2 % (4171)</td>
</tr>
</tbody>
</table>

1) Event = recurrence and/or local recurrence and/or metastases
Fig. 3: Survival probabilities of the patients treated with mistletoe extract and of the external reference population using the Kaplan-Meier model (Stages I to IV)

Key:
EKRS = Saarland Epidemiological Cancer Registry

Prognostic factors

Possible prognostic factors for survival time which were looked at were the group to which the patient belonged, tumour stage, age and sex. The distribution of factors relevant for prognosis between the two groups (patients who received mistletoe therapy vs. external reference population) was only homogenous for the factor sex (female 50 %/51.2 %, male 50 %/48.8 %). For the factor tumour stage, there were more patients in the mistletoe therapy group with advanced tumour stages than in the external reference population group (Stages I/II 35.4 %/44.3 %, Stages III/IV 64.6 %/55.7 %). The age of the patients who received mistletoe therapy was 57 at the time of diagnosis, which was less than that of the external reference population (68).

The statistical analysis of the importance of the prognostic factors for survival time was carried out by univariate and multivariate analyses (Cox regression, Table 4). A statistically significant influence on survival time was found for all factors studied. In both the univariate and multivariate analyses (i.e. adjusted for the other factors) the tumour stage had the greatest influence on survival (patients with tumour Stages III or IV had a
2.8-fold higher risk of dying of cancer than patients with tumour Stages I and II), whilst age was the second most important influencing factor (patients who were 68 years of age or older had a 1.6-fold higher adjusted risk of dying than patients who were under 68 years of age). The group to which the patients belonged also had a statistically significant influence on survival time. Patients from the Saarland Epidemiological Cancer Registry had a 1.3-times higher risk of dying (adjusted for the other factors) than the patients on mistletoe therapy. It was confirmed that women survive longer than men (0.86-fold, adjusted).

Table 4: Univariate and multivariate Cox regression of the prognostic factors for survival time in the mistletoe treatment group of patients (n = 328) and external reference population (n = 8151)

<table>
<thead>
<tr>
<th>Variable (risk group given)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis (n = 8477*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Relative risk</td>
</tr>
<tr>
<td>“Non-mistletoe” group</td>
<td>8479</td>
<td>1.51 (1.30-1.75)</td>
</tr>
<tr>
<td>Tumour Stages III + IV</td>
<td>8479</td>
<td>2.66 (2.50-2.83)</td>
</tr>
<tr>
<td>Age ≥ 68 years</td>
<td>8479</td>
<td>1.68 (1.58-1.77)</td>
</tr>
<tr>
<td>Female sex</td>
<td>8477</td>
<td>0.94 (0.89-0.99)</td>
</tr>
</tbody>
</table>

*No information on the sex of the patient was given for 2 patients in the external reference population

Discussion

Depending on the stage of the tumour, either chemotherapy or a combination of chemotherapy and radiotherapy are established post-operative treatments for colorectal cancer. Mistletoe extracts have been used as adjuvant therapy to conventional therapies for many years for this type of tumour [3, 4, 7-9, 12-14, 16, 19, 20, 24]. In order to verify the efficacy of our own therapeutic use of this treatment in colorectal cancer, we carried out the retrospective analysis presented here, in which all the colorectal cancer patients (n = 1354) who consulted or were treated at the Outpatient Oncology Clinic of the Herdecke Communal Hospital, for whom both the tumour stage and the survival time were known, were included.

Of the known distorting effects which can occur as a result of retrospective data collection, the following were addressed in the interpretation of the results: “error as a result of patient selection”, “lack of representativeness of the patient population because the Herdecke Communal Hospital is known nation-wide as an anthroposophic hospital” and “error as a result of unknown cause of death”.

There was no patient selection during patient screening, as without exception all patients with colorectal cancer who attended the Outpatient Oncology Clinic during the period 1981 to 2001 were documented. A possible sociological selection before patient screening cannot be ruled out because of the generally expected higher social status of patients who turn to complementary medicine.
A selection effect as a result of the Herdecke Communal Hospital being known nationwide as an anthroposophic hospital could not be verified. 84.5 % of the patients (n = 402) came from the immediate vicinity and the neighbouring regions of the hospital.

For ethical reasons, the questionnaire did not ask about the cause of death. In the analysis of the data, it was always assumed that the cause of death was the colorectal cancer. This assumption distorts the result in the case of patients with a longer survival time in particular, as the risk of dying of another cause increases with time. This can lead to an increased systematic underestimation of the actual survival times of patients who received mistletoe therapy. Conversely, patients from whom no questionnaire was received and/or whose date of death was unknown, were excluded from the analysis. It is debatable whether on the other hand relatives of patients who died early did not want to answer the questionnaire because of the early death, making a positive selection a possibility.

No suitable retrospective study carried out during the same period could be found in the literature for a comparison of the results of the present study with a control population. The patient data were therefore compared with data from the Saarland Epidemiological Cancer Registry from the same period (1981 - 2001). The average age of the external group, which was 11 years higher, should also be taken into account, as the probability of a “non-cancer death” was clearly higher.

**Local recurrence-free time**

In the comparison of the local recurrence-free time of patients in the study population who received mistletoe therapy with the patients in the external reference group, the probability of recurrence in the mistletoe therapy group is statistically significantly higher (p = 0.0013). A link to the mistletoe therapy cannot be deduced here, as some of the patients attended the Herdecke Outpatient Oncology Clinic with an existing local recurrence in order to receive mistletoe therapy there. Thus the mistletoe group had a clear negative bias as regards the frequency of local recurrence. Despite the negative bias, the survival time of the mistletoe patients is markedly higher.

Account must also be taken of the fact that in the external patient group from the Saarland Epidemiological Cancer Registry, only a single date was given for a recurrence and for metastases, so that it was not possible to differentiate reliably between local recurrence and metastases.

**Metastasis-free time**

In the external reference group, it was not possible to distinguish between the time of occurrence of metastases and the date of local recurrence, so that the date given for metastases is not immediately reliable.

In the study population which received mistletoe therapy, the proportion of patients with metastases was 46.6 % (n = 155). Although amongst the patients in the external reference group, 57.2 % (n = 4665) had metastases, the date on which the metastases first occurred was given for only 10.6 % (n = 496), so that a comparison of the two groups in terms of metastasis-free time is likely to be clearly biased.
Almost half of the “events” (for definition, see Table 3, mainly metastases) in the mistletoe group occurred before the start of mistletoe therapy. This may have been one of the reasons for wanting mistletoe therapy. Since there can hardly be a causal relationship between mistletoe therapy which was not received by 25.3% of the patients who experienced an event before the start of mistletoe therapy and the efficacy of mistletoe therapy, the two groups are not really comparable in terms of the number of events causally related to mistletoe therapy, especially as there was no information on the time of the event for over half the patients in the reference group who experienced an event (Table 3). Furthermore, the lack of differentiation between the date of local recurrence and date of metastases also contributes to the data relating to recurrence-free time and metastasis-free time not being regarded as valid.

Survival time

When the two groups were compared in terms of survival time, the probability of longer survival in the mistletoe extract group was statistically significantly higher (median 59 versus 38 months, p < 0.0001, log-rank test). In contrast to the times given for local recurrence and metastases, there can be no criticism of the information given on survival time, as the date of death is documented in the Saarland Epidemiological Cancer Registry. If the multiple test problem is considered in the overall analysis (3 primary endpoints), the difference between the groups remains statistically significant (α/3 = 0.0167) even with strictly conservative adjustment of the significance level. The mistletoe group was superior to the external reference population in all stages (Fig. 3).

With regard to the 5-year survival rate, the comparison with the data of the Saarland Epidemiological Cancer Registry shows that the result of this retrospective data survey with 48.9% compared to the data from the Saarland Epidemiological Cancer Registry with 40.3% gives a survival advantage for the patients in the mistletoe therapy group. Even after differentiation according to tumour stage, the results for the mistletoe therapy sub-group in this study are superior to the data from the Saarland Epidemiological Cancer Registry for stages I - IV (Table 2).

The 10-year survival rate for patients treated with mistletoe extracts was much higher at 42.7% than the 27.2% for the Saarland Epidemiological Cancer Registry patients. This difference can also be seen for the 10-year survival rates differentiated according to tumour stages (Table 2). The differences are all the more remarkable as some of the patients only started mistletoe therapy after the first recurrence or metastasis.

Even the internal comparison between the patients who received mistletoe therapy and those who could not provide information on their treatment or definitely did not receive mistletoe therapy showed that the 5 and 10-year survival rates, median survival time and the probability of the occurrence of metastases were superior in the mistletoe extract group. There was no significant difference between these subgroups in terms of the probability of a recurrence.
Prognostic factors

In the multivariate analysis (Cox regression), tumour stage, age at diagnosis, group to which the patient belonged and sex were determined as factors relevant to prognosis. As the distribution of the prognostic factors in the two patient groups was very different in some cases, the CART method [29] was used in a subsequent exploratory analysis to identify prognostically homogenous sub-groups, for whom the survival time was then analysed. Even with this analytical procedure, it could be seen that the tumour stage had the greatest influence on survival time, followed by age and sex. Of the previously defined conditions for sub-group formation [29], only the factors tumour stage and age remained. This gave 4 sub-groups: tumour Stage I or II and age < 68 years, tumour Stage I or II and age ≥ 68 years, tumour Stage III or IV and age < 68 years and tumour stage III or IV and age ≥ 68 years. In the analysis of survival time for these 4 sub-groups, a statistically significant effect of group difference on survival time was only found for sub-group 3 - patients with tumour Stage III or IV and age < 68 years. In this sub-group the patients benefited from mistletoe therapy. In all other sub-groups no statistical difference could be determined between the groups in terms of survival time.

Even if the group to which the patients belonged had a statistically significant effect on survival time in the overall analysis (1.3 times, p < 0.0001, adjusted), account must also be taken of the fact that in addition to the effect of the prognostic factors tumour stage and age, there was no information available on the treatments given in the external reference group and that the patients in the mistletoe group were also given other therapies in addition.

Acknowledgements

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Literature


