Mistletoe therapy in oncology (Review)

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[Intervention Review]

Mistletoe therapy in oncology

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ABSTRACT

Background

Mistletoe extracts are commonly used in cancer patients. It is claimed that they improve survival and quality of life (QOL) in cancer patients.

Objectives

To determine the effectiveness, tolerability and safety of mistletoe extracts given either as monotherapy or adjunct therapy for patients with cancer.

Search strategy

Search sources included the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2007) Cochrane Complementary Medicine Field Registry of randomized clinical trials (RCTs) and controlled clinical trials, MEDLINE, EMBASE, HEALTHSTAR, INT. HEALTH TECHNOLOGY ASSESSMENT, SOMED, AMED, BIOETHICSLINE, BIOSIS, CancerLit, CATLINE, CISCOM (August 2007).

For the search the Standard Operating Procedures of the Information System in Health Economics at the German Institute for Medical Documentation and Information (DIMDI) were utilized. Reference lists of relevant articles and authors extensive files were searched for additional studies. Manufacturers of mistletoe preparations were contacted.

Selection criteria

We included randomised controlled trials (RCTs) of adults with cancer of any type. The interventions were mistletoe extracts as sole treatments or given concomitantly with chemo- or radiotherapy. The outcome measures were survival times, tumor response, QOL, psychological distress, adverse effects from antineoplastic treatment and safety of mistletoe extracts.

Data collection and analysis

Three review authors independently assessed trials for inclusion in the review. All review authors independently took part in the extraction of data and assessment of study quality and clinical relevance. Disagreements were resolved by consensus. Study authors were contacted where information was unclear. Methodological quality was narratively described and additionally assessed with the Delphi list and the Jadad score. High methodological quality was defined if six out of nine Delphi criteria, or four out of five Jadad criteria were fulfilled. Results were presented qualitatively.

Main results

Eighty studies were identified. Fifty-eight were excluded for various reasons, usually as there was no prospective trial design with randomised treatment allocation. Of the 21 included studies 13 provided data on survival, 7 on tumour response, 16 on measures of QOL or psychological outcomes, or prevalence of chemotherapy-related adverse effects and 12 on side effects of mistletoe treatment; overall comprising 3484 randomised cancer patients. Interventions evaluated were 5 preparations of mistletoe extracts from 5 manufacturers and one commercially not available preparation. The general reporting of RCTs was poor.

Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The results of two trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival.

Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QOL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality.

Data on side effects indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects.

Authors' conclusions

The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trails.

PLAIN LANGUAGE SUMMARY

Mistletoe treatment in cancer patients

Preparations from the European mistletoe (Viscum album L.) are among the most prescribed drugs in cancer patients in several European countries. Proponents claim that mistletoe extracts stimulate the immune system, improve survival, enhance quality of life and reduce adverse effects of chemo- and radiotherapy in cancer patients. The review found that there was not enough evidence to reach clear conclusions about the effects on any of these outcomes and it is therefore not clear to what extent the application of mistletoe extracts translates into improved symptom control, enhanced tumour response or prolonged survival. Adverse effects of mistletoe extracts were reported, but appeared to be dose-dependent and primarily confined to reactions at injection site and mild, transient flu-like symptoms. In the absence of good quality, independent trials, decisions about whether mistletoe extracts are likely to be beneficial for a particular problem should rely on expert judgement and practical considerations.

BACKGROUND

Please refer to the glossary for the definitions of the technical terms
(Table 1).

The treatment of cancer with extracts from mistletoe was first introduced at the beginning of the 20th century by Rudolf Steiner as part of a holistic and human-centred therapeutic approach within anthroposophically-extended medicine (Heusser 1998).

Today, preparations from mistletoe extracts are the most frequently used, so-called complementary and alternative methods (CAM) in the treatment of cancer patients in German-speaking countries (Horneber 2009). In 2002, mistletoe extract was the most frequently prescribed substance in out-patient oncology clinics in Germany; health insurance companies paid for 465,000 mistletoe prescriptions. In comparison, the second most frequently prescribed substance in out-patient oncology treatment was Tamoxifen, prescribed 329,000 times (Schwabe 2003).

All commercially available mistletoe extracts are prepared from the semi-parasitic plant Viscum album Loranthaceae (Viscum album L. or European mistletoe). Brand names in Europe include ABNOBAviscum®, Cefalektin®, Eurixor®, Helixor®, Iscador®, Iscucin®, Isorel® and Lektinol®. Mistletoe grows on several types of trees, and the extracts derived from it contain numerous ingredients in varying concentrations depending on the species of the host tree, the time of year harvested and the pharmaceutical process according to which the extracts are prepared (Becker 2000).

Mistletoe preparations contain several biologically active substances: mistletoe lectins, viscotoxins, amino acids, flavonoides, polysaccharides, membrane lipids (vesicles) and other substances in low concentrations. Although studies showed a broad range of immunomodulating, cytotoxic, and antiviral effects of different extracts or isolated agents from mistleote extracts, their precise mode of action is poorly understood. Many researchers attribute therapeutic efficacy to the mistletoe lectins (ML). Therefore most investigations have been carried out on the structure and profile of action of those lectins, especially of ML-I. Mistletoe lectins induce apoptosis by inhibiting protein synthesis in ribosomal RNA (Bussing 1996; Bussing 1999). In vitro, mistletoe lectins induced several cytokines (Joller 1996; Ribereau-Gayon 1996) and in animals to an increase of neutrophils, large granular lymphocytes, and higher levels of phagocytosis as well as cytotoxic activity of natural killer-cells (NK-cell) were found (Hajto 1989). In breast cancer patients, intravenous application also lead to an increase of the number of neutrophils and a significant rise in NK-cell activity (Hajto 1989). In healthy adults increasing numbers of blood granulocytes especially eosinophils were found after application of a lectin-rich mistletoe preparation, as well as an increased production of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-5 (IL-5) and interferon gamma (IFNgamma) (Huber 2005), and the induction of tumour necrosis factor- alpha (TNF-alpha) and interleukin-12 (IL-12), which was partly mediated via cell marker CD14. (Heinzerling 2006) There is clear evidence that the application of mistletoe extracts induced anti-lectin antibodies, typically of the subclasses IgG1 and IgG3 (Heinzerling 2006; Kaiser 2001; Klein 2002).

In practice, mistletoe extracts are applied both in adjuvant and in palliative treatment situations, mainly complementing conventional tumour therapy. The generally stated therapeutic objectives are to improve QOL, to strengthen the immune system and to reduce adverse effects of chemo- or radiotherapy, and to a lesser extent to prolong survival and to enhance tumour response (Kienle 2003b).

Currently, there are two different approaches to the production and clinical application of mistletoe preparations (Kienle 2003b):

- Phytotherapeutic mistletoe preparations which are applied at a constant dose (Cefalektin®, Eurixor®, Lektinol®). From these mistletoe preparations Lektinol® is adjusted for the content of mistletoe lectin.
- Mistletoe preparations which are being produced according to pharmaceutical guidelines from anthroposophical medicine (abnovaVISCUM®, Helixor®, Iscador®, Iscucin®, Isorel®). It is assumed here that the overall pharmacological effects and therapeutic efficacies do not derive from a single component but from several compounds acting together additively or synergistically. With this approach, the doses of the mistletoe preparation are continually increased, depending on the patient's general condition, the extent of the local reaction at the site of injection and the regulation of body temperature. Some physicians also adjust the dosage, depending on certain immunological parameters. The preparations are usually applied by subcutaneous injection, two to three times a week.

Despite the existence of elaborated therapeutic concepts, numerous clinical studies and the experiences from a long and widespread use, there is considerable debate about the efficacy of this treatment modality (Cordier 2004; Mansky 2002). A recent editorial and the subsequent discussion vividly depicted that debate (Ernst 2006). The existing reviews used different approaches to collect and appraise the evidence and varied in their interpretations of the data (Ernst 2003; Hauser 1993; Kiene 1991; Kienle 2003a; Kleijnen 1994; Lange-Lindberg 2006). Therefore, we felt the need to systematically and comprehensively review the available evidence regarding the use of mistletoe extracts in the treatment of cancer patients.

OBJECTIVES

To assess the evidence for the effectiveness of mistletoe extracts for prolonging survival, preventing recurrences, reducing treatment toxicity and/or improving QOL in patients with cancer.

Specifically:

(1) Do mistletoe extracts given alone or in combination with tumour-specific therapies prolong disease-free survival (DFS) and/or overall survival (OS)?

(2) Do mistletoe extracts given alone or in combination with tumour-specific therapies enhance tumour response?

(3) Do mistletoe extracts alleviate adverse effects from chemo- or radiotherapy?

(4) Do mistletoe extracts improve the QOL of cancer patients?

(5) Do mistletoe extracts produce adverse effects?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults diagnosed with cancer, without restriction to the type or stage of the disease.

Types of interventions

Comparison of mistletoe extracts, whether or not standardized for the content of mistletoe lectin with placebo or no treatment or any type of tumour-specific treatment.

Types of outcome measures

Reporting of at least one of the following outcomes: survival, tumor remission, different aspects of QOL, adverse effects from antineoplastic treatment and/or from mistletoe extracts. Trials which only reported physiological measures (e.g. immune parameters etc.) were excluded.

Search methods for identification of studies

Electronic searches

For the search the Standard Operating Procedures of the Information System in Health Economics at the DIMDI was utilized applying a combination of text and keyword (MeSH terms) in each database. MeSH/keyword terms were modified as necessary for each electronic database searched. Restrictions by study methodology were not included in order not to eliminate the 'best available' evidence, in the event that there were no RCTs or controlled clinical trial that fully met the inclusion criteria. The following databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 4, 2006)
- EMBASE (1980 to 2007)
- MEDLINE
- AMED
- BIOETHICSLINE
- BIOSIS
- CancerLit
- CATLINE
- CISCOM
- Cochrane Complementary Medicine Field Registry of randomized clinical trials and controlled clinical trials
- HEALTHSTAR
- INT. HEALTH TECHNOLOGY ASSESSMENT
- SOMED

For identifying unpublished material, institutions and subjects known to have expertise in cancer treatment with mistletoe preparations and respective manufacturers were contacted for further information. Beyond this the bibliographies of the identified studies were checked for further trials on the topic which may not be found by the search strategy described above.
In addition, the Cochrane Gynaecological Cancer Review Group searched their Specialised Register and Non-Trials Database for new records.
See Appendix 1 for search terms applied.
An update of the search in 2008 yielded eight RCTs, which are listed in the Studies awaiting classification section and will be assessed in an upcoming update of the review (Enesel 2005; Grossarth 2006b; Grossarth 2006a; Grossarth 2007b; Grossarth 2007c; Grossarth 2007a; Tröger 2007).

Searching other resources

Reference lists

The reference lists of articles retrieved by electronic searches and contained in the authors databases were searched for additional citations.

Unpublished studies

Unpublished reports were sought through searches of conference proceedings, references in published literature, and through contact with institutions and subjects known to have expertise in cancer treatment with mistletoe extracts and to manufacturers of mistletoe preparations.

Language

No language restrictions were applied to study selection.
We tried to contact all the trial authors and replies were received supplying data for nine studies (Dold 1991; Grossarth 2001a; Grossarth 2001b; Heiny 1997; Kleeberg 2004; Lange 1993; Piao 2004; Schwiersch 1999; Semiglasov 2004). Other data had to be extracted and assessed as outlined in the methods section.

Data collection and analysis

Selection of studies

Two review authors (GB, MH) screened titles and abstracts, and eliminated records obviously not relevant to this review. Three review authors (GB, MH, MR) then independently screened the remaining titles and abstracts for their eligibility for inclusion in accordance with the criteria set up in the section 'Criteria for considering studies for this review', reviewing full paper copies where necessary. Trial authors were contacted where information was unclear.

Full texts of all possibly eligible studies were obtained for independent review by at least two review authors (GB, MH, RH, KL and

If data were not reported in extractable form, the authors were contacted for additional information. If the authors could not be contacted or did not provide data or if the information is no longer available, this is being reported.

Assessment of risk of bias in included studies

The methodological quality of each study was assessed by the criteria suggested by Jadad 1996, the Delphi List (Verhagen 1998) and the approach of the Cochrane Collaboration (Higgins 2006). All review authors participated in the assessment. Information on the quality of included studies is reported in the validity assessment table (Table 2).

The Jadad scale consists of three items:

- one point is provided for randomisation, blinding, and description of withdrawals and drop-outs
- two extra points are added for well-described and appropriate methods of randomisation and blinding
- studies which use a clearly inappropriate method of randomisation or blinding (such as alternating patients) forfeit the respective point
- studies which only state the numbers of withdrawn patients without reporting the reasons lose the respective point

Thus the maximum obtainable score is five points and studies scoring below three points are usually regarded as being of low methodological quality (Jadad 1996). For example the presentation in the validity assessment table (Table 2) reads as follows: 2-2-1 (full score for each item); 1-0-0 (randomisation only stated; no further details obtained).

The Delphi list has nine items where one point is provided if:

- words such as random and randomisation are used
- the treatment allocation was concealed, meaning that an unpredictable assignment sequence was generated by an independent person not responsible for determining eligibility of the patients
- the groups are regarded as similar in terms of prognostic indicators

MR). Studies that failed to meet the inclusion criteria are listed in the 'Characteristics of excluded studies' table. Disagreements over inclusion were resolved by discussion between the review authors.

Data extraction and management

Data extraction of descriptive characteristics and study results were performed independently by all five review authors.

In addition to information relating to study quality, information on the setting, the participants' characteristics, the interventions, the results, and any reported side effects of the therapies were recorded using a standardised data extraction sheet. These details are reported in the Characteristics of included studies table and table and validity assessment table (Table 2).

- the eligibility criteria were reported
- patient, care provider and/or outcome assessor were adequately blinded (three points in total)
- point estimates and measures of variability were presented
- all randomised patients were analysed for the most important outcome measures, irrespective of noncompliance and co-interventions

Thus the maximum obtainable score is nine points (Verhagen 1998). For example the presentations in the validity assessment table (Table 2) reads as follows: 1-0-1-1-0-0-0-1-0 (randomisation stated; concealment of allocation unclear, relevant prognostic indicators evenly distributed between groups, criteria for in- and exclusion of patients reported, no blinding, estimates presented as medians with confidence intervals (CI), no intention-to-treat analysis).

For the definition of high methodological quality we used an arbitrary cut-off point of six out of nine fulfilled Delphi criteria, or four out of five fulfilled Jadad criteria.

The methodological quality of trials was also assessed with particular emphasis on the allocation concealment, which was ranked using the Cochrane Collaboration approach (Higgins 2006):

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

Grade D: Not used

Simple agreement and kappa statistics were applied to measure concordance among evaluators using the three scoring methods. Consensus on quality scores was established by discussion. No trial was excluded based on its quality score.

Data synthesis

Due to the strong clinical heterogeneity of the studies (range of mistletoe preparations, differences in dosage and application modes and concomitant conventional antineoplastic treatments, variation in patients' characteristics) and insufficient reporting it

was not possible to perform a meta-analysis or to summarize the results of single studies in effect size measures. Therefore, the review findings had to be presented as a descriptive, narrative qualitative synthesis.

A rating system consisting of five levels of evidence was used (van Tulder 2003)

1. Strong evidence - consistent findings among multiple high quality RCTs
2. Moderate evidence - consistent findings among multiple low quality RCTs and/or one high quality RCT
3. Limited evidence - one low quality RCT
4. Conflicting evidence - inconsistent findings among multiple RCTs
5. No evidence from trials - no RCTs

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Electronic and manual searches identified 80 potential trials and reviews.

Of these, duplicates were identified and, on initial review, 37 were excluded for the following reasons:

- not concerned with mistletoe treatment
- no original data (editorials, reviews and discussion papers)
- observational studies
- animal or in-vitro studies
- no clinical outcomes

Details of the above excluded studies are available on request from the review authors.

Forty-three full text articles were evaluated for inclusion. Twenty-two of these did not meet the inclusion criteria (for details see Characteristics of excluded studies table). The remaining 21 studies were RCTs and used parallel groups (for details see Characteristics of included studies table).

1. Diagnoses/treatment situations

The 21 identified trials provided data from 3484 patients from Austria, Bulgaria, China, Germany, Italy, Romania, Russia and Ukraine. The median number of patients per trial was 107, the mean number was 166 (range 23 to 408). All studies were restricted to adults.

Patients with various forms of cancer were included in the trials:

- cancer of the gastrointestinal tract (Cazacu 2003; Douwes 1986a; Heiny 1997;Salzer 1983)
- breast cancer (Auerbach 2005; Borrelli 1999; Grossarth 2001a; Heiny 1991; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006)
- glioblastoma (Lenartz 2000)
- cancer of the bronchus (Dold 1991; Salzer 1991)
- urinary bladder cancer (Goebell 2002)
- head-and-neck cancer (Steuer-Vogt 2001)
- melanoma (Kleeberg 2004)
- renal cell cancer (Luemmen 2001)
- various cancer (Grossarth 2001b; Lange 1993; Piao 2004)

Seven studies used mistletoe extracts in adjuvant treatment situations (Auerbach 2005; Goebell 2002; Kleeberg 2004; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001). Another seven studies used mistletoe extracts in palliative treatment situations (Borrelli 1999; Dold 1991; Douwes 1986a; Heiny 1991; Heiny 1997; Lange 1993; Luemmen 2001). In the additional seven trials, the study population included both, patients in adjuvant and in palliative treatment situations (Cazacu 2003; Grossarth 2001a; Grossarth 2001b; Lenartz 2000; Piao 2004; Salzer 1983; Salzer 1991)

2. Types of mistletoe extracts

Preparations of mistletoe extracts of five manufacturers were tested. Nine trials used mistletoe extracts adjusted for the content of mistletoe lectin with constant dosage from two different manufacturers. The brands used in these studies were Eurixor (Goebell 2002; Heiny 1991; Heiny 1997; Lenartz 2000; Luemmen 2001; Steuer-Vogt 2001) and Lektinol (Schwiersch 1999; Semiglasov 2004; Semiglasov 2006). One trial used a commercially not available mistletoe extract standardized for the content of mistletoe lectin (Borrelli 1999).

In 11 trials mistletoe extracts standardized for the pharmaceutical production process with varying dosages from three different manufacturers were used. The brands used in these studies were Helixor (Auerbach 2005; Douwes 1986a; Lange 1993; Piao 2004), Iscador (Dold 1991; Grossarth 2001a; Grossarth 2001b; Kleeberg 2004; Salzer 1983; Salzer 1991) and Isorel (Cazacu 2003).

Across the studies, not only mistletoe extracts with different pharmaceutical manufacturing processes and hence varying compounds were applied, but also the application modes and doses varied considerably. In 17 studies, mistletoe extracts were applied subcutaneously (Auerbach 2005; Borrelli 1999; Douwes 1986a; Dold 1991; Goebell 2002; Heiny 1997; Kleeberg 2004; Lange 1993; Lenartz 2000; Luemmen 2001; Piao 2004; Salzer 1983; Salzer 1991; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001), 1 intravenously (Cazacu 2003), 1 intravenously and subcutaneously (Heiny 1991) and 2 no information on the mode of application was available (Grossarth 2001a; Grossarth 2001b).

3. Intervention/Control treatment

3.1 Mistletoe extracts as sole treatment

3.1.1. Compared with no-treatment or placebo

Two 2-arm trials compared mistletoe extracts with no treatment (Goebell 2002; Salzer 1991) and two trials with a placebo treatment (Borrelli 1999; Schwiersch 1999). Kleeberg 2004 comprised of two trials, a 3-arm trial comparing interferon-a2b with interferon-g with no treatment (EORTC 18871 trial) and a 4-arm trial in which a fourth arm was added where patients received mistletoe extracts for one year (DKG 80-1 trial). The efficacy analysis concerning mistletoe extracts was confined to the comparison with the no-treatment group of the EORTC 18871 trial.
In Steuer-Vogt's 4-arm trial patients were stratified into two groups that underwent either radiotherapy after surgery or no further treatment. Patients of both strata were then allocated to either mistletoe extracts or no additional treatment (Steuer-Vogt 2001).

3.1.2. Compared with other immunomodulatory drugs and placebo

In a 3-arm trial, Dold 1991 compared mistletoe extracts with organ extracts from sheep spleen and a vitamin B mixture, which served as placebo.

3.1.3. Compared with chemotherapy and no-treatment

In a 3-arm trial, Salzer 1983 compared mistletoe extracts with chemotherapy or no treatment. In 1979 they reported on the results of two interim analyses after three years and four years of follow-up. The final publication in 1983 (Salzer 1983) only reported about the results from the comparison between the mistletoe and the no-treatment group.

3.1.4. Compared with chemoimmunotherapy

In Luemmen 2001 mistletoe extracts were compared with a chemoimmunotherapy comprising IFN-alpha, IL-2 and 5-Fluorouracil.

3.2 Mistletoe extracts during chemotherapy or radiotherapy

3.2.1. Compared with no-treatment or placebo

In five trials the basic oncological treatment for all groups was chemotherapy (Auerbach 2005; Heiny 1991; Heiny 1997; Semiglasov 2004; Semiglasov 2006). Three of them compared an additional treatment with mistletoe extracts with a placebo (Auerbach 2005; Heiny 1991; Semiglasov 2006) and one compared it with no additional treatment (Heiny 1997). Semiglasov (Semiglasov 2004) compared mistletoe extracts at three different doses (low, medium and high) with a placebo treatment. In a 3-arm trial, Cazacu 2003 compared chemotherapy and mistletoe extracts with chemotherapy alone with no treatment. In Lange's trial, the basic oncological treatment for both groups was chemo- and radiotherapy and the additionally given mistletoe extracts were compared with no treatment (Lange 1993). In Lenartz's trial the basic oncological treatment was radiotherapy and additional mistletoe extracts were compared with no concomitant treatment (Lenartz 2000). All patients in stratum B of the Steuer-Vogt trial received radiotherapy and a concomitant treatment with mistletoe extracts was compared with no treatment (Steuer-Vogt 2001).

3.2.2. Compared with other drugs and no-treatment

In a 3-arm trial, Douwes et al compared mistletoe extracts with xenogenic peptides (organ extracts from different animal species) and no-treatment. In this trial the basic oncological treatment for all groups was chemotherapy (Douwes 1986a).

3.2.3. Compared with other drugs

In a 2-arm trial, in which both groups received chemotherapy, Piao et al compared mistletoe extracts with lentinan, a polysaccharide from lentinus edodes (Piao 2004).

3.3. Mistletoe extracts in an unclear therapeutic setting

In two 2-arm trials, patients of the intervention group were requested to ask their physician for a treatment with mistletoe extracts. Comparisons were made with the group which was not requested to ask their physician for a treatment with mistletoe extracts. Both the intervention treatment and the control treatment was not further described (Grossarth 2001a; Grossarth 2001b - these trials are published in one paper, but will be cited separately henceforth).

4. Outcomes

Most trials investigated several outcomes, and 16 prespecified their outcome of greatest importance (Auerbach 2005; Borrelli 1999; Dold 1991; Douwes 1986a; Goebell 2002; Grossarth 2001a; Grossarth 2001b; Heiny 1997; Kleeberg 2004; Lange 1993; Luemmen 2001; Salzer 1991; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001). Two trials were designed as pilot studies (Auerbach 2005; Lange 1993).

4.1. Studies reporting on survival

Eleven studies reported on measures of OS (Cazacu 2003; Dold 1991; Douwes 1986a; Grossarth 2001a; Grossarth 2001b; Heiny 1997; Kleeberg 2004; Lenartz 2000; Luemmen 2001; Salzer 1983; Salzer 1991). Four studies used measures of DFS (Goebell 2002; Heiny 1997; Kleeberg 2004; Lenartz 2000) and one study reported on disease-specific survival (Steuer-Vogt 2001)

4.2. Studies reporting on tumor response

Three studies stated how categories of response were defined (Dold 1991; Douwes 1986a; Lange 1993). Lange 1993 applied evaluation criteria according to Hayward 1978.

Dold 1991 classified response to treatment in four categories:
1) remission: disappearance of all signs of tumor at two follow-ups
2) uncertain remission: disappearance of all signs of tumor at one follow-up
3) regression: decrease in the size of the primary tumor
4) uncertain regression: decrease in the size of the primary tumor after a preceding increase.
Douwes 1986a classified response to treatment in five categories:
1) complete remission was defined as disappearance of all signs of tumor (CR)
2) partial remission as a decrease in the size of a tumor of more than 50% of the initial extent (PR)
3) minimal remission as shrinkage or partial disappearance of less than 50% (MC)
4) no definition was given for stable disease (NC) and progressive disease was defined as any tumor growth (PD).
Four studies reported on tumour response without stating how response categories were defined (Borrelli 1999; Heiny 1997; Luemmen 2001; Piao 2004).

4.3. Studies reporting on health related QOL, psychological measures, performance index, symptom scales or adverse effects of chemo- or radiotherapy

4.3.1. Assessment during chemotherapy

Auerbach 2005 assessed QOL with the QLQ-C30 and a visual analogue scale and reported on hematological toxicity of chemotherapy without further details. Cazacu 2003 reported on adverse effects of chemotherapy without presenting any details. Douwes 1986a reported on rates of chemotherapy-associated side effects without further details. Heiny 1991 assessed QOL by Befindlichkeitsskala, Beschwerdeliste, Eigenschaftswörterliste, FLIC and merged the results into an Index of well-being and anxiety with Therapieangstskala and Catell-Angstskala, the results of which were also merged into an Index of anxiety and measured chemotherapy-related toxicity by means of peripheral leukocytes. Heiny 1997 assessed QOL with the FACT and reported on numerous typical chemotherapy-associated side effects. Lange 1993 assessed performance index (Karnofsky), used symptom scales and reported on hematological, hepatic and renal toxicity of chemotherapy. Piao 2004 measured QOL with the FLIC and symptoms with a TCM Index and reported on chemotherapy-related side effects. Semiglasov 2004 assessed QOL with GLQ-8, Spitzer's QOL uniscale and the QLQ-C30 and reported on hematological and gastrointestinal side effects of chemotherapy. Semiglasov 2006 measured QOL with FACT-G, GLQ-8 and Spitzer's QOL Uniscale, assessed performance index (Karnofsky) and reported on chemotherapy-related side effects.

4.3.2. Assessment during radiotherapy

Lenartz 2000 assessed QOL with Spitzer's QOL Index.
In patients of stratum B of Steuer-Vogt 2001, QOL was assessed during radiotherapy with QLQ-C30.

4.3.3. Assessment after completion of chemotherapy/radiotherapy

Borrelli 1999 assessed QOL with Spitzer's QLI

4.3.4. Assessment during sole mistletoe treatment

Dold 1991 assessed overall well-being, Karnofsky's performance index and degree of discomfort by numerous symptom scales. Steuer-Vogt 2001 assessed QOL with QLQ-C30.

4.3.5. Assessment during oncological rehabilitation

Schwiersch 1999 measured psychological distress with the FBK, life satisfaction with the FLZ, QOL with the SF-36 and MDBF, psychological symptoms with the SCL-90R, and performance index (Karnofsky).

4.3.6. Assessment in an unclear therapeutic setting

Grossarth 2001a and Grossarth 2001b measured psychosomatic self-regulation.

4.4. Studies reporting on adverse effects of mistletoe extracts

Twelve of the 21 studies reported adverse events associated with the study medication (Auerbach 2005; Dold 1991; Goebell 2002; Heiny 1991; Heiny 1997; Kleeberg 2004; Luemmen 2001; Piao 2004; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001).

5. Comparability of studies

Semiglasov 2004 and Semiglasov 2006 had comparable study populations, used the same study medication and measured similar outcomes. Dold 1991 and Salzer 1991 also had comparable study interventions and endpoints, but patients in Dold 1991 suffered from all stages of inoperable lung cancer, whereas Salzer 1991 included patients with all stages of lung cancer after surgery. Douwes 1986a and Heiny 1997 included both patients with advanced stages of colorectal cancer, applied palliative chemotherapies with the same substances but different doses and used different preparations of mistletoe extracts.
In all other studies, the differences in the study populations, outcome measures, basic and intervention treatments hampered any sort of comparison.

6. Published and unpublished data

Ten studies were published in Medline-listed journals (Cazacu 2003; Goebell 2002; Grossarth 2001a; Grossarth 2001b; Kleeberg 2004; Lenartz 2000; Piao 2004; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001), whereof four went through a formal peer-review process (Goebell 2002; Grossarth 2001a; Grossarth 2001b; Kleeberg 2004; Steuer-Vogt 2001). Six trials were published in journals not listed in Medline (Borrelli 1999; Douwes 1986a; Heiny 1991; Heiny 1997; Salzer 1983; Salzer 1991). One study was published in the proceedings book of a symposium and another one in a book (Auerbach 2005; Dold 1991). Two studies were only available as unpublished manuscripts (Lange 1993; Schwiersch 1999) and one study only in abstract form (Luemmen 2001).

The following authors did not provide further information (e.g. study protocol) despite of repeated application (Auerbach 2005; Goebell 2002; Kleeberg 2004; Lenartz 2000; Luemmen 2001).
The manufacturer of the mistletoe extract used in Kleeberg 2004 (Weleda) provided the study protocol and additional information after a second application in 2004. Lange 1993 was provided as an unpublished manuscript from the manufacturer (Helixor Heilmittel GmbH&Co) in 2006 after repeated application. The manufacturer of the mistletoe brand in Piao 2004 (Helixor Heilmittel GmbH&Co) kindly provided the submission manuscript and the medical study report. Schwiersch 1999 was provided as an unpublished submission manuscript and sourced directly from the authors. According to the authors, the study will not be published. The manufacturer (MADAUS) kindly provided the study protocol of Semiglasov 2004.
Borrelli 1999 was republished in English in 2001.
Heiny 1997 was republished in 1998 with referencing the original report, and with a third author.
Lenartz 2000 comprised data on different outcomes of one study after different follow-ups of the same trial published in 1996 and 2000. Data from the 1996 publication were republished in 1999 with differing number of included patients. Data from the 2000 publication were republished in 2001. Both double publications did not reference the corresponding original reports. After repeated application, the authors stated in a personal communication in 2005 that the 1996 and the 2000 publication reported on the same trial with different outcomes and follow-up times.
Results from Luemmen 2001 were presented at three international meetings in 2000 and 2001. Coauthors of Luemmen 2001 published results of a probable subgroup of these study patients in 2004 (Brinkmann 2004).

In 1979, Salzer et al published the results of two interim analyses during recruitment of the Salzer 1983 trial. The second author was not listed in the Salzer 1983 publication. In 1988, the first author published a comment on the number of withdrawals and drop-outs.
Data of Semiglasov 2004 were published in 2000 in form of an abstract and widely distributed as an advertising report from the manufacturer (Wetzel 2000). Wetzel and Schaefer, who authored the 2000 abstract, were not involved in the 2004 publication.
Data from Steuer-Vogt 2001 was published in 2000 as part of a professorial dissertation. Data of the QOL analysis were published in 2006.

7. Conflict of interest

As we found no reports on conflicts of interest in any of the trials, we assessed the issue by looking at funding sources and whether an author was employed by a pharmaceutical manufacturer. No information about sources of funds was found in Borrelli 1999, Douwes 1986a, Heiny 1991, Heiny 1997, Lenartz 2000, Luemmen 2001, Schwiersch 1999. Dold 1991, Goebell 2002, Grossarth 2001a, Grossarth 2001b. The DKG 80-1 trial of Kleeberg 2004, Salzer 1983, Salzer 1991 and Steuer-Vogt 2001 were funded by public grants. Cazacu 2003 was funded by a public grant and by a pharmaceutical company (Novipharm GmbH, Pörtschach, Austria). Semiglasov 2004 and Semiglasov 2006 were funded by a pharmaceutical company (MADAUS AG, Köln). In Borrelli's trial the experimental medicine was supplied by Dr. med.Tibor Hajto, Abt. Naturheilkunde, Universität Zürich (Borrelli 1999). The study medication in Steuer-Vogt 2001 was supplied by a company (Biosyn Arzneimittel GmbH, Fellbach). In 6 trials, at least one author was employed by a pharmaceutical company (Auerbach 2005; Cazacu 2003; Grossarth 2001a; Grossarth 2001b; Semiglasov 2004; Semiglasov 2006).
Details on patients, methods, interventions, and outcomes of all included studies are described in the Characteristics of included studies table, details of the results can be found in Table 3 and details of the validity assessment in Table 2.

Risk of bias in included studies

Initially, several ratings for the fullfilment of methodological quality criteria for individual studies varied between review authors. Specifically, there were 38 disagreements on 294 individual ratings, for a raw agreement rate of 83%. A total of 24 of the disagreements resulted from different interpretations of the methodological quality items and the additional 14 resulted from reading errors in the studies. All disagreements were resolved through discussion among the review authors without the need for a third party.

The results of the validity assessement according to the Delphi and Jadad criteria are given and commented on in Table 2.

Randomisation and concealment of allocation

All of the included studies reported on random treatment allocation. Publications of 11 studies specified the method of sequence generation (Dold 1991; Goebell 2002; Grossarth 2001a; Grossarth 2001b; Heiny 1991; Heiny 1997; Piao 2004; Salzer 1991; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001), and in all of them we judged the method to allow for truly random allocation. Heiny 1997 reported matching after randomisation. In a personal correspondence the author stated, that there was no matching but a randomisation after stratification for sociodemographic factors. Methods to conceal allocation of treatment were reported in eight studies and in seven of them the concealment was jugded as adequate to prevent foreseement of assignement. The allocation took place at a central core facility in six studies (Dold 1991; Goebell 2002; Kleeberg 2004; Lange 1993; Salzer 1983; Steuer-Vogt 2001), one study used sealed envelopes (Salzer 1991).

Blinding

In principle, blinding of the patient and the care provider is problematic in trials with mistletoe extracts, as these extracts often evoke skin reaction at injection site. Only four of the 21 trials were described as double-blind (Auerbach 2005; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006), but all authors reported either full (Auerbach 2005) or partial deblinding of allocated treatment (Schwiersch 1999; Semiglasov 2004; Semiglasov 2006). Borrelli 1999 blinded the patient, but provided no data on whether blinding was successful. Only one publication explicitely reported a blinded outcome assessment (Dold 1991).

Completeness of data

All authors reported on the number of patients withdrawing or dropping out. Five studies reported that no patients had dropped out of or withdrawn from the study (Borrelli 1999; Cazacu 2003; Douwes 1986a; Grossarth 2001b; Luemmen 2001). Reasons for dropping out or withdrawing were described in nine studies (Auerbach 2005; Dold 1991; Grossarth 2001a; Heiny 1991; Kleeberg 2004; Lange 1993; Salzer 1983; Salzer 1991; Semiglasov 2004).

Composite scales

The mean Delphi score of all included studies was 4 with a median of 4 and a range of 1 to 6. The mean Jadad score was 2.6, with a median score of 3 and a range of one to 4. No study fulfilled all quality criteria in either one of the composite scales. Using an arbitrary cut-off point of 6 out of 9 fulfilled Delphi criteria, 4 of the 21 trials (19%) were of high methodological quality (Dold 1991; Kleeberg 2004; Goebell 2002; Steuer-Vogt 2001). Applying the Jadad score as a measure for methodological quality and a cut-off point of 4 out of 5 fulfilled criteria, 3 of the 21 trials (14%) were of high methodological quality (Schwiersch 1999; Semiglasov 2004; Semiglasov 2006).

See scores and description of validity criteria of the single trials in Table 2.

From a clinical point of view, limitations of the majority of trials include a lack or insufficient description of prognostic relevant factors for the outcome of interest, staging not corresponding to international standards, outdated oncological treatment regimens, comparability of basic treatment (chemotherapy/radiotherapy) between groups being unclear, and a lack of control for equal provision of care apart from the treatment under evaluation.

Effects of interventions

1. Studies reporting on survival

Of the 21 included studies 13 provided data on survival. Results suggesting a benefit were found in six trials (Cazacu 2003; Douwes 1986a; Grossarth 2001a; Grossarth 2001b; Lenartz 2000; Salzer 1983) and results that do not in seven (Dold 1991, Goebell 2002; Heiny 1997; Kleeberg 2004; Luemmen 2001;Salzer 1991; Steuer-Vogt 2001). Four of those 13 trials were considered to be of high methodological quality and belong to the group in which no evidence for a benefit was reported (Dold 1991; Goebell 2002; Kleeberg 2004; Steuer-Vogt 2001).

1.1. Breast cancer

In Grossarth 2001b, women with different stages of breast cancer had a mean survival of 4.79 years compared to 2.41 years in women who were in the control group (SD not reported; p = 0.02, log-rank test) . Median survival data (extracted from a plot) was 6.2 years for patients of the mistletoe group and 2.3 for controls.

1.2. Colorectal cancer

In Cazacu 2003, patients with Dukes C stage who were treated with 6 cycles of chemotherapy and additional mistletoe extracts survived a median of 757 days, those who received chemotherapy alone survived 547 days, and those without a postoperative adjuvant treatment 502 days (no confidence intervals (CIs) presented; $p < 0.05$). Patients with Dukes D colorectal cancer who received chemotherapy and mistletoe extracts survived a median of 505 days, those who were treated with chemotherapy alone survived 214 days, and those without a postoperative antineoplastic treatment 451 days (no CIs,;$p < 0.05$).

In Heiny 1997, patients with metastatic diseases received chemotherapy and lived a mean of 53 weeks when additionally treated with mistletoe extracts compared with 50 weeks in the control group. The mean progression-free survival (PFS) was 30.8 weeks and 31.2 weeks respectively. Authors performed no statistical analysis.

In Douwes 1986a, patients with metastatic diseases were treated with chemotherapy and survival data were reported for responders (patients with a complete, partial or minimal response) and non-responders (patients with a no-change or progression of the disease). On average, responders of the mistletoe group lived 26.7 months (standard deviation (SD) 11.9), non-responders of this group 11.9 months (SD 4.7), responders of the group which was only treated with chemotherapy lived on average 13.6 (SD 4.4), and non-responders of this group 4.8 months (SD 4.1). A statistical analysis was not performed.

1.3. Head and neck cancer

In Steuer-Vogt 2001, participants with operable diseases were stratified into one group that underwent surgery (stratum A) and a second one with surgery followed by radiotherapy (stratum B). The five-year Kaplan estimates of the disease-specific survival and DFS were not significantly different between a) the groups both in the main analysis and b) in that of the two strata. Also, no significant differences were found in the five year survival rates, the relapse incidence, the development of distant metastases and second primaries.

1.4. Lung cancer

In Dold 1991, participants with previously untreated, inoperable non-small cell lung cancer had a median survival time of 9.1 months (95% CI 6.8 to 10.7) when treated with mistletoe extracts compared to 7.6 months (95% CI 6.0 to 8.9) in the placebo group ($p = 0.24$ [log rank]). The rate of patients in the mistletoe group surviving 6 months was 62.7% (SD 4.6), one year 36.0% (SD 4.6) and two years 11.5% (SD 3.2). The respective rates for patients in the control group were 59.0% (SD 4.7), 32.2% (SD 4.4) and 10.1% (SD 3.0). The authors reported having reanalyzed the data including the 48 patients who dropped out due to protocol violations without having found differences to the per-protocol analysis (data not presented).

In Salzer 1991, patients with all stages of lung cancer after surgery were included and the median survival time in the mistletoe group was 33 months compared with 31 months in the control group (n.s., log-rank test). A post-hoc analysis of subgroups revealed no difference in median survival for patients with stage IV (16.5 versus 17 months) and stage I/II without positive lymph nodes (44 versus 43 months). There was, however, a difference for the subgroup of patients with stage II or III with positive lymph nodes (T1-3, N1-2): Patients in this subgroup who had received mistletoe extracts experienced a median survival of 31 months compared to 24 months without treatment and 38% of the mistletoe group survived 5 years compared to 20% of the control group (n.s., log-rank test).

1.5. Malignant glioma

Lenartz 2000 reported the OS and relapse-free survival of patients with malignant glioma after a follow-up of 50 weeks. Though stated in the 1996 publication that only patients with stage III/IV were included, in the 2000 publication of the trial, survival data were separately analysed for all stages and for stage III/IV without reporting the numbers of patients in each group. The mean OS of patients from the all stages group who had received mistletoe extracts was 21.71 (SD 3.7) months and for the controls 17.32 (SD 3.9). Patients with stage III or IV of the disease were reported as having survived a mean of 20.05 (SD 3.5) months if they had received mistletoe extracts, and 9.90 (SD 2.1) months if they did not ($p = 0.035$, Breslow test).

The DFS of patients from the all stages group who had received mistletoe extracts was 14.41 (SD 2.7) months and for the controls 14.76 (SD 3.6). Patients with stage III or IV of the disease survived a mean of 17.43 (SD 8.2) months if they had received mistletoe extracts, and 10.45 (SD 3.9) months if they did not.

1.6. Melanoma

In the DKG 80-1 part of Kleeberg 2004, patients with melanoma either received mistletoe extracts for one year or no treatment after all had curative surgery. The univariate analysis of the Cox Proportional Hazards model revealed an estimate for the disease-free interval of 1.32 (95% CI 0.93 to 1.87; $p = 0.12$, [Wald test]) and 1.21 (95% CI 0.84 to 1.75; $p = 0.31$) for the OS.The multivariate analysis was adjusted for stage, number of positive lymph nodes, localisation of primary and Breslow thickness. The hazard ratio (HR) estimate for the disease-free interval was 1.34 (95% CI 0.95 to 1.91; $p = 0.10$) and 1.27 (95% CI 0.87 to 1.84; $p = 0.21$) for the OS.

1.7. Renal cell carcinoma

In Luemmen 2001, the patients of the mistletoe group had a median survival of 21 months compared with a median survival of

13 months in patients of the chemoimmunotherapy group (p = 0.14), after a median follow-up of 19 months. Measures of variability and information on the statistical test were not presented.

1.8. Gastric cancer

In Salzer 1983, patients with all stages of gastric cancer after surgery either received chemotherapy, mistletoe extracts or no treatment. In 1979 data from the interim analyses after three years and four years of follow-up were published. Survival data had to be extracted from two Kaplan-Meier diagrams: After three years of follow-up more than 50% of patients of both the mistletoe and chemotherapy group were alive and the median survival of the control group was 1.9 years. After four years of follow-up, more than 50% of patients of the mistletoe group were still alive, the median survival time of patients in the chemotherapy group was 3.1 yrs. and 1.1 years for patients of the control group respectively. The final publication in 1983 reported only data from patients of the mistletoe and the control group and of those with stage II and III. Furthermore, for the comparison of survival times, patients of both stages were grouped into those with or without affected lymph-nodes: Patients with stage II or III and affected lymph-nodes who had received mistletoe extracts lived a median of 660 days on average whereas the same subgroup of patients of the control group lived 324 days (p < 0.05, Breslow test). For lymph-node negative stage II-III patients no difference in terms of survival was found.

1.9. Urinary bladder cancer

After transurethral surgery and an eighteen-months treatment with subcutaneous mistletoe extracts, the number of recurrences were assessed. Thirty-one were found in the mistletoe group, and 30 in the control group with a mean time to recurrence of 6.3 and 6.4 months, respectively (Goebell 2002). Nine patients in each group of this study remained without evidence of disease during follow-up. Patients receiving mistletoe extracts had a median disease-free interval of 9 months and patients of the control group one of 10.5 months. None of these estimates showed statistical significance.

1.10. Various cancer

In Grossarth 2001a, for patients with mixed cancer who had been treated with mistletoe extracts a mean survival of 3.49 years was reported compared to 2.45 years for patients of the control group (p = 0.04, log-rank test). Median survival data had to be extracted from a plot and showed similar results for both groups: 2.5 years for patients of the mistletoe group and 2.4 for controls.

2. Studies reporting on tumour response

Of the 21 included studies 7 provided data on tumour response. Results suggesting a benefit were found in 2 trials (Borrelli 1999; Lange 1993) and results that did not in 5 (Dold 1991; Douwes 1986a; Heiny 1997; Luemmen 2001; Piao 2004). Only one trial was judged as being of high methodological quality (Dold 1991) and pertained to the latter group.

2.1. Breast cancer

Borrelli 1999 reported on tumour response after three months treatment with mistletoe extracts. Assessment revealed 4 patients showing a partial remission (20%), 10 with a stable disease (50%) and 6 with progressive disease (30%) in the mistletoe group compared with 4 stable diseases (40%) and 6 progressive diseases (60%) in the control group.

2.2. Colorectal cancer

In Douwes 1986a assessment of treatment response found 13 tumour responses in the mistletoe group (3 complete and 6 partial remissions) and 12 in the group without a concomitant treatment (3 complete and 5 partial remissions). Heiny 1997 found complete and partial remissions in 21.4% of the group treated with mistletoe extracts and chemotherapy and in 22.6% of patients in the control group (only chemotherapy).

2.3. Lung cancer

In Dold 1991, 30 patients in the mistletoe group experienced a tumor response compared to 22 in the placebo group (p = 0.10, Chi ^{2} test). Remissions, were reported in four patients of the mistletoe group and thtee patients of the control group.

2.4. Renal cell cancer

Luemmen 2001 reported a response rate of 2% in the mistletoe group (no complete and 2 partial remissions) compared with 25% in the chemoimmunotherapy group (7 complete and 15 partial remissions).

2.5. Various types of cancer

Lange 1993 evaluated tumour responses after 2 cycles of chemotherapy and found 8 complete and 10 partial remissions (78%) in patients of the mistletoe group, 10 and 3 respectively (62%) in the control group. Application of the combination chemotherapy with cisplatinum and ifosfamide was possible in the first cycle in 17 out of 23 patients of the mistletoe group compared to 14 out of 21 of the control group and in the second cycle in 14 out of 23 patients of the mistletoe group compared to 9 out of 21 of the control group. In the remaining patients, cisplatinum was omitted. Combination chemotherapy could be given at full dose (defined as equal to 85% of the scheduled dose) in the first cycle in 12 out of 17 patients of the mistletoe group compared to 9 out

of 14 of the control group and in the second cycle the numbers were 11 out of 14 and 6 out of 9 respectively.
Piao 2004 reported complete and partial remissions in 21.4% of patients in the mistletoe group and 20.5% in the control group.

3. Studies reporting on health related QOL, psychological measures, performance index, symptom scales or adverse effects of chemotherapy

Of the 21 included studies 16 provided data on QOL, psychological outcomes, symptom scales, performance index and 11 on chemotherapy-related side effects.

3.1. Assessment during chemotherapy

Results suggesting a benefit for at least one of these outcomes during a treatment with chemotherapy were found in all nine trials (Auerbach 2005, Cazacu 2003; Douwes 1986a; Heiny 1991; Heiny 1997; Lange 1993; Piao 2004; Semiglasov 2004; Semiglasov 2006). Two of these trials were of high methodological quality (Semiglasov 2004; Semiglasov 2006).

3.1.1. Breast cancer

In Auerbach 2005, health-related QOL was assessed in patients with early stage breast cancer with the QLQ-C30 and a visual analogue scale. Authors stated that there had been no difference in QOL between the mistletoe and the placebo group, but presented no data of the assessment. No episodes of leukopenia were found in patients who had received mistletoe extracts.
In Heiny 1991 well-being and anxiety during chemotherapy were measured. For the assessment of well-being, four instruments were distributed (Befindlichkeitsskala, Beschwerdeliste, Eigenschaftswörterliste, FLIC) and the results of these instruments were merged into a 5-point scale named Index of well-being (Befindlichkeitsindex). Anxiety was measured with two instruments (Therapieangstskala and Catell-Angstskala) and the results were merged into a 10-point scale named the Index of anxiety (Angstindex). The authors did not report the methods of how the patient-reported outcomes were merged into the physician-rated indices. In patients receiving additional mistletoe extracts the physician-assessed index of well-being decreased from a mean of 4 (out of 5) at baseline to 2.8 after 6 cycles of chemotherapy, whereas in patients of the placebo group the mean index fell from 4 to 2 (measures of variability not reported; $p < 0.01$, t-test). The mean values of the physician-assessed index of anxiety showed the following course in patients of the mistletoe group: 5 (out of 10) at baseline, 6 before second cycle of chemotherapy, 6 before 3rd, 5 before 4th, 4 before 5th, 4 before 6th and 4 at 10 days after completion of chemotherapy. The corresponding estimates in patients of the control group were: 5 at baseline, 6 before 2nd cycle: 6 before 3rd, 7 before 4th and 5th, and 7.5 before 6th and 7.5 at 10 days after completion of chemotherapy (no measures of variability; p </= 0.01, unclear which estimates were tested).
In Semiglasov 2004, QOL was assessed during chemotherapy. The changes of the GLQ-8 sum score were combined with those of Spitzer's Uniscale (QLU) score by means of a nonparametric rank-sum (O'Brien) and tested for statistical significance. The changes from baseline to week 15 were found to be significantly different in patients from the medium and high dose mistletoe group compared with those who were treated with low dose mistletoe or placebo ($p = 0.0035$, O'Brien rank sum test). Pair-wise comparisons between placebo and each single mistletoe group revealed significance only for the medium dose mistletoe group ($p = 0.007$). For the medium dose mistletoe group, all changes in the 8 items of the GLQ-8 were larger than those in the placebo group. Significance was reached for changes in tiredness, sexual interest and anxiety related to treatment. For the results of the QLQ-C30 assessment, the authors reported no relevant difference without presenting data. An analysis of covariance, which had been carried out due to baseline inhomogeneities in the GLQ-8 and QLU score, revealed significant differences in week 15 between the medium dose mistletoe group and the placebo group for both measures ($p = 0.012$ and $p = 0.0021$ respectively).
Concerning the incidence of chemotherapy-induced adverse effects the authors reported no differences in white blood cells among the four groups. However, in red blood cells they found changes in 6% of the placebo group versus 3% in the low and medium dose mistletoe group and 12% in the high dose mistletoe group. Adverse effects related to the gastrointestinal tract were found in 9% of the placebo, the low dose and the medium dose mistletoe group compared to 15% in the high dose mistletoe group.
In Semiglasov 2006, pre-post changes of QOL during chemotherapy were measured with FACT-G, GLQ-8 and QLU. The rank sums of changes of all three instruments from baseline to week 15 and from baseline to a follow-up of another two months after completion of chemotherapy were significant different between groups. Authors stated, that all results were confirmed in a baseline-adjusted analysis of covariance, which had been carried out due to baseline inhomogeneities, but presented no data. No significant changes were found in Karnofsky's performance indices between groups after 15 weeks and after the 2 months follow-up (no data presented).

3.1.2. Colorectal cancer

The authors of Cazacu 2003 stated that adverse effects of chemotherapy pertaining to the gastrointestinal tract and/or bone marrow had been found in four patients of the group exclusively treated with chemotherapy and in none of the patients who had received mistletoe extracts in addition to chemotherapy, but without reporting further details. Douwes 1986a reported inconsistently on the rates of chemotherapy-associated side effects and a referenced table was not included in the publication.
In Heiny 1997, health related QOL during chemotherapy was as-

sessed every 6 weeks with the FACT questionnaire. After the second cycle of chemotherapy, authors reported a significantly higher FACT sum score for patients of the mistletoe group. Concerning adverse effects of chemotherapy, a lower incidence of grade III mucositis in the mistletoe group was reported, but no differences were found for rates of nausea, vomiting, diarrhoea and hand-foot syndrome. A lower rate of leukopenia (32.1% versus 38.7%) was reported for patients of the mistletoe group without presentation of further details.

3.1.3. Various types of cancer

Lange 1993 investigated 44 participants with inoperable cancer of the ENT tract, lung or ovary. Evaluation was restricted to two cycles of chemotherapy. Application of the combination chemotherapy with cisplatinum and ifosfamide at full dose (defined as equql to 85% of the scheduled dose) was possible more frequently in patients of the mistletoe group. Mean performance index (Karnofsky) rose in both groups during the first cycle of chemotherapy, but the increase was significantly higher in the mistletoe group. All symptom scores for nausea, pain and vomiting were lower in the patients who had received mistletoe extracts. The difference was statistically significant for nausea and pain during the 5 following days after the first cycle of chemotherapy. Leukocytes regenerated to significant higher values after the second cycle of chemotherapy in patients who had received mistletoe extracts (p = 0.003, test not stated). No differences between the mistletoe and control group were found for chemotherapy-related hepato- and renotoxicity.

Piao et al evaluated the influence of mistletoe extracts compared to lentinan on chemotherapy-related side effects, performance index and QOL in patients with all stages of breast, ovarian or non-small cell lung cancer (Piao 2004). The authors evaluated all outcomes before start of chemotherapy and after termination. Changes in Karnofsky's performance Index during the treatment period were classified as reduced or increased in case of a difference of at least 10%, otherwise as stable. A significantly larger rate of increased or stable performance indices was found in the mistletoe group compared with the control group (96.5% versus 89%).
Twenty-eight adverse events related to chemotherapy were reported for the mistletoe group compared to 77 for the control group, but were not further described. Health-related QOL was measured with the FLIC and a median improvement of the sum score of 6.0 points was reported for the mistletoe group compared with 3.0 points for the control group. Changes in the TCM score showed a median improvement for the mistletoe group of -1 compared to 0 for the control group.

3.2. Assessment during radiotherapy

In Lenartz 2000, a better QOL in patients with malignant glioma of the mistletoe group was reported 12 and 24 weeks after surgery. Data were not statistically analysed and the results of the five subscales of the questionnaire were not presented.

3.3. Assessment during rehabilitation

Schwiersch 1999 assessed measures of psychosocial distress and QOL in women with breast cancer during a 4-week oncological rehabilitation after completion of adjuvant therapy. No significant differences between the groups were found in psychosocial distress (FBK-KF), Karnofsky's performance index and overall QOL (SF-36). However, for the subscale vitality of the SF-36, significantly higher values were found in the mistletoe group. Also for the subscale energy/joie de vivre of the questionnaire on life satisfaction significantly higher values were found in the mistletoe group.

3.4. Assessment during sole mistletoe treatment

Borrelli 1999 assessed QOL with Spitzer's Quality of Life Index (QLI) (Spitzer 1981) in women with metastatic breast cancer who had completed chemo-/radiotherapy. QLI mean scores increased in the mistletoe group from baseline to follow-up after one and three months, whereas corresponding mean scores in the control group decreased. Differences in estimates at three-months follow-up were statistically significant.
Dold 1991 assessed wellbeing, Karnofsky's performance index and symptom scales in patients with lung cancer. Fifty-nine percent of patients receiving mistletoe extracts perceived an improvement in their wellbeing (patient statement documented by the physician) compared to 45% in the placebo group. The difference was statistically significant (p = 0.018). No significant difference was found between the mistletoe and the placebo group for Karnofsky's performance index. Assessement of QOL by means of symptom scales (patient's degree of discomfort documented by the physician) including fatigue, pain, loss of appetite, dyspnea, fever and others revealed no significant differences.
Steuer-Vogt 2001 assessed QOL with the QLQ-C30 over a maximum period of 156 weeks (median 95 weeks) and 399 patients completed 3611 questionnaires. Data were analysed in a repeated-measurement model which differentiated between treatment effects, time effects and treatment-time interaction. Although one group of patients received mistletoe extracts during radiotherapy (stratum B) data of the comparison between the mistletoe group and the control group were presented unstratified. Authors reported no significant differences between groups for overall QOL and five subscales.

3.5. Assessment in an unclear therapeutic setting

In both of Grossarth et al's trials, psychosomatic self-regulation was assessed after three months of treatment with mistletoe extracts (Grossarth 2001a; Grossarth 2001b). In patients with various types of cancer, mean score for self-regulation increased significantly within three months in the mistletoe group, whereas a decrease was found in the control group. The difference in the change in

self-regulation values was statistically significant (p = 0.02, Mann-Whitney test) (Grossarth 2001a). In patients with breast cancer, mean scores for self-regulation increased within three months from 2.92 at baseline to 3.70 in the mistletoe group (p = 0.01, Wilcoxon test) compared with an nonsignificant increase from 2.87 to 2.99 in the control goup. The difference in the change in self-regulation values between groups was not statistically significant (p = 0.13, Mann-Whitney test) (Grossarth 2001b).

4. Studies reporting on adverse effects of mistletoe extracts

Twelve studies reported on side effects related to the treatment with mistletoe extracts (Auerbach 2005; Dold 1991; Goebell 2002; Heiny 1991; Heiny 1997; Kleeberg 2004; Luemmen 2001; Piao 2004; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001) All authors recorded local or systemic reactions, with the exception of one in which no patient experienced adverse effects of mistletoe extracts (Goebell 2002). Local reactions were most commonly rubor, prurigo and induration at injection site, typical systemic reactions were mild fever and flue-like symptoms. Patients in Schwiersch's trial experienced no systemic side effects. Five patients in Kleeberg 2004, 1 in Semiglasov 2006 and 43 in Steuer-Vogt 2001 discontinued mistletoe treatment due to adverse effects. In the Piao 2004 trial they described one patient with angioedema and urticaria which was related to mistletoe application and recovered two days after discontinuation of study medication. In Semiglasov 2004, mistletoe extracts evoked reactions at injection site in 9% of patients of the low dose mistletoe group, in 18% of those who were in the medium dose mistletoe group, and in 32% of those treated with high doses.

DISCUSSION

The aims of this review were to examine the outcomes of mistletoe therapy in patients with cancer in RCTs. The review includes data from 21 trials investigating the treatment of various malignancies with mistletoe extracts. The number and range of interventions and outcomes included in this review indicate the special situation surrounding cancer treatment with mistletoe extracts. The trials evaluated mistletoe preparations with different pharmaceutical manufacturing processes, varying compositions of ingredients, different dosage schedules, modes of application and durations of treatment and the authors measured a multiplicity of outcomes.

Overall, there is a lack of independent duplication of studies investigating the same interventions which limits the strength of evidence and generalisability. Only two studies included matchable patient populations, used similar interventions and measured comparable outcomes (Semiglasov 2004; Semiglasov 2006).

1. Methodological Quality

The methodological quality of included studies was described narratively (Table 2) and assessed by means of three criteria lists (the Delphi list, the Jadad score and the Cochrane Collaboration approach). In this context, criteria lists do not define what quality entails and consists of, but rather they describe in a short and concise way which criteria regarding internal or external quality have been met. This way, they facilitate an oriented overview and classification of studies according to different criteria of methodological quality.

When applying the Jadad score one needs to consider that it was originally developed in order to appraise studies in pain research. This is one of the reasons why this instrument places a special value on the blinding of the intervention. In studies where unblinded administration does not have such a great influence on the results (for instance, in clinical studies assessing OS) the sole application of the Jadad score can lead to an underestimation of the methodological quality of studies. The Delphi list also assesses blinding of the intervention with two items and blinding of the outcome assessment with one item.

The assessment of the methodological quality of trials is always linked to its reporting quality, that is, the extent to which a publication reports on the design, conduct and analysis of a clinical trial. Although recent evidence suggested that the quality of RCTs of herbal medicine is superior to that of comparable trials of conventional medicine (Nartey 2007), RCTs of herbal interventions have been found to report less than half of the required information as outlined by the CONSORT statement (Gagnier 2006; Moher 2001).

The eligible trials for this review varied in their design and quality and it was unfortunate that many studies reported data in an intransparent form. The use of structured abstracts and application of the CONSORT guidelines, to which only one study adhered to, would have improved the reporting quality considerably.

Though it is encouraging that 21 RCTs were available for review, we observed many methodological difficulties. Sample sizes were small (less than 100 patients) in 10 trials (48%), and bias could not be ruled out in the following percentages of included studies:

- In 10 trials (48%) we could not rule out biases based on influences by the individuals carrying out the treatment allocation.
- In only three trials blinding of the care provider and the patient was reported. Given that in two of these studies a partial deblinding due to mistletoe-induced skin reactions was reported, the influence of participant or observer bias cannot be ruled out in nearly any of the included studies in which subjectively rated outcomes were assessed.
- Only one trial explicitely reported blinding of the outcome assessor. Through blinding of the outcome assessor the influence of an assessment bias is being decreased. This regards, for instance, studies with tumour response as an investigator-rated outcome measure.

- In only 9 of the 16 trials (56%) from which patients had dropped out or had no complete follow-up, we found remarks on the reasons for it. Moreover, it is noteworthy that especially in studies with small numbers of included patients the drop-out rates were low and that these studies often included patients with advanced disease stages, which usually are to be accounted for to contribute to a high number of drop-outs.
- In 75% of the studies, in which mistletoe extracts were used during chemo- or radiotherapy (n = 12) it was not possible to judge whether the provision of these treatments was carried out equally.

While some of these problems are difficult to avoid (e.g., the problems with blinding) the quality of reporting of methodological and clinical details could easily be improved.
Concerning publication bias, several studies without positive results have been published and of the two unpublished trials, one reported benefits (Lange-Lindberg 2006) and the other did not (Schwiersch 1999).

2. Efficacy on survival

Overall, there was no consistent effect of mistletoe extracts on DFS or OS for any of the included malignant diseases and for any of the applied preparations of mistletoe extracts.

2.1. Breast Cancer

For breast cancer the evidence that mistletoe extracts positively influence survival is limited and is based on one trial of 34 adult patients. Apart from other methodological shortcomings, particularly the lack of details on the treatment of patients of both the mistletoe and the control group in Grossarth 2001b constricts the informational value of the reported positive results.

2.2. Gastrointestinal cancer

Concerning metastasized colorectal cancer there is conflicting evidence from two small trials that a treatment with mistletoe extracts given concomitantly to chemotherapy adds benefit in terms of survival (Douwes 1986a; Heiny 1997). Douwes 1986a, who reported benefits, used a preparation containing higher concentration of mistletoe compounds compared with Heiny 1997, who found no benefits, and in Douwes' trial mistletoe extracts were applied daily, whereas Heiny et al. applied them twice weekly. These differences between the interventional treatments notwithstanding, the effects reported in Douwes 1986a should be interpreted with caution due to its small size and risk of bias.
Due to its low methodological quality, Cazacu 2003 adds only limited evidence in that the addition of mistletoe extracts to the adjuvant treatment of colorectal cancer has a positive impact on survival. The comparison of Cazacu's results with other trials is furthermore hampered by the fact that the authors applied the study medication intravenously. Moreover, the poor survival of Dukes D patients treated with chemotherapy alone raises concerns about the influence of chemotherapy-related toxicity on the survival rates.
In patients with gastric cancer, mistletoe extracts were compared with chemotherapy or no treatment after surgery in one trial with 238 patients (Salzer 1983). In the first publication in 1979 a benefit in terms of survival in comparison with no treatment was reported, but the short follow-up period and the scant presentation of data without a statistical analysis impede a final conclusion. In the second publication of the trial in 1983, survival data were only presented for subgroups without the chemotherapy group and a benefit was reported only for the subgroup of patients with positive lymph-nodes. Based on these results, the evidence that patients with gastric cancer benefit from a postsurgical treatment with mistletoe extracts is weak.

2.3. Lung cancer

For non-small cell lung cancer there is limited to moderate evidence from two trials with 337 patients with inoperable lung-cancer (Dold 1991) and with 183 patients after surgery (Salzer 1991) that used mistletoe extracts have no significant effect concerning survival. It cannot be ruled out that the sample size in Dold's trial was too small to detect a realistic difference in survival (Hoffmann 1992), where a comparison with a sample size of 200 patients can only detect a 15-20% absolute survival difference, assuming a type I error of 5%, a power of 80% and a baseline survival function of 40% to 60%. Obviously, such differences are unrealistic in this type of disease. Consequently, even if a 5% to 10% absolute survival benefit was present, it would probably have been missed by the trial. In contrast, it cannot be ruled out that the results of the post-hoc analyses in Salzer 1991, which suggested benefits for subgroups of patients, were spurious findings.

2.4. Cancer of the urinary bladder, head and neck region and melanoma

From three trials with high methodological quality there is moderate evidence suggesting that the used mistletoe extracts influence neither survival times nor recurrence rates in transurethrally resected urinary bladder cancer (Goebell 2002), resected squamous cell carcinoma of the head and neck region (Steuer-Vogt 2001) and high risk melanoma after curative surgery (Kleeberg 2004). Although these results stem from trials with higher methodological quality, one should be careful in generalizing the results to other mistletoe preparations or other forms of application and dosage of mistletoe extracts. Recent evidence from a phase I/II trial suggests that intravesical application of high-dose mistletoe extracts might be efficacious in the treatment of superficial urinary bladder cancer (Elsasser-Beile 2005) and evidence from an observational study suggests that mistletoe extracts could prevent

recurrences and prolong survival in patients with melanoma after curative surgery (Augustin 2005).

2.5 Renal cell carcinoma

There is limited evidence from one study with 176 patients with metastatic renal cell cancer showing that the treatment with mistletoe extracts was associated with a distinct but non-significant longer median survival compared to immunochemotherapy (Luemmen 2001). This result could be ascribed to the treatment with mistletoe extracts (although virtually no tumour response was seen) or to an excess mortality due to toxicities of the immunochemotherapy.

2.6. Malignant glioma

Data of one trial with 38 patients receiving radiotherapy (Lenartz 2000) seem to suggest that the concomitant application of mistletoe extracts might prolong the DFS and OS. As the trial was poorly reported and we considered it to be at high risk of bias, the evidence that mistletoe extracts contribute to a prolongation of survival in glioma patients is weak.

2.7. Various types of cancer

Also the data of Grossarth 2001a adds little evidence that mistletoe extracts positively influence survival. Particularly the lack of details on the treatment of patients with various types of cancer of both the mistletoe and the control group limits the informational value of this trial.

3. Efficacy on tumour response

There is moderate evidence from two trials that mistletoe extracts have no beneficial influence on tumour response in lung cancer patients (Dold 1991; Piao 2004) and limited evidence that this is also the case in patients with metastatic renal cell carcinoma (Luemmen 2001).

For patients with advanced colorectal cancer, advanced stages of breast and ovarian cancer, there is contradictory evidence concerning an influence of mistletoe extracts on the tumour response (Borrelli 1999; Douwes 1986a; Heiny 1997; Lange 1993; Piao 2004).

4. Efficacy on measures of QOL and of psychosocial distress

When we analysed the studies that had investigated the influence of mistletoe extracts on QOL we found considerable heterogeneity between studies. Potential problems leading to this heterogeneity include: different types of instruments, no assessment before randomisation, lack of clarity whether measures were patient- or physician-rated. In addition to the possible biases from these methodological shortcomings, the timing of the assessment and the time scale of the chosen questionnaire were problematic. Since acute side effects of chemotherapy are usually expected within a few days of treatment it seems inappropriate to collect data three weeks later on the patient's next visit with questionnaires refering to symptoms during the previous week.

4.1. Treatment during chemotherapy

Multidimensional scales measuring health-related QOL were used in 10 studies. From two studies, there is weak evidence that mistletoe extracts positively impact QOL during palliative chemotherapy in patients with advanced breast cancer (Heiny 1991), and advanced colorectal cancer (Heiny 1997). In both trials sample sizes were small, and the lack of care provider and patient blinding opened the results to the influence of bias. Furthermore, in Heiny 1991, it was not clear, whether the outcomes were patient- or physician-rated.

The authors of Piao 2004 compared mistletoe extracts with Lentinan. This study was designed as an approval trial for the mistletoe extract and the Chinese health authorities ordered lentinan, a biologic response modifier, to act as a control treatment for this study. As the direction of effect of lentinan on QOL is unclear, the positive effects of mistletoe extracts compared to lentinan cannot be definitely attributed to the mistletoe therapy. Also in this unblinded study it was not clear, whether the outcomes were patient- or physician-rated.

From three other studies, there is conflicting evidence, that mistletoe extracts may positively influence health related QOL during adjuvant chemotherapy of breast cancer (Auerbach 2005; Semiglasov 2004; Semiglasov 2006). In Auerbach's small and unblinded pilot trial (Auerbach 2005) and in Semiglasov 2004, no changes in the QLQ-C30 questionnaire were detected, whereas in both of Semiglasov's trials, significant improvements were reported in health-related QOL as measured by the GLQ. In Semiglasov 2004 this positive effect, however, was limited to that patient group, which received mistletoe extracts in a medium dose. This dose was also used in the follow-up study (Semiglasov 2006). In both studies, the absolute changes of the outcome measures were small, however, many investigators found that, for a variety of scales assessing overall QOL, changes between 5% and 10% were noticed by patients and were regarded by them as significant changes. Though Semiglasov's trials were the only ones with a double-blind study design, authors reported that the mistletoe-evoked skin reactions led to a substantial percentage of unblinding of the intervention treatment (Semiglasov 2004; Semiglasov 2006).

From Lange's small and unpublished pilot trial there is limited evidence that mistletoe extracts have beneficial effects on tumor-related pain (Lange 1993). But in this study the effect size was also small and the intervention unblinded.

4.2. Treatment after chemotherapy

From one trial with 30 patients, there is evidence that women with metastatic breast cancer benefit in terms of QOL and anxiety from a three-month treatment with mistletoe extracts after completion of chemotherapy (Borrelli 1999). As the intervention was not blinded and the number of patients was small, we considered the trial at risk of bias and the evidence that mistletoe extracts contribute to an increase in QOL and a decrease of measures of anxiety in this setting as limited. Furthermore, it was not clear, whether the subjective outcomes were patient-reported or physician-rated.

From another trial with 151 breast cancer patients in a rehabilitation setting after completion of adjuvant chemotherapy (Schwiersch 1999), there is evidence that a four-week treatment with mistletoe extracts had no significant impact on disease specific aspects of stress (FBK) and overall QOL (SF-36). Nevertheless, in this unpublished study, there were significant changes in the vitality subscale of the SF-36 in the mistletoe group. As the outcome assessments were conducted after a very short treatment period and the influence of the non-reported concomitant rehabilitation program on the subjective outcomes were unclear, also the evidence about the effects of mistletoe extracts in this setting remains unclear.

4.3. Treatment during radiotherapy

In malignant glioma, one small study reported a benefit concerning QOL when patients were treated with mistletoe extracts during radiation (Lenartz 2000). As mentioned above, this study has many methodogical flaws and a poor reporting quality, therefore the evidence for a benefit due to a treatment with mistletoe extracts is weak.

4.4. Sole mistletoe treatment

There is limited to moderate evidence from Steuer-Vogt 2001 that patients with head and neck-cancer did not benefit from a treatment with constantly dosed mistletoe extracts in their QOL. From a methodological point of view, one has to criticize that the intervention in this study was not blinded, and thus principally the influence of a participant bias on the results could not be ruled out. However, if in this study measures of QOL were influenced by a participant bias, a benefit in favour of the intervention group would have been expected. Unfortunately, the results of the QOL analysis were so poorly presented that no further statement can be made regarding the course of the assessed parameters.

From one trial with 337 patients there is limited evidence that patients with advanced lung carcinoma benefit in their overall well-being from a treatment with mistletoe extracts (Dold 1991). However, results from this trial also add limited evidence that a treatment with mistletoe extracts did not alleviate disease-related symptoms. The evidence was judged as limited for both outcomes, as the assessment was done by the physician and the provision of care was unblinded.

5. Efficacy on adverse effects of radio-/chemotherapy

The assessment of efficacy of mistletoe extracts for chemo- or radiotherapy induced adverse effects is only possible to a limited extent due to the low methodological quality with which the outcome parameters were reported. Authors of five studies stated lower rates of chemotherapy related adverse effects in the mistletoe group without presenting further data (Auerbach 2005; Cazacu 2003; Douwes 1986a; Heiny 1991; Piao 2004)

Data from Semiglasov 2004 seem to suggest that organ toxicities of chemotherapy might increase depending on the dose of the used mistletoe extracts. Compared with the low and medium dose mistletoe group and the placebo group, patients in the high dose mistletoe group experienced higher rates of adverse effects on the gastrointestinal tract and on red blood cells.

The results from Lange's unpublished trial give limited evidence that variably dosed mistletoe extracts diminish symptoms from radiochemotherapy (Lange 1993). Although the authors assessed symptoms on a daily basis, the unblinded application of the study medication opened the results to bias. Furthermore, the absolute changes of the outcome measures were small.

Although Heiny et al. stated a significant difference in the incidence of mucositis between the groups, the corresponding table listed a p-value of 0.321 (Heiny 1997). Edler even disclosed a calculation error in this piece of work and corrected the p-value for the duration of the mucositis from 0.033 to 0.64 (Edler 2004). Collectively, the low methodological quality of the study prevents the drawing of any reliable conclusion.

6. Safety of mistletoe extracts

From twelve studies there is moderate evidence that mistletoe extracts are usually well tolerated and have only few side effects (Auerbach 2005; Dold 1991; Goebell 2002; Heiny 1991; Heiny 1997; Kleeberg 2004; Luemmen 2001; Piao 2004; Schwiersch 1999; Semiglasov 2004; Semiglasov 2006; Steuer-Vogt 2001). Depending on the dose, local reactions with rubor, prurigo and induration at injection site occur in up to one third of patients, as well as systemic reactions with mild fever and flue-like symptoms in 10%. Severe, life-threatening symptoms were rare events. There is no evidence from RCTs that mistletoe extracts negatively impact survival in cancer patients (Eggermont 2001; Kiene 2001; Silver 2001). As RCTs, however, often do not suffice to detect adverse effects, reviews must go beyond the data from RCTs and include such from observational studies in order to reliably appraise the safety of mistletoe extracts.

7. Available evidence from systematic reviews

Ernst 2003 addressed the question of the safety and effectiveness of mistletoe extracts in cancer treatment. We found inconsistencies in this review between the numbers of trials that were included and from which the authors presented results. Though the authors claimed a comprehensive search strategy, they missed three published studies (Borrelli 1999; Luemmen 2001; Salzer 1983) and two unpublished studies (Lange 1993; Schwiersch 1999). The authors were using the criteria suggested by Jadad for assessment, however for their review they fail to define the cut-off points between good and mediocre methodological quality. When discussing the safety of mistletoe extracts, the authors presented prevalence rates of low grade adverse effects linked with a list of severe ones. Through this, the review suggested a bad tolerability of mistletoe extracts, which did not comply with the data from the included RCTs.

Kienle 2003a also addressed the question of safety and effectiveness of mistletoe extracts in cancer and reported a comprehensive search strategy. They failed to include one published study (Borrelli 1999). According to their inclusion criteria, also studies with quasi-random allocation of treatment and non-randomised, prospective trials were included. Compared to our review, the following differences exist regarding inclusion of studies: Kienle 2003a did not include unpublished studies (Lange 1993; Schwiersch 1999), but three trials, which were excluded from our review: A small study with lung cancer patients, scantily reported in a bookchapter (Salzer 1987), a quasi-randomised study with breast cancer patients (Günczler 1971) and one further study with breast cancer patients in which randomisation had failed (Günczler 1974; Gutsch 1988). In Jach 2003, which was included in Kienle's review, women with cervical intraepithelial neoplasia were treated, which is a precancerous condition but not cancer. This was the reason why this study was not included in our review. Kienle 2003a evaluated the internal and external validity of studies according to an extensive list of criteria. The influence of bias on the trials' results were comprehensively discussed. However, their critical verdict that only a few studies were reasonably well conducted was incomprehensible, since the authors neither stated how they defined reasonably well, nor which studies fulfilled their definition.

A recently published health technology assessment (HTA) addressed the question of the potential of mistletoe extracts in alleviating the side effects of chemotherapy and on QOL during chemotherapy (Lange-Lindberg 2006). The authors confined their comprehensive literature search to RCTs and found eight eligible trials (six published and 2 unpublished), of which all are also included in our systematic review. However, Lange-Lindberg et al. missed one published trial that should have been included (Douwes 1986a) and did not take into account the most recent publication from Auerbach's trial (Auerbach 2005). The authors of the HTA concluded that the evidence is insufficient to reliably appraise the question whether mistletoe extracts could be helpful in diminishing the side effects of chemotherapy but that there is some evidence that mistletoe extracts standardized for the content of mistletoe lectin could have beneficial effects on the QOL of breast cancer patients during chemotherapy.

8. Strengths and limitations

The strength of this systematic review lies in the wide-ranging literature search and the comprehensive assessment and reporting of all clinical outcomes evaluated in the included studies.

The qualitative analysis used here may be regarded as a strength and a drawback at the same time. That is, although it would have been incorrect to statistically combine data from a sample of such heterogeneous trials, the qualitative method used does not provide information on the size of the treatment effect.

The conclusiveness of this review is limited by the small sample size and methodological shortcoming in the majority of included studies. Apart from the often low methodological quality, three issues particularly limited our ability to interprete the data. One was the clinical heterogeneity of the included patients which impeded the grouping of study data. The second was the lack of comparability with current treatment situations due to outdated or unusual methods of cancer treatment and diagnosis. The third limitation was the pharmaceutical heterogeneity in the applied mistletoe extracts, and the varying dosages and modes of application.

AUTHORS' CONCLUSIONS

Implications for practice

The majority of the included trials reported benefits for patients treated with mistletoe extracts in one or more outcome measures. However, most trials were found to have major methodological drawbacks that raise doubts about the validity and generalizability of the findings and there is no clear evidence for the superiority of one preparation or treatment schedule over another. Therefore, based on the results of RCTs, the evidence is insufficient to provide clear guidelines for the use of mistletoe extracts in oncological practice and it does not support mandatory use of mistletoe extracts.

Safety data indicate that, depending on the dose, mistletoe extracts are usually well tolerated and have only few adverse effects. Although they comprise rare events, caution is advised to allergic reactions and care should be taken to monitor signs of systemic immune stimulation like fever and chills.

Decisions about whether mistletoe extracts are likely to be effective and safe for a particular problem as well as the mode of use must rely on expert judgement and practical considerations. This should be discussed with patients before they give their consent

and where possible, patients should be offered entry into well-designed clinical trials.

Implications for research

Given the widespread use of mistletoe extracts for cancer patients, the small number of informative trials for some tumour entities, and the limited evidence concerning effects of different mistletoe extracts on clinical relevant outcomes, there is a need for good quality independent clinical evaluation of this treatment modality. It is imperative that trials with positive outcomes should be repeated by other research groups and in different settings.

Concerning the design of future studies with mistletoe extracts the following issues should be taken into account:

- the results of two trials suggesting beneficial effects of mistletoe extracts on QOL of breast cancer patients during chemotherapy need independent replication;
- the results of some trials give reasonable evidence that the used mistletoe extracts are not effective for the purpose for which they have been used;
- the availability of mistletoe extracts and their wide-spread use in cancer patients, especially in German-speaking countries, impede the recruitment of controlled clinical trials in this field and expose the trial to the risk of bias through contamination of the control group;
- compliance and/or contamination could be controlled by measuring the formation of mistletoe-lectin antibodies;
- the lectin content of the investigational mistletoe extracts should be specified in the publications;
- treatment schedules adjusted to the individual's local and systemic reaction, which are recommended by some manufacturers, cannot be properly blinded;
- the context variables between different forms of mistletoe therapy (i.e. anthroposophical, phytomedical) vary in clinical practice and should be considered in future study designs;
- better reporting of study methods, targeted outcomes, characteristics of participants and interventions is needed.

Finally, authors should bear in mind that positive or negative results obtained with a specific mistletoe preparation or application schedule in a defined type of cancer cannot be extrapolated to "mistletoe therapy" in general.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Auerbach 2005

Methods	Design: Double-blind 2-arm RCT Recruitment period: unclear Observation period: 12 months Ethical approval: yes
Participants	Number of patients: 23 patients were randomised, 16 finished the study per protocol Condition: breast cancer (T1-2, N0-1,M0), pre- and postmenopausal, adjuvant treatment situation, eligible for CMF chemotherapy Demographics: not reported Recruitment: unclear Setting: Departement of Gynecology, AKH Wien, Austria Informed consent: yes
Interventions	Intervention (MT): Helixor A, increasing doses of 1, 5, 10, 20, 30, 50 to 100mg, s.c., thrice weekly, for 6 months Control: placebo (NaCl 0,9%) Basic treatment: 6 cycles of adjuvant polychemotherapy (CMF) + radiotherapy for patients with breast conserving surgery (50Gy after the 3rd CMF cycle, 13 pats.)
Outcomes	Primary outcome measure: feasibility of doubleblind care provision Other: Quality of life (QLQ C30), Karnofsky performance status (outcomes assessed at screening and before each CMF cycle), well-being (visual analogue scale; assessed each day); treatment related toxicity, adverse effects of mistletoe extracts, immunological parameters
Notes	Methods: Feasibility study Interventions: Type of mistletoe extract: pharmaceutical process standardized. Comparability of sum doses of basic treatment (chemotherapy/radiotherapy) between groups unclear Quality Scores (Delphi List/Jadad Score): 3/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Borrelli 1999

Methods	Design: 2-arm RCT with a placebo control (PT) Recruitment period: unclear Observation period: 3 months Ethical approval: unclear
Participants	Number of patients: 30 patients randomised, 30 analysed (MT: 20 patients, PT: 10 patients) Condition: metastasized breast cancer (sites of metastases not reported) Demographics: mean age 54 (range 45-65) Recruitment: unclear Setting: unclear Informed consent: yes
Interventions	Intervention (MT): Lectin standardized mistletoe extract (brand not commercially available) 1ng/kg of body weight, three times weekly for three months Control (PT): placebo (distilled water)
Outcomes	Primary outcome measure: Quality of life Index (Spitzer) Other: Tumor response
Notes	Participants: 2:1 randomisation Outcomes: Definition of tumor response not given Quality Scores (Delphi List/Jadad Score): 4/2

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Cazacu 2003

Methods	Design: Open-label 3-arm RCT with a no-treatment control (NT) Recruitment period: 1997-2000 Observation period: unclear Ethical approval: unclear
Participants	Number of patients: 64 included and analysed (Arm A [CT]: 21 patients, 16 Dukes C, 5 Dukes D; arm B [MT]: 29 patients, 18 Dukes C, 11 Dukes D; arm C [NT]: 14 patients, 6 Dukes C, 8 Dukes D) Condition: colorectal cancer patients (40 Dukes C, 24 Dukes D), previously operated Demographic: Dukes C: 20 men, 20 women, mean age 54.2 years; Dukes D: 15 men, 9 women, mean age 59.9 years Recruitment and setting: one university departement of surgery, Romania Informed consent: unclear
Interventions	Intervention (MT): Isorel 5mg/kg in saline solution, 1 hour infusion, 3 days/week + similar chemotherapy as control group CT Control (CT): 6 cycles of a 5-FU based chemotherapy according to either the DeGramont or Mayo protocol (not further described). Control (NT): no treatment.

Cazacu 2003 (*Continued*)

	Basic treatment (see footnotes): surgery (curative or palliative)
Outcomes	Primary outcome measure: not clearly stated Other: Overall survival, treatment related toxicity
Notes	Poor reporting quality Participants: Numbers of pats in groups differ Interventions: Type of mistletoe extract: pharmaceutical process standardized. Dosage and application of Isorel not consistent with the recommendations of the manufacturer. Outcomes: Number of chemotherapy cycles/chemotherapy sum doses between groups unclear. Statistical analyses for different Dukes stages without prior stratification Quality Scores (Delphi List/Jadad Score): 2/2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dold 1991

Methods	Design: Open-label, 3-arm RCT with a BRM control (PT) and a placebo control (BT) Recruitment period: 1978-1986 Observation period: 6 months - 11 years Ethical approval: yes
Participants	Number of patients: 408 included and 337 analysed ([MT]: 114 patients, [PT]: 110 patients, [BT]: 113 patients) Condition: inoperable non-small-cell lung cancer, all stages, previously untreated Demographic: 315 men, 22 women, mean age 66,8 years. Recruitment and setting: most part of patients were recruited in 3 rehabilitation clinics and 1 university hospital departement of pulmonology, and a few outpatients of oncological practices, Germany. Informed consent: yes
Interventions	Intervention (MT): Iscador Ulmi cum Hydrargyro D8 and Iscador Querci cum Hydrargyro D8 in different dilutions, thrice weekly in varying dosages. Treatment duration not limited. Control (PT): 'Polyerga Neu' 1ml, containing 30µl glycopeptides (extracted from animal spleen) once a week i.m. Control (BT): 'BVK Roche' (7 vitamins of the B-group) once a week 1 amp. i.m. (served as placebo)
Outcomes	Primary outcome measure: Overall survival Other: Tumour response; Patient-reported subjective well-being; Physician-rated Karnofsky performance status, and symptom scales; Adverse effects of mistletoe extracts. Outcomes measured at beginning of treatment and every 2 weeks
Notes	Large and comprehensively reported study. Methods: Long recruitement period. Interventions: Type of mistletoe extract: pharmaceutical process standardized. Control treatment with

Dold 1991 (*Continued*)

	vitamins (BT) functioned as placebo treatment. Treatment duration unclear Outcomes: Uncommon definition of tumor response Quality Scores (Delphi List/Jadad Score): 6/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Douwes 1986a

Methods	Design: Open-label 3-arm RCT with a BRM (XT) and a no-adjunctive treatment control (CT) Recruitment period: not reported Observation period: 2-38 months Ethical approval: unclear
Participants	Number of patients: 60 included and analysed Condition: advanced colorectal cancer (partly pretreated) Demographics (intervention group): mean age 59, 10 men, 10 women; (control group XP): mean age 60, 12 men, 8 women; (control group): mean age 61, 11 men, 9 women Recruitment and setting: not reported, presumably one rehabilitation clinic, Germany Informed consent: unclear
Interventions	Intervention (MT): Helixor, daily s.c. slowly increasing doses until 200mg reached, then 200mg daily continued. Control (XT): Xenogenic peptides (organ extracts from fetal and young pigs and cows [NeyTumorin]) twice weekly i.v. or s.c. slowly increasing doses, until 30mg reached, 30mg continued Control (CT): no adjunctive treatment. Basic treatment: 5-FU 200mg/m2 bolus + 5-FU 370mg/m2 infusion 6h + FA 200mg/m2 on day 1-5; repeated every 4 weeks
Outcomes	Primary outcome measure: Tumour response Other: Survival; treatment related toxicity
Notes	Interventions: Type of mistletoe extract: pharmaceutical process standardized. High dosage of mistletoe extracts. Comparability of sum doses of basic treatment (chemotherapy) between groups unclear Outcomes: Definition of tumour response not given. Uncommon rates of tumour responses/drop-outs in view of the advanced disease stages. Quality Scores (Delphi List/Jadad Score): 4/2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Goebell 2002

Methods	Design: Two open-label, parallel, 3-arm (EORTC 18871) and 4-arm (DKG 80-1) RCTs each with a no-treatment control Recruitement period: 1/88 - 3/96 Observation period: 6 years Ethical approval: unclear
Participants	Number of patients: 45 included, 44 analysed Condition: bladder cancer, transurethrally resected (pTa G1-2; stage 0a [AJCC]) Demographics: mean ages 65 years, 33 men, 12 women Recruitment: unclear Setting: 1 university hospital departement of urology, Essen, Germany Informed consent: yes
Interventions	Intervention (MT): 1ml mistletoe extract standardized for ML-1 (Eurixor) s.c. twice weekly for three months followed by a therapy-free interval of 3 months (one treatment cycle), max. 3 cycles. Control (NT): no treatment Basic treatment: transurethral resection
Outcomes	Primary outcome measure: Disease-free survival/Tumor recurrence Other: adverse effects of mistletoe extracts
Notes	Methods: Pilot study designated as phase II study. Quality Scores (Delphi List/Jadad Score): 6/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Grossarth 2001a

Methods	Design: Open label, randomized, 2-arm, matched-pair trial nested within a large cohort study Recruitment period: 1973-1982 Observation period: 16 - 25 years Ethical approval: unclear
Participants	Number of patients: 98 included, 78 analysed Condition: mixed cancer (all stages) Demographics: unclear Recruitment: 49 matched-pairs of participants of a longterm prospective epidemiological cohort study, Germany Setting: unclear Informed consent: unclear
Interventions	Intervention (MT): Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts (type of Iscador brand documented, dosage and duration of treatment not) Control (CT): unclear Basic treatment: unclear

Grossarth 2001a (*Continued*)

Outcomes	Primary outcome measure: Overall survival Other: psychosomatic self-regulation
Notes	Methods: Long recruitement period Interventions: Type of mistletoe extract: pharmaceutical process standardized. Patients of the MT group were reported as having received Iscador treatment Quality Scores (Delphi List/Jadad Score): 3/2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Grossarth 2001b

Methods	Design: Open label, randomized, 2-arm, matched-pair trial nested within a large cohort study Recruitment period: 1974-1988 Observation period: 10 - 24 years Ethical approval: unclear
Participants	Number of patients: 34 included and analysed Condition (matching criteria): breast cancer, pre- or postmenopausal, stage IIa,IIIA,IIIB, before or after chemo- and/or radiotherapy Demographics: unclear Recruitment: 17 matched-pairs of participants of a longterm prospective epidemiological cohort study, Germany Setting: unclear Informed consent: unclear
Interventions	Intervention (MT): Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts (type of Iscador brand documented, dosage and duration of treatment not) Control (CT): unclear Basic treatment: unclear
Outcomes	Primary outcome measure: Overall survival Other: psychosomatic self-regulation
Notes	Methods: Long recruitement period Interventions: Type of mistletoe extract: pharmaceutical process standardized. Patients of the MT group were reported as having received Iscador treatment Quality Scores (Delphi List/Jadad Score): 4/2

Risk of bias

Item	Authors' judgement	Description

Grossarth 2001b (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Heiny 1991

Methods	Design: Open-label, 2-arm RCT with a placebo-control (CT), Recruitment period: not reported Observation period: 6 months Ethical approval: unclear
Participants	Number of patients: 46 included, 40 analysed. Condition: advanced breast cancer (no detailed description) Demographics: unclear Recruitment: unclear Setting: not reported, probably outpatients of 1 oncological practice, Germany Informed consent: unclear
Interventions	Intervention (MT): 1ng per kg body weight Eurixor in 100ml salt solution i.v. on day 1,2,4,5 of each chemotherapy cycle followed by 1ng per kg body weight s.c. once or twice a week Control (CT): 100ml salt solution (not further described) Basic treatment: VDS 3mg per m2, EADM 40mg per m2 and CTX 750mg per m2 on day 1 repeated 6 times every 4 weeks
Outcomes	Primary outcome measure: not clearly stated Other: Quality of life measured as 'Befindlichkeitsindex' by a 5-point scale, Befindlichkeitsskala, Beschwerdeliste, Eigenschaftswörterliste, FLIC. Outcomes measured at baseline and after 6 cycles of chemotherapy; Anxiety measured by a 10-point scale 'Angstindex' and by 'Therapieangstskala', and 'Catell-Angstskala'. Outcomes measured 4-5 days before each treatment cycle. Treatment related toxicity, adverse effects of mistletoe extracts
Notes	Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Unusual indications for chemotherapy (obstruction of the ureter, ileus). Placebo intervention insufficiently described. Comparability of sum doses of basic treatment (chemotherapy) between groups unclear. Outcomes: Assessment of baseline quality of subjective outcomes after randomisation. Procedure of quality of life/anxiety assessment unclear (physician-/patient-rated?). Data only for 'Befindlichkeitsindex' and 'Angstindex' presented. Response rates to oncological therapy not stated. Despite repeated application, author did not comment on the assessment of subjective outcomes. Quality Scores (Delphi List/Jadad Score): 2/2

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Heiny 1997

Methods	Design: Open-label, 2-arm RCT + matched pairs Recruitment period: study initiated in 1993 Observation period: unclear Ethical approval: unclear
Participants	Number of patients: 107 included, 79 analysed ([MT]: 38 patients, [CT]: 41 patients) Condition: advanced colorectal cancer (metastasized) Demographics: CT: mean age 53.2 ys., 23 men, 18 women; MT: mean age 54.7 ys., 22 men, 16 women Recruitment: unclear Setting: not reported, probably outpatients of 1 oncological practice, Germany Informed consent: unclear
Interventions	Intervention (MT): Eurixor, 0.5-1ng ML-I per kg body weight s.c. twice weekly, treatment cycles of 8 weeks followed by a break of 4 weeks. Control (CT): no concomitant treatment Basic treatment: 5-FU 600mg/m2 + FA 200mg/m2 on day 1-5; repeated every 4 weeks
Outcomes	Primary outcome measure: Quality of life, measured by FACT (version 3.0) . Outcome measured at beginning of treatment and every 6 week during the following treatment period. Other: Overall survival, disease-free and progression-free survival; tumour response; treatment related toxicity, adverse effects of mistletoe extracts
Notes	Methods: In a personal correspondence it was clarified, that there was no matching after randomisation as erroneously reported but a randomisation after stratification for sociodemographic factors. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Comparability of sum doses of basic treatment (chemotherapy) between groups unclear. Outcomes: Baseline assessment of quality of life after randomisation Quality Scores (Delphi List/Jadad Score): 4/1

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kleeberg 2004

Methods	Design: Two open-label, parallel, 3-arm (EORTC 18871) and 4-arm (DKG 80-1) RCTs each with a no-treatment control Recruitement period: 1/88 - 3/96 Observation period: 6 years Ethical approval: unclear Flow chart according to the CONSORT guidelines.
Participants	Number of patients: overall 830 included and analysed, 423 in the EORTC 18871 trial and 407 in the DKG-80-1 trial. 102 patients in the control arm were compared with 102 in the Iscador-M arm. Condition: resected primary melanoma (stage II [>3mm] + stage III [curative dissection of regional lymph node metastases]).

Kleeberg 2004 (*Continued*)

	Demographics: age 14-80; males 64,4% (MT), 53,5 % (CT) Recruitment: unclear Setting: 45 institutions in 13 countries Informed consent: unclear
Interventions	DKG 80-1 trial: Intervention (MT): 1ml Iscador M s.c. twice weekly, starting with series 0 for two weeks, then, after 3 days break, series II for 12 months (7 days break after every 4 weeks of treatment). Control (NT): no tumour-specific treatment Basic treatment: resection of primary melanoma (stage II) and curative resection of regional lymph node metastases (stage III); elective lymph node-dissection in stage IIb patients EORTC 18871 trial: IFNa vs. IFNg vs (similar doses/application as in DKG 80-1 vs no treatment
Outcomes	Primary outcome measure: disease-free interval Other: overall survival, treatment related toxicity, adverse effects of mistletoe extracts
Notes	Methods: Authors stated in a comment that the study comprises in fact "two parallel phase III trials, a three-arm trial comparing rIFn-a2b with rIFN-g with observation after surgery (423 pats.) [EORTC 18871] (...) and a four-arm trial comparing rIFN-a2b to rIFN-g with Iscador with observation after surgery" (total no. of pats. 407) [DKG 80-1]. Participants: slight preponderance of males in MT. Flow chart according to the CONSORT guidelines. Quality Scores (Delphi List/Jadad Score): 6/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lange 1993

Methods	Design: Open-label, 2-arm RCT Recruitement period: 4/83-12/83 Observation period: 5-24 weeks Ethical approval: yes
Participants	Number of patients: 68 included, 44 analysed Condition: unresectable squamous cell carcinoma of ENT (MT 11, CT 7) and lung (MT 8, CT 8), ovarian carcinoma (MT 4, CT 6) Demographics: 18 female, 26 male patients, age range 39-79 (mean 59,2) Recruitment and setting: Robert Janker Klinik, Bonn, Germany Informed consent: yes
Interventions	Intervention (MT): Helixor s.c., daily increasing doses (1-200mg) over two weeks, then daily doses of 50mg over 1 week, then increasing doses until 150mg over 1 week, then twice daily 100mg for 1 week, followed by twice daily 150mg for 1 week, followed by 200mg twice daily for 1 week, then a break of 1 day and repetition of the last 3 weeks.

Lange 1993 (*Continued*)

	Control (CT): no concomitant treatment Basic treatment: IFO 60mg/kg body weight day 1,3,5,7,9 and PDD 20mg/m2 body surface, day 2,4,6,8,10. Repeated max. 3 times every 4 weeks. Radiotherapy with 40Gy (ovarian cancer, daily doses of 2 Gy), 60Gy (ENT and lung cancer, daily doses of 2 Gy); omission of cisplatin and dose reduction of ifosfamide in case of Karnofsky index <30%
Outcomes	Primary outcome measure: Performance index (Karnofsky), bone marrow toxicity of chemotherapy, and tumor response Other: applicable chemotherapy dose Performance was assessed at beginning of each treatment cycle, symptom scales daily during the treatment period
Notes	Unpublished study Methods: Trial designed as pilot study Outcomes: Results difficult to interprete because of differing chemotherapy sum doses between groups, and differing radiotherapy fields due to uneven distribution of tumor types between groups. Quality Scores (Delphi List/Jadad Score): 5/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lenartz 2000

Methods	Design: Open-label, 2-arm RCT Recruitment period: 1/94-12/95 Observation period: 24 weeks (1996 publication) and 50 months (2000 publication) Ethical approval: unclear
Participants	Number of patients (1996 publication): 35 included, 26 analysed ([MT]: 13 patients, [RT]: 13 patients) Number of patients (2000 publication), 38 included, 29 analysed Condition (1996 publication): malignant glioma (stage III/IV) Condition (2000 publication): malignant glioma ("all stages") Demographics (1996 publication): mean age 52 years, 20 male, 15 female (2000 publication) Recruitment: unclear Setting: unclear, probably patients of Departement of Neurosurgery, Städtische Kliniken, Cologne, Germany Informed consent: unclear
Interventions	Intervention (MT): Eurixor 1ng ML-1 per kg body weight, s.c. twice weekly, for 3 months, starting after surgery Control (RT): no concomitant treatment Basic treatment: standard neurosurgery, perioperative dexamethasone (24mg/day, duration unclear), radiotherapy (60Gy)

Lenartz 2000 (*Continued*)

Outcomes	Primary outcome measure: not clearly stated Other: Quality of life Index (Spitzer Index), immunological parameters (1996 publication); Relapse-free and overall survival (2000 publication)
Notes	Poor reporting quality Participants: Number of included patients differ among publications Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Concomitant application of a high-dose immunosuppressive agent (dexamethasone) Comparability of sum doses of radiotherapy and extent of surgery between groups unclear Outcomes (Lenartz 1996): Study author (LD) stated in a personal correspondence that patients rated their quality of life with the help of a study nurse. Quality Scores (Delphi List/Jadad Score): 1/1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Luemmen 2001

Methods	Design: Open-label, 2-arm RCT Recruitment period: unclear Observation period: 19 months (median) Ethical approval: unclear
Participants	Number of patients: 176 included and analysed Condition: metastatic renal cell carcinoma Demographics: unclear Recruitment and Setting: 10 urologic centers, Germany Informed consent: unclear
Interventions	Intervention (MT) : Eurixor 1ml s.c. twice weekly till progression Control (IT): IFN-alpha s.c 4.5MU/m2 day 1 of week 1 and 4 and day 1, 3 and 5 of week 2 and 3; and 9 MU/m2 day 1, 3 and 5 of week 5 to 8; IL-2 9 MU/m2 day 3,4 and 5 of week 1 and 4; 4.5MU/m2 day 1, 3 and 5 of week 2 and 3; 5-FU 750mg/m2 i.v. day 1 of week 5 to 8; treatment was repeated two times and in case of succes a third cycle was added
Outcomes	Primary outcome measure: tumour response and overall survival Other: treatment related toxicity, adverse effects of mistletoe extracts
Notes	Assessment based on three abstract publications, two of them with different follow-up times. Methods: Option to cross-over in case of progression mentioned, no further information given. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Quality Scores (Delphi List/Jadad Score): 3/2

Risk of bias

Luemmen 2001 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Piao 2004

Methods	Design: Open-label, 2-arm RCT with a BRM treatment as control (LT) Recruitement period: 15 months Observation period: 5 - 12 weeks Ethical approval: yes
Participants	Number of patients: 233 included and 224 analysed Condition: breast (n=68), ovarian (n=71), non-small-cell lung cancer (n=94), all stages Demographics: mean age Recruitment and setting: inpatients of 3 cancer clinics in China Informed consent: yes
Interventions	Intervention (MT): Helixor A, three times per week s.c. slowly increasing doses starting 1mg up to 200mg (mean tretment duration: 6.4 weeks) Control (LT): Lentinan, daily 4mg i.m. (mean tretment duration: 6.6 weeks) Basic treatment: two courses of combination chemotherapy. Breast cancer: CAP or CAF. Non-small cell lung cancer: NVB + PDD or MVP. Ovarian cancer: CP or CBP +IFO/PDD
Outcomes	Primary outcome measure: Chemotherapy-related toxicity Other: Karnofsky performance index; tumour response; adverse effects of mistletoe extracts, immunological parameters. All outcomes measured at screening and after two cycles of chemotherapy
Notes	Approval study for the Peoples Republic of China Interventions: Participants: Numbers/estimates in tables and between publications inconsistent. Interventions: Type of mistletoe extract: pharmaceutical process standardized. Concomitant supportive medication unclear. Comparability of sum doses of basic treatment (chemotherapy) between groups unclear. Short treatment period, highly variable observation/treatment periods Outcomes: Procedure of quality of life assessment unclear (physician-/patient-rated?) Quality Scores (Delphi List/Jadad Score): 4/2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Salzer 1983

Methods	Design: Open-label, 3-arm RCT with a no-treatment control (NT) Recruitment period (1979 publication): 1974-77 Recruitment period (1983 publication): 1974-79 Observation period (1979 publication): 1-3 years Observation period (1983 publication): 3-5 years Ethical approval: unclear
Participants	Number of patients (1979 publication): 271 included, 238 analysed in 12/1977 (67 [MT], 62 [CT], 109 [NT]) Number of patients (1983 publication): 359 included, 137 analysed (62 [MT], 75 [NT], patients of the CT group were not included in this publication) Condition: stomach cancer: 1979 publication: stage I : 10, stage II: 72, stage III: 102, stage IV: 46 patients 1983 publication: stage I: no. of patients not reported+not included in analysis, stage II (T1/2N1M0 + T2N0M0): 54, stage III (T1/2N2M0 + T3N0M0 + T3N1/2M0): 83, stage IV: no. of patients not reported+not included in analysis. Demographics (1979 publication): unclear. 1983 publication: 64 men, 73 women, mean age 66 years. Recruitment: postoperative allocation Setting: 3 departements of surgery of 3 general hospitals in Austria Informed consent: unclear
Interventions	Intervention (MT): Iscador, varying concentrations between 1% and 5%, applications three times weekly s.c. for one year, continued by twice weekly injections over the 2nd year. Treatment duration partly over 5 years. Control (NT): no postoperative tumour-specific treatment Control (CT): 5-FU 120mg/kg BW i.v., once weekly for 7 weeks, repeated every 6 weeks (data on this group reported only in the 1979 publication) Basic treatment: surgery
Outcomes	Primary outcome measure: not clearly stated Other: overall survival
Notes	Participants: In the 1983 publication, patients of the chemotherapy group (CT) were not included and patients with stage I and IV were excluded from analysis. In the 1979 publication no TNM classification was reported for the stages. In the 1979 publication, numbers of patients indicated in the text did not correspond with those in the tables. Interventions: Omission of CCNU after 10 patients, which had been added to 5-FU for the lymph-node positive cases, because of severe side effects. Type of mistletoe extract: pharmaceutical process standardized. Quality Scores (Delphi List/Jadad Score): 4/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Salzer 1991

Methods	Design: Open-label, 2-arm RCT with a no-treatment control Recruitment period: 1981-86 Observation period: unclear Ethical approval: unclear
Participants	Number of patients: 218 included, 183 analysed Condition: Non-small cell lung cancer (all stages) Demographics: mean age 60 years, 150 men, 33 women Recruitment and setting: 4 departements of surgery of 3 general hospitals in Austria and 1 in Germany Informed consent: unclear
Interventions	Intervention (MT): Iscador, applications three times weekly s.c. for six months, continued by twice weekly injections. Treatment duration 4-5 years. Control (NT): no postoperative tumour-specific treatment Basic treatment: surgery
Outcomes	Primary outcome measure: overall survival
Notes	Open discussion of shortcomings concerning design and implementation of trial. Interventions: Type of mistletoe extract: pharmaceutical process standardized. Quality Scores (Delphi List/Jadad Score): 4/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Schwiersch 1999

Methods	Design: Double-blind, placebo-controlled 2-arm RCT Recruitment period: unclear Observation period: 8 weeks Ethical approval: yes
Participants	Number of patients: 171 patients were randomised, 166 treated and 154 patients finished the study per protocol Condition: breast cancer (stage I-III, adjuvant treatment finished) Demographics: unclear Recruitment: unclear Setting: 1 rehabilitation clinic, Germany Informed consent: yes
Interventions	Intervention (MT): subcutaneously injected mistletoe extract standardized for ML-1 (Lektinol), 2.5µl per kg body weight twice weekly over 4 weeks Control (PT): placebo Basic treatment: complex rehabilitation program

Schwiersch 1999 (*Continued*)

Outcomes	Primary outcome measure: Distress as measured by FBK-KF (short version of the questionnaire for determination of distress in cancer patients) Secondary outcome measure: Quality of life as measured by SF-36, MDBF, SCL-90R, FLZ. Performance index (Karnofsky), immunological parameters. Adverse effects of mistletoe extracts Outcomes measured at admission, every week during the 4-week treatment period and 4 weeks after discharge;
Notes	Unpublished study which, according to the authors, will not be published. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Short treatment period. Quality Scores (Delphi List/Jadad Score): 5/4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Semiglasov 2004

Methods	Design: Double-blind, placebo-controlled 4-arm RCT Recruitment period: unclear Observation period: 16 weeks Ethical approval: yes
Participants	Number of patients: 272 patients were randomised, treated and 261finished the study per protocol Condition: breast cancer (stage II-III), pre- and postmenopausal, adjuvant situation, eligible for CMF chemotherapy Demographics: age range 18-55, school education > 7 years Recruitment: unclear Setting: 9 centres in Russia, Bulgaria, Ukraine Informed consent: yes
Interventions	Intervention (MT1-3): three groups with 0,5ml s.c. injected mistletoe extract standardized for ML-1 (Lektinol), contaning 10 [MT1], 30 [MT2], 70ng [MT3] ML/ml, twice weekly over 15 weeks Control (PT): placebo Basic treatment: 4 cycles of adjuvant polychemotherapy (CMF) and supportively 10mg dexamethasone i.v. and 10mg metoclopramide per os q.i.d. on the day of chemotherapy
Outcomes	Primary outcome measure: Quality of life measured by GLQ-8 and Spitzer's uniscale Other: Quality of life as measured by QLQ C30 (EORTC), treatment related toxicity, concomitant supportive medication; adverse effects of mistletoe extracts; immunological parameters (measured in a subset of 43 pats.) All outcomes measured at start of chemotherapy, before each new treatment cycle every 4 weeks and during week 2+ and 3 of the 4th cycle
Notes	Methods: Trial with dose finding and confirmatory study design. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Manufacturer adapted dosage

	recommendation according to the results of this trial. Stated that >90% received 4 cycles of chemotherapy, but comparability of sum doses of basic treatment (chemotherapy) between groups unclear. Quality Scores (Delphi List/Jadad Score): 4/4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Semiglasov 2006

Methods	Design: Double-blind, placebo-controlled 2-arm RCT Recruitment period: unclear Observation period: 6-8 months Ethical approval: yes
Participants	Number of patients: 352 patients were randomised. 337 were evaluable for 4 cycles of chemotherapy and 207 for six cycles. Condition: breast cancer (stage I-III), pre- and perimenopausal, adjuvant situation, eligible for CMF chemotherapy Demographics: age range 25-55, school education > 7 years Recruitment: unclear Setting: 6 centres in Russia, Bulgaria, Ukraine Informed consent: yes
Interventions	Intervention (MT): 0,5ml s.c. injected mistletoe extract standardized for ML-1 (Lektinol), contaning 30ng ML/ml, twice weekly for 24-32 weeks (16-24 weeks during chemotherapy and 8 weeks during follow-up) Control (PT): placebo Basic treatment: 4-6 cycles of adjuvant polychemotherapy (CMF) and supportively 10mg dexamethasone i.v. and 10mg metoclopramide per os q.i.d. on the day of chemotherapy
Outcomes	Primary outcome measure: Quality of life measured by FACT-G (subscales physical, emotional and functional well-being), Secondary outcome measure: GLQ-8 and Quality of Life Uniscale (Spitzer) uniscale Other: performance index (Karnofsky), treatment related toxicity, concomitant supportive medication; adverse effects of mistletoe extracts; immunological parameters QoL outcomes were measured on days 1 of each chemotherapy cycle and after 4 and 6 cycles of chemotherapy respectively and after further 2 months after chemotherapy. Other parameters were also determined on days 8 of chemotherapy
Notes	Follow-up study of Semiglasov 2004. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Manufacturer used medium dosage following the results of Semiglasov 2004. Quality Scores (Delphi List/Jadad Score): 4/4

Risk of bias

Semiglasov 2006 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Steuer-Vogt 2001

Methods	Design: Open-label 2-arm RCT with two strata in each arm (stratum A: surgery without/with mistletoe treatment; stratum B: surgery+radiotherapy without/with mistletoe treatment) with a no treatment control Recruitment period: 1993-97 Observation period: 6 years (treatment period 1 year, follow-up 5 years) Ethical approval: yes
Participants	Number of patients: 495 included, 477 randomised and analysed Condition: operable head-and-neck squamous cell cancer (stage I-IV [AJCC]) Demographics: mean ages range between 54 and 58 years (four strata), 437 men, 40 women Recruitment and setting: 4 university hospital departements of Otorhinolaryngology, Germany Informed consent: yes
Interventions	Intervention (MT, stratum A + B): Eurixor, 1ng ML-1 per kg body weight twice weekly for 60 weeks, treatment cycles of 12 weeks followed by a break of 4 weeks. Control: no treatment (stratum A)/ radiotherapy (stratum B) Basic treatment: surgical procedure
Outcomes	Primary outcome measure: disease-free survival Other: disease-specific survival, quality of life (EORTC QLQ-C30), adverse effects of mistletoe extracts; immunological parameters
Notes	Participants: Flow chart according to the CONSORT guidelines. Interventions: Type of mistletoe extract: standardized for mistletoe-lectin I. Comparability of sum doses of radiotherapy in stratum B between groups unclear. Quality Scores (Delphi List/Jadad Score): 6/3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

5-FU = 5-Fluorouracil; ADM = Adriamycin; Basic treatment = tumor specific treatment given in all groups; BRM = Biologic response modifier; CBP = C-PPD = Carboplatin; CTX = Cyclophosphamid; EADM: Epiadriamycin; EORTC = European organisation for research and treatment of cancer; FA = Folinic acid; FACT = Functional assessment of cancer treatment; IFO = Ifosfamid; MMC = Mitomycin; n.a./n.r. = not assessed or not reported; NVB = Vinorelbin; PDD = cis-Diaminodichloroplatinum; POM = Primary outcome measure; QLQ-C30 = EORTC Quality of life questionnaire; QLI = Quality of Life Index (Spitzer); QLU = Quality of LIfe Uniscale (Spitzer); QoL = Quality of life; TCM = Traditional chines medicine; VDS = Vindesine;

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bar-Sela 2004	
Dohmen 2004	No control arm
Douwes 1986b	No mistletoe treatment
Douwes 1988	Allocation not randomised (randomization failure)
Esch 1985	Information from principal investigator: study cancelled shortly after start of recruitement, data not analysed
Friess 1996	uncontrolled trial
Gorter 1996	uncontrolled phase I/II trials
Gutsch 1988	Study mentioned in Salzer 1987. Randomisation failure mentioned in the publication ("Randomisation nicht voll durchgehalten worden war"). Personal communications with the author (11/2004 and 1/2009): the study "should not be regarded as randomised"
Günczler 1968	no RCT
Günczler 1971	Study mentioned in Salzer 1987. Allocation quasi-randomized (alternation)
Günczler 1974	Study mentioned in Salzer 1987. Patients identical with Gutsch 1988
Jach 1999	precancerous lesions
Jach 2003	precancerous lesions
Kaiser 2001	analysis of quality of life data not finished
Kjaer 1989	uncontrolled trial
Klopp 2005	uncontrolled trial
Krause 1983	uncontrolled trial
Mansky 2005	interim report of Mansky 2007
Mansky 2007	ongoing phase I trial
Salzer 1987	Bookchapter with short descriptions and scarce data of several clinical trials with mistletoe extracts. In four of the mentioned trials the author alluded a randomised allocation of treatment: two trials with breast cancer patients (Günczler 1971 and Günczler 1974/Gutsch 1988), two trials with lung cancer patients from which one 'yielded no useful results' (page 186: "Leider lieferte diese Studie keine brauchbaren Ergebnisse.") and the second was included as Salzer 1991

(*Continued*)

Salzer 1990	no RCT; retrospective evaluation
Schoeffski 2005	Phase I trial
Schuppli 1990	allocation not randomized
von Hagens 2005	no RCT
Yoon 2005	allocation not randomized

Characteristics of studies awaiting assessment *[ordered by study ID]*

Enesel 2005

Methods	Open-label, 2-arm RCT with a no treatment control
Participants	70 patients with undergoing digestive tract cancer surgery
Interventions	Isorel (s.c.) for two weeks preoperatively and two weeks postoperatively
Outcomes	Anxiety scale, performance index (Karnofski), immune parameters
Notes	

Grossarth 2006a

Methods	Open-label, randomized 2-arm matched-pair trial nested within a large cohort study
Participants	34 patients with breast cancer
Interventions	Intervention: Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts
Outcomes	Survival, psychosomatic self-regulation
Notes	Reanalysis of Grossarth 2001b

Grossarth 2006b

Methods	Open-label, randomized 2-arm matched-pair trial nested within a large cohort study
Participants	76 patients with breast cancer
Interventions	Intervention: Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts
Outcomes	Survival, psychosomatic self-regulation

Grossarth 2006b (*Continued*)

Notes	

Grossarth 2007a

Methods	Two open-label, randomized 2-arm matched-pair trial nested within a large cohort study
Participants	42 patients with localised and 40 patients with metastasized ovarian cancer
Interventions	Intervention: Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts
Outcomes	Survival, psychosomatic self-regulation
Notes	

Grossarth 2007b

Methods	Open-label, randomized 2-arm matched-pair trial nested within a large cohort study
Participants	38 patients with cervical cancer
Interventions	Intervention: Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts
Outcomes	Survival, psychosomatic self-regulation
Notes	

Grossarth 2007c

Methods	Open-label, randomized 2-arm matched-pair trial nested within a large cohort study
Participants	44 patients with melanoma
Interventions	Intervention: Patients were advised to ask their doctor for treatment with one brand of mistletoe extracts
Outcomes	Survival, psychosomatic self-regulation
Notes	

Tröger 2007

Methods	Open label, 3-arm RCT with no treatment control
Participants	96 patients with breast cancer scheduled for adjuvant chemotherapy
Interventions	Helixor or Iscador, s.c., three times weekly during chemotherapy

Tröger 2007 (*Continued*)

Outcomes	Quality of life, neutropenia, immune parameters
Notes	according to GCP criteria

Wollermann 2002

Methods	Open-label, 2-arm RCT with an active treatment control
Participants	40 patients with malignant pleural effusions
Interventions	Several intrapleural instillations of Helixor
Outcomes	Tolerability, success of pleurodesis, laboratory parameters
Notes	unclear if patients identical with Kim 1999 (see 'Classification pending references')

Characteristics of ongoing studies *[ordered by study ID]*

Bar-Sela 2007

Trial name or title	Mistletoe as Complementary Treatment in Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC) , Treated With Carboplatin/Gemcitabine Chemotherapy Combination: Randomized Phase II Study
Methods	Single center study, randomized phase II, open label, active control
Participants	Pats with NSCLC
Interventions	Iscador in combination with Gemcitabine/Carboplatin vs. Gemcitabine/Carboplatin alone
Outcomes	QOL, toxicity profile of the chemotherapy treatment, time to tumor progression (TTP), survival, safety profile of mistletoe extracts
Starting date	April 2007
Contact information	http://clinicaltrials.gov/ct2/show/NCT00516022?term=mistletoe&rank=1
Notes	

LaRocca 2006

Trial name or title	Randomized Pilot Study of Supplemental Iscar in Combination With Gemcitabine vs. Gemcitabine Alone as Second Line Treatment for Advanced Non-Small Cell Lung Cancer
Methods	Randomized, Open Label, Active Control, Parallel Assignment
Participants	Adults with non-small cell lung cancer
Interventions	Iscar in combination with Gemcitabine vs. Gemcitabine alone
Outcomes	Immune function and quality of life
Starting date	May 2004
Contact information	http://clinicaltrials.gov/ct2/show/NCT00283478?term=mistletoe&rank=8
Notes	study completed

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Glossary of terms

Befindlichkeitsskala	Mood scale introduced 1976 by von Zerssen
Beschwerdeliste	Questionnaire to assess the extent of subjective impairment through symptoms general health impairment
CAM	Complementary and Alternative Medicine
CCT	Controlled Clinical Trial
DKG	German Cancer Society (Deutsche Krebsgesellschaft)
Eigenschaftswörterliste	Mood Rating by using all German adjectives that describe moods
EORTC	European Organization for Research and Treatment of Cancer
FLIC	Functional Living Index - Cancer (=Quality of Life Questionnaire)
HRQoL	Health-related Quality of Life
IgG	Immunoglobulin G
QLQ-C30	Quality of Life Questionnaire
Therapieangstskala	Rating scale for treatment-related anxiety
Catell-Angstskala	Anxiety rating scale
TCM Index	Traditional Chinese Medicine Index (=Quality of Life Questionnaire)
FACT-G	Functional Assessment of Cancer Therapy: General (=Quality of Life Questionnaire)
SF-36	Short Form-36 (=Quality of Life Questionnaire)
MDBF	Rating scale of moods
SCL-90-R	Symptom Checklist (90 items)
Cox Proportional Hazards model	Survival model in statistics describing how risk changes over time and relates to other factors

Table 1. Glossary of terms (*Continued*)

Breslow thickness	Measuring of the depth of penetration of a melanoma into the skin in mm
Rank-sum (O'Brien)	Statistical test for paired data developed by O'Brien (1984) based on rank-sums
FBK-KF	Questionnaire to assess coping with illness (Fragebogen zur Belastung von Krebspatienten - Kurzform)
Spitzer's Quality of life Uniscale (QLU)	Single-item rating scale for overall quality of life
Spitzer's Quality of Life Index (QLI)	5-item questionnaire to assess Quality of Life
Dukes	Staging score for Colorectal cancer
GLQ-8	Global Life Quality (8 items)

Table 2. Validity assessment

Study	Randomisation	Concealment	Comparability	Eligibility	Blinding	Attrition	Scores	Comment
Auerbach 2005	Method of sequence generation not reported	Unclear	No information about relevant prognostic factors given	In-/exclusion criteria reported	Patient: unclear Care provider: designed as double-blind, but deblinding in 16/20 patients due to local reactions Outcome assessor: unclear	7 drop-outs, 3 after screening, 4 during study (2 of each study arm), reasons reported	Delphi List: 1-1-0-1-0-0-0-0-0 Jadad List: 2-0-1	Selection bias possible: allocation concealment unclear, comparability of groups unclear Participant/observer bias possible: unblinding of intervention in the majority of patients. Poor reporting quality.
Borrelli 1999	Method of sequence generation not reported; 2: 1 randomi-	Unclear	Baseline QoL similar between groups. Distribution of prognostic	In-/exclusion criteria reported	Patient: study probably designed as single-blind (use of a placebo	No drop-outs or withdrawals reported	Delphi List: 1-0-0-1-0-0-0-1-1 Jadad List: 1-0-1	Selection bias possible: allocation con-

Table 2. Validity assessment (*Continued*)

	sation		factors unclear		treatment), but no further information presented (intervention probably unblinded due to local reactions) Care provider: no (see above) Outcome assessor: unclear			cealment unclear. Participant/observer bias possible: unblinded evaluation of QoL. Poor reporting quality
Cazacu 2003	Method of sequence generation not reported	Unclear	Uneven distribution of Dukes stages between groups, no further information on relevant prognostic factors	No in-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	No drop-outs or withdrawals reported	Delphi List: 1-0-0-0-0-0-0-0-1 Jadad List: 1-0-1	Selection bias possible: allocation concealment unclear, uneven numbers of patients in groups, comparability of groups unclear. Poor reporting quality
Dold 1991	Balanced randomisation lists, stratified	Central randomisation	Groups comparable regarding important prognostic factors	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: assessment performed centrally	71 Drop-outs/withdrawals, balanced between the groups, detailed record of reasons. Reasons imbalanced among groups	Delphi List: 1-1-1-1-1-0-0-1-0 Jadad List: 2-0-1	Attrition bias possible due to number of drop-outs Performance bias possible: Concomitant treatments unclear Participant/

Table 2. Validity assessment (*Continued*)

								observer bias possible: unblinded investigation of measures of subjective outcomes
Douwes 1986a	Method of sequence generation not reported	Unclear	Distribution of relevant prognostic factors among groups unclear	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: no	No drop-outs or withdrawals reported	Delphi List: 1-0-0-1-0-0-0-1-1 Jadad List: 1-0-1	Selection bias possible: allocation concealment unclear/ comparability of groups unclear, chemotherapeutic pretreatment not further described (intervention group 4/20, control (XP) goup 2/20, control (CX) group 3/20) . Participant/ observer bias possible: unblinded outcome assessment. Poor reporting quality.
Goebell 2002	Permuted blocks	Biostatistic core facility	Slight imbalance regarding tumour characteristics at resection: 11 recurrent lesions (intervention	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: no	Except of one death in the control group no dropouts/ withdrawals	Delphi List: 1-1-1-1-0-0-0-1-1 Jadad List: 2-0-1	Observer bias possible: no blinding of outcome assessment

Table 2. Validity assessment (*Continued*)

			group) vs. 8 in the control group and 13 multiple lesions in the intervention group vs. 10 in the control group					
Grossarth 2001a	Blinded drawing of lots	Unclear	Matching procedure did not warrant balanced distribution of relevant prognostic factors	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	Dropouts/withdrawals: 10 patients in the intervention group (+ their 10 respective matches), reasons stated	Delphi List: 1-0-0-1-0-0-0-1-0 Jadad List: 1-0-1	Performance bias possible: not controlled for concomitant oncologic therapies Long recruitement period (>9 years).
Grossarth 2001b	Blinded drawing of lots	Unclear	Matching procedure did not warrant balanced distribution of relevant prognostic factors	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	No dropouts and withdrawals reported	Delphi List: 1-0-0-1-0-0-0-1-1 Jadad List: 1-0-1	Statistical analyses which show favorable results for the "intervention group" are based on mean survival times, whereas no difference is to be seen regarding the median survival presented in the curves
Heiny 1991	Random table	Unclear	No data of the baseline quality of life assessment reported	In-/exclusion criteria reported	Patient: study probably designed as single-blind (use of a placebo	Four dropouts in the intervention and 2 in the control group, rea-	Delphi List: 1-0-0-1-0-0-0-0-0 Jadad List: 1-0-1	Selection bias possible: unblinded allocation of treatment/

Table 2. Validity assessment (*Continued*)

					treatment), but no further information presented (intervention probably unblinded due to local reactions) Care provider: no Outcome assessor: unclear	sons stated		unclear distribution of prognostic factors at baseline, exclusion of patients with allergic reactions to mistletoe extracts during pretest Participant/observer bias possible: unblinded analysis of quality of life and anxiety Attrition bias possible: numbers of drop-outs unevenly distributed between groups Statistics: Data presented only in figures without standard deviations. Poor reporting quality
Heiny 1997	Random generator	Unclear	No difference in baseline quality of life between groups stated (no data presented)	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: no	Overall, 28 drop-outs/withdrawals, distribution between groups unclear, reasons not reported	Delphi List: 1-0-1-1-0-0-0-1-0 Jadad List: 1-0-0	Selection bias possible: unblinded allocation of treatment Participant/observer bias possible: un-

Table 2. Validity assessment (*Continued*)

								blinded assessment of quality of life. Attrition bias possible: reasons for and number of patients dropping out from each group not reported. Statistics: Incorrect calculation of P-value concerning reduction of mucositis in intervention group [see 'Results']) Poor reporting quality
Kleeberg 2004	Stratified, method of sequence generation not reported	Central randomisation	Balanced distribution of key factors, but slightly imbalanced distribution of males, localisation of primary and initial stage between groups	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	Dropouts/ withdrawals: 30 in the intervention (mistletoe) group, 18 in the control group. Reasons partly reported	Delphi List: 1-1-1-1-0-0-0-1-1 Jadad List: 2-0-1	No sample size calculation reported for the DKG-80-1 trial (4-arm trial including the mistletoe group) Selection bias possible: slight imbalance in prognostic relevant factors. Contamina-

Table 2. Validity assessment (*Continued*)

								tion possible: not controlled for concurrent mistletoe treatment in control groups (ML antibodies etc.) Slight preponderance of males (64,4 vs 53,5%), non-limb localisation of primary melanoma 54,9 vs. 52,9%), initial stage III (15,4 vs. 9,4%) in the intervention group (MT)
Lange 1993	Method of sequence generation not reported	Central randomisation	Baseline performance index, gender distribution, pretreatment similar between groups, mean age slightly higher in the control group (60,2 vs 58,3) , sightly unequal distribution of tumour types between groups	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: no	24 Drop-outs/withdrawals (6 died within 1st chemotherapy, 6 refused further chemotherapy, 3 refused Helixor, 1 refused radiotherapy, 8 incomplete histories)	Delphi List: 1-1-1-1-0-0-0-1-0 Jadad List: 2-0-1	Participant/observer bias possible: no patient/care provider blinding, no placebo control

Table 2. Validity assessment (*Continued*)

Lenartz 2000	Method of sequence generation not reported	Unclear	No information on prognostic relevant factors; baseline QoL (presented in a figure) comparable between groups	Only histological verification of diagnosis as inclusion criteria reported	Patient: no Care provider: no Outcome assessor: no	Both publications of the trial mentioned 9 patients who were excluded during the trial, but no further information reported	Delphi List: 1-0-0-0-0-0-0-0-0 Jadad List: 1-0-0	Selection bias possible: method and concealment of allocation not reported/ no data concerning the balance of prognostic relevant data given. Attrition bias possible: no detailed description of drop-outs. Participant/ observer bias possible: no patient/care provider blinding, no placebo control Statistics (survival) : Number of patients in the subgroups analysed unclear. Poor reporting quality.
Luemmen 2001	Method of sequence generation not reported	Unclear	Balanced distribution of metastatic sites, age and sex stated	No eligibility criteria reported	Patient: no Care provider: no Outcome assessor: unclear	No drop-outs/withdrawals reported	Delphi List: 1-0-1-0-0-0-0-0-1 Jadad List: 1-0-1	Quality assessment based on three abstract publications Selection bias possible: no informa-

Table 2. Validity assessment (*Continued*)

								tion on concealment of treatment allocation Observer bias possible: no blinding of outcome assessment
Piao 2004	Computer generated lists with varying block size	Unclear	Baseline FLIC score balanced between groups with a tendency to higher scores in 3 subscales in the mistletoe group. TCM baseline score balanced. Groups balanced in terms of age, gender, recruitement centers. Due to the way of presentation (separately for pT, pN, and M status), comparability in terms of stage unclear	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	9 dropouts/withdrawals, slightly unbalanced (6 in control, 3 in intervention group), reasons not stated	Delphi List: 1-0-1-1-0-0-0-1-0 Jadad List: 1-0-1	Selection bias possible: no information on concealment of treatment allocation. Participant/observer bias possible: unblinded assessment of quality of life. Poor reporting quality.
Salzer 1983	Method of sequence generation not reported; 3:3:4 randomisation	Central randomisation	Slight imbalance among distribution of stages and histologic subtypes be-	No eligibility criteria reported	Patient: no Care provider: no Outcome assessor: unclear	118 dropouts/withdrawals (intervention group 43, control group 38)	Delphi List: 1-1-1-0-0-0-0-1-0 Jadad List: 2-0-1	Selection bias possible: staging not corresponding to thenintterna-

Table 2. Validity assessment (*Continued*)

			tween groups			, reasons reported		tional standards. Attrition bias possible: in 13 patients intervention treatment not applicated (reason not stated) Statistics: Survival data only analysed within subgroups (post-hoc analyses)
Salzer 1991	Randomisation lists	Sealed envelopes	Slight imbalance among distribution of histologic subtypes between groups. Slightly more men in intervention group. Age evenly distributed	No eligibility criteria reported	Patient: no Care provider: no Outcome assessor: unclear	35 dropouts/withdrawal, balanced between the groups, reasons for non-participation reported	Delphi List: 1-1-1-0-0-0-0-1-0 Jadad List: 2-0-1	Selection/attrition bias possible: staging not corresponding to then-international standards Statistics: no stratification, but subgroup analysis (i.e. post hoc analysis)
Schwiersch 1999	Computer-generated random lists	Unclear	No significant difference in the quality of life between groups at baseline	In-/exclusion criteria reported	Patient: designed as double-blind, but intervention unblinded due to local reactions Care provider:	8 dropouts/withdrawals in the intervention group, 4 in the control group, reasons not reported	Delphi List: 1-1-1-1-0-0-0-0-1 Jadad List: 2-1-1	Quality assessment and data extraction limited to submission manuscript Quality of life analysis prelimi-

Table 2. Validity assessment (*Continued*)

					unclear (see above) Outcome assessor: unclear			nary. Performance bias possible: Not controlled for the rehabilitation interventions. Comparison of the sociodemographic parameters of both groups indicates balanced randomisation
Semiglasov 2004	Computer-generated random lists	Unclear	Baseline QoL data of both instruments different among groups	In-/exclusion criteria reported	Patient: designed as double-blind, but intervention unblinded due to local reactions Care provider: unclear (see above) Outcome assessor: unclear	18 dropouts and withdrawals because of major protocol violations, 11 withdrawals (4 adverse events, 4 decision of the patient, 3 other reasons)	Delphi List: 1-1-0-1-0-0-0-1-0 Jadad List: 2-1-1	Selection bias possible: considerable inhomogeneities of baseline QoL data Participant/observer bias possible: local reactions deblinded partly for mistletoe treatment
Semiglasov 2006	Computer-generated random lists	Unclear	Inhomogeneities among baseline QoL data stated (no data reported)	In-/exclusion criteria reported	Patient: designed as double-blind, but intervention unblinded due to local reactions Care provider: unclear (see	15 dropouts during chemotherapy (reasons not reported) . 6 dropouts during 2-months follow-up after chemotherapy (MT 2 pats, PT 4	Delphi List: 1-1-0-1-0-0-0-1-0 Jadad List: 2-1-1	Selection bias possible: inhomogeneities of baseline QoL data Participant/observer bias possible: local reactions

Table 2. Validity assessment (*Continued*)

					above) Outcome assessor: unclear	pats.)		deblinded partly for mistletoe treatment. Attrition bias possible: 15 dropouts (balance between groups unclear) Statistics: no intention-to-treat analysis
Steuer-Vogt 2001	Balanced randomisation lists; block randomisation within both strata	Central allocation	No significant differences among groups regarding important prognostic factors	In-/exclusion criteria reported	Patient: no Care provider: no Outcome assessor: unclear	45 dropouts/withdrawal, balanced between the groups; reasons stated in CONSORT figure	Delphi List: 1-1-1-1-0-0-0-1-1 Jadad List: 2-0-1	Performance bias possible: Intervention not blinded, Contamination possible: No measurement of ML-I antibodies in the control group, therefore provision of unintended treatment with mistletoe extracts not controllable. Participant/observer bias possible: unblinded investigation of quality of life

Table 3. Results

Study	Survival	Tumor response	Quality of life	Treatment toxicity	AE mistletoe extract
Auerbach 2005	n.a./n.r.	n.a./n.r.	Patient-rated (QLQ-C30): no differences between groups stated (no data presented) Physician-rated: No differences in Karnofsky's performance index between groups stated (no data presented)	Chemotherapy: In comparison with the CT group, pats. of the MT group had no therapy-related leukopenia (no details reported)	3 pats. reported skin reactions >5cm at injection site, 2 pats. had headaches
Borrelli 1999	n.a./n.r.	Total no. of tumor responses after 3 months follow-up: MT: partial remissions 4/20, stable disease 10/20; PT: stable disease 4/10	Patient-rated (all data had to be extracted from three figures): QLI (five-item scale, each item score 0-2, maximum 10 points, higher scores indicate better quality of life): MT mean (SD) at baseline: 5.2 (±1), after 1 month: 6.8 (±1), after 3 months 7.4 (±0.6) ; PT mean (SD) at baseline: 5 (±1.4) , after 1 month: 4.6 (±1.6), after 3 months 4.2 (±1.4) . Difference after 3 months statistically significant ($p<0.05$; Student t-test). The scores of the subscales were only presented for the mistletoe group. At baseline, mean scores of subscale (±SD) were: 1.02 (±0.88)	n.a./n.r.	n.a./n.r.

Table 3. Results (*Continued*)

			for 'activity', 1.02 (±0.61) for 'daily living', 1.12 (±1.1) for 'health', 1.1 (±1.32) for 'support', and 0.84 (±0.72) for 'outlook'. After one month, mean scores of subscale (±SD) were: 1.6 (±1.1) for 'activity', 1.42 (±0.65) for 'daily living', 1.4 (±1.1) for 'health', 1.24 (±1.21) for 'support', and 1.08 (±0.77) for 'outlook'. After three months, mean scores of subscale (±SD) were: 1.62 (±0.99) for 'activity', 1.64 (±0.65) for 'daily living', 1.56 (±1.1) for 'health', 1.02 (±1.21) for 'support', and 1.06 (±0.66) for 'outlook'		
Cazacu 2003	Overall survival (median/after surgery): Dukes C : intervention group (MT) 757 days, control group (CT) 547 days, control group (NT) 502 days (no confidence intervals presented; p<0.05). Dukes D: intervention group (MT) 505 days, control group (CT) 214 days, control group (NT) 451 days (no confidence intervals presented; p<0.05)	n.a./n.r.	n.a./n.r.	Chemotherapy: 4 of 21 patients in the control group (CT) experienced gastrointestinal/hematological toxicities (no further details reported) and none were registered in the patients from the mistletoe group (MT)	Authors found no side effects

Table 3. Results (*Continued*)

Dold 1991	Overall survival (median): MT 9.1 months (95% CI 6.8-10.7), BT 7.6 months (95% CI 6.0-8.9) (p=0.24, log-rank). Survival rates at 6 months: MT 62.7% (±4.6) vs BT 59.0% (±4.7), at 1 year: MT 36.0% (±4.6) vs. BT 32.2% (±4.4), at 2 years: MT 11.5% (±3.2) vs BT 10.1% (±3.0)	Total no. of tumour responses: MT 30/114, BT 22/113. Remissions (defined as twice-confirmed disappearance at primary site + disappearance of metastases): MT 4/110, BT 3/113	Patient-rated: Well-being: Intervention group (MT) 59% improvement, control group (PT) 43% , control group (BT) 45% (MT vs. BT p=0.018). Physician-rated: Karnofsky Performance Status (mean): Intervention group (MT) 53 (SD 47-64), control group (PT) 61 (SD 53-67), control group (BT) 57 (SD 49-63). Symptom scales: no significant differences among the groups.	n.a./n.r.	Only few and mild adverse effects reported. No drop-outs due to study medication.
Douwes 1986a	Overall survival (mean): data presented separately for "responders" ([R] i.e. patients with a complete, partial or minimal respone) and "non-responders" ([NR] i.e. patients with a no-change or progressive disease). Intervention group (MT): R: 26.7±11.9 months, NR: 11.9±4.7, control group (XT): R: 23.7±9.6, NR: 12.4±5.1, control group (CT): R 13.6±4.4, NR 4.8±4.1. No statistical analysis	Overall response rates (including "minimal response") : MT 13/20, XT 13/20, CT 12/20	n.a./n.r.	Chemotherapy: Inconsistent report of side effects without presentation of data	n.a./n.r.

Table 3. Results (*Continued*)

Goebell 2002	Disease-free interval (median) : intervention (MT) 9 months, control (NT) 10.5 months (p=0.76). Number of recurrences (after 18 months): intervention 31, control 30 (p=0.48)	n.a./n.r.	n.a./n.r.	n.a./n.r.	No systemic or local adverse effects
Grossarth 2001a	Overall survival (mean) : MT 3.49 years vs CT 2.45 years (no standard deviation reported; p= 0.04, log-rank test). Median overall survival (extracted from Kaplan-Meier figure): MT ~2.5 years vs CT 2.4 years	n.a./n.r.	Patient-rated: Self-regulation (higher values indicate better self-regulation): MT increase of mean value after 3 months from 3.41 (baseline) to 3.87, CT decrease from 3.85 to 3.62 (p= 0.022, Mann-Whitney)	n.a./n.r.	n.a./n.r.
Grossarth 2001b	Overall survival (mean) : MT 4.79 years vs CT 2.41 years (no standard deviation reported; p= 0.02, log-rank test). Median overall survival (extracted from Kaplan-Meier figure): MT ~6.2 years vs CT 2.3 years	n.a./n.r.	Patient-rated: Self-regulation (higher values indicate better self-regulation): MT increase of mean value after 3 months from 2.92 (baseline) to 3.70, CT from 2.87 to 2.99 (p=0.13, Mann-Whitney)	n.a./n.r.	n.a./n.r.
Heiny 1991	n.a./n.r.	n.a./n.r.	Unclear whether patient-/or physician-rated: 'Befindlichkeitsindex" (5-point scale, higher values indicate better quality of life): MT higher sum score after 6 cycles of chemotherapy: base-	Chemotherapy: Higher hematological toxicity in the control group reported (measured as numbers of peripheral leukocytes, mean values without STD of only 4 cycles presented, p<=	13 of 21 patients experienced fever <39.5C and flue-like symptoms

Table 3. Results (*Continued*)

			line 4/5, post 2.8/5, CT: baseline 4/5, post 2/5 (p<=0.01). "Angstindex" (10-point scale, higher values indicate higher anxiety strain): MT: lower levels after third cycle: baseline: 5/10, before second cycle: 6/10, third: 6/10, 4th: 5/10, 5th: 4/10, 6th 4/10, 10 days after chemotherapy: 4/10), CT: baseline: 5/10, before second cycle: 6/10, 3rd: 6/10, 4th: 7/10, 5th: 7/10, 6th: 7.5/10, 10 days after chemotherapy: 7.5/10. (p<=0.01, unclear which estimates were tested)	0,001, unclear which estimates were tested)	
Heiny 1997	Overall survival (unclear whether mean or median): Intervention (MT) 52.8 weeks, control (CT) 50 weeks. Progression-free survival (unclear whether mean or median): intervention (MT) 30.8 weeks, control (CT) 31.2 weeks. Stated as not significant (data of analysis not presented)	Remission rates: intervention (MT) 21.4% , control (CT) 22.6%. Duration of remission (unclear whether mean or median): intervention (MT) 23.1 weeks, control (CT) 21.4. Stated as not significant (data of analysis not presented)	Patient-rated: The FACT mean sum scores (±SD) in patients of the mistletoe group were 69.8 out of 100 (±6.1) at baseline, 69.6 (±4.9) after 6 weeks, 60.9 (±4.3) after 12 weeks, 60.5 (±3.4) after 18 weeks, 60.9 (±2.7) after 24 weeks, 64.0 (±4.2) after 30 weeks, 59.7 (±3.0) after 36 weeks, and 39.0 (±5.1) after 42 weeks. The respective mean sum scores of the control group were 67.8 (±6.1) at baseline, 69.1	Chemotherapy: Incidence of mucositis grade III (WHO): MT 17.9%, CT 25.8% (p=0.03 reported, but correct p-value should be 0.64), nausea/vomiting (14.4% vs 16.1%), diarrhea (25% vs 29%), hand-foot syndrom (0% vs 3.2%), chest pain (3.6% vs 4.5%), leukopenia (32.1% vs 38.7% [p=0.01]), thrombopenia (10.7% vs 12.9%). Duration of mucositis (method of assessment not stated)	Local inflammation and a small number of mild systemic reaction (fever, flue-like symptoms) stated (no further data). No drop-outs due to study medication

Table 3. Results (*Continued*)

			(±5.8) after 6 weeks, 50.4 (±4.7) after 12 weeks, 41.4 (±3.7) after 18 weeks, 41.9 (±3.4) after 24 weeks, 41.4 (±3.6) after 30 weeks, 33.9 (±3.6) after 36 weeks, 21.1 (±2.7) after 42 weeks. The p-value for the comparisons of the estimates of week 12 - 42 were <0.0001 (Wilcoxon test). No data were published for the 5 subdomains of the FACT questionnaire. Intransparent presentation of data.	: MT 12.3 days (SD 2.7) vs CT 16.8 (SD 1.8), severity of mucositis (method of assessment not stated): MT 7.2 (SD 1.1) vs CT 7.4 (SD 0.9) (units not reported)	
Kleeberg 2004	Overall survival: estimated hazard ratios (Cox Proportional Hazards model) for MT vs. NT (DKG 80-1 trial): 1.21 with a 95% CI of 0.84-1.75 in the univariate analysis (p= 0.31) and 1.27 with a 95% CI of 0.87-1.84 in the multivariate analysis (p= 0.21). Disease-free interval: estimated hazard ratio for MT vs. NT: 1.32 with a 95% CI of 0.93-1.87 in the univariate analysis (p=0.12) and 1.34 with a 95% CI of 0.87-1.84 in the multivariate analysis (p=0.10)	n.a./n.r.	Patient-rated: No data presented.	Immunotherapy (EORTC 18871 trial): Discontinuation of treatment in 4,6% in the ITa and 7,8% in the ITg group due to WHO grade 3-4 toxicities (e.g. fever, local skin inflammation at the site of injection). No organ toxicity observed	DKG 80-1 trial: Discontinuation of treatment in 4.9% of patients in the intervention (MT) due to WHO grade 3-4 toxicities (e.g. fever, local skin inflammation at the site of injection). No organ toxicity observed

Table 3. Results (*Continued*)

Lange 1993	n.a./n.r.	Remission rates (evaluation after two cycles of radiochemotherapy): 34,8% complete remissions + 43,5% partial remissions in the intervention group (MT) vs 47,6% and 14,3 % in the control group (CT)	Patient-rated: Nausea, emesis and tumour-related pain were assessed daily (5-point scale, higher values indicate higher intensity/frequency of symptoms) and two mean values were calculated for each cycle: symptoms during chemotherapy (C1/C2) and symptoms during the 5 following days (F1/F2). Mean scores and standard errors of the mean had to be extracted from three figures. Nausea C1 in mistletoe group was 1.15 (±), in the control group 1.14 (±), nausea F1 in the mistletoe group was 0.5 (±), in the control group 0.86 (±); nausea C2 in mistletoe group was 1.1 (±), in the control group 1.29 (±), nausea F2 in the mistletoe group was 0.52 (±), in the control group 1.0 (±). The difference in nausea scores between mistletoe and control group after the first cycle of chemotherapy (F1) was statistically significant (p=0.033, test not stated). Emesis C1	Chemotherapy: Application of the combination chemotherapy with cisplatinum and ifosfamide was possible in the first cycle in 17/23 patients of the mistletoe group compared to 14/21 of the control group and in the second cycle in 14/23 patients of the mistletoe group compared to 9/21 of the control group. In the remaining patients cisplatinum was omitted. Combination chemotherapy could be given at full dose (defined as = 85% of the scheduled dose) in the first cycle in 12/17 patients of the mistletoe group compared to 9/14 of the control group and in the second cycle the numbers were 11/14 and 6/9 respectively. Leukocytes regenerated to significant higher values after the second cycle of chemotherapy in patients who had received mistletoe extracts (p=0.003, test not stated) . No differences between mistletoe and control group were	n.a./n.r.

Table 3. Results (*Continued*)

			in mistletoe group was 0.65 (±), in the control group 0.9 (±), emesis F1 in the mistletoe group was 0.2 (±), in the control group 0.52 (±); emesis C2 in mistletoe group was 0.75 (±), in the control group 0.87 (±) , emesis F2 in the mistletoe group was 0.52 (±), in the control group 0.65 (±) . Pain C1 in mistletoe group was 0.48 (±), in the control group 0.78 (±), pain F1 in the mistletoe group was 0.2 (±), in the control group 0.75 (±); pain C2 in mistletoe group was 0.35 (±), in the control group 0.55 (±), pain F2 in the mistletoe group was 0.35 (±), in the control group 0.46 (±) . The difference in pain scores between mistletoe and control group after the first cycle of chemotherapy (F1) was statistically significant (p=0.04, test not stated). Physician-rated: Mean performance index (Karnofsky) increased from 67% (±3.2) at baseline to 76% (no SD reported) be-	found for chemotherapy-related hepato- and renotoxicity	

Table 3. Results (*Continued*)

			fore the second cycle in patients of the mistletoe group (p=0.0008, test not stated), and from 69% (±3.5) to 74% (no SD reported) in those of the control group (p=0.12, test not stated)		
Lenartz 2000	Overall survival (mean): intervention (MT) 21.71 ± 3.7 months, control (RT) 17.32 ± 3.9. Subgroup analysis (stage III/IV) : intervention 20.05 ± 3.5 months, control 9.90 ± 2.1 (p= 0.035) Disease-free survival (mean) : intervention 14.41 ± 2.7 months, control group 14.76 ± 3.6. Subgroup analysis (stage III/IV): intervention 17.43 ± 8.2 months, control 10.45 ± 3.9	n.a./n.r.	QLI Spitzer (five-item scale, each item score 0-2, maximum 10points, higher scores indicate better quality of life): MT: mean at baseline 8/10, at one, 12 and 24 weeks after surgery: 6/10, 6/10 and 8/10. RT: mean at baseline 8/10, at 1, 12, 24 weeks: 7/10, 5/10, 5/10 (sum scores presented in a figure, no data on subscales, no standard deviations, no statistical analysis)	Radiotherapy: n.a.	n.a./n.r.
Luemmen 2001	Overall survival (median) : intervention (MT) 21 months, control (IT) 13 months (no confidence intervals presented; p=0.14)	Remission rates: intervention (MT) 2% (2 partial responses) , control (CT) 25% (7 complete, 15 partial responses) . Stated as significant (data of analysis not presented)	n.a./n.r.	Chemoimmunotherapy: 26 patients (30%) experienced grade III WHO toxicities.	6 patients (7%) experienced grade III WHO toxicities
Piao 2004	n.a./n.r.	Remission rates: 12,5% complete remissions + 8,9% partial remissions in the intervention group vs 11,6%	Physician-rated: Performance index: MT 'increased' in 58 patients (50.4%) , 'stable' in 53 (46.1%), 're-	Chemotherapy: 28 not nearer described adverse events in the intervention group vs. 77 in the control group	Fever was reported in 4 patients, rubor and pruritus at injection site in 7, angioedema and urticaria in one patient

Table 3. Results (*Continued*)

		and 8,9% in the control group (no transparent presentation of data)	duced' in 4 (3.5%) . CT 'increased' in 35 (33%), 'stable' in 61 (56%), 'reduced' in 12 (11.1%) (p= 0.002; Fisher's exact test). Numbers of patients in the analysis of performance index varied slightly between the journal publication and the Medical Study Report. Unclear whether patient-/or physician-rated: Health-related quality of life was measured with the FLIC (22 items each scoring from 1-7 relating to 6 domains: physical well-being, psychological well-being, hardship due to cancer, social well-being, nausea and pain) A median improvement of the FLIC sum score of 6.0 points (CI not reported, mean: 9.0, SD 16.6) was reported for the mistletoe group and a median improvement of 3.0 points (mean: 4.7, SD 17.5) for the lentinan group (p= 0.0141, Wilcoxon test). Changes in the TCM score (sum of five symptom scales: anorexia, fatigue, in-		

Table 3. Results (*Continued*)

			somnia, nausea and pain, each scoring 0-3, higher values indicate higher intensity) showed a median improvement for the mistletoe group of -1 (mean: -1.3, SD 2.4), compared to 0 (mean: -0.2, SD 2.3) for the control group (p=0,0007)		
Salzer 1983	1979 publication: Overall survival (data extracted from two Kaplan-Meier diagrams): as at 12/1977: intervention group [MT], median not reached (>2.5 yrs.), chemotherapy group [CT], median not reached (~3 yrs), control group [NT], median ~1.9 years. As at 9/1978: MT >3 yrs. (median not reached), CT ~3.1 yrs., NT ~1.1 years (no statistical analysis). 1983 publication: Overall survival (median survival; data presented only as subgroup analyses): lymph-node positive subjects: intervention [MT] 660 days (119-2010), control [NT] 324 days (37-2394) (p<0.05) ; lymph-node negative subjects: MT	n.a./n.r.	n.a./n.r.	n.a./n.r.	n.a./n.r.

Table 3. Results (*Continued*)

	median not reached (64-2371) , NT 1201 days (40-2345) (n.s.)				
Salzer 1991	Overall survival (median): Total population: MT 33 months, CT 31 (n.s., log-rank test). Subgroup analysis for lymph-node positive patients with Stage II-III: median overall survival MT 31 months, CT 24 months; overall survival rate after 5 years: MT 38%, CT 20%. Subgroup analysis for lymph-node negative patients with stage I-II: overall survival rate after 6 years, MT 48%, CT 27% (data presented as Kaplan-Meier diagrams, no statistical analysis)	n.a./n.r.	n.a./n.r.	n.a./n.r.	n.a./n.r.
Schwiersch 1999	n.a./n.r.	n.a./n.r.	Patient-rated: The FBK-KF mean sum scores (range 0-50, higher values indicate higher distress) in patients of the mistletoe group were 19.44 out of 50 at screening, 19.61 at day 0 of the study, 16.62 after 2 weeks, 15.57 after 4 weeks and 16.21 at follow-up after 8 weeks. The respective scores of the control group were 18.06 at screening, 17.88 at day 0,	n.a./n.r.	Pretest of medication without either allergic reactions, or local reaction at injection site in 150 pats (88%)

Table 3. Results (*Continued*)

			15.27 after 2 weeks, 14.93 after 4 weeks and 15.64 at follow-up after 8 weeks. The differences between groups were not significant (p=0.72, t-test, ANCOVA). No significant differences between the groups were found in the overall analysis of the questionnaire on life satisfaction (FLZ). Details were only reported for two subscales of the FLZ: The scores of the FLZ subscale 'ability to relax' (range -16 to 20, higher values indicate the ability to better relax) in patients of the mistletoe group were 0.5 at day 0 of the study, 3.74 after 4 weeks, and 2.07 at follow-up after 8 weeks. The respective scores of the control group were 1.52 at day 0, 3.6 after 4 weeks and 2.57 at follow-up after 8 weeks. The differences were not significant, measures of variability not reported. The scores of the FLZ subscale 'energy/joie de vivre' (range -16 to 20, higher values indicate higher energy) in patients of		

Table 3. Results (*Continued*)

			the mistletoe group were 3.2 at day 0 of the study, 6.67 after 4 weeks, and 4.31 at follow-up after 8 weeks. The respective scores of the control group were 4.42, 5.65, and 4.89 (p= 0.025, t-test, ANCOVA). The analysis of the questionnaires B-L, MDBF, SCL-90R, and of performance index (Karnofsky) revealed no significant differences between groups. No significant differences were found in the overall analysis of the questionnaire SF-36, but for the subscale 'vitality', significant higher values are found in the mistletoe group (no details presented)		
Semiglasov 2004	n.a./n.r.	n.a./n.r.	Patient-rated: Changes in the GLQ-8 (baseline to 1 week after completion of chemotherapy (4 cycles)): MT1 from 157.2 (101.4 [mean and SD in mm]) to 173.8 (142.5), MT2 from 171.5 (109.1) to 134.2 (122.9), MT3 from 158.5 (119.8) to 149.3 (132.1), PT from 128.9 (99.1) to 152.4 (117.3). Changes in Spitzer's	Chemotherapy: Incidence of adverse effects concerning white blood cells: PT 20%, MT1 22%, MT2 16%, MT3 21%; red blood cells: PT 6%, MT1 3%, MT2 3%, MT3 12%; related to the gastrointestinal tract: PT 9%, MT1 9%, MT2 9%, MT3 15%	Dose-dependent local reactions: placebo goup: 0%; low dose mistletoe group (MT1): 9%; medium dose mistletoe group (MT2): 17,9%; high dose mistletoe group (MT3): 32,4%. Lower grade systemic reactions (chills, muscle pain, allergic skin reaction, headache) were seen in 4 patients

Table 3. Results (*Continued*)

			Quality of Life Uniscale (QLU): MT1 from 39.5 (28.3) to 35.8 (29.9), MT2 from 46.4 (26.3) to 27.4 (28.9), MT3 from 37.9 (26.7) to 33.8 (30.0), PT from 35.1 (27.5) to 32.5 (29.1). For the QLQ-C30, the authors reported 'no relevant' difference without presenting data. Physician-rated: No data for Karnofsky's performance index presented.		
Semiglasov 2006	n.a./n.r.	n.a./n.r.	Patient-rated: Changes from baseline to week 15: in FACT-G sum score (only subscales for physical, emotional and functional well-being were evaluated; increase means better qol; mean [±SD]) : MT (169 pats.) 4.40 (±11.28), PT (168 pats.) -5.11 (±11.77), p<0.0001 (U-test); in FACT-G physical well-being: MT 2.03 (±5.07) , PT -2.33 (±5.10) p<0.0001 (U-test); in FACT-G emotional well-being: MT 1.44 (±4.11) , PT -1.17 (±4.36) p<0.0001 (U-test); in FACT-G func-	Chemotherapy: Changes from baseline to week 15: GLQ-3 (3 scales considered as tolerability variables for chemotherapy, increase means worse qol): 'feeling sick (nausea or vomiting) ': MT 1.8 (±28.9) , PT 15.1 (±25.9) p<0.0001 (t-test); ' numbness or pins and needles': MT 1.6 (±21.9), PT 6.8 (±22.4) p=0.03 (t-test); 'loss of hair': MT 10.5 (±23.5), PT 12.5 (±23.5) p= 0.44 (t-test). No significant differences in the incidences of other adverse reactions or laboratory test (data	Injection site reactions: MT 31 patients, PT 2 patients.

Table 3. Results (*Continued*)

			tional well-being: MT 0.94 (±4.15) , PT -1.61 (±4.66) p<0.0001 (U-test) ; in GLQ-8 (sum of 8 scales, increase means worse qol): MT -28.9 (±154.6) , PT 94.8 (±141.1) p<0.0001 (U-test); in GLQ-5 (sum of 5 scales): MT -42.9 (±125.0), PT 60.3 (±94.0) p<0.0001 (U-test); in Spitzer's uniscale (increase means worse qol): MT -12.2 (±30.7) , PT 10.8 (±26.1) p<0.0001 (U-test) Changes from baseline to end of follow-up (2 months after end of chemotherapy): FACT-G sum score (only subscales for physical, emotional and functional well-being were evaluated; mean [±SD]): MT (103 pats.) 8.55 (±12.27), PT (104 pats.) 0.34 (±10.14) , p=0.03 (U-test). Mean change in the GLQ-8: MT -70.7±166.3 vs PT 34.2± (p<0.0001, t-test). Mean change in QLU: MT -16.3±30.6 vs 2.7±22.9 in CT (p<0.001, t-test). Physician-rated:	shown in a table)	

Table 3. Results (*Continued*)

			No differences in performance index (Karnofsky) between groups stated (no data reported)		
Steuer-Vogt 2001	Both strata: Disease-free survival (adjusted hazard ratio, alpha=0.05, intention-to-treat analysis): 0.96 (95% CI 0.73-1.27 Per-protocol analysis: 0.88 (95% CI 0.63-1.21) and for the Disease-specific survival: 0.96 (95% CI 0.66-1.38). Relapse rate (after 4 years): Stratum A (surgery without radiotherapy): intervention (MT) 24/97 (25%), control (NT) 35/105 (33%) . Stratum B (surgery + radiotherapy): intervention (MT) 75/138 (54%), control (NT) 66/137 (48%) . Stratum A: Disease-free survival: 5-year Kaplan estimate in MT 0.74 (95% CI: 0.64-0.83), in CT 0.59 (95% CI: 0.47-0.71) (P=0.18) . Crude and adjusted hazard ratios for the treatment effects (Cox proportional hazards model): 0.70	n.a./n.r.	Patient-rated: EORTC QLQ-C30 (subsample 399 pats., 173 [stratum A, 226 [stratum B]): Mean estimates (i.e. 'treatment effects') for the overall quality of life (range 0 [worse] to 100 [best]) in patients of the control group was 60.0 and in patients of the mistletoe group 61.7 (p=0.360, F-test). In the functional scales (range 0 [worse] to 100 [best]) the mean estimates of the control group compared with the mistletoe group were 81.7 vs. 82.3 for physical functioning (p=0.766), 70.7 vs. 69.6 for role functioning (p=0.712), 68.2 vs. 73.6 for emotional functioning (p=0.017), 86.3 vs. 87.2 for cognitive functioning (p=0.631), 80.2 vs. 81.2 for social functioning (p=0.671). The mean values of the symptom scales and single items (range 0 [best] to 100 [worse]) for the control group	Radiotherapy: n.a./n.r.	Low grade systemic and/or local side-effects were numerous at beginning of therapy, but decreased markedly with continued treatment. 43/231 patients dropped out due to side-effects of mistletoe treatment

Table 3. Results (*Continued*)

	(95% CI: 0.42-1.18, P=0.18) and 0.63 (95% CI: 0.33-1.09, P=0.09). Disease-specific survival: 5-year Kaplan estimate in MT 0.84 (95% CI: 0.76-0.92), in CT 0.78 (95% CI: 0.69-0.88) (P=0.37) . Crude and adjusted hazard ratios for the treatment effects: 0.73 (95% CI: 0.37-1.45, P=0.37) and 0.63 (95% CI: 0.30-1.30, P=0.21). Stratum B: Disease-free survival: 5-year Kaplan estimate in MT 0.42 (95% CI: 0.32-0.52), in CT 0.46 (95% CI: 0.37-0.56) (P=0.32) . Crude and adjusted hazard ratios for the treatment effects: 1.18 (95% CI: 0.85-1.65, P=0.32) and 1.05 (95% CI: 0.75-1.48, P=0.78). Disease-specific survival: 5-year Kaplan estimate in MT 0.46 (95% CI: 0.36-0.55) in CT 0.56 (95% CI: 0.36-0.55) (P=0.13) . Crude and adjusted hazard ratios for the treatment effects: 1.32 (95% CI: 0.92-1.88, P=0.13) and 1.16 (95% CI: 0.80-1.67, P=0.44).		compared with the mistletoe group were 28.9 vs. 25.6 for fatigue (p=0.159, F-test), 7.2 vs. 4.9 for nausea/vomiting (p=0.071), 26.3 vs. 23.3 for pain (p=0.191), 21.6 vs. 19.5 for dyspnoea (p=0.382), 28.3 vs. 24.7 for sleep (p=0.170) , 20.8 vs. 17.7 for appetite (p=0.185), 6.3 vs. 5.9 for constipation (p=0.758), 6.6 vs. 8.1 for diarrhea (p=0.323), and 17.9 vs. 20.1 for financial issues (p=0.433). The corresponding p-values (F-test) for the estimated differences in the treatment-time interactions for the overall quality of life was 0.144, for physical functioning 0.679, for role functioning 0.591, for emotional functioning 0.055, for cognitive functioning 0.650, for social functioning 0.063, for fatigue 0.930, for nausea/vomiting 0.472, for pain 0.697, for dyspnoea 0.773, for sleep 0.726, for appetite 0.232), for constipation 0.914, for diarrhea 0.226, and for financial issues 0.119		

Table 3. Results (*Continued*)

	Adjustment was made in both strata for tumour stage, primary tumour site, treatment centre and histologic grade				

APPENDICES

Appendix 1. Search terms applied

The following search terms were applied:
1 (CANCER? OR KREBS? OR TUM?R# OR NEOPLASM# OR ONKOLOG? OR ONCOLOG####)
2 (THERAP? OR MEDICINE?)
3 2 AND 1
4 (MISTEL? OR MISTLE? OR VISC? ALB? OR ISCADOR OR HELIXOR OR ISCUCIN OR ABNOBAVISCUM OR EURIXOR OR PLENOSOL OR LEKTINOL OR VYSOREL OR ISOREL OR CEFALEKTIN)
5 3 AND 4
6 5 AND (RANDOMI? AND STUD? AND (CONTROL? OR KONTROLL?))
7 5 AND (SYSTEMAT? AND (REVIEW? OR ##BERSICHT))
8 5 AND (META? AND ANALYS###)
9 5 AND (META? AND ANALYS?)
10 6 OR 7 OR 8 OR 9
11 unique in 10

FEEDBACK

Reply, 9 February 2009

Summary

Date of Submission: 29-Oct-2008
Name: Dr. Gunver S. Kienle
Email Address: gunver.kienle@ifaemm.de
Personal Description: Occupation Clinical researcher, physician

Feedback: Comment on: Mistletoe therapy in oncology (Cochrane-Review 2008)
(Horneber MA, Bueschel G, Huber R, Linde K, Rostock M: Mistletoe in oncology (Review). 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd)

The Cochrane-Review 'Mistletoe therapy in oncology' (2008) concludes that the available evidence is not sufficient to support mandatory administration of mistletoe therapy. This summation will no doubt generally find agreement. However, the additional conclusion that trial evidence is generally weak requires critical examination.

The Cochrane-Review is neither complete nor updated, the formal evaluation procedure is inadequate, and the factual assessments are not consistent and often incorrect. Appropriate correction of the assessments leads to a different overall picture of the mistletoe trials. (For details see www.mistel-therapie.de).

How complete and updated is the Cochrane-Review?
The Cochrane-Review covers 21 randomized trials (RCTs). One HTA report and two system-atic reviews are also discussed.
The following relevant publications were not taken into account: 9 RCTs investigating survival time, tumour behaviour and quality of life; 1 re-analysis of an RCT; 1 meta-analysis; 1 systematic review; 1 HTA report. The publications are distributed as follows:

- published 1987 [1]: 1 RCT
- published 1999 [2]: 1 RCT
- published 2005 [3]: 1 RCT
- published 2006 [4-7]: 1 RCT, 1 re-Analysis of an RCT, 1 HTA report
- published 2007 [8-12]: 5 RCTs und 1 systematic review
- published 2008 [13]: 1 meta-analysis.

(For further details, see www.mistel-therapie.de)

The Cochrane-Review is therefore incomplete and outdated.

The formal procedure for evaluation of study quality The procedure chosen for evaluation of study quality in this Cochrane-Review is inadequate:
A number of formal evaluation scores are available. Different scores yield different results when applied to identical studies (see e.g. [14]). The Cochrane-Review employs two scores (the Jadad score and the Delphi list) which give the greatest weight to blinding of the study intervention: blinding is allocated 2 points (40%) of the maximum 5 Jadad points, and 3 points (30%) of the maximum 9 Delphi points. By selecting these particular evaluation scales, a poor performance of the mistletoe trials was predetermined, irrespective of how good or bad they actually are. The reason is: Subcutaneous mistletoe injections regularly cause painful swelling and reddening. Therefore, in principle, this therapy cannot be blinded. When blind-ing is attempted, unblinding certainly occurs. (This has been repeatedly investigated and con-firmed in clinical trials. For this reason many mistletoe trials refrain from using pro-forma blinding.) Consequently, the Cochrane-Review disqualifies all mistletoe trials on this point, including the trials formally conducted as double-blind trials. But the dilemma is not men-tioned: Namely that trials investigating subcutaneous mistletoe therapy will, in principle, per-form poorly in the evaluation scores used by the Cochrane-Review (because blinding is im-possible). The formal evaluation procedure chosen for this review is therefore inadequate.

It may be inconvenient that mistletoe therapy is so incompatible with blinding. However, the same problem arises with other therapy forms such as physiotherapy, surgery and psychother-apy. It would be absurd if all these treatments should be disqualified a priori. The Cochrane-Review should have at least acknowledged that the evaluation procedure did not allow for mistletoe studies to be classified as a high-quality research. Furthermore, the general requirement of blinding (of patient, physician and observer) has bi-zarre consequences: It assumes, amongst other things, that a physician can only reliably de-termine a patient's time of death if he or she does not know whether the patient received mis-tletoe therapy or not (i.e. is blinded).

Inconsistencies in evaluation
For evaluation of study quality, cut-off values were set arbitrarily. Following the subtraction of 'blinding points' mentioned above, no mistletoe trial could perform positively on the Jadad score, and on the Delphi list the subtraction of one additional point was sufficient for the trial to receive a poor quality rating. Therefore the remaining methodological evaluations require particular accuracy and balancing Furthermore, errors, lack of transparency, subjective ten-dencies, lack of recourse to the author of the trial etc. can quickly and unjustly tip the balance towards a positive or negative trial rating.

Thus the question arises as to why, in the Cochrane Review, the trials with negative results (i.e. no superiority of mistletoe therapy over the control group) were so positively evaluated, and why the weaknesses of these studies, in part severe limitations, were not presented

or dis-cussed. And why, on the other hand, trials with positive results (i.e. where mistletoe therapy was superior) were disqualified sometimes with regard to aspects which they dealt with equally well or better than the trials with negative results. Or why trials with positive results were disqualified because some study features were not clearly described in the primary pub-lication, when the respective features were described in a secondary publication or trial report, or could have been identified by contacting the study authors.

These issues will be illustrated with the following examples:
Example 1: Handling of drop-outs in the Piao (2004) [15] und Steuer-Vogt (2001) [16;17] trials.
Assessment in the Cochrane-Review: The Piao trial, which shows superiority of mistletoe therapy, is criticised on the following grounds that not all patients completed the trial ('drop-outs' are ubiquitous in almost all clinical trials), that according to the Cochrane review, the reason for the drop-outs was not mentioned, that the number of drop-outs was unbalanced in the two groups, and that these drop-outs were not part of the trial evaluation. In contrast, the Steuer-Vogt trial, where mistletoe therapy showed no superiority, received a plus point with respect to drop-outs.
The facts:
1.) Both studies were evaluated according to the intention-to-treat-principle, i.e. all patients were evaluated as if they actually received the treatment assigned by randomization, inde-pendently of whether this actually was the case or not. This is the contemporary standard evaluation technique.
2.) Furthermore, the drop-out rate in the Piao trial was only 4%. This rate is so marginal that any influence of dropout on the trial result would appear to be theoretical. In the Steuer-Vogt trial, the drop-out rate for survival was 9%; for quality of life, it was 32% and 53% after one and two years, respectively. In fact, the Piao study states the reasons for drop-outs very clearly (presented in a biometric trial report available on the Internet). In the Steuer-Vogt trial, however, the dropouts are for the most parts not even listed separately for the mistletoe and control groups. Therefore, contrary to the Cochrane-Review's statements, 'balance' of drop-outs in the two groups of the Steuer-Vogt trial cannot be assessed at all.
The Cochrane-Review criticises the Piao trial for failure to include data of excluded patients in the quality of life evaluation. This does not make sense: quality of life can only be evalu-ated for available questionnaires, as opposed to outcomes such as survival time, time of death and tumour behaviour which can also be assessed outside of trial participation. In the litera-ture this problem is well-known and is still unsolved (see e.g. [18;19]). Therefore, there is no convincing factual basis for an a priory disqualification of the Piao trial in this respect. More-over, the same problem is also present in the Steuer-Vogt trial: With regard to the trial's pri-mary outcome measure, a subset of the drop-outs (namely 4%: 495 randomized, 477 assessed) was also not included in the analyses, although this would have been technically possible in contrast to Piao's 4%. Furthermore, the 32% and 53% drop-out-rate concerning quality of life were not considered in the respective analyses of the Steuer-Vogt trial.
In conclusion: With regard to handling of dropouts, the Steuer-Vogt trial is definitely not superior to the Piao trial. At best, the two trials are comparable in this respect but under close scrutiny the Steuer-Vogt trial clearly comes off worse because of its high dropout rates for quality of life assessment. Nonetheless, the Steuer-Vogt trial receives a plus point in this regard and the Piao trial a minus point. This is not in accordance with the factual data and creates an impression of biased assessment.

Example 2: Assessment of prognostic comparability in the Grossarth (2001a/b) [20;21] and Kleeberg (2004) [22] trials.
Assessment in the Cochrane-Review: The assessment of comparability of trial groups regard-ing prognostic factors results in a minus point for the Grossarth trials (that show superiority of mistletoe therapy), in contrast to a plus point for the Kleeberg trial (no superiority).
The facts:
In the breast cancer trial by Grossarth, the patients (Mamma Ca., N>1, M=O) were matched systematically into pairs according to stage (IIIA and IIIB), menopause status, chemotherapy, radiation therapy, hormone therapy, age, and year of first diagnosis; the other Grossarth trial applied similar matching criteria. Accordingly, patients were comparable concerning these prognostic parameters. After matching had been completed, each patient in a matched and comparable pair was randomized to either mistletoe or control group. It is inexplicable why the Cochrane-Review assessed comparability of these studies as not guaranteed.
The Kleeberg trial, on the other hand, had marked differences in gender distribution: Women were clearly under-represented in the mistletoe group (35.6% of patients) compared to the control group (46.5%), a relevant difference for survival time. For example, among patients in Stage IIb (half of the study patients: 49% and 48% respectively), women had a highly signifi-cant better survival (p=0.0009) than men. This uneven gender distribution between mistletoe and control groups disadvantages the mistletoe group. If the imbalance had been taken into account in the final multivariate analyses, a positive result for survival time in the mistletoe group might have occurred.
In conclusion: Regarding comparability of prognostic factors, the Kleeberg trial is not at all superior to the Grossarth trial. In fact, the Kleeberg trial shows a markedly uneven distribu-tion relevant for survival time. It is inexplicable why the Kleeberg trial received a plus point and the Grossarth trial a minus point in this respect. This assessment creates an impression of bias.

Example 3: Blinding in the Borrelli (1999) [23] and Dold (1991) [24] trials Assessment in the Cochrane-Review: In the Borrelli trial (which showed superiority of mis-tletoe therapy), according to Dr. Borrelli (first author), the physicians and patients were blinded towards mistletoe therapy. Nevertheless the trial was evaluated as 'not blinded'.
On the other hand, in the Dold trial (which shows no superiority of mistletoe therapy concern-ing tumour remission and survival time) the physicians and patients were not blinded towards mistletoe therapy this trial was devised and conducted as a non-blinded placebo-controlled trials. Yet, the Cochrane-Review allocates the Dold trial a plus point in the Delphi list regard-ing 'adequate blinding of patients'. This is inexplicable.
Furthermore, according to the Cochrane review's description of the Dold trial, there was sup-posedly a genuine blinding of the 'outcome assessor'. This claim also does not reflect the facts: The trial report states that the physicians were not blinded, and that these (not blinded) physicians collected the outcome data and entered them into the case report forms.

Further inconsistencies
Grossarth trials [20;21], Borrelli trial [23]: The Cochrane-Review subtracts a quality point for each of these trials because randomization was not concealed. Allocation concealment is intended to prevent the physicians enrolling patients from guessing or estimating the group to which each patient will be randomized, knowledge of which could lead to manipulation of patient enrolment. The fact is, however: In the Borrelli trial randomization was carried out by an independent person who had no contact with the enrolling physicians (= definition crite-rion for 'concealment' according to the Delphi list). In the Grossarth trials each unit to be randomized (the matched patient pair) was already fully included in the trial before randomi-zation. Because randomization took place after enrolment had been completed, randomization was certainly concealed from the personnel enrolling patients. Therefore subtracting a point for supposed lack of concealment of allocation was indisputably incorrect for the Borrelli trial and at least questionable regarding the Grossarth trials.

In addition, the Cochrane-Review claims that in the Grossarth trials it is unclear whether the patients had consented to participation. The fact is: All patients were informed about the trial. (Consent to participate in the study was assumed after comprehensive information about the study objectives and the study design and the patient's explicit expression of willingness to participate [4]. Randomization procedures were carried out according to Zelen's Random-ized Consent Design.) The Cochrane-Review restricted inclusion criteria to randomized trials. This limitation is not without problems, as can be seen with the Grossarth trials: Both Grossarth RCTs considered in the Cochrane-Review (as well as other mistletoe RCTs by Grossarth) are part of a large epidemiological cohort study comprising approximately 10,000 patients, within which several large prospective matched-pair studies are embedded [4;5;8-10;13;20;25]. RCTs normally have a very limited external validity, i.e. they provide very little evidence of the effectiveness of a therapy in practice. For example, RCTs encompass highly selected patients (mostly less than 1% of the relevant diagnosis group [26]), they exclude the most relevant concomitant diseases; and RCTs differ markedly from real-world treatment conditions with respect to di-agnosis, therapy, adjunctive therapies and follow-up [26;27]. The Grossarth cohort study, on the other hand, is characterised by an extremely high external validity. The study does not interfere with the therapy, nor does it intervene in the natural course of treatment with exten-sive study documentation and diagnostic procedures. In this way, the Grossarth study enables a comprehensive and undistorted evaluation of the patients' treatment under everyday clinical conditions. These features are combined with other design elements to assess and strengthen the internal validity (that is, the highest possible distortion-free therapy evaluation), by em-bedding a number of smaller RCTs within this larger cohort study. Thus Grossarth achieves what almost all experimental trials are incapable of: to maximise internal and external validity within a single research project. This achievement is lost when single embedded RCTs are isolated and assessed independently from their research context, as in the Cochrane-Review. In this respect the Cochrane Review represents a reductionistic tunnel vision that does not enable any realistic evaluation of the Grossarth studies.

Against this background, the Cochrane-Review's statement that lack of detailed information about the therapies provided would limit the informational value of the Grosarth RCTs is also put into perspective. Although the trials do not provide any information as to whether, for example, Iscador A or Iscardor M is more effective for a particular indication, or whether mis-tletoe dosage should be increased rapidly or slowly, they do assess the question of whether mistletoe therapy administered in regular clinical settings has any benefit at all. Similarly, the Cochrane-Review summary concludes with a global analysis and does not differentiate ac-cording to mistletoe host tree and dosage. The Grossarth trials were also criticised for the lack of detailed information about adjunct therapies administered apart from the investigational therapy, but this represents customary practice in clinical trials. Similarly, in the Kleeberg or Steuer-Vogt trials, there is no documentation on therapies administered apart from the trial therapy, although one can assume that the patients did receive other therapies in the time span from surgery to death.

Piao trial (2004) [15]: If blinding is not reliably possible, an active, effective therapy is a rea-sonable and well-established alternative for the control group. This may lead to an underesti-mation of the effects of the test therapy, which would not be in conflict with the prevailing conservative attitude in clinical research. This solution was adopted in the Piao trial. In the Cochrane-Review, however, the use of active control therapy was not acknowledged as a rea-sonable alternative: the therapy benefit of mistletoe extracts was deemed unassessable since the effects of the control therapy (Lentinan) were unclear. This statement is not quite cor-rect because a number of clinical trials on Lentinan are available.

Gutsch trial (1988) [28]: This trial was excluded from the Cochrane-Review because of a putative randomization error. However, no such error is reported in the publication by Gutsch; instead protocol violations are described, i.e. the allocated therapy was not administered to all patients. This occurs frequently in clinical trials. (For this reason analyses are mostly made according to intention-to-treat and per-protocol; Gutsch analysed as treated [29]). Therefore this trial should have been included as an RCT.
Kienle-Review (2003) [30]: According to the Cochrane Review, Kienle 2003 'failed to' in-clude two unpublished trials, Lange 1993 and Schwiersch 1999. The fact is: 'Unpublished' was an exclusion criterion for the Kienle Review from 2003. Furthermore, Kienle was said to have also failed to include Borrelli's published trial. This is true for Kienle 2003 but not for Kienle's HTA-report of 2006 [6;7] and the Kienle Review from 2007 [12]. According to the Cochrane Review, Kienle 2003 also mistakenly included the above-mentioned Gutsch trial as an RCT; in fact, however, this trial was indeed an RCT. Kienle is said to have included Sal-zer 1987 twice: Once as a randomized trial and once as a non-randomized trial. The fact is: Two different trials were involved here, concerning bronchial carcinoma and breast cancer, respectively. The Cochrane-Review is also of the opinion that the trial described in the Kienle Review 2003 as Salzer 1987 is identical to Gutsch 1988 (in the Cochrane-Review also described as Gunczler 1974). This is also incorrect: Neither is Gutsch 1988 identical with the RCT of bronchial carcinoma, nor with the quasi-randomized trial for breast carci-noma which was carried out before the Gutsch trial. The randomized trial of bronchial carci-noma in question was overlooked by the Cochrane Review and not included.

Further issues
The Cochrane Review has a substantial number of other errors of details, but not every prob-lematic aspect can be dealt with here.
All non-randomized trials were excluded a priori, which is questionable since tumour re-sponse to mistletoe therapy was an explicit outcome parameter in the Cochrane Review and since tumour remission has been far more thoroughly investigated and represented in the non-randomized trials than in the randomized trials.

Strangely, the decision to conduct this Cochrane Review is described as resulting from discrepancies between earlier reviews (e.g. Kienle 2003 [30], Ernst 2003 [31], Lange-Lindberg 2006 [32]), whereas the protocol for the Cochrane Review was already available in the Cochrane Library long before these reviews were accessible.

Overall picture of mistletoe trials
When the criticism against the Cochrane Review presented here is taken fully into account, a different overall picture of the mistletoe trials emerges.

While most of the trials have strengths and weaknesses to varying extent, as is the case with other clinical trials, there are indeed a number carefully conducted trials (Furthermore, the mistletoe trials with a negative result, ranked as 'high quality' by the Cochrane Review have ' in part substantial ' quality deficiencies not discussed in the Review. See further details at www.mistel-therapie.de or [33]). Currently, the best evidence of mistletoe effects concerns improvement of quality of life and improved tolerance of conventional oncological therapies. Survival benefit from mistletoe therapy has been found in many trials, but not beyond cri-tique. Tumour remissions have been reported, often in detail, in non-randomized trials, and seem to depend on the type of administration and dosage of mistletoe extracts.

Hopefully the evidence base will be further broadened by future trials. However, 'high quality' trials are frequently called for, but their practical implementation is subject to consider-able difficulties. Due to huge bureaucratic hurdles today, industry-independent trials are hardly feasible. (The cost per clinical RCT in the USA have been estimated at US$ 12 million [34]). In Germany larger trials for mistletoe therapy are almost infeasible because of recruit-ment problems and randomization refusals. For this reason, trials have to be conducted in other countries. Blinding poses problems discussed above. Nonetheless, mistletoe therapy is subject to vigorous research activities, the number of clinical trials has increased markedly in recent years, and this trend is likely to continue in the future.

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Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We would like to thank Kienle & Kiene for their comments on the review. We have considered their points carefully. The cited trials and reviews will be assessed among others in the upcoming update of the review. This update was already planned as the review was first published in the Cochrane Library. In this update, the assessment of risk of bias will be done according to the new approach of the Cochrane Collaboration. This approach relies neither on a scale nor a checklist, but on a 'domain-based evaluation', in which the assessments are made separately for different domains and outcomes (see Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions).
Concerning the assessment of the validity of findings of clinical trials within a systematic review, we are aware to the fact that such an assessment always involves a certain degree of subjectivity. Nevertheless, we reject the allegation of double standards in the appraisal of the included studies in our review.
The informative value of our review is limited by the fact that the majority of the included trials have restricted internal and/or external validity. We will change the conclusions of our review, if we find conclusive reasons for it. The points which Kienle & Kiene raised were insufficient for it and did not convince us.
To address some of Kienle & Kiene's specific comments:

'That the following publications were not taken into account'

Cited reference [1]: Salzer G. 30 Jahre Erfahrung mit der Misteltherapie an öffentlichen Krankenanstalten. In: Leroi R, editor. Misteltherapie. Eine Antwort auf die Herausforderung Krebs. Stuttgart: Verlag Freies Geistesleben, 1987: 173-215.
This reference relates to a book chapter in which experiences with and results of clinical investigations with mistletoe extracts from the 1960ies to the 80ies were narratively reported and supplemented with few table data and figures. On page 179 of this book chapter a trial

with breast cancer patients is mentioned that was initiated in 1971 and in which the treatment was allocated in a quasi-random manner. This trial was listed in the review as Günczler 1971 and excluded. On page 180 a second randomised trial with breast cancer patients is mentioned ("*1974 wurde eine neue, prospektive, randomisierte Studie operierter Mammakarzinome (...) auf breiter Basis gestartet. (...) Bis 1978 wurden 724 Fälle randomisiert und eine erste Zwischenbilanz im Sommer 1979 gezogen*.") which was analysed and published by J. Gutsch (page 181: "*1985 hat J. Gutsch in Zusammenarbeit mit der statistischen Abteilung der Universität Witten-Herdecke (G. Scholz) eine Schlußbilanz dieser Arbeit gezogen (20).*"). This trial was listed in the review as Günczler 1974 and Gutsch 1988 and excluded because J. Gutsch affirmed in a personal communication that the random allocation to the treatment groups had failed which he already had reported in the publication (Gutsch 1988). The initiators of this study (G. Salzer and M. Günczler) were not listed as authors of Gutsch 1988.

On page 186/187, two clinical trials with lung cancer patients are mentioned. According to G. Salzer, the author of the book chapter and initiator of the trials, one of them yielded no 'useful results' ("*Leider lieferte diese Studie keine brauchbaren Ergebnisse (...)*"). Due to this statement, it was decided to not include the scarce data of this trial. The second trial was included in the review (Salzer 1991).

Cited reference [2]: Kim M-H, Park Y-K, Lee S-H, Kim S-C, Lee S-Y, Kim C-H et al. Comparative study on the effects of a Viscum album (L.) extract (mistletoe) and doxycycline for pleurodesis in patients with malignant pleural effusion. 51th Meeting of The Korean Association of Internal Medicine. Translation by Helixor Heilmittel GmbH. Korean Journal of Medicine 1999; 57(Suppl. II):S121.

This abstract publication was i) not listed in one of the databases which were searched for the review, ii) not mentioned by one of the manufacturers of mistletoe extracts which we had contacted and iii) was not included or even mentioned in one of the systematic reviews published until 2006. Also Kienle & Kiene did not include this trial in their systematic review published in 2003. In Nov, 2008, again, the reference could neither be found in any of the databases listed in the review, nor on a search engine for the 'Korean Journal of Medicine' (http://www.koreamed.org/SearchBasic.php?KM=1&DT=0&DC=20&DisplaySearchResult=1&SS=2) nor on the web site of the 'Korean Association of Internal Medicine' (http://www.kaim.or.kr).

The cited reference was included in the 'Classification pending references' section of the review for now.

Cited reference [3]: Enesel MB, Acalovschi I, Grosu V, Sbarcea A, Rusu C, Dobre A, et al. Perioperative application of the Viscum album extract Isorel in digestive tract cancer patients. Anticancer Res 2005;25:4583-90.

This paper was checked for eligibility in 2006 but the phrase in the abstract, i.e. "*The study involved 70 cancer patients, divided into two groups: Isorel-treated group of 40 patients who received Isorel* (...) *and the age- and sex-matched control group of 30 patients that did not receive Isorel* (...)" and the number of patients in the two study groups raised doubts about the way the groups were constituted. As we had not received any additional information on the allocation procedure from the first author, the study was not included in the review, which was not mentioned by an oversight.

In 2008 we received an authenticated document from the manufacturer of the used mistletoe brand in which the first author of the study certified the randomised allocation to the treatment groups. The study is now included in the 'Studies awaiting classification' section and will be assessed in the upcoming update of the review.

Cited references [4, 5, 8-11]: These clinical trials are also included in the 'Studies awaiting classification" section and will be assessed in the upcoming update of the review.

'That the procedure chosen for evaluation of study quality is inadequate'

The validity assessment in the review was geared to common practice in systematic reviews. For the purpose of enabling a transparent view on the possible risks of bias in the included studies, key domains of methodological quality were not only assessed by means of widely used criteria lists but also described narratively and annotated with comments. Trials were grouped according to the scores of the criteria lists, and the levels of evidence were judged accordingly. No trial was excluded due to low methodological quality and the results of all outcomes of all included studies were appraised. Moreover, the limitations of checklists of methodological quality were discussed.

Kienle & Kiene themselves used in both of their systematic reviews on mistletoe extracts a "*criteria based analysis*" to assess the methodological quality of included studies. The criteria were adapted from the approach of the Centre for Reviews and Dissemination, University of York and from Kleijnen 1994. Both approaches rely on the same key domains used in our review.

'That two scores were employed which give the greatest weight to blinding of the study intervention'

The Jadad scale consists of three items relating to the issues randomisation, blinding, and description of withdrawals and drop-outs. Two points are given if randomisation is well-described and the method appropriate, the same is true for blinding and one point is given for the issue of withdrawals and drop-outs. Thus, in the strict sense, the issues of randomisation have unambiguously the same weight than those of blinding.

The maximum score in the Delphi list is nine points. A study could obtain three points for issues related to blinding (patient, care provider, outcome assessor) but also three points could be obtained for issues related to the homogeneity of the study groups (randomisation, allocation concealment, distribution of prognostic indicators between groups). Thus, in this list, issues concerning selection and allocation of the study group have the same weight than those related to blinding.

'That by selecting the evaluation scales, a poor performance of the mistletoe trials was predetermined as in principle this therapy cannot be blinded'

This statement is wrong. A well designed and properly conducted open-label study could fulfil a maximum of seven criteria of the Delphi list. Given our arbitrary cut-off point of six out of nine fulfilled Delphi criteria for high methodological quality, blinding of the patient and the care provider is not a prerequisite for receiving this label. Concerning the assessment with the Jadad scale, a well designed and properly conducted study in which the authors at least attempt to double blind the intervention could fulfil a maximum of four criteria of this scale. Given our arbitrary cut-off point of four out of five Jadad criteria for high methodological criteria, a successful blinding of the patient and the care provider is not a prerequisite for receiving this label.

'That the Cochrane-Review disqualifies all mistletoe trials on this point [blinding], including the trials formally conducted as double-blind trials'

Again, this statement is wrong. All trials that were classified as of higher methodological quality according to the Jadad scale were designed as double blind (Schwiersch 1999; Semiglasov 2004; Semiglasov 2006).

'That the problem with blinding of the treatment with mistletoe extracts is not mentioned'

This is not correct. The problem is addressed in three sections: 'Results', 'Discussion' and 'Implications for research'.

'That the general requirement of blinding has bizarre consequences'

It was unclear to whom Kienle & Kiene addressed this statement as no one would seriously claim a "*general requirement of blinding*"in all clinical trials.

'That Piao 2004 was evaluated according to the intention-to-treat-principle'

Kienle & Kiene cited for Piao 2004 a "*biometric trial report available on the Internet*" (see Klose et al. [2003] listed in Piao 2004). In this report the following comments concerning the statistical methods of Piao 2004 could be found: Page 12: "*In the clinical trial protocol primary and secondary endpoints as well as an analysis strategy are not specified*". Page 14: "*The analysis has to be interpreted as explorative and has no confirmative power* (...) *The statistical analysis of the efficacy criteria, safety criteria and quality of life questionnaires follows the as-treated principle (AT analysis).*"

'That double standards were applied concerning the assessment of Piao 2004 and Steuer-Vogt 2001'

Piao 2004 was an open-label, 2-arm parallel RCT with an active treatment as control. In the original publication, the aim of the study was described as "*to evaluate the impact of a standardized mistletoe extract administered complementary to the standard treatment of patients with breast, ovarian and non-small cell lung cancer.*" Outcome measures were quality of life, performance status, tumour response, immunological parameters and a safety analysis. It was unclear whether the quality of life outcomes were patient- or physician rated. A primary outcome measure was not defined. Our assessment of this study was based on the original publication and a medical study report.

According to our judgment, the validity and generalizability of the findings of Piao 2004 were primarily limited due to:

- possible influences of selection bias (no information on concealment of treatment allocation) and participant/observer bias (unblinded assessment of patient-/physician-rated outcomes),
- lack of details on whether concomitant supportive medication and sum doses of chemotherapy were comparable between groups,
- variability of length of observation/treatment periods.

This was reflected in the respective criteria of the validity assessment.

Steuer-Vogt 2001 was an open-label, 2-arm RCT with two strata in each arm with a no treatment control. The study was reported according to the CONSORT statement. Concerning the aim of the study, the authors stated: "*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 leads to an increased DFS compared with patients receiving no additional therapy.*" Outcome measures were disease-free survival (primary outcome measure), disease-specific survival, quality of life, immunological parameters and a safety analysis. Our assessment of the study was based on two original publications of the study and two further papers. Concerning withdrawals/drop-outs both trials received one point on the Jadad scale. Concerning intention-to-treat analysis, Piao 2004 received no point on the Delphi list due to the above mentioned reason and Steuer-Vogt 2001 received one point, as the analysis of the primary outcome measure (disease-free survival) followed the intention-to-treat principle. Concerning the quality of life analysis in Steuer-Vogt 2001, we not only judged the results as at risk for the influence of participant bias due to the unblinded investigation but also critically discussed the findings.

'That double standards were applied concerning the assessment of similarity of groups in Kleeberg 2004 and Grossarth-Maticek 2001'

We judged the Delphi criterion concerning the similarity of groups at baseline regarding the most important prognostic indicators in both Grossarth-Maticek trials, as 'unclear' because the matching criteria did not ensure that the matched patients had comparable risks related to survival. For example, given the definition of 'stage III colon carcinoma' as "*N>0 M0*" (see p. 61 of the original publication), two patients matched for this stage could mean that one patient had a tumor directly invading other organs with lymph node metastases in four or more regional lymph nodes (T4, N2, M0), whereas the other had a tumor invading the muscularis propria with metastases in one to three regional lymph nodes (T2, N1, M0).
In Kleeberg's trial there was indeed a slight imbalance of patient's characteristics between the groups. However, the key factors, TNM stage and Breslow thickness, were quite similarly distributed and the higher number of males and patients with non-limb localisation of the primary melanoma in the intervention group could be contrasted with the higher number of patients with ulcerations in the primary tumour in the control group. Considered together, we decided that the groups should be regarded as similar at baseline regarding the most important prognostic indicators.

'That blinding was not properly assessed in Borrelli 1999 and Dold 1991'

The assessment of Borrelli's trial was based on two original publications of the study. This trial, which we had found through handsearching, was not included in any of the systematic reviews published until 2006 (including that of Kienle & Kiene) and the manufacturers of the mistletoe brand used in Borrelli's trial did not even provide information on the existence of this trial.
There is no statement concerning blinding of the interventions in either of the publications.
As the author reported the use of a placebo in the control group (see p. 28 in the original publication), we at least assumed a single blinded design. Nevertheless, due to the lack of information we judged the respective criteria of the validity assessment as 'unclear'.
For the upcoming update of the review, the author will be contacted and the study will be reappraised provided that reliable information will be made available concerning blinding of the intervention and concealment of allocation.
Kienle & Kiene claimed that "*the Cochrane-Review allocates the Dold trial a plus point in the Delphi list regarding adequate blinding of patients*". This statement is wrong. Dold 1991 reported a central, independent and anonymous outcome assessment and therefore the criteria of the Delphi list concerning a concealed outcome assessment was judged as being fulfilled.

'That concealment of allocation was not properly assessed in Borrelli 1999 and Grossarth-Maticek's trials

Concerning the assessment of concealment of allocation in Borrelli 1999 see the precedent comment.
In Grossarth-Maticek's trials drawing of lots was used to assign participants to the intervention (see p. 4 in the original publication). This procedure is transparent before allocation, and, according to the criteria of the Cochrane Reviewer's Handbook, this method does not ensure concealed allocation. Therefore, we assessed the criterion of the Delphi list related to concealment of allocation as 'unclear'.

'That it was improper to claim that in the Grossarth trials it was unclear whether the patients had consented to participate'.

The assessment of the trials of Grossarth-Maticek et al. in our review was based on two original publications, and in none of these publications a statement could be found that patients of the nested RCTs had given their informed consent for participation.

'That Grossarth achieves what almost all experimental trials are incapable of: to maximise internal and external validity within a single research project'

The two included studies of Grossarth-Maticek et al. had the following design:

- participants of a large cohort study were matched,
- a small number of the matched pairs formed the basis for a nested RCT,
- in this RCT, one of the matched participants was randomly allocated to the intervention,
- the intervention was the advise "*to ask their doctor for treatment with Iscador*" (see p. 60 in in the original publication),
- during follow-up, participants were "*questioned about well-being, progression of disease, further diseases, continuation of treatment, and new therapies.*" (see p. 62, l.c.).
- concerning the intervention, "*only the basic fact of an Iscador treatment and its global duration were documented. The type of Iscador that was used (…) the dosage, and temporary interruptions of treatment were not documented.*" (see p. 62, l.c.).

No information was given (if collected at all) concerning any tumour-related or other treatments. The conclusion of the authors of the trials was: "*Iscador treatment can achieve a clinically relevant prolongation of survival time of cancer patients.*" If this causal inference indeed possessed the alleged high degree of external validity then the life of many cancer patients could be prolonged by the simple advice "*to ask their doctor for treatment with Iscador*" irrespective of what other treatments would be applied. Such a reasoning appears not only overconfident but somewhat cynical regarding the daily efforts of all parties concerned with oncological treatment and care. With their claim of a 'maximised internal and external validity' the authors overlook not only that basic criteria of internal validity are not fulfilled in Grossarth-Maticek's trials, but also that the generalizability is severely limited because important factors (i.e. tumour-related therapies) interacting with the independent variable (i.e. survival) are not assessed. Furthermore, the critical discussion of the underlying cohort studies (see: Issue 3 of Psychological Inquiry [Vol. 2, 1991]) is not mentioned by Kienle & Kiene.

'That the use of active control therapy in Piao 2004 was not acknowledged as a reasonable alternative and the therapy benefit of mistletoe extracts was deemed unsuitable for assessment since the effects of the control therapy (Lentinan)'

In Piao 2004, the groups were compared concerning the changes of the scores of the quality of life questionnaires. The authors found a significant higher improvement in the mistletoe group compared with the group in which lentinan, a biologic response modifier, had been given. However, the direction of the effect of lentinan on issues of quality of life is unclear, at least in this study. Therefore, we concluded that the differences in the quality of life scores between the groups could be attributed either to positive effects of mistletoe extracts or to negative effects of lentinan. To reliably clarify this issue a placebo or no-treatment group would have been necessary.

'That the status "unpublished" was an exclusion criterion for the Kienle Review from 2003 and as a consequence, Schwiersch 1999 and Lange 1993 were not included'

In this review the authors stated "*Publication as a manuscript or abstract (e.g. conference report)*" as inclusion criteria. This was misinterpreted by us, as Schwiersch 1999 and Lange 1993 were both available, though unpublished, as submission manuscripts. The respective section in the review was changed.

'That the trials mentioned in Salzer 1987 were not properly handled'

Please see the first specific comment of this reply concerning the trials mentioned in Salzer 1987. The respective section in the review was changed.

'That the decision to conduct this review was described as resulting from discrepancies between earlier reviews (e.g. Kienle 2003, Ernst 2003, Lange-Lindberg 2006) whereas the protocol for this review was already available in the Cochrane Library long before these reviews were accessible.'

The protocol of the review was first published in the Cochrane Library in 2001. The passage in the background section of the protocol to which the statement of Kienle & Kiene alludes was: "*Despite this widespread use of mistletoe preparations, there is considerable dispute about the efficacy of this treatment modality and the results of the existing reviews concerning the efficacy and effectiveness of this treatment are inconsistent (Kiene 1991, Hauser 1993, Kleijnen 1994).*

For several reasons it seems necessary to systematically review the available evidence of mistletoe treatment of cancer:

- *The results of the present reviews are inconsistent.*
- *Several new clinical trials with mistletoe preparations have been published recently.*
- *The therapeutic paradigm of this treatment modality and thus the endpoints of the clinical studies have shifted during the last years from tumor response towards quality of life and alleviation of side effects of chemo- and radiotherapy.*
- *A new treatment approach emerged over the last years, which contrasts with the classical treatment modality. Both concepts are subject of substantial debate. The latter works with mistletoe preparations standardized for the manufacturing process and are applied at individual doses whereas the new approach applies preparations standardized for the b-galactoside-specific mistletoe lectin I in a constant dosage schedule.*"

In the review, we adjusted the passage to the topical discussion, which still is characterised in that "*The existing reviews used different approaches to collect and appraise the evidence and varied in their interpretations of the data*" (see last passage of the review).

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 3 February 2008.

Date	Event	Description
15 March 2010	Amended	Contact author address amended

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 2, 2008

Date	Event	Description
9 February 2009	Feedback has been incorporated	Feedback and reply added to review
26 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All reviewers participated in the development of the protocol, the identification of studies, the data extraction and quality assessment of the included studies, the interpretation of the results and the review of the manuscript. Markus Horneber coordinated the review and wrote the draft of the manuscript.

DECLARATIONS OF INTEREST

RH and MR received research funding for clinical and preclinical research on mistletoe extracts from mistletoe manufacturers. All research projects were independent from this review . RH and MR received honoraria for scientific lectures from mistletoe manufacturers

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INDEX TERMS

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*Mistletoe; Antineoplastic Agents, Phytogenic [*therapeutic use]; Neoplasms [*drug therapy]; Phytotherapy [*methods]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans