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The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial

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Abstract

The effect of an adjuvant mistletoe extract treatment was tested in a prospective, randomised controlled clinical trial involving 477 patients with head and neck squamous cell carcinoma. The patients were stratified into two treatment groups that underwent surgery or surgery followed by radiotherapy and both groups were randomised for additional treatment with mistletoe extract. Patients treated with a mistletoe lectin-1 (ML-1) standardised mistletoe preparation had no lower risk of local/locoregional recurrences, distant metastases or second primaries. In the main analysis based on 202 patients treated with surgery and 275 patients treated with surgery and radiotherapy the adjusted hazard ratio for the disease-free survival (DFS) was 0.959 (95% confidence interval (CI) 0.725–1.268). The 5-year survival rates of patients from the mistletoe group were no better than the survival rates of patients from the control group. Furthermore, no significant changes in the cellular immune reaction or in quality of life could be detected. We conclude that the used mistletoe preparation has no indication in the adjuvant treatment of patients with head and neck cancer.

Keywords: Head and neck carcinoma; Herbal medicine; Mistletoe lectin-1; Mistletoe extract; Disease-free survival; Disease-specific survival

1. Introduction

The use of complementary or alternative medicine (CAM) for the treatment of cancer has become increasingly popular [1–4]. In Germany, 45–60% of all cancer patients use unconventional medical products at least some time during their treatment, and the figures for other countries are similar [5]. Some of the most common CAM products are mistletoe preparations which are used either alone or combined with other alternative medical methods [6]. The yearly expenditure for these preparations is estimated to be over $30 million in Germany alone with an annual increase of 20% [7]. Despite the general popularity in central Europe only a few controlled trials have been carried out to evaluate the efficacy of mistletoe extract treatment. The results of a total of 10 trials favour mistletoe treatment. However, the general quality of these completed trials is disappointing [8]. The trial which achieved the highest methodological score [8] did not reveal any beneficial effects and was published without a peer review process [9]. With the exception of a pilot trial in patients with advanced pancreatic cancer [10], no further comprehensive studies in humans have been published that apply sufficient methodologies such as a predefined study design and a disease-free survival (DFS) time as the primary endpoint. Therefore, the present study was designed to evaluate the clinical effectiveness of additional mistletoe therapy in two groups of head and neck cancer patients who either underwent surgery alone or surgery combined with postoperative radiotherapy.

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Mistletoe therapy is believed to cause immunostimulation with cytokine release affecting both cytotoxic lymphocytes and macrophages [11–14]. The stimulation is thought to boost the immune system, which is known to be depressed in patients with head and neck cancer [15–17], thereby promoting tumour defence by eliminating minimal residual cancer cells [18]. Immunosuppression, which increases with stage grouping, comprises cell-mediated defects including T-lymphocytopenia, as well as dysfunction of T cells and mononuclear phagocyte system cells [19,20].

A mistletoe lectin-1 (ML-1) standardised preparation (Eurixor®) was chosen from currently available approved preparations for therapy since the following data suggest that ML-1 is the active component with immunomodulatory properties in a low-dose range as used in our trial: (i) ML-1 has been found to increase the number of large granular lymphocytes and the phagocytic activity of granulocytes in rabbits, healthy persons and breast cancer patients [21]; (ii) it has been found to enhance the cytotoxicity of natural killer (NK) cells *in vitro* and the phagocytic activity of polymorphonuclear granulocytes from rabbits and patients [21]; (iii) a limited number of patients with breast cancer had an increased number of T-lymphocytes as well as T helper/inducer cells [13,22]; (iv) in cultures of peripheral blood lymphocytes, ML-1 induced cytotoxicity of CD8+ T cells [11]; (v) ML-1-specific lectin binding [14] increased the secretion of tumour necrosis factor α, interleukin 1 and interleukin 6 from human mononuclear cells; (vi) the antitumour efficacy of ML-1 was shown in animal experiments [12].

Based upon the observed *in vitro* and *in vivo* effects of ML-1, our study was designed to answer the question of whether an additional treatment of head and neck cancer patients with a ML-1 standardised mistletoe extract (Eurixor®) leads to an increased DFS compared with patients receiving no additional therapy.

2. Patients and methods

2.1. Patients

A total of 588 patients with head and neck squamous cell carcinoma were initially registered into the study at four University hospital departments of otorhinolaryngology between 1993 and 1996 (stratum A), and 1993 and 1997 (stratum B), respectively. 495 patients were randomised into the study. Following a drop-out of 18 patients, 477 patients received the study treatment (Fig. 1). Patients with protocol violations in the primary treatment ($n=48$) received modified conventional tumour treatment, e.g. a simultaneous radiochemotherapy or refused the proposed surgery (e.g. total laryngectomy), discontinued the radiotherapy or agreed to a one-off radiotherapy only. Due to an overestimation of the true accrual rates, the protocol was amended to prolong the accrual period by approximately 1 year. Power calculations confirmed that the original assumptions remained valid. All relevant baseline variables are listed in Table 1.

The study was approved by the Medical Ethics Committee of the Technical University of Munich and informed, written consent was obtained from all patients. Patients with previously untreated resectable tumours of T1–T4 and N0–N3 classifications were included, with the following exclusion criteria: age greater than 70 years or less than 18 years, simultaneous distant metastases, a second synchronous or previous malignancy, previous chemotherapy or radiotherapy, co-existing disease which contra-indicated surgery, prior treatment with a biological response modifier, and serious hepatic or renal dysfunction.

2.2. Preoperative examination and randomisation

The extent of the tumour was clinically evaluated in each patient by physical examination, panendoscopy, abdominal ultrasonography, isotopic bone scans and computed tomography and/or magnetic resonance tomography. The diagnosis of carcinoma was preoperatively confirmed. After cTNM classification (the International Union Against Cancer (UICC) 1992) [23], patients were stratified into one of the two primary treatment regimens (Fig. 1). Stratum A comprised patients with resectable head and neck cancer who were treated with surgery alone, while stratum B consisted of patients, mostly with a higher stage grouping, who received surgery followed by radiotherapy. Within both strata, randomisation was performed permuting random blocks of 4 or 6 patients to the control group (standard treatment) or mistletoe group (standard plus mistletoe treatment). Balanced randomisation lists for each hospital were generated at the statistical analysis centre and treatment assignments remained masked to all other study personnel until the patients had been judged eligible for enrolment.

2.3. Surgical treatment

88.4% Of the patients received peri- and postoperative antibiotics. The surgical procedure was dependent on the size, lymph node status and location of the tumour and included uni- or bilateral neck approaches with selective, modified radical or radical neck dissection as well as laser microsurgery. 124 Patients (62.6%) in stratum A, and 174 patients (67.4%) in stratum B, underwent laser microsurgery. Conventional surgery was performed in 74 cases (37.4%) in stratum A and in 84 patients (32.6%) in stratum B. 105 Patients in stratum A and 13 patients in stratum under-

went resection of the primary tumour without a neck dissection. 44 and 107 patients in stratum A and B, respectively, underwent a unilateral neck dissection. 49 Patients in stratum A and 138 patients in stratum B underwent a bilateral neck dissection. The tumours of 198 patients in stratum A, who underwent primary tumour surgery, were completely resected (UICC R0 category), while 22 patients in stratum B had microscopic tumour involvement of their resection margins (UICC R1).

2.4. Postoperative radiotherapy

The postoperative radiotherapy in stratum B consisted of isocentric treatment of the primary tumour bed and draining lymphatic system with 6-MV photons and parallel opposed lateral portals. A single dose of 2.0 Gy per fraction was applied once daily with five sessions per week for a total of 6 weeks. Suspected N+ lymph nodes in the lower neck were treated using a single anterior field with midline blocking to prevent spinal cord overlap. The spinal cord was also blocked in both lateral fields. The total radiation dose ranged from 50 to 75 Gy (median 60 Gy) at the primary site and in the draining lymphatics, 50 Gy for N0, 60 Gy for N+ and 66 Gy for N3 cases.

2.5. Mistletoe treatment and follow-up

The aim was to start the mistletoe treatment before surgery in order to improve the antitumour immune reaction at the time of surgery. However, this could only be achieved in 72% of the patients 1–4 days before surgery. The remaining patients received their first injections shortly after surgery. The therapy consisted of subcutaneous (s.c.) injections of a mistletoe extract (Eurixor®, biosyn) with a standardised amount of ML-1 (1 ng ML-1 per kg of body weight, twice weekly over a 60-week period, in treatment cycles of 12 weeks followed by a break of 4 weeks between weeks 12 and 16, 28 and 32 and 44 and 48) as is common practice and recommended by the manufacturer.

Follow-up examinations were carried out in all hospitals according to a standard protocol. The first postoperative examinations were carried out in weeks 8, 12, 16, 22, 28, 32, 44, 48 and 60, followed by further

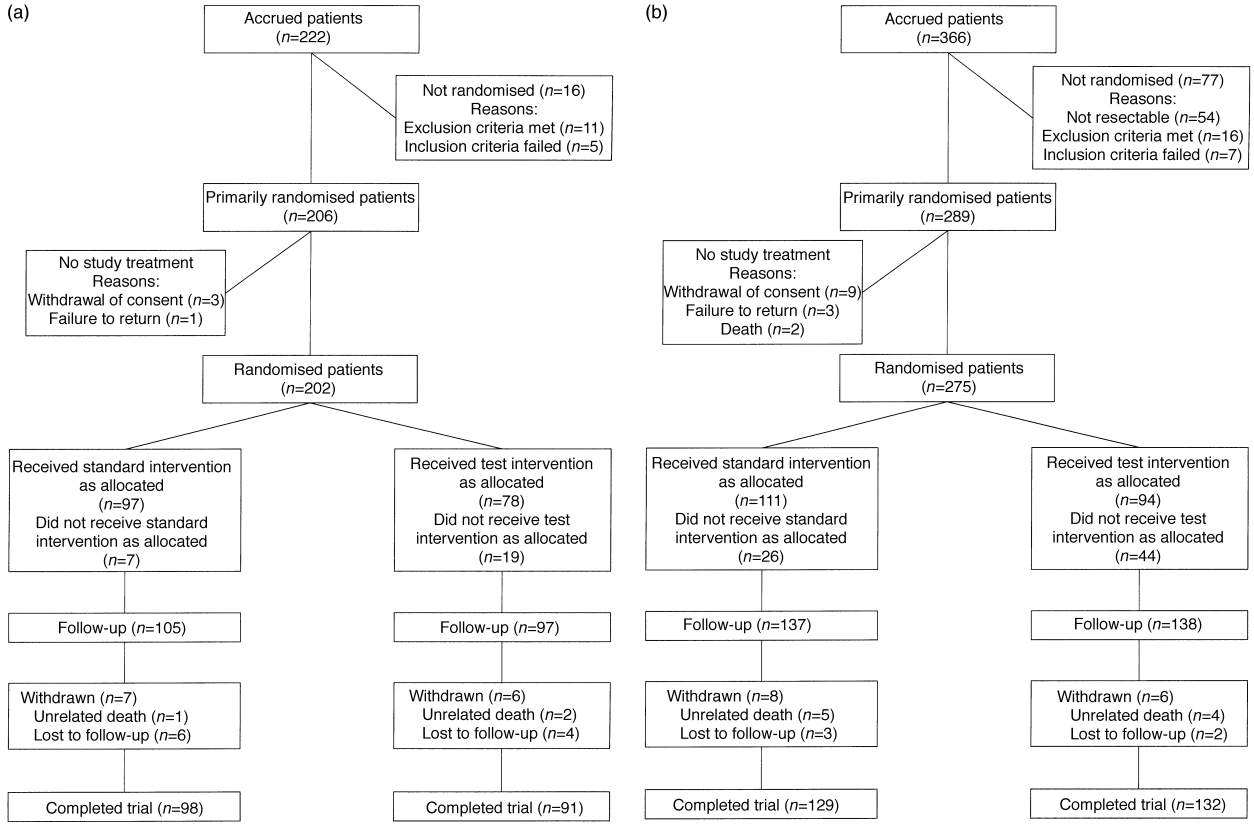

Fig. 1. Flow chart of the progress of all patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.) Patients with protocol violations in the primary treatment ($n=48$) received modified conventional tumour treatment, e.g. a simultaneous radiochemotherapy or refused the proposed surgery (e.g. total laryngectomy), discontinued the radiotherapy or agreed to a one-off radiotherapy only. (a) Stratum A — surgery without and with mistletoe treatment. (b) Stratum B — surgery and radiotherapy without and with mistletoe treatment.

examinations at quarterly intervals until the third year and at half-yearly intervals until the fifth year. At each examination, a history was taken and a physical examination and ultrasonographic examination of the neck was performed. A computed tomography (CT) or NMR spectroscopy of the primary tumour site and neck, as well as a chest X-ray, were performed yearly. In addition to the documentation of adverse drug reactions, the following haematological and biochemical studies were performed until week 84, to exclude any toxic reactions due to mistletoe treatment: differential blood count, haemoglobin, γ-glutamyltransferase, glutamic–oxaloacetic transaminase, glutamic–pyruvic transaminase, fibrinogen, haptoglobin, α1-glycoprotein, C-reactive protein and blood alcohol concentration.

2.6. Determination of outcome/sample size

The primary endpoint for evaluating the treatment efficacy was DFS. Disease-specific survival (DSS) time was considered to be a secondary measure of efficacy. The outcome measure was the time span between randomisation and the first occurrence of local/loco-regional recurrences, distant metastases or second primaries. The sample size calculation for the two identically designed strata was based on the comparison of two survival distribution functions using the log-rank test for the analysis of the primary endpoint DFS. The study assumed a 1:1 randomisation, a 0.05 two-sided significance level, an accrual period of 2 years with a maximum follow-up time of 5 years, proportional

Table 1
Clinical and pathological factors in the 477 patients with head and neck cancer

Outcome[a]	All patients ($n=477$) no. (%)	Stratum A Control group ($n=105$) no. (%)	Stratum A Mistletoe group ($n=97$) no. (%)	Stratum B Control group ($n=137$) no. (%)	Stratum B Mistletoe group ($n=138$) no. (%)
Age (years)					
Median (range)		58 (31–70)	57 (30–70)	54 (29–70)	55 (36–70)
Sex					
Male	437 (92)	96 (91)	87 (90)	127 (93)	127 (92)
Female	40 (8)	9 (9)	10 (10)	10 (7)	11 (8)
Site of primary tumour					
Oral cavity	78 (16)	20 (19)	14 (14)	19 (14)	25 (18)
Oropharynx	136 (29)	15 (14)	19 (20)	53 (39)	49 (36)
Hypopharynx	78 (16)	6 (6)	3 (3)	34 (25)	35 (25)
Larynx	185 (39)	64 (61)	61 (63)	31 (23)	29 (21)
Tumour classification[b]					
T1	119 (25)	48 (46)	48 (49)	14 (10)	9 (7)
T2	159 (33)	36 (34)	35 (36)	43 (31)	45 (33)
T3	97 (20)	15 (14)	6 (6)	31 (23)	45 (33)
T4	102 (21)	6 (6)	8 (8)	49 (36)	39 (28)
Nodal classification[b]					
N0	268 (56)	90 (86)	86 (89)	45 (33)	47 (34)
N1	60 (13)	9 (9)	7 (7)	23 (17)	21 (15)
N2a	13 (3)	1 (1)	2 (2)	5 (4)	5 (4)
N2b	92 (19)	5 (5)	2 (2)	38 (28)	47 (34)
N2c	35 (7)	0	0	19 (14)	16 (12)
N3	9 (2)	0	0	7 (5)	2 (1)
Stage[b]					
I	103 (22)	47 (45)	44 (45)	7 (5)	5 (4)
II	95 (20)	31 (30)	32 (33)	15 (11)	17 (12)
III	82 (17)	16 (15)	9 (9)	28 (20)	29 (21)
IV	197 (41)	11 (10)	12 (12)	87 (64)	87 (63)
Histological grade[c]					
G1	34 (7)	16 (15)	8 (8)	5 (4)	5 (4)
G2	314 (66)	72 (69)	79 (81)	83 (61)	80 (58)
G3	129 (27)	17 (16)	10 (10)	49 (36)	53 (38)
Resection margin[d] (UICC R status)					
R1	22 (5)	0	0	10 (7)	12 (9)

[a] There were no significant differences between groups for any of the factors listed.

[b] Primary tumours and lymph nodes were staged according to criteria of the International Union Against Cancer (UICC) [23].

[c] All 477 tumours were graded histologically. Grade 1 indicates a well-differentiated tumour, grade 2 a moderately well-differentiated tumour, and grade 3 a poorly differentiated tumour.

[d] Percentages refer to the 198 patients of stratum A and/or to the 258 patients of stratum B, who underwent surgery for their primary tumour.

hazards and an exponential DFS distribution. The expected baseline 2 year DFS rate for both strata was 40%.

In stratum B, it was planned to achieve a statistical power of 0.80 at a hazard ratio of 1.5, corresponding to a 50% improvement under mistletoe treatment in median DFS. For stratum A, a 20% improvement in 2-year DFS should be detected with a power of 0.80. With an assumed drop-out rate of 20%, 314 patients (stratum B) and 170 patients (stratum A) had to be randomised to meet the required 125 patients per group (stratum B) and 65 patients per group (stratum A) [24].

2.7. Statistical methods

The main analysis was conducted on an intention-to-treat basis including all randomised patients who had not dropped out after the initial examination. DFS was estimated by the Kaplan–Meier product limit method and compared using a two-sided log-rank test. Crude and adjusted hazard ratios for the treatment effect were estimated using the Cox proportional hazards model. In addition, reference bands [25] were drawn to examine graphically whether the data supported the null hypothesis. The bands represent an acceptance region for the 'no difference' hypothesis between groups and are derived from the standard error of the difference at each time point. General patient characteristics were compared using the χ^2-test or Fisher's exact test for categorical and the Student t-test for continuous variables. All calculations were performed with SAS software (Release 6.12).

2.8. Interim analysis

Two interim analyses, 1 and 2 years after the last accrual date, and a final analysis at the end of the follow-up time were planned. The strata were monitored using the sequential O'Brien–Fleming alpha-adjustment approach [26]. The results of each interim analysis were reviewed by an internal monitoring committee, which kept the results confidential as long as no recommendation for early termination was made.

Table 2
Incidence of relapses and death in the mistletoe and control groups of head and neck cancer patients after a median follow-up period of 4 years

Factor[a]	All patients ($n=477$) n (%)	Stratum A Control group ($n=105$) n (%)	Stratum A Misletoe group ($n=97$) n (%)	Stratum B Control group ($n=137$) n (%)	Stratum B Mistletoe group ($n=138$) n (%)
All relapses	200 (42)	35 (33)	24 (25)	66 (48)	75 (54)
Recurrence[a] (general)	118 (25)	23 (22)	14 (14)	32 (23)	49 (36)
Local recurrence	97	16	13	25	43
Lymph node metastasis					
Unilateral	23	7	2	7	7
Bilateral	26	4	0	9	13
Recurrence[a] (stage related)					
Stage (UICC 1992)					
I	11 (9)	5 (22)	4 (29)	0	2 (4)
II	14 (12)	6 (26)	4 (29)	1 (3)	3 (6)
III	18 (15)	4 (17)	1 (7)	6 (19)	7 (14)
IV	75 (64)	8 (35)	5 (36)	25 (78)	37 (76)
Distant metastasis[a]	57	3	2	30	22
Stage					
II	5 (9)	1 (33)	2 (100)	2 (7)	0
III	7 (12)	1 (33)	0	2 (7)	4 (18)
IV	45 (79)	1 (33)	0	26 (87)	18 (82)
Secondary tumour[a]	46	10	9	15	12
Stage					
I	9 (20)	5 (50)	2 (22)	1 (7)	1 (8)
II	8 (17)	4 (40)	1 (11)	1 (7)	2 (17)
III	8 (17)	1 (10)	3 (33)	2 (13)	2 (17)
IV	21 (46)	0	3 (33)	11 (73)	7 (58)
Tumour-related death	157	20	14	54	69
Stage					
I	8 (5)	3 (15)	3 (21)		2 (3)
II	17 (11)	6 (30)	3 (21)	4 (7)	4 (6)
III	26 (17)	5 (25)	2 (14)	9 (17)	10 (14)
IV	106 (68)	6 (30)	6 (43)	41 (76)	53 (77)

[a] Patients with different synchronous local and locoregional relapses, distant metastases and/or secondary tumours are included in the groups.

3. Results

3.1. Efficacy analysis

A total of 200 of the 477 patients (42%) suffered a relapse during the follow-up period (median 4 years for surviving patients). The total relapse incidence and the development of distant metastases and second primaries did not significantly differ between the control and mistletoe groups and were strongly dependent on the stage grouping (Table 2). The largest percentage of relapse patients developed local and/or regional recurrences (25%; $n=118$), followed by distant metastases (12%; $n=57$), and second primaries (10%; $n=48$). Lymph node metastases were more often unilateral in stratum A, and bilateral in stratum B. Of the 157 patients (33%) with tumour-related deaths during the follow-up period, 74 were in the control groups and 83 were in the mistletoe groups.

The results of the efficacy analyses are summarised in Fig. 2 and Table 3. No significant differences were detected at an α-level of 0.05. In the main analysis based on 477 patients, the adjusted hazard ratio for the DFS was 0.959 (95% confidence interval (CI) 0.725–1.268). These results were confirmed by a per-protocol analysis with 364 patients: the adjusted hazard ratio for the DFS was 0.88 (95% CI 0.63–1.21) and for the DSS 0.96 (95% CI 0.66–1.38).

3.2. Immune parameters

We could not detect any significant changes in the following lymphocyte subsets (cluster of differentiation (CD)3+, CD4+, CD8+, CD19+, CD16+56+3+, CD16+56+3, CD25+, CD3+DR+) determined for a randomly taken subsample by flow cytometry comparing control and treatment group samples. The detailed results of 1230 analysed blood samples from 230 patients (stratum A 45 control/44 mistletoe, stratum B 73 control/68 mistletoe) with a median of six longitudinal measurements between week 0 and 84 will be summarised in a forthcoming report.

3.3. Quality of life score

To assess the quality of life the general cancer-specific European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-score 30 (QLQ-C30) instrument was applied in a randomly taken subsample of 443 study patients. The results of 3800 questionnaires from these patients (stratum A 99 control/94 mistletoe, stratum B 126 control/124 mistletoe) with a median of nine longitudinal measurements between week 0 and 156 also failed to show any improvement in the patient's quality of life compared with the control group and will be presented elsewhere in detail.

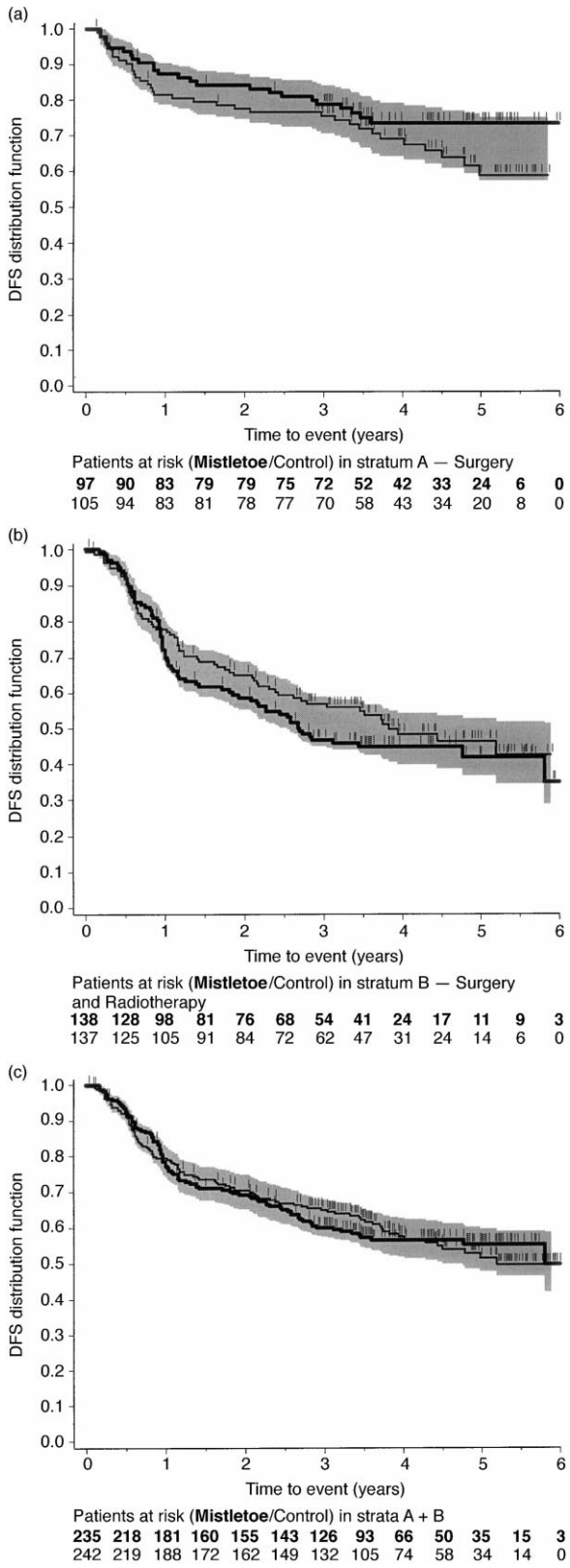

Fig. 2. Kaplan–Meier estimates of disease-free survival (DFS) distribution function with the reference band (grey shading): (a) DFS distribution function of patients of stratum A in patients with surgery; (b) DFS distribution function of patients of stratum B in patients with surgery and radiotherapy; (c) DFS distribution function of all patients.

3.4. Safety considerations

Haematological or biochemical parameters did not change significantly during mistletoe therapy. At the onset of mistletoe therapy, a total of 47 patients (48%) in stratum A and 54 patients (39%) in stratum B developed local and/or systemic side-effects upon mistletoe extract injections into the abdominal wall. However, the number of patients showing adverse reactions steadily decreased with continued treatment to 1–4% in stratum A and 4–8% in stratum B at week 32 or later. The most common local adverse drug reactions were rubor and prurigo. 44 (45%) cases of rubor around the injection site with median diameters of 25–30 mm were monitoring in stratum A and 54 (39%) in stratum B at the beginning of mistletoe therapy. These numbers dropped to 1–4% and 1–5% (stratum A and B, respectively) at week 32 or later. Prurigo was seen at the start of therapy in 30% of the patients in both strata ($n=29$ and 41, respectively), but decreased to 1–3% in stratum A and 3–7% in stratum B at week 32 or later. Another local adverse reaction was induration which occurred in 6% ($n=6$) and 8% ($n=11$) of the patients (stratum A and B, respectively) at the start of therapy and decreased to 1–5% of the patients (stratum A and B, respectively) at week 22 or later. Vesiculation was seen in 1–3% of the patients from both strata over the therapy period. General drug reactions like melalgia, fever (not above 39.0°C), sleeplessness, tiredness, coldness or heat sensation and sneezing occurred only in 1–4% of the patients. 16 patients in stratum A (16%) and 27 patients in stratum B (20%) refused further injections because of mistletoe-induced adverse reactions.

4. Discussion

The present study was designed to apply good clinical practice standards to further clarify the therapeutic benefit of mistletoe extracts in cancer therapy. With the exception of double blinding, the trial fulfils all criteria of good methodology as described by Kleijnen and Knipschild and the concept systematically meets the rigorous standards of safety and efficacy of the Food and Drug Administration (FDA) [8,27]. Present claims concerning the positive effect of mistletoe treatment have been based on trials which clearly have not employed these standards. Double blinding was not applied in this study, since it is known that local side-effects arise in a high percentage of treated patients making the stratification obvious. The ethics committees also did not agree to such a double-blind phase III study for this reason.

According to different standard treatment modalities for resectable head and neck cancer [28], this mistletoe trial consisted of two treatment strata: surgery alone and surgery followed by radiotherapy. The study included squamous cell carcinomas of the larynx, hypopharynx, oropharynx and oral cavity. Regional lymph node metastases, which are known to be the most important prognostic factor for these tumours [29], were present in 44% of patients. This factor, the type of surgical approach, as well as the histopathological factors were equally represented in the corresponding treatment groups (Table 1). The description of the treatment effect in this study was limited to the management of the primary tumour, as well as its regional metastases, and did not include the treatment of subsequent tumour recurrences.

Table 3
Results of efficacy analyses on primary and secondary outcome measures

Outcome	Trial	Group	5-year Kaplan–Meier estimates (95% CI)	*P* value logrank		Hazard ratio[a] (95% CI)	*P* value CoxPH[b]
DFS	A	Mistletoe	0.74 (0.64; 0.83)	0.18	crude	0.702 (0.417; 1.180)	0.18
		Control	0.59 (0.47; 0.71)		adj.[c]	0.627 (0.326; 1.087)	0.09
	B	Mistletoe	0.42 (0.32; 0.52)	0.32	crude	1.184 (0.850; 1.649)	0.32
		Control	0.46 (0.37; 0.56)		adj.	1.051 (0.746; 1.480)	0.78
	A + B	Mistletoe	0.55 (0.49; 0.62)	0.97	crude	1.005 (0.761; 1.326)	0.98
		Control	0.52 (0.44; 0.59)		adj.	0.959 (0.725; 1.268)	0.77
DSS	A	Mistletoe	0.84 (0.76; 0.92)	0.37	crude	0.734 (0.371; 1.453)	0.37
		Control	0.78 (0.69; 0.88)		adj	0.626 (0.302; 1.301)	0.21
	B	Mistletoe	0.46 (0.36; 0.55)	0.13	crude	1.316 (0.921; 1.879)	0.13
		Control	0.56 (0.46; 0.65)		adj.	1.158 (0.801; 1.674)	0.44
	A + B	Mistletoe	0.62 (0.55; 0.69)	0.35	crude	1.161 (0.849; 1.589)	0.35
		Control	0.66 (0.59; 0.73)		adj.	1.065 (0.775; 1.463)	0.70

DFS, disease-free survival; DSS, disease-specific survival (only tumour-related deaths); CI, confidence interval.

[a] Hazard ratio of mistletoe versus control groups; estimates below 1 indicate superior effect of adjuvant mistletoe treatment.

[b] *P* value according to likelihood-ratio test from Cox's proportional hazard regression model.

[c] Adjustment due to tumour staging, primary tumour site, centre, grading.

Overall, the relapse distribution did not differ from previous data [30,31], with more local and/or regional recurrences being seen than distant metastases or second primary tumours. We observed 5-year survival rates of 35, 50, 46 and 67% for patients with carcinomas of the hypopharynx, oropharynx, oral cavity and larynx, respectively, which are higher rates than those published in the EUROCARE study which were 19, 33, 46 and 57%, respectively [32]. 5-year DSS for the same sites was 34, 56, 68 and 75% in our study compared with 31, 46, 56 and 67% according to the National Cancer Data Base Report [33]. These differences are probably due to the exclusion of unresectable tumours from our study.

From the patients receiving mistletoe treatment, 43 did not finish 1 year of therapy as recommended by the commercial suppliers. The time between the start and interruption of the injections was in a range from 12 to 60 weeks (median 12 weeks). Until today, no data supporting the clinical benefit of long-term administration in humans are available. The likelihood of patients in the control group utilising mistletoe extracts or some other form of alternative treatment, independent of the study, was infinitely small, since all applied drugs were noted at each consultation over the 5-year follow-up. We saw only 5 patients who received other aqueous mistletoe extracts from their family doctor. 43 patients had to be withdrawn from the per-protocol analysis due to an interruption of the adjuvant treatment. It has been previously noted that local side-effects occur when mistletoe treatment is applied for the first time [10]. In our study, adverse drug reactions such as rubor, prurigo, induration and vesiculation were observed initially, but decreased with continued treatment. No toxic [34] or anaphylactic reactions [10] were seen.

Although basic research experiments clearly suggest an antitumour efficacy of ML-1 [11–14,21,35,36], the long-term administration of such a ML-1 standardised aqueous mistletoe extract failed to show any significant differences in either of the treatment groups. Neither stage I and II tumour patients (predominant in stratum A) nor stage III and IV tumour patients (predominant in stratum B) benefited from this alternative treatment programme. These results are in accordance with the recently published experiments of Kunze and colleagues where long-term administration of ML-1 with the same schedule of bi-weekly s.c. injections failed to delay, reduce, inhibit or prevent chemically induced cancer development in rat urinary bladders [37,38].

Immune parameters determined for a randomly taken subsample of the study patients have also been analysed in order to detect immunostimulation in mistletoe patients. However, we were unable to detect any significant changes between the control and treatment group samples in any of the lymphocyte subsets or activation markers studied. The final results of 1230 analysed blood samples from 230 patients will be summarised in a forthcoming report. Büssing and coworkers were also unable to detect significant changes in the cellular immune reaction in 23 tumour subjects within 2–3 months after the onset of treatment with Helixor®A [39].

Mistletoe extracts have also been described to improve the quality of life in breast cancer patients [40]. To assess this aspect the general cancer-specific EORTC-QLQ-C30 instrument with high validity, reliability and sensitivity was applied in a randomly taken subsample of the study patients. The results of this testing also failed to show any improvement in patient quality of life compared with the control group and details will also be presented in a forthcoming report.

Various *in vitro* and *in vivo* experiments using a variety of phytotherapeutic substances have led to unsubstantiated claims of positive health outcomes in patients with solid cancers. In this large clinical trial, with an appropriate randomisation and follow-up, the long-term application of a commercially recommended mistletoe extract was investigated with respect to clinical outcome. No statistically significant differences between standard treatment regimes and additional mistletoe treatment could be detected and the results suggest that there is no more than equivalent efficacy between standard and additional mistletoe therapy. We conclude that this mistletoe preparation can not be recommended as a complementary treatment modality in patients with head and neck squamous cell carcinoma. In addition, the application of CAM may not be harmless and should not be regarded as front-line cancer treatment [27]. As this study has demonstrated, further controlled randomised clinical trials with defined mistletoe extracts or defined active compounds, as well as a further pharmacological investigation of mistletoe components, are necessary to give a definite and clear statement about the antitumour activity of mistletoe compounds in humans.

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