Thymic peptides for treatment of cancer patients (Review)

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TABLE OF CONTENTS

[Intervention Review]

Thymic peptides for treatment of cancer patients

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ABSTRACT

Background

Purified thymus extracts (pTE) and synthetic thymic peptides (sTP) are thought to enhance the immune system of cancer patients in order to fight the growth of tumour cells and to resist infections due to immunosuppression induced by the disease and antineoplastic therapy.

Objectives

To evaluate the effectiveness of pTE and sTP for the management of cancer.

Search strategy

We searched CENTRAL (*The Cochrane Library* 2010, Issue 3), MEDLINE, EMBASE, AMED, BIOETHICSLINE, BIOSIS, CATLINE, CISCOM, HEALTHSTAR, HTA, SOMED and LILACS (to February 2010).

Selection criteria

Randomised trials of pTE or sTP in addition to chemotherapy or radiotherapy, or both, compared to the same regimen with placebo or no additional treatment in adult cancer patients.

Data collection and analysis

Two authors independently extracted data from published trials. We derived odds ratios (OR) from overall survival (OS) and disease-free survival (DFS) rates, tumour response (TR) rates, and rates of adverse effects (AE) related to antineoplastic treatments. We used a random-effects model for meta-analysis.

Main results

We identified 26 trials (2736 patients). Twenty trials investigated pTE (thymostimulin or thymosin fraction 5) and six trials investigated sTP (thymopentin or thymosin α_1). Twenty-one trials reported results for OS, six for DFS, 14 for TR, nine for AE and 10 for safety of pTE and sTP. Addition of pTE conferred no benefit on OS (RR 1.00, 95% CI 0.79 to 1.25); DFS (RR 0.97, 95% CI 0.82 to 1.16); or TR (RR 1.07, 95% CI 0.92 to 1.25). Heterogeneity was moderate to high for all these outcomes. For thymosin α_1 the pooled RR for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, P = 0.15) for DFS, with moderate heterogeneity. The pTE reduced the risk of severe infectious complications (RR 0.54, 95% CI 0.38 to 0.78, P = 0.0008; I^2 = 0%). The RR for severe neutropenia in patients treated with thymostimulin was 0.55 (95% CI 0.25 to 1.23, P = 0.15). Tolerability of pTE and sTP was good. Most of the trials had at least a moderate risk of bias.

Authors' conclusions

Overall, we found neither evidence that the addition of pTE to antineoplastic treatment reduced the risk of death or disease progression nor that it improved the rate of tumour responses to antineoplastic treatment. For thymosin α_1, there was a trend for a reduced risk of dying and of improved DFS. There was preliminary evidence that pTE lowered the risk of severe infectious complications in patients undergoing chemotherapy or radiotherapy.

PLAIN LANGUAGE SUMMARY

Thymic peptides for treatment of cancer patients in addition to chemotherapy or radiotherapy, or both

The immune system plays a key role in the body's own defences against cancer cells. The thymus gland plays a central part in this and modifies T-cells, a subset of lymphocytes. Studies with thymic peptides have shown a variety of effects on the immune system. There are two groups of thymic peptides available for use in treatment: purified extracts from animal (mostly calf) thymus glands and synthetically produced thymus gland peptides.

This review aims to answer the question whether having thymic peptides can improve the response to and tolerability of standard chemotherapy or radiotherapy, or combined treatment. Further questions are whether the peptides inhibit or reduce the progression and recurrence of disease, whether they prolong the life of cancer patients and whether quality of life is improved.

This review looked at the evidence from 26 clinical trials with a total of 2736 adult cancer patients. Many of the trials were small and of moderate quality. Only three studies were less than 10 years old. Thymosin α_1 is a synthetic peptide that shows some promise as a treatment option for patients with metastatic melanoma when used in addition to chemotherapy. Severe problems occur during chemotherapy and radiotherapy due to low white blood cell counts and infections. These were reduced by using purified thymus extracts. However, the use of purified thymus extracts should be investigated more thoroughly before the extracts are used routinely in patients. The findings were not conclusive and caution is advised. Overall, thymic peptides seem to be well tolerated.

BACKGROUND

By the late 1950s and early 1960s the role of the thymus as a lymphoid organ became clearer based on observations of a decreased immune response and consequent lowered resistance to infectious disease that resulted from damage to or experimental removal of the gland (Seybold 1950). It is now well established that the thymus gland is a central lymphoid organ in which bone marrow-derived T-cell precursors undergo differentiation within the context of a specific cellular and extracellular microenvironment. The thymus gland is also responsible for the production of various peptides with hormone-like activity and purified extracts from animal thymus glands have been used to treat primary immunodeficient states (Goldstein 2009).

The role of the immune system to recognize and destroy tumour cells has been hypothesized since the early 1950s and is now generally accepted (Dunn 2002). One of the approaches to treat cancer is via stimulation or modulation of the immune system with extracts and peptides from the thymus gland, which was first introduced in the 1970s (Costanzi 1977).

Thymus derived pharmaceuticals can be divided into two groups:

1. purified extracts from animal thymus glands containing peptide mixtures; and

2. synthetically produced single thymic peptides.

Historically these two groups represent two steps in the investigation of thymic peptides involved in T-cell maturation and activation. The first step is to produce cell-free extracts, the second is to characterize and analyse single components of these extracts.

Purified thymus extracts

Extracts from calf thymus glands were further processed in different steps of purification, fractionation and filtration to result in peptide mixtures. The exact composition and character of the peptides are not completely known and are subject to biological variation. Different preparations are not defined by their components but by the respective standardization of the extraction procedure. Two purified thymus extracts (pTE) were investigated in

clinical trials and are included in this review, thymosin fraction 5 and thymostimulin (Table 1).

Table 1. Type of interventional treatment

Type	Name	Ingredients	Provider	Applied in study
Purified thymus extracts	Thymosin fraction 5	Peptide mixture, range 1-15 kDa	Hoffmann-La Roche	Bedikian 1984; Cohen 1979; Scher 1988; Wara 1981
	Thymostimulin	Peptide mixture, range 1-12 kDa	Serono S.A.	Airoldi 1987; Canovas 1988; Canovas 1991; De Serdio 1997; Del Giacco 1988; Federico 1995; Gonnelli 1995; Guzman 1988; Iaffaioli 1994; Luzi 1984; Macchiarini 1989; Mantovani 1988; Mustacchi 1994; Pavesi 1993; Salvati 1984; Sanchiz 1996
Synthetic thymic peptides	Thymosin α_1	Polypeptide (28 amino acids)	SciClone Pharmaceuticals	Cheng 2004; Gish 2009; Maio 2010; Schulof 1985
	Thymopentin	Oligopeptide (5 amino acids)	Italfarmaco	Gebbia 1994; GISOT 1987

Thymosin fraction 5

Thymosin fraction 5 was produced by US investigators in 1966. Goldstein et al extracted a so called 'lymphocytopoietic factor' from calf thymus, referring to its capacity to stimulate proliferation of lymphocytes both in vitro and in animal models, and termed it thymosin, which was initially thought to be a single polypeptide (Goldstein 1966). A further 5-step purification led to 'thymosin fraction 5', then identified as a mixture of 30 to 40 small polypeptide components with a molecular weight ranging from 1 to 15 kilodalton (Goldstein 1977).

Thymostimulin

Thymostimulin, also extracted from calf thymus, was first produced by Italian investigators in 1976. It consists of a group of peptides with molecular weights ranging from 1 to 12 kilodalton (Falchetti 1977). The way of processing differs from that of thymosin fraction 5 in several steps, which presumably results in a different composition of peptides (reviewed in Schulof 1985a).

Synthetic thymic peptides

Synthetically produced thymic peptides (sTP) are derivatives of peptides that have been isolated from thymus extracts and sequenced. Two synthetically produced thymic peptides were used in clinical trials included in this review, thymosin α_1 and thymopentin (Table 1).

Thymosin α_1

Thymosin α_1 is a peptide of 28 amino acids that was first isolated from thymosin fraction 5 in 1977 (Goldstein 1977). It is highly conserved among species and the amino acid sequence of human and bovine thymosin α_1 are identical (reviewed in Hannappel 2003). Thymosin α_1 has been sequenced and produced synthetically. Nowadays it is approved, mainly in countries of Asia and South America, for the treatment of chronic hepatitis B and C as a vaccine enhancer and in few countries of Southeast Asia for the treatment of cancer (Billich 2002). Pharmacokinetic studies in healthy volunteers showed good absorption after subcutaneous injection with a peak serum level at between one and two hours

and a half live of less than three hours (Rost 1999).

Thymopentin

Thymopentin is a fragment of a larger peptide called thymopoietin. Thymopoietin was initially isolated from calf thymus and consists of 49 amino acids. It had been shown to induce differentiation of T-cell precursors both in vitro and in vivo (Schlesinger 1975). In the search for a smaller peptide with the same immunologic properties that was suitable for large-scale synthesis, the five amino-acid peptide thymopentin was identified (Goldstein 1979). Pharmacokinetic studies in humans showed a short half live of 30 seconds (reviewed in Singh 1998).

Preclinical and clinical studies with pTE and sTP

Preclinical studies with pTE and sTP showed a variety of modulatory effects on the immune system (Bodey 2000; Chretien 1978; Goldstein 2009; Schulof 1985a). They were tested with other substances in the Biological Response Modifiers Program of the National Cancer Institute for their efficacy in the treatment of human cancers in the 1980s (Schulof 1985a). Surveys from the late 1990s showed ample dissemination of information on the treatment of cancer with purified thymus extracts as part of a 'complementary and alternative treatment' of cancer (Grothey 1998; Hardell 1998; Kullmer 1999; Moschen 2001; Sehouli 2000; Soellner 1997). Clinical studies investigated the effects on various clinical endpoints as well as immunological effects in a broad range of malignant diseases. The findings of controlled trials of pTE and sTP in cancer have not been conclusive. The height of research activity was in the 1980s and early 1990s and then seemed to wane but very recently published studies with thymosin α_1 indicate that it is still topical (Maio 2010).

The purpose of this review was to summarize the available evidence from clinical trials which investigated pTE and sTP in combination with chemotherapy or radiotherapy, or both, in order to determine whether the addition of thymic peptides had a beneficial effect on survival outcomes and quality of life in cancer patients as well as whether it improved the response to and tolerability of conventional cancer therapies. Given the diversity of pTE and sTP we also intended to elucidate their probable differential effects.

OBJECTIVES

To determine the effectiveness and tolerability of purified thymus extracts (pTE) and synthetically produced thymic peptides (sTP) for the treatment of cancer patients during chemotherapy or radiotherapy. The objectives of the review were to assess the following.

- The effects of thymic peptides on:
    - overall survival (OS) and disease-free survival (DFS) or progression-free survival (PFS),
    - tumour response,
    - adverse effects of chemotherapy and radiotherapy,
    - patient-reported quality of life.
- Adverse effects of pTE and sTP;

and to make recommendations for future research.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs (for example trials which used alternation, allocation by date of birth, etc.).

Types of participants

Adult patients with histologically proven malignant diseases of all stages who were submitted to treatment with chemotherapy, chemo-immunotherapy or radiotherapy (that is standard care).

Types of interventions

Intervention group

Standard care plus treatment with any kind of parenterally applied pTE or sTP.

Control group

Standard care plus placebo treatment or no additional treatment. Standard care was required to be similar between groups.

Types of outcome measures

The outcomes of interest were:

- OS;
- DFS and PFS;
- tumour response (parameters for response had to be defined or follow standard criteria (WHO (Miller 1981), RECIST (Therasse 2000));
- hematologic toxicities or infectious complications related to antineoplastic treatment (chemotherapy, radiotherapy) of at least grade 3, scored using standardized criteria (CTC version 2 or later) (CTC 2009);
- adverse events related to pTE and sTP.

Quality of life (QoL), measured with validated instruments, was an outcome for which data were sought but no data for this outcome were found in any of the included RCTs. Trials which only reported physiological measures (for example immune parameters etc.) were excluded.

For a glossary of terms please see Appendix 1.

Search methods for identification of studies

The last systematic search was performed in February 2010.

Electronic searches

We searched the following databases without language restrictions: Cochrane Complementary Medicine Field Registry of randomised clinical trials and controlled clinical trials, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3), MEDLINE, EMBASE, PubMed, AMED, BIOETHICSLINE, BIOSIS, CATLINE, CISCOM, HEALTHSTAR, INTERNATIONAL HEALTH TECHNOLOGY ASSESSMENT, SOMED, LILACS. Synonyms of the specific terms were identified by looking up the thesaurus of each database, if available. Search strategies and terms are listed in Appendix 2. All databases were searched from inception to February 2010.

Duplicates were removed from the search results and bibliographies from retrieved articles were searched for additional studies. The search strategies used were developed and executed by the author team.

Searching other resources

To minimize the impact of publication bias, we searched conference abstracts and unpublished material. Inquiries were sent to the investigators or institutions of included studies and respective manufacturers of pTE and sTP requesting information on additional trials. Our own files were searched for further studies.

Data collection and analysis

All discrepancies between two authors in the process of data collection and analysis were discussed and, if not agreed upon, the opinion of a third review author was sought.

Selection of studies

All publications identified by the search were screened by one review author (SM), who excluded those that were clearly irrelevant (for example diseases other than cancer, reviews, etc.). The titles and abstracts of the remaining articles were independently checked by two review authors (KB, MH, SM, EW). When articles could not be excluded with certainty, full text material was obtained. At least two review authors (KB, MH, SM, EW) of the team independently assessed full text material by means of a standard eligibility form that applied the inclusion and exclusion criteria. All results of the selection process were documented and disagreements resolved by discussion with a third review author (MH, EW).

Data extraction and management

Data extraction was performed non-blinded to the study authors and independently by at least two review authors using a pretested extraction form. For included studies, data were extracted as recommended in Higgins 2009. This included data on the following.

- Author, year of publication (if published), journal citation and language.
- Country.
- Setting.
- Study design, methodology.
- Study population: total number enrolled, patient characteristics (inclusion and exclusion criteria, age, stage, histological cell type, co-morbidity, previous treatment), number enrolled in each arm.
- Intervention and control details: no treatment, composition of placebo.
- Standard care: type of chemotherapy, number of cycles and dose; timing and dose of radiotherapy.
- Risk of bias in study: see below.
- Duration of follow up.
- Deviations from protocol.
- Outcomes, where data on all outcomes were extracted for:
    - time to event data, we extracted the median or mean survival times and their spread or confidence interval;
    - dichotomous outcomes (e.g. adverse events, deaths, disease recurrence, disease progression, tumour response), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at the endpoint in order to estimate a risk ratio (RR). If necessary, data were extracted from Kaplan-Meier curves;
    - adverse events, type of event and grade of toxicity.

The time points at which outcomes were collected and reported were noted. Data were entered from the forms into a Microsoft Access database and double-checked using descriptive database methods and plausibility checks by two review authors (MH, EW). If more than one report from a study was available, the most recent was considered as the primary publication and was used primarily for data extraction; information from other reports were extracted if not reported in the primary reference. Data from non-english articles were extracted with the help of a native speaker.

Assessment of risk of bias in included studies

The assessment of risk of bias was carried out according to the approach of The Cochrane Collaboration (Higgins 2009). In a first step, information relating to study quality that was essential for the judgment of risk of bias was extracted onto a prespecified form. Two review authors (MH, EW) then independently judged the risk of bias for each criterion as being low, high or unclear. Disagreements were resolved by discussion. The 'blinding' item was split up in order to allow for differential assessment of the outcomes dependent or independent of outcome assessors. The risk of bias was scored 'low' to 'high' with three intermediates ('low to moderate', 'moderate', and 'moderate to high'), with 'high' indicating the highest risk of bias.

Dealing with missing data

Where information was missing in the study reports, lacked detail or there was a discrepancy between different reports, we tried to obtain the required information from the study authors. Contacting study authors helped to clarify our questions for only one publication (Maio 2010).

Assessment of heterogeneity

Heterogeneity was assessed according to the standard method using the I^2 statistic, calculated for each comparison on each outcome. I^2 values above 50% indicated high heterogeneity, between 25% and 50% moderate heterogeneity, and below 25% low heterogeneity.

Data synthesis

For both survival outcomes, OS and DFS, we analysed the number of patients in each treatment arm who experienced deaths from all causes or relapse or progression of their cancer disease at one year ± four months. Tumour response was analysed if studies reported events of complete or partial, or both, responses. Pooled random-effects model estimates and their 95% confidence intervals (CI) were calculated. Analyses were run separately for pTE and sTP trials.

A decision regarding whether to combine treatment-related symptoms was made depending on how this information was collected in each trial. Results were expressed as relative risks or risk ratios (RR) with 95% CIs. In survival and tumour response analyses a RR higher than 1.0 favoured the intervention group, indicating that patients in the intervention group (pTE or sTP) had a greater chance of survival or for having a response to treatment. In the analysis of adverse effects of chemotherapy and radiotherapy, RR less than 1.0 favoured the intervention group, indicating that fewer patients experienced adverse events in the intervention groups than in the control group.

In studies reporting the median survival time, we recalculated the number of events up to median survival time in the intervention group for both the intervention and the control group assuming one-parametric exponential survival time. This assumption is equivalent to assuming a constant event hazard Ê. Therefore, the formulae developed by Kirkwood 2003 were used (Appendix 3). Due to the variable study methods, all meta-analyses were considered as being explorative and pooled effects sizes have to be interpreted with great caution.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed according to type of pTE or sTP if at least three studies reported data on the respective outcome and carried out sensitivity analyses as described below.

Sensitivity analysis

We performed sensitivity analyses taking account of different intervention treatments within one study (that is low dose or high dose of thymic peptides).

RESULTS

Description of studies

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

Results of the search

From electronic searches and handsearches we retrieved 326 relevant publications. Out of 326 publications, 23 publications were unclear or the abstracts were not retrievable and 251 publications were ineligible for this systematic review. Reasons for ineligibility were: trial design other than RCT (for example historical control

group); participants other than adult cancer patients (for example children, other disease conditions); no thymic peptides; application mode other than subcutaneous or intramuscular (for example oral or topical) or combination with other substances; no control for thymic peptides; and no chemotherapy or radiotherapy or different regimes in the control and intervention groups.

Included studies

Twenty-six randomised controlled trials were included in this review. Thirteen were conducted in Italy (Airoldi 1987; Del Giacco 1988; Federico 1995; Gebbia 1994; GISOT 1987; Gonnelli 1995; Iaffaioli 1994; Luzi 1984; Macchiarini 1989; Mantovani 1988; Mustacchi 1994; Pavesi 1993; Salvati 1984), six in the USA (Bedikian 1984; Cohen 1979; Gish 2009; Scher 1988; Schulof 1985; Wara 1981), four in Spain (Canovas 1988; Canovas 1991; De Serdio 1997; Sanchiz 1996), one in Argentina (Guzman 1988), one in China (Cheng 2004), and one study recruited patients from several countries (Maio 2010). Studies with thymosin fraction 5 were published between 1979 and 1988, with thymostimulin between 1984 and 1997, with thymopentin between 1987 and 1994, and with thymosin α_1 between 1985 and 2010.

Participants

A total of 2931 adult patients were randomised (and 2744 evaluated) in the studies (median 49, range 28 to 650). The studies included the following number of randomised (and evaluated) cancer patients:

- four studies with 427 (372 evaluated) breast cancer patients (Gonnelli 1995; Mantovani 1988; Pavesi 1993; Sanchiz 1996),
- five with 314 (304) non-small cell lung cancer patients (Bedikian 1984; Del Giacco 1988;Iaffaioli 1994; Luzi 1984; Schulof 1985),
- four with 220 (192) small cell lung cancer patients (Cohen 1979; Macchiarini 1989; Salvati 1984; Scher 1988),
- three with 236 (207) lymphoma patients (Canovas 1988; Canovas 1991; Federico 1995),
- three with 160 (159) head and neck cancer patients (Airoldi 1987; De Serdio 1997; Wara 1981),
- two with 267 (243) colorectal cancer (Guzman 1988; Mustacchi 1994),
- two with 69 (66) hepatocellular carcinoma patients (Cheng 2004; Gish 2009),
- two with 750 (705) patients with various types of cancer (Gebbia 1994; GISOT 1987), and
- one with 488 (488) melanoma patients (Maio 2010).

Treatments

Intervention

In 20 studies pTE was used as interventional treatment: 16 used thymostimulin and four used thymosin fraction 5. Thymostimulin was applied intramuscularly and single doses ranged from 25 mg to 150 mg. Most study authors (n = 9) used a dose of 1 mg/kg body weight. Thymosin fraction 5 was applied subcutaneously with single doses of 60 mg in all trials. However, treatment schedules varied considerably among trials. Cohen 1979 had two interventional arms with different doses of thymosin fraction 5 (20 mg and 60 mg).

Six study authors used sTP as the interventional treatment: four used thymosin α_1 and two used thymopentin. Thymosin α_1 was applied subcutaneously with single doses of 1.6 mg in three trials and 0.9 mg/m² in one trial. Treatment schedules varied among these trials. Maio 2010 compared different doses of thymosin α_1 (1.6, 3.2 and 6.4 mg); Schulof 1985 compared a 14-day 'loading' dose of thymosin α_1 with a maintenance therapy for up to one year; thymopentin was given intramuscularly in Gebbia 1994 and subcutaneously in GISOT 1987, both studies using single doses of 50 mg.

Control

Twenty studies had two arms and two of these studies used a placebo control (Iaffaioli 1994; Schulof 1985). Three studies had three arms (Cheng 2004; Cohen 1979; Schulof 1985). Cohen 1979 compared two different thymosin fraction 5 doses with no treatment; Cheng 2004 compared intrahepatic chemotherapy, with or without thymosin α_1, with no intrahepatic chemotherapy; and Schulof 1985 compared two different regimen of thymosin α_1 with placebo. Gebbia 1994 had four arms and compared thymopentin with or without granulocyte colony-stimulating factor (G-CSF) versus placebo and G-CSF. Maio 2010 had five arms: three compared different doses of thymosin α_1 in addition to chemotherapy plus interferon α, one arm had 3.2 mg thymosin α_1 in addition to chemotherapy alone and the fifth arm had only chemotherapy plus interferon α. The comparison between 3.2 mg thymosin α_1 and interferon α was not included in the analysis as interferon α was not a control treatment in accordance with our protocol.

Basic treatment

The chemotherapy or radiotherapy regimen was described in all but one of the studies (GISOT 1987). In 23 studies patients received chemotherapy alone, in combination with radiotherapy or immunotherapy, or applied as transcatheter arterial embolization. In two studies patients received radiotherapy alone (Schulof 1985; Wara 1981).

Outcomes

Survival

Twenty-one studies reported OS. One author did not present estimates but described the results narratively (Iaffaioli 1994). Six studies reported DFS (Cohen 1979; De Serdio 1997; Federico 1995; Guzman 1988; Mantovani 1988; Scher 1988), although none gave a definition of how this was measured. Nine studies reported on PFS (Airoldi 1987; Cheng 2004; Macchiarini 1989; Maio 2010; Mustacchi 1994; Pavesi 1993; Salvati 1984; Schulof 1985; Wara 1981) although none gave a definition of how this was measured. Terminology of the measures of relapse and recurrence differed considerably between trials (Table 2, Table 3).

Table 2. Purified thymus extracts: survival, response, toxicity

Study	Survival rates		Tumour response		Toxicity (no. of patients)	
	Overall survival (OS)	**Disease-/progression-free survival (DFS/PFS)**	**Complete remission**	**Partial remission**	**Grade 3/4 neutropenia**	**Grade 3/4 infection**
Airoldi 1987	*After a median time of survival in IG of 7.9 months§:* IG: 12/24 (50%) CG: 10/24 (42%)	*After a median time of DFS in IG of 3.8 months§:* IG: 7/14 (50%) CG: 2/6 (33%)	*After 8 cycles of chemotherapy:* IG: 3/24 (12.5%) CG: 1/24 (4%)	IG: 11/24 (46%) CG: 5/24 (21%) (p< 0.05 chi² test)	n.r.	
Bedikian 1984	*After 1 year#:* IG: 8/46 (17%) CG: 16/53 (30%) (P = 0.14)	n.r.	IG: 0/46 CG: 2/53 (4%)	IG: 10/46 (22%) CG: 22/53 (42%)	n.r.	
Canovas 1988	*After 4 cycles of chemotherapy (approximately 3 to 4 months):* IG: 23/23 CG: 20/23 (87%)	n.r.	n.r.		n.r.	
Canovas 1991	*After 6 cycles of chemotherapy (approximately 4 to 6 months):* IG: 19/20 (95%) CG:17/20 (85%)	n.r.	n.r.		n.r.	("life threatening infections") IG: 2/20 (10%) CG: 4/20 (5%)

Table 2. Purified thymus extracts: survival, response, toxicity (*Continued*)

Cohen 1979	*After 1 year#:* IG1 (60 mg/m²) : 10/18 (56%) IG2 (20 mg/m²) : 2/12 (17%) CG: 3/16 (19%)	*After 1 year (complete responders):* IG1: 6/9 (67%) IG2: 1/2 (50%) CG: 2/8 (25%)	*After 3 months of chemotherapy:* IG1: 9/18 (50%) IG2: 2/12 (17%) CG: 8/16 (50%)	n.r.	n.r.	
De Serdio 1997	n.r.	*After a mean time of observation of 18 months:* IG: 15/18 (83%) CG: 14/18 (78%)	*After approximately 2 months of radiochemotherapy:* IG: 17/18 (94%) CG: 17/18 (94%)	n.r.	n.r.	
Del Giacco 1988	*After 12 to 33 months observation time:* IG: 8/25 (32%) CG: 8/23 (35%)	n.r.	*After induction chemotherapy (only reported in preliminary publication):* IG: 0/10 CG: 0/12	IG: 0/10 CG: 0/12	n.r.	(lethal infections) IG: 0/25 CG: 2/23 (9%)
Federico 1995	*After 1 year#:* IG: 51/66 (72%) CG: 48/68 (71%) (P = 0.62)	*Pats. with CR* IG: 35/39 (90%) CG: 24/29 (83%)	*After completion of chemotherapy (approximately 3 to 6 months):* IG: 39/66 (59%) CG: 29/68 (43%) (P = 0.05 log-rank)	IG: 14/66 (21%) CG: 22/68 (32%)	n.r.	
Gonnelli 1995	n.r.		*At 3 months of chemotherapy (40 patients evaluated):* IG: 0/20 CG: 0/20	IG: 1/20 (5%) CG: 0/20	n.r.	
			At 6 months of chemotherapy (36 patients evaluated):	IG: 6/19 (32%) CG: 4/17 (24%)		

Table 2. Purified thymus extracts: survival, response, toxicity (*Continued*)

			IG: 0/19 CG: 0/17			
Guzman 1988	*After 18 to 42 months observation time:* IG: 14/16 (87.5%) CG: 11/16 (69%)	IG: 11/16 (69%) CG: 10/16 (62.5%)	n.r.		n.r.	
Iaffaioli 1994	n.r.		n.r.		(grade 3/4) IG: 7/37 (19%) CG: 12/32 (37.5%) (P = 0.074)	n.r.
Luzi 1984	*After 1 year#:* IG: 8/25 (32%) CG: 6/25 (24%)	n.r.	*At 40 days (response was defined as CR, PR or radiologic improvement of atelectasis):* IG: 13/23 (57%) CG: 21/24 (88%)		n.r.	
Macchiarini 1989	*After 1 year#:* IG: 10/15 (67%) CG: 2/11 (18%) (log rank p<0,0032)	*After a median time of DFS/PFS in IG of 6 months§:* IG: 7/15 (47%) CG: 3/11 (27%)	*After approximately 6 months of chemotherapy:* IG: 7/15 (47%) CG: 1/11 (9%) (P = 0.45, Fisher exact)	IG: 4/15 (27%) CG: 3/11 (27%) (n.s.)	(grade 3) IG: 0/15 CG: 3/11 (27%) (grade 4) IG: 0/15 CG: 1/11 (9%)	n.r.
Mantovani 1988	*After 1 or 2 years:* IG: 18/20 (90%) CG: 16/17 (94%) (n.s.)	*After 1 year:* IG: 6/11 (55%) CG: 3/10 (30%) *After 2 years:* IG: 2/9 (22%) CG: 4/7 (57%)	n.r.		n.r.	
Mustacchi 1994	*After a median time of survival in IG of 10 months§:* IG: 53/106 (50%) CG: 60/105 (57%)	*After a median time of DFS/PFS in IG of 6.5 months§:* IG: 62/106 (58%) CG: 62/105 (59%)	IG: 6/106 (6%) CG: 3/105 (3%)	IG: 26/106 (25%) CG:16/105 (15%) (P = 0.02, chi²)	n.r.	
Pavesi 1993	*After a median time of survival*	*After a median time of*	"Overall response" (not further described):		n.r.	

Table 2. Purified thymus extracts: survival, response, toxicity (*Continued*)

	in IG of approximately 16 to 17months§: IG: 74/148 CG: 85/148	*survival in IG of 15 months§:* IG: 74/148 CG: 86/148	IG: 77/148 (52%) CG: 88/148 (60%)			
Salvati 1984	*After a median time of survival in IG of 6 for extensive and 18 months for limited disease§:* IG: 12/23 (52%) CG: 7/23 (30%)	*After a median time of survival in IG of 2.1 for extensive and 2.8 months for limited disease§:* IG: 11/23 (48%) CG: 3/23 (13%)	IG: 6/20 (32%) CG: 3/20 (16%)	IG: 6/20 (30%) CG: 9/20 (45%)	n.r.	
Sanchiz 1996	n.r.		*After 1 cycle of chemotherapy:* IG: 0/27 CG: 0/27	IG: 1/27 (3%) CG: 0/27	(grade 4) IG: 20/27 (74%) CG: 27/27 (p<0.01)	(ANC <500/mm² and fever > 38°C) IG: 6/27 (22%) CG: 16/27 (59%) (P = 0.0119)
Scher 1988	*After 1 year#: Limited disease:* IG: 11/17 (65%) CG: 16/18 (89%) (P = 0.38, log rank)	*After 1 year#: Limited disease:* IG: 10/17 (59%) CG: 11/15 (73%) (P = 0.32, log rank)	*After induction and consolidation radiochemotherapy (at approximately 6 months):* IG:18/41 (44%) CG:17/39 (44%)	IG:23/41 (56%) CG: 20/39 (51%)	n.r.	*(Admission for neutropenia and sepsis)* *Limited disease:* IG: 5/17 (29%) CG: 11/15 (73%)
	After 1 year#: Extensive disease: IG: 12/28 (43%) CG: 15/28 (54%) (P = 0.49, log rank)	*After 1 year#:Extensive disease: approximately 28 to 60 months observation time#:* IG: 8/23 (35%) CG: 10/24 (42%) (P = 0.49, log rank)				*Extensive disease:* IG: 12/24 (50%) CG: 15/24 (63%)
Wara 1981	n.r.	*After 1 year#:* IG: 22/33 (67%) CG: 25/42 (60%) (p<0.08)	n.r.		n.r.	

Abbreviations: # survival rates extracted from Kaplan-Meier curves, § survival rates estimated from median survival times, CR: complete remission, PR: partial remission, SD: stable disease, NC: no change, PD: progressive disease, n.r.: not reported

Table 3. Synthetic thymic peptides: survival, response, toxicity

Study	Survival rates		Tumour response		Toxicity (no. of patients)	
	OS	DFS	**CR**	**PR**	**Grade 3/4 neutropenia**	**Grade 3/4 infection**
Maio 2010	*At 1 year:* IG1 (IFN Éž+1.6 mg thymosin α_1) : 39/97 (40%) IG2 (IFN Éž+3.2 mg thymosin α_1) : 36/97 (37%) IG3 (IFN Éž+6.4 mg thymosin α_1) : 45/98 (46%) IG4 (3.2 mg thymosin α_1)*: 38/99 (39%) total IG (IG1-3): 120/292 (41%) CG (IFN Éž): 33/97 (34%)	*At 1 year#:* IG1: 4/97 (4%) IG2: 10/97 (10%) IG3: 3/98 (3%) IG4*: 10/99 (10%) total IG (IG1-3): 17/292 (5%) CG: 0/97	*Best response within 12 months (measured at various time points):* IG1: 2/97 (2%) IG2: 3/97 (3%) IG3: 2/98 (3%) IG4*: 2/99 (2%) total IG (IG1-3): 7/292 (2%) CG: 0/97	IG1: 5/97 (5%) IG2: 7/97 (7%) IG3: 4/98 (4%) IG4*: 10/99 (10%) total IG (IG1-3): 16/292 (5%) CG: 4/97 (4%)	n.r.	
Cheng 2004	*After a median time of survival in IG of 10 months§:* IG: 9/18 (50%) CG: 9/23 (39%)	*At 1 year:* IG: 3/18 (17%) CG: 3/23 (13%) (n.s.)	n.r.		n.r.	
Gebbia 1994	n.r.		n.r.		n.r.	(ANC<1,000/mm² and fever>38°C) IG1 (thymopentin): 12/23 (52%) IG2 (thymopentin+G-CSF): 4/22 (18%) IG1+IG2: 16/45 (36%) CG1 (placebo): 18/28 (64%) CG2 (G-CSF):

Table 3. Synthetic thymic peptides: survival, response, toxicity (*Continued*)

						5/23 (22%) CG1+CG2: 23/51 (45%)
Gish 2009	*At 6 months* IG: 12/14 (86%) CG: 7/11 (64%) *At 12 months* IG: 9/14 (64%) CG: 7/11 (64%) *At 2 years* IG: 8/14 (57%) CG: 5/11 (45%)	n.r.	*Best response within 18 months (measured at various time points):* IG: 0/14 CG: 0/11	IG: 2/14 (14%) CG: 2/11 (18%)	n.r.	(severe bacterial infections) IG: 0/14 CG: 4/11 (36%)
GISOT 1987	*After 3 months mean observation time:* IG: 432/447 (97%) CG:197/203 (97%) (P = 0,068, chi²)	n.r.	n.r.		n.r.	
Schulof 1985	*After 1 year#*: IG1 (maintenance therapy): 8/15 (53%) IG2 (loading dose): 4/13 (31%) CG: 1/13 (8%)	*After 1 year#:* IG1: 3/15 (20%) IG2: 4/13 (31%) CG: 0/13	n.r.		n.r.	

Abbreviations: # survival rates extracted from Kaplan-Meier curves, § survival rates estimated from median survival times, * not included in metaanalysis; CR: complete remission, PR: partial remission, SD: stable disease, NC: no change, PD: progressive disease

Tumour response

Seventeen studies reported on tumour response and 14 of them referred to defined response criteria mostly in accordance with standard criteria. In Iaffaioli 1994 tumour response data were not reported but the author summarised the results in the text. Pavesi 1993 reported data on an 'overall response rate' but did not define it any further and Sanchiz 1996 presented data on response referring to the first cycle of chemotherapy only (Table 2, Table 3).

Toxicity (adverse effects of chemotherapy and radiotherapy)

The two outcomes which were reported in a way that allowed us to include them in our analyses were severe neutropenia and infectious complications. Nine studies (Canovas 1991; Del Giacco 1988; Federico 1995; Gebbia 1994; Gish 2009; Iaffaioli 1988; Macchiarini 1989; Sanchiz 1996; Scher 1988) reported on one or both of these outcomes according to the National Cancer Institute Common Toxicity Criteria (CTC 2009) or gave a sufficient description of the outcomes, which allowed us to apply grading

criteria. Three of them reported on the incidence of grade 3 to 4 neutropenia per patient, one per chemotherapy cycle; and seven on the incidence of grade 3 to 4 infectious complications (Table 2, Table 3).

Safety (adverse effects of purified thymus extracts (pTE) and synthetic thymic peptides (sTP)

Ten trials commented on the 'tolerability' of pTE or sTP (Bedikian 1984; Canovas 1988; Canovas 1991; Cohen 1979; Del Giacco 1988; Gebbia 1994; Gish 2009; Luzi 1984; Salvati 1984; Sanchiz 1996). The numbers of patients with local or systemic adverse effects were given in three studies (Macchiarini 1989; Scher 1988; Schulof 1985) (Table 4, Table 5).

Table 4. Purified thymus extract: safety

Study	Adverse effects of purified thymus extracts	
	local	*systemic*
Bedikian 1984	Erythema and induration of site of injection	Generalized skin rash, febrile reaction
Canovas 1988	Authors stated that thymostimulin was well tolerated, but 2 patients were excluded because of allergic reaction to TP-1	
Canovas 1991	Authors stated that thymostimulin was well tolerated and no adverse reactions were observed	
Cohen 1979	"Toxic effects of thymosin were confined to local irritation at the injection site manifested by greater or lesser degrees of pain and swelling. All reactions subsided within 12-72 hours of injection."	
Del Giacco 1988	"No side effects were observed with thymostimulin,[...]."	
Luzi 1984	"(...) no allergic reactions or toxic effects were noted during TS treatment."	
Macchiarini 1989	"No local or systemic thymostimulin-related clinical toxicities were noted."	
Salvati 1984	Authors stated that no toxic effects attributable to thymostimulin treatment were observed.	
Sanchiz 1996	"(...) GCS-F and TS were well tolerated without adverse events related to these drugs."	
Scher 1988	Dose reduction because of local reactions (pain and inflammation at injection site): 9/45 patients	chills and fever within 24 h of injection in 5/45 patients

Table 5. Synthetic thymic peptides: safety

Study	Adverse effects of synthetic thymic peptides	
	local	*systemic*
Gebbia 1994	"Thymopentin treatment did not cause any significant side effects."	
Gish 2009	"Of the 23 adverse events the author judged possibly or probably related to thymalfasin, most were mild and resolved without sequelae. Only three of these events occurred in more than one patient: nausea (n=2), fatigue (n=2), and nipple pain (n=2).(...) Overall, thymalfasin was well tolerated."	
Schulof 1985	mild burning at the injection site in 3 patients.	mild transient loss of muscle mass in1 patient.

Quality of life

None of the included studies reported on patient-reported QoL.

Excluded studies

Of the remaining 52 publications considered to be of possible relevance, nine papers were duplicates and 17 did not fulfil inclusion criteria. Reasons for exclusion of studies are described in the table Characteristics of excluded studies.

Risk of bias in included studies

The quality of the included studies and the subsequent risk of bias were assessed separately for the different outcomes of interest using the criteria defined in the Cochrane Handbook (Higgins 2009). The assessments and grades given are shown in Table 6 and Table 7. The studies are grouped below by the grades for risk of bias. The grading is a basic judgement and does not account for the complexity of many of the trials studied.

Table 6. Purified thymus extracts: risk of bias

Study	Sequence generation	Allocation concealment	Blinding	Attrition	Selective reporting	Risk of Bias	
						OS	DFS/Tox
Airoldi 1987	Quote: "i pazienti sono stati stratificati (...) prima di essere randomizzati al trattamento (...)" Comment: sequence generation not reported; no earlier reports from the same investigators found that clearly describe the use of random sequences	Not reported; prognostic factors similarly distributed	No blinding reported	No dropouts or withdrawals	Comprehensive report of outcomes	moderate	moderate - high

Table 6. Purified thymus extracts: risk of bias (*Continued*)

Bedikian 1984	Quote: "Patients (...) were randomized (...)." Comment: sequence generation not reported	Probably not done: no concealment reported, dissimilarities in baseline prognostic factors	No blinding reported	Quote: Three of 49 thymosin patients have been excluded from the subsequent evaluation of response and survival of the thymosin group (...) Comment: differential loss in comparison groups, but extent of possible bias unclear	No indication for selective reporting	moderate - high	high
Canovas 1988	Quote: "La asignación de los pacientes.....se realizó mediante el sistema de numeros aleatorios." Comment: probably done, table of random numbers used	Not reported. Equal distribution of characteristics/prognostic factors stated in text, but no detailed data provided	No blinding reported	All patients analysed	All intended outcomes were reported	moderate	moderate - high
Canovas 1991	Quote: " (...) se realizó mediante la aplicación de la tabla de numeros aleatorios (...)." Comment: probably done, table of random numbers used	Not reported. Equal distribution of characteristics/prognostic factors stated in text, but no detailed data provided	No blinding reported	All patients analysed	All intended outcomes were reported	moderate	moderate - high

Table 6. Purified thymus extracts: risk of bias (*Continued*)

Cohen 1979	Quote: " (...) randomly received (...)" Comment: sequence generation not reported	No concealment reported. Dissimilarities in baseline characteristics; small sample size	No blinding reported	Quote:"Statistical analysis was also (...) of 55 patients. All results (..) in the 46 protocol-eligible patients were also significant for (...) 55 patients." Comment: number of withdrawals/ drop-outs balanced, reasons for exclusions described, PP and ITT performed	Comprehensive report of outcomes	moderate	moderate - high
De Serdio 1997	Quote: "Las tablas de azar nos suministra- tron (...) siguiente esquema de randomización (...) " Comment: adequate sequence generation	No concealment reported. Detailed list of disease localisation and stage given; other patient related characteristics not reported	No blinding reported	All patients analysed	All intended outcomes were reported	Outcomes not assessed	moderate - high
Del Giacco 1988	Quote:" (...) patients were randomised between (...)" Comment: sequence generation not reported	No concealment reported.	No blinding reported	Quote: "31 could be randomised (...) but only 22 are completely evaluable (the other 9 having an incomplete follow-up (..) " Comment: 9 patients lost to follow-up, rea-	Discrepancy between intended and reported outcome measures, results on quality of life were not reported, tumour response only reported in the prelim-	high	high

Table 6. Purified thymus extracts: risk of bias (*Continued*)

				sons not commented, distribution between intervention and control group unclear	inary publication		
Federico 1995	Quote: "(...) patients were randomised (...)." Comment: sequence generation not reported	No concealment reported. Dissimilarities in baseline prognostic factors, which were discussed by study authors as possibly having influenced the outcomes	No blinding reported	Equal numbers of drop-outs/exclusions in both groups	Comprehensive report of outcomes	moderate - high	high
Gonnelli 1995	Quote: "(...) were randomly selected (...)" Comment: sequence generation not reported	No concealment reported.	No blinding reported	4 patients inevaluable, 1 in IG, 3 in CG, reasons not stated, ITT for tumour response and rate of infection	Intended outcomes not stated	Outcome not assessed	high
Guzman 1988	Quote: "(...) were randomised." Comment: sequence generation not reported	No concealment reported. No data on distribution of risk factors	No blinding reported	All patients analysed	All intended outcomes were reported	moderate - high	high
Iaffaioli 1994	Quote: "(...) and randomised (...)" Comment: sequence generation not reported	No concealment reported; prognostic factors similarly distributed	No blinding reported	All patients analysed	Intended outcomes were not comprehensively reported	Outcome not assessed	moderate

Table 6. Purified thymus extracts: risk of bias (*Continued*)

Luzi 1984	Quote: "(...) in a randomized controlled study; (...)" Comment: sequence generation not reported	No concealment reported. Slight imbalances in patient-related factors. Small sample size. (direction of possible risk unclear)	No blinding reported	Three patients with adenocarcinoma were excluded afterwards for unknown reasons, (two in IG and on in CG)	Intended outcomes were not comprehensively reported	moderate - high	high
Macchiarini 1989	Quote: "The randomization was performed by assigning a prerandomized sequential number to each patient (...)" Comment: probably done, table of random numbers used	No concealment reported. Dissimilarities in disease stage. Small sample size.(possible risk of bias in favor of the intervention group)	No blinding reported	Two patients from the control group excluded because of death within the first 2 weeks of treatment; no ITT; (possible risk of bias concerning mortality outcomes in favor of the control group)	All intended outcomes were reported	high	high
Mantovani 1988	Quote:"(...) enrolled for study and randomized (...)" Comment: sequence generation not reported	No concealment reported. Dissimilarities in disease characteristics. Small sample size.(possible risk of bias in favour of the control group)	No blinding reported	All patients analysed	All intended outcomes were reported	high	high
Mustacchi 1994	Quote: "(...) entering this prospective randomized multicenter trial (...) "Comment: sequence gen-	Quote: "(...) were randomly allocated over the phone by the Central Office (...)"Comment: proba-	No blinding reported	Quote: "(...) 25 out of 235 patients were lost due to cancellation, ineligibility or proto-	All intended outcomes reported	low - moderate	moderate

Table 6. Purified thymus extracts: risk of bias (*Continued*)

	eration not reported	bly done (central allocation)		col violations (..)"Comment: distribution between groups similar, outcome measure not likely to be influenced			
Pavesi 1993	Quote: "(...) and randomly allocated (...) "Comment: sequence generation not reported	Quote: "(...) and randomly allocated over the phone (...) "Comment: probably done (central allocation)	No blinding reported	Quote: "(...) in 245 fully evaluable patients (..) "Comment: 51 randomised patients not included in analy- sis, reasons not reported, distribution between groups unclear	Intended outcomes were reported (only abstract publication available)	moderate	moderate - high
Salvati 1984	"(?) hanno ricevuto a random (?) "Comment: sequence generation not reported	No concealment reported. Distribution of possible risk factors/disease characteristics unclear. Small sample size	No blinding reported	Quote: "I pazienti valutabili sono stati 40 (..)"Comment: six patients not included in analy- sis, reasons not reported, distribution between groups unclear	Intended outcomes were reported (but report was not very detailed)	high	high
Sanchiz 1996	Quote: "(...) were randomly assigned (by means of tables of random numbers) (...) "Com-	No concealment reported. Slight imbalances in possible risk factors/ disease characteristics. Small sample size	No blinding reported	No dropouts/ withdrawals reported but unclear whether all patients were included in the analyses	All intended outcomes were reported	Outcome not assessed	moderate - high

Table 6. Purified thymus extracts: risk of bias (*Continued*)

	ment: probably done, table of random numbers used						
Scher 1988	Quote: "Randomization was by the method of random permuted blocks (...)"Comment: probably done	No concealment reported. Dissimilarities in prognostic factors between groups	No blinding reported	All randomised patients were included in the survival analysis and the reasons for the exclusion of three patients from the response analysis were reported and unlikely to introduce bias	Outcomes comprehensively reported	low - moderate	moderate
Wara 1981	Quote: "(?) were randomly assigned (?) "Comment: sequence generation not reported	No concealment reported. Dissimilarities in prognostic factors.	No blinding reported	All but one randomised patients included in the analyses, reason for exclusion not reported	All intended outcomes reported	Outcome not assessed	moderate - high

Table 7. Synthetic thymic peptides: risk of bias

Study	Sequence generation	Allocation concealment	Blinding	Attrition	Selective reporting	Risk of Bias	
						OS	DFS/Tox
Cheng 2004	Quote: "(...) were randomly divided (...) based on the date of admission." Comment: Quasi-randomisation	Probably not done; study authors did not use adequate sequence generation and baseline prognostic factors dissimilarly distributed.	No blinding reported	All patients analysed.	All intended outcomes were reported.	high	high

Table 7. Synthetic thymic peptides: risk of bias (*Continued*)

Gebbia 1994	Quote: "(...) were randomised (...)" Comment: sequence generation not reported	Not reported. Similar distribution of age, gender, performance status, but no data on site of primary tumour for the placebo group	No blinding reported	Quote: "(...) 4 patients were excluded from final analysis due to major protocol violation." Comment: unclear distribution of drop-outs between groups	Incomplete reporting of hematological and infectious outcomes	Outcome not assessed	moderate - high
Gish 2009	Quote: "Randomization was carried out centrally using a randomization table (...)" Comment: probably done, table of random numbers used	Quote: "Randomization was carried out centrally using a randomization table (...)" Comment: probably done (central allocation)	Quote: "tumour measurements and interpretation (...) performed centrally by radiologists blinded to treatment assignment	28 randomised, 25 treated and evaluated, 3 withdrawals in CG before beginning of treatment	All intended outcomes reported	low - moderate	low - moderate
GISOT 1987	Quote:" (...) per mezzo di una lista di randomizzazione;" Comment: probably done, table of random numbers used	Not reported. No data on characteristics/ risk factors	No blinding reported	Inconsistent numbers of drop-outs/ withdrawals	All intended outcomes were reported	moderate	moderate - high
Maio 2010	Quote: "The randomization list was produced by the Internal QualityControl Unit of Biostatistics and Data Management (...)" Comment: adequate se-	Quote: "Randomization was blinded and centralized (...). Comment: probably done (central allocation)	Quote: "tumour response was evaluated (...) utilizing a central review." Comment: although central review performed, unclear whether assessor was	For tumour response all patients were analyzed, authors assumed that this was the case for the outcomes OS and PFS as well	Comprehensive report of outcomes	low	low - moderate

Table 7. Synthetic thymic peptides: risk of bias (*Continued*)

	quence generation		blinded				
Schulof 1985	Quote: "(...) was performed using a randomized, double-blind design (...) "Comment: sequence generation not reported	No concealment reported. Dissimilarities in prognostic factors between groups (possibly in favour of intervention group). Small sample size	Quote: "The code did not have to be broken because of toxicity in any patient (...) "Comment: Successful blinding of patients and care provider likely Quote: "(...) and administered (...) for a period of up to 1 year or until relapse."Commen Outcome was assessed during the blinded study phase in the majority of patients	All but one randomised patients included in the analyses, reason for exclusion reported	All intended outcomes reported	moderate	moderate

Mortality outcomes

Studies with pTE were judged as having the following risk of bias concerning OS:

- low to moderate: Mustacchi 1994; Scher 1988,
- moderate: Airoldi 1987; Canovas 1988; Canovas 1991; Cohen 1979; Pavesi 1993,
- moderate to high: Bedikian 1984; Federico 1995; Guzman 1988; Luzi 1984,
- high: Del Giacco 1988; Macchiarini 1989; Mantovani 1988; Salvati 1984.

Studies with sTP were judged as having the following risk of bias concerning OS:

- low: Maio 2010,
- low to moderate: Gish 2009,
- moderate: GISOT 1987; Schulof 1985,
- high: Cheng 2004.

Outcome assessor-related outcomes

Studies with pTE were judged as having the following risk of bias concerning DFS and toxicity outcomes:

- moderate: Iaffaioli 1994,
- moderate to high: Airoldi 1987; Canovas 1988; Canovas 1991; Cohen 1979; De Serdio 1997; Gebbia 1994; Mustacchi 1994; Pavesi 1993; Sanchiz 1996; Scher 1988; Wara 1981,
- high: Bedikian 1984; Del Giacco 1988; Federico 1995; Gonnelli 1995; Guzman 1988; Luzi 1984; Macchiarini 1989; Mantovani 1988; Salvati 1984.

Studies with sTP were judged as having the following risk of bias concerning DFS and toxicity outcomes:

- low to moderate: Gish 2009; Maio 2010,
- moderate: Schulof 1985,
- moderate to high: GISOT 1987,
- high: Cheng 2004.

Overall, the reasons for higher grades of risk of bias were due to

inadequate reporting of the methods used for random allocation, unbalanced risk factors for the outcome of interest and small sample sizes. For outcome assessor-related outcomes, inadequate reporting of the methods used for blinding were an additional reason for assuming higher risk of bias.

Effects of interventions

Survival

Overall survival (OS)

Purified thymus extracts (pTE)

Fifteen trials with pTE reported OS data with observation periods ranging from three to over 60 months. Data for meta-analysis of OS at one year could be obtained from eight trials. The analysis included a total of 705 patients and 355 events and the RR did not show a difference in the risk of survival between the thymic peptides regimen and no treatment or placebo (RR 1.00, 95% CI 0.79 to 1.25) (Analysis 1.1). Heterogeneity was moderate (I^2 = 44%).

Subgroup analysis

The thymostimulin group included five trials with 469 patients and the thymosin fraction 5 group had three trials including 236 patients. In the thymostimulin group, the pooled RR was above 1 (RR 1.07, 95% CI 0.85 to 1.35), whereas in the thymosin fraction 5 group the RR was 0.84 (95% CI 0.49 to 1.45).

Synthetic thymic peptides (sTP)

Five trials with sTP reported OS data with observation periods from three months to two years. Data for meta-analysis of OS at one year could be obtained from four trials (Cheng 2004; Gish 2009; Maio 2010; Schulof 1985). All four trials used thymosin α_1. The analysis included 496 patients and 200 events. The RR for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14) without statistical heterogeneity (I^2 = 0%).

Disease-free survival (DFS)

Purified thymus extracts (pTE)

Twelve trials with pTE reported DFS data with observation periods ranging from three to over 60 months. Data for meta-analysis of DFS at one year could be obtained from six trials (Cohen 1979; Federico 1995; Mantovani 1988; Pavesi 1993; Scher 1988; Wara 1981). The DFS analysis included a total of 511 patients and 308 events. The RR did not show a difference in the risk of DFS between the thymic peptides regimen and no treatment or placebo (RR 0.97, 95% CI 0.82 to 1.16) (Analysis 1.2). Heterogeneity was moderate (I^2 = 30%).

Subgroup analysis

The thymostimulin group included three trials with 385 patients and the thymosin fraction 5 group had three trials including 126 patients. The subgroup analysis showed no difference between the two subgroups (thymostimulin: RR 0.93, 95% CI 0.73 to 1.19; thymosin fraction 5: RR 1.06, 95% CI 0.71 to 1.60).

Synthetic thymic peptides (sTP)

Data were obtained for meta-analysis of DFS at one year from three trials. All trials used thymosin α_1. A total of 471 patients with 30 events were included in analysis. The RR was 3.37 (95% CI 0.66 to 17.30, P = 0.15) with moderate heterogeneity (I^2 = 37%) (Analysis 2.2).

Tumour response

Purified thymus extracts (pTE)

Data could be obtained for response analysis from 11 trials with pTE. A total of 825 patients with 423 events were included in the analysis. There was no difference in the overall chance of achieving a complete or partial response between the intervention and the control groups (RR 1.07, 95% CI 0.92 to 1.25) (Analysis 1.3). Heterogeneity among the trials was rather high (I^2 = 53%).

Subgroup analysis

The thymostimulin group included eight trials with 553 patients and 258 events; the thymosin fraction 5 group had three trials including 225 patients with 131 events.
The pooled RR of trials using thymostimulin was 1.25 (95% CI 0.96 to 1.62, P = 0.09), whereas in the thymosin fraction 5 group the RR was below 1 (RR 0.73, 95% CI 0.24 to 2.19, P = 0.57).

Synthetic thymic peptides (sTP)

Only two trials with thymosin α_1 reported data on tumour response (Gish 2009; Maio 2010). Therefore we did not pool data. Both trials showed no significant difference between the intervention and the control groups (RR 0.79, 95% CI 0.13 to 4.72; RR 1.91, 95% CI 0.68 to 5.39 respectively) (Analysis 2.3).

Sensitivity analyses

Sensitivity analyses were performed using data from treatment arms with higher doses of thymic peptides (Cohen 1979; Maio 2010) or maintenance regime instead of the loading dose (Schulof 1985). Overall, no significant changes were found in risks for survival and tumour response and in statistical heterogeneity. Details are shown in Table 8.

Table 8. Sensitivity analyses

Purified thymus extracts - overall survival		
Outcome	**Random effects model**	**Single intervention groups in studies with more doses/regimes tested**
pTE	RR 1.00, 95% CI 0.79 to 1.25, P = 0.98, I^2=44%	60 mg thymosin fraction 5 (Cohen 1979) RR 1.02, 95% CI 0.80 to 1.31, P = 0.87, I^2=52%
Thymostimulin (subgroup)	RR 1.07, 95% CI 0.85 to 1.35, P = 0.57, I^2=35%	not applicable
Thymosin fraction 5 (subgroup)	RR 0.84, 95% CI 0.49 to 1.45, P = 0.53, I^2= 48%	60 mg thymosin fraction 5 (Cohen 1979) RR 0.95, 95% CI 0.46 to 1.95, P = 0.89, I^2=69%
Purified thymus extracts - disease-free survival		
pTE	RR 0.97, 95% CI 0.82 to 1.16, P = 0.77, I^2= 30%	60 mg thymosin fraction 5 (Cohen 1979) RR 0.97, 95% CI 0.82 to 1.16, P = 0.78, I^2=32%
Thymostimulin (subgroup)	RR 0.93, 95% CI 0.73 to 1.19, P = 0.59, I^2= 54%	not applicable
Thymosin fraction 5 (subgroup)	RR 1.06, 95% CI 0.71 to 1.60, P = 0.76, I^2= 38%	60 mg thymosin fraction 5 (Cohen 1979) RR 1.07, 95% CI 0.70 to 1.64, P = 0.48, I^2=41%
Purified thymus extracts - tumour response		
pTE	RR 1.07, 95% CI 0.92 to 1.25, P = 0.37, I^2= 53%	60 mg thymosin fraction 5 (Cohen 1979) RR 1.04, 95% CI 0.89 to 1.21, P = 0.64, I^2=56%
Thymostimulin (subgroup)	RR 1.25, 95% CI 0.96 to 1.62, P = 0.09, I^2=66%	not applicable
Thymosin fraction 5 (subgroup)	RR 0.73, 95% CI 0.24 to 2.19, P = 0.57, I^2=94%	60 mg thymosin fraction 5 (Cohen 1979) RR 0.81, 95% CI 0.32 to 2.07, P = 0.65, I^2=92%

Table 8. Sensitivity analyses (*Continued*)

Synthetic thymic peptides - overall survival		
sTP	RR 1.21, 95% CI 0.94 to 1.56, P = 0.14, I^2=0%	6.4 mg thymosin α_1(Maio 2010) and maintenance regime (Schulof 1985) RR 1.30, 95% CI 0.92 to 1.85, P = 0.14, I^2=23%
Synthetic thymic peptides - disease-free survival		
sTP	RR 3.37, 95% CI 0.66 to 17.30, P = 0.15, I^2= 37%	6.4 mg thymosin α_1 (Maio 2010) and maintenance regime (Schulof 1985) RR 2.22, 95% CI 0.67 to 7.37, P = 0.19, I^2=0%

Toxicity

Purified thymus extracts (pTE)

Infectious complications

Data could be obtained from four studies for pooled analysis of severe infections (at least CTC grade 3 or 4). Three investigated thymostimulin and one thymosin fraction 5. A total of 214 patients were included and 73 experienced a severe infectious complication at any site. The RR indicated a lower risk of severe infectious complications (RR 0.54, 95% CI 0.38 to 0.78, P = 0.0008) (Analysis 1.4). Heterogeneity among the trials was low (I^2 = 0%).

Neutropenia

Data for analysis of severe neutropenia (at least CTC grade 3 or 4) could be obtained from three trials, which all used thymostimulin. Overall, 72 of 149 patients experienced severe neutropenia. The RR was 0.55 (95% CI 0.25 to 1.23, P = 0.15) (Analysis 1.5) with high heterogeneity among the trials (I^2 = 63%).

Synthetic thymic peptides (sTP)

Only two trials with sTP reported data on infectious complications or neutropenia (Table 3). Therefore pooling of data was not feasible. Gebbia 1994 found a non-significant reduction in the number of patients experiencing neutropenia during chemotherapy by treatment with thymopentin. Gish 2009 reported a non-significant reduction in the rate of patients with severe bacterial infections by treatment with thymosin α_1.

Safety

Ten out of 20 studies with pTE and three out of six trials with sTP reported on adverse effects of the interventional treatments. Seven authors reported that the interventional treatments were well tolerated. Adverse events reported by the other authors were mild, transient local reactions at the injection site with systemic reactions in few patients. Details are shown in Table 4 and Table 5.

DISCUSSION

This review included data from 26 trials (2736 patients) investigating the treatment of various malignancies with pTE or sTP while receiving basic oncologic treatment consisting of chemotherapy alone or in combination with radiotherapy or immunotherapy, chemotherapy applied as transcatheter arterial embolization, or radiotherapy alone. These 26 studies included both published and unpublished trials and represented all RCTs matching the inclusion criteria at the time of the literature search. The last trial was identified in March 2010. Twenty studies used one of two pTE, thymostimulin or thymosin fraction 5, and six one of two sTP, thymopentin or thymosin α_1, as investigational treatments.

We did not find evidence that the addition of pTE or sTP to antineoplastic treatment reduces the risk of death or disease progression, nor that it improves the rate of tumour response to antineoplastic treatment. However, there was preliminary evidence that pTE lowered the risk of severe infectious complications in patients undergoing chemotherapy or radiotherapy. There was no evidence of significant side effects either with pTE or sTP.

The pTE was used to treat 1436 patients, and 372 breast cancer patients from three studies was the largest group. There were

1300 participants treated with sTP, 488 patients with metastasised melanoma were from one study. There were sufficient numbers to assess treatment impact of both pTE and sTP on survival outcomes, and of pTE on tumour response. There were only a few trials with small numbers of patients that assessed the effects of pTE and sTP on adverse effects of chemotherapy or radiotherapy scored according to standardized criteria (CTC), therefore the trials in this review have low power to assess the impact of the intervention on this outcome. We had planned to perform subgroup analyses with respect to different types of cancer. After appraisal of the included studies, however, subgroup analysis was only possible for the different investigational drugs applied.

Other major problems for this review were the poor methodological quality of many of the included trials, variability in entry criteria, the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to different treatment schedules and doses of both the investigational and the basic oncologic treatments across the trials, as well as a general failure to report data suitable for comparison of survival over time. Only four trials reported adequate methods of allocation concealment, which could have introduced bias. None of the trials with pTE and only one with sTP reported blinding of outcome assessors, which could have introduced bias in the assessment of DFS, tumour response and toxicity outcomes. Another limitation of this systematic review was the small sample size of many of the trials. In particular, two thirds of trials had a sample size of less than 60 participants and may have yielded inconclusive results because they were small and therefore did not have adequate statistical power. Only six trials included more than 100 participants.

The included trials were published over a 31-year period, up to 2010, and mainly involved participants from Italy, Spain and the USA. Studies with pTE were conducted from 1979 until the late 1990s. Thereafter this treatment concept was seemingly abandoned and clinical investigations became orientated towards the application of sTP. All studies (n = 3) which were conducted after 1997 used the sTP thymosin α_1.

Pooling of data was possible for a number of clinical outcomes of interest. For thymosin α_1 there was a slight trend toward an overall reduction in the risk of dying (RR 1.21, 95% CI 0.94 to 1.56, P = 0.14) and improved DFS (RR 3.37, 95% CI 0.66 to 17.30, P = 0.15). Data from one large trial with low risk of bias on patients with metastatic melanoma mainly contributed to these results. Two trials with thymosin α_1 compared either different doses (Maio 2010) or different regimes of application (Schulof 1985). Results from these individual studies indicated a possible dose-dependent effect. A further finding from Maio's trial that was not included in our analysis but which could be of interest was that thymosin α_1 added to chemotherapy seemed to be as effective as interferon α but better tolerated.

The different RR for tumour response of thymostimulin (above 1) and thymosin fraction 5 (below 1) might be regarded as a possible indication of differential effects of the two different pTE. However, such an interpretation should be made with caution because the suggested negative effect of thymosin fraction 5 is mainly caused by one study at high risk of selection bias that involved patients with advanced non-small cell lung cancer (Bedikian 1984). Nevertheless, true opposite effects of different pTE, for instance caused by differences in the peptide composition, could not be ruled out based on our data. Thymostimulin and thymosin fraction 5 have dissimilar manufacturing processes and while there were little to no efforts to analyse the components of thymostimulin, those of thymosin fraction 5 came under scrutiny. One oligopeptide identified from the thymosin fraction 5 is thymosin ß$_4$, which was recently discussed due to its possible stimulating effects on tumour metastasis by activating cell migration and angiogenesis (Cha 2003). The heterogeneity within the two groups might also be attributable to different reactions of the various cancer entities to pTE. Lack of sufficient studies with the same disease conditions hampers further evaluation of this aspect.

Pooled estimates of trials of pTE suggest an advantage on the risk of experiencing serious infectious complications or, as a trend, severe neutropenia during basic oncological treatment. Two trials with sTP reported similar findings on these outcomes but were not included in the meta-analysis (Gebbia 1994; Gish 2009). Two of the four arms in Gebbia 1994 compared thymopentin with G-CSF. Although there was some evidence that thymopentin might reduce the risk of infections, G-CSF was significantly more effective (Gebbia 1994). Given the safety profile of sTP, they could still be of investigational interest for this indication.

All of these findings are subject to a potential publication bias. While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. For instance Schulof referred, in a systematic review from 1985, to one trial of thymosin fraction 5 with negative effects on tumour response where the information was obtained by personal communication (Schulof 1985). We could not trace a publication.

Only one systematic review on thymic peptides in cancer patients has been published so far (Ernst 1997). The author addressed the question of clinical effectiveness of 'thymus therapy' in cancer patients and included 13 of 21 RCTs published between 1979 and 1996. Inclusion criteria were similar to those used in our review but additionally included oral thymus preparations as interventional treatments and immunologic parameters as outcomes. There was no tool for assessment of methodological quality and study results were interpreted narratively. The author criticised the trials because of low methodological quality, small sample sizes, heterogeneous study populations and statistical shortcomings. The overall conclusion saw no 'compelling' evidence for the efficacy of thymus

extracts but regarded some results as 'promising' and deserving of further investigation. This overall conclusion is in accordance with the results of our review pertaining to the set of trials included in Ernst's review.

AUTHORS' CONCLUSIONS

Implications for practice

Data provided by four small RCTs suggest that purified thymus extracts (pTE) might reduce the risk of infectious complications in patients undergoing chemotherapy or radiotherapy, or both. The effect of synthetic thymic petides on the same outcome is only supported by weak evidence. Findings that thymosin α_1 might have beneficial effects on survival were mainly supported by one larger study with low risk of bias of patients with metastatic melanoma. Given the limited treatment options for this condition and the safety profile of thymosin α_1, treatment with thymosin α_1 could be considered assuming that the decision about its use was based on expert clinical judgement. 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

There is a case for well-designed randomised trials to assess the possible value of the application of thymosin α_1, suggested by one large trial in patients with metastasised melanoma. Future trials must employ up-to-date antineoplastic and supportive treatment regimens in both arms; should take into account a possible dose-dependent effect of thymosin α_1, evaluate appropriate sample sizes with power to detect expected differences and apply effective and explicit blinding of treatment allocation. Examined outcome measures should include QoL measured with validated instruments and careful elucidation of any adverse effects.

Clinical trials with purified thymus extracts should not be advocated in the management of cancer until the exact compositions of the extracts are scrutinized and components are identified that might confer possible effects on host immunity and tumour biology.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Airoldi 1987

Methods	**Design:** 2-arm parallel trial with a no-treatment control group; stratification by type of pretreatment, location and grading of tumour, disease status (non-responsive or recurrent) **No of centres:** 1 **Recruitment and setting:** Medical Clinic and Department of Radiotherapy, University of Turin, Italy **Recruitment period:** 01/84-08/85 **Observation period:** median: 14 months, minimum: 11 months **Ethical approval:** unclear
Participants	**No of patients:** 48 randomised, 48 evaluated **Condition:** squamous cell cancer of the oral cavity non-responsive or recurrent after conventional therapy with surgery and/or irradiation **Demographics**: men: 39, women: 9; mean age (range): 58 (37-71) years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin, dose/schedule: 1 mg/kg/day i.m. starting 7 days before chemotherapy treatment, thereafter 2x/week for 4 weeks and 1x/week until tumour progression **Control treatment:** no treatment **Basic treatment:** vincristine 1.2 mg/m² i.v. (d1), bleomycin 18 mg/m² i.m. (d1), methotrexate 30 mg/m² i.v. (d2); every week for 8 weeks
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), other
Notes	**Outcomes:** side effects of chemotherapy were not scored using standardized criteria

Bedikian 1984

Methods	**Design:** 2-arm parallel trial with a no-treatment control group; stratification by histological type of disease and performance status **No of centers:** 1 **Recruitment and setting:** M.D. Anderson Cancer Center, University of Texas, USA **Recruitment period:** 01/79-05/80 **Observation period:** max. 104 weeks **Ethical approval:** unclear
Participants	**No. of patients:** 105 randomised, 99 evaluated **Condition:** advanced stage non-small cell lung cancer (NSCLC) **Demographics:** men: 70, women: 29; median age (range): IG: 55 (37-77), CG: 57 (35-80) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymosin fraction 5; dose/schedule: 60 mg/m² s.c. every chemotherapy cycle (d1,4,8,12,16) **Control treatment:** no treatment **Basic treatment:** vindesine 3 mg/m² (d1), doxorubicin 50 mg/m² (d1), cisplatin 60 mg/m² (d1) every 3-4 weeks

Bedikian 1984 (*Continued*)

Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), chemotherapy dose/schedule modifications, other
Notes	**Participants**: first 13 patients were not randomised because of unavailability of thymosin fraction 5 and allocated to the no-treatment arm, thereafter to equalise the two arms a randomisation scheme favouring the thymosin arm was used **Outcomes:** side effects of chemotherapy were not scored using standardized criteria **Funding:** sponsored by the National Cancer Institute (NCI)

Canovas 1988

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No of centres:** 1 **Recruitment and setting:** outpatients department, Hospital de Cruces, Bilbao, Spain **Recruitment period:** unclear **Observation period:** 4 chemotherapy cycles **Ethical approval:** unclear
Participants	**No. of patients:** 46 randomised, 41 evaluated **Condition:** multiple myeloma (28 patients), non-Hodgkin lymphoma (NHL) (11 patients), Hodgkin lymphoma (2 patients) **Demographics:** unclear **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 25 mg i.m., 6x within 2 weeks at beginning of the study, thereafter 4x within 2 weeks before each chemotherapy cycle **Control treatment:** no treatment **Basic treatment:** multiple myeloma: VCAP/VMCP, MP or M-2; NHL: Promace MOPP, CVP or CHOP; Hodgkin lymphoma: MOPP/ABVD
Outcomes	**Outcome measures:** survival, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides/extracts), other
Notes	**Outcomes:** side effects of chemotherapy were not scored using standardized criteria; pre/post analysis of performance status (ECOG)

Canovas 1991

Methods	**Design:** 2-arm parallel trial with a no-treatment control group; patients stratified by diagnosis **No of centres:** 1 **Recruitment and setting:** Hospital de Cruces, Bilbao, Spain **Recruitment period:** unclear **Observation period:** approximately 4-6 months (6 cycles of chemotherapy) **Ethical approval:** unclear
Participants	**No. of patients:** 40 randomised, 32 evaluated **Condition:** multiple myeloma (13 patients), NHL (11 patients), Hodgkin lymphoma (8 patients) **Demographics:** unclear

Canovas 1991 (*Continued*)

	Informed consent: unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg body weight i.m., daily for one week; thereafter 2x/week for 6 chemotherapy cycles **Control treatment:** no treatment **Basic treatment:** multiple myeloma: VCAP/VMCP, MP or M-2; NHL: Promace MOPP, CVP, LSA2Ls, C-MOPP or IMVP-16; Hodgkin lymphoma: MOPP MOPP/ABVD
Outcomes	**Outcome measures:** survival, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	**Outcomes:** side effects of chemotherapy were not scored using standardized criteria; pre/post analysis of performance status (ECOG)

Cheng 2004

Methods	**Design:** 3-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China **Recruitment period:** 01/00-12/02 **Observation period:** 6-32 months **Ethical approval:** yes
Participants	**No. of patients:** 57 for the whole trial, 41 randomised, 41 evaluated in the two relevant arms **Condition:** hepatocellular carcinoma after hepatectomy; Edmondson´ s stage II-IV **Demographics:** men: 34, women: 7; median age (range): 48 (30-66) years for whole study population **Informed consent:** unclear
Interventions	**Interventional treatment:** thymosin α_1 (thymalfasin; Zadaxin) dose/schedule: 1.6 mg/day s.c., 2x/week from the first week after hepatectomy for 6 months **Control treatment:** no treatment **Basic treatment:** transcatheter hepatic arterial chemoembolisation (TACE) with carboplatin: 100 mg, epidoxorubicin 10 mg and mitomycin C 10 mg, starting 1.5 months after hepatectomy. In patients with recurrence, treatment was repeated max. four times
Outcomes	**Outcome measures:** survival
Notes	**Design**: 2 arms were relevant for this review, the third arm compares transcatheter hepatic arterial chemoembolisation with no treatment **Participants:** imbalance in stage of disease, with a higher proportion of patients with stage IV in the intervention group; distribution of patients with radical and palliative resection unclear **Funding:** supported by Shanghai Science and Technology Committee and Shanghai Hospital New Star Plan

Cohen 1979

Methods	**Design:** 3-arm parallel with placebo control **No of centres:** unclear **Recruitment and setting:** NCI-VA Medical Oncology Branch, Veterans Administration Hospital, Washington, D.C.; Surgery Branch, National Cancer Institute, Bethesda, USA **Recruitment period:** 07/75-01/77 **Observation period:** approximately 2 years for survival, 12 weeks for response **Ethical approval:** unclear
Participants	**No. of patients:** 55 randomised, 46 evaluated **Condition:** small cell lung cancer (SCLC), limited (15) or extensive (31) disease **Demographics:** men: 34, women: 12; median age (range): IG1: 58 (49-69), IG2: 61 (47-69), CG: 53 (41-67) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymosin fraction 5; dose/schedule: IG1: 60 mg/m² s.c., IG2: 20 mg/m² s.c., 2x/week during induction chemotherapy **Control treatment:** no treatment **Basic treatment:** induction therapy: cyclophosphamide 1500 mg/m² (d1), lomustine 100 mg/m² (d1), cyclophosphamide 1000 mg/m² (d22), methotrexate 15 mg/m² 2x/week for 10 doses; maintenance therapy: cyclically alternating two or three drug chemotherapy regimes for 2 years; starting on week 6
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	**Participants:** as stated by study authors patients in the IG2 tended to have a lower performance status **Outcomes:** side effects of chemotherapy were not scored using standardized criteria **ITT analysis:** was performed **Funding:** thymosin fraction 5 was provided by Hoffmann-La Roche

De Serdio 1997

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** Hospital Nuestra SeÅŁora de la Cruz, Santa Cruz de Tenerife, Spain **Recruitment period:** 03/93-09/95 **Observation period:** mean 18 months, max. 30 months **Ethical approval:** unclear
Participants	**No. of patients:** 36 randomised, 36 evaluated **Condition:** locally advanced head and neck cancer, stage III or IV **Demographics:** men: 35, women: 1; age (range): 30-66 years (no median given) **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1.5 mg/kg/day i.m. for 7 days before radiochemotherapy, 1.5 mg/kg/day i.m. 2x/week during treatment, 1 mg/kg/day i.m. 2x/week for 2 years or until recurrence **Control treatment:** no treatment **Basic treatment :** radiochemotherapy with 1.15 Gy per fraction up to 80.5 Gy (cumultative dose), carboplatin 5 mg/m² per fraction up to 700 mg (cumulative dose); 2x/day, 5 days/week
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), other

De Serdio 1997 (*Continued*)

Notes	

Del Giacco 1988

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** Institute of Internal Medicine, University of Cagliari, Italy **Recruitment period:** starting 01/81; duration unclear **Observation period:** 12-33 months **Ethical approval:** unclear
Participants	**No. of patients:** 48 randomised, 48 evaluated (22 evaluated for tumour response) **Condition:** NSCLC or SCLC after incomplete resection or unresectable, classified as immunodepressed by various immunologic tests **Demographics** (only reported in the preliminary publication for 22 patients): men: all patients; mean age (SD): IG: 58 (±8), CG: 57 (±11) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1.5 mg/kg i.m. daily between cycles for 2 months; on alternate days for 4 months; thereafter 2x/week **Control treatment:** no treatment **Basic treatment:** doxorubicin 50 mg/m² (d1), vincristine 1,2 mg/m² (d1), cyclophosphamide 400 mg/m² (d1), lomustine 30 mg/m² (d1); every 4 weeks; until demonstrable response for max 6 cycles; maintenance chemotherapy: NSCLC: cyclophosphamide 400 mg/m² (d1,d8), methotrexate 15 mg/m² (d1,d8), procarbazine 100 mg/m² (d1-10); every 4 weeks; SCLC: cyclophosphamide 1000-1500 mg/m²; every 3 weeks, methotrexate 10 mg/m² every 2 weeks, lomustine 50 mg/m² d1; thereafter VP16+adriamycin and methotrexate (no exact description given by authors)
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	Various inconsistencies regarding inclusion criteria and dose of thymostimulin **Participants:** in an earlier publication (1984) preliminary results were published on 22 patients 1 year after terminating an enrolment phase of 21 months; patients with SCLC were not included at the beginning of the trial and inclusion criteria were later changed **Interventions:** there are differing doses stated in the two publications, the preliminary publication refers a dose of 1 mg/kg i.m. **Outcomes:** side effects of chemotherapy were not scored using standardized criteria

Federico 1995

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 6 **Recruitment and setting:** 2 university hospitals (Modena and Pavia) and 4 other hospitals in Italy **Recruitment period:** 11/88-12/90 **Observation period:** 4 years, median follow up 38 months **Ethical approval:** unclear
Participants	**No. of patients:** 150 randomised, 134 evaluated **Condition:** intermediate- or high-grade NHL, stage II-IV and stage I with bulky disease **Demographics:** men: 73, women: 65 (mistake in publication); median age: IG: 52, CG: 51 years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg i.m.; for pats. treated with MACOP-B: (d22-29, 50-57, 77-85), for pats. treated with ProMACE-CytaBOM (d22-28) of each chemotherapy cycle **Control treatment:** no treatment **Basic treatment:** comparative study of 2 chemotherapy regimes: MACOP-B and ProMACE-CytaBOM: in both regimes doxorubicin was replaced by a 20% higher dose of epidoxorubicin
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), other
Notes	The study was designed by the Italian Lymphoma Study Group **Participants:** performance status significantly better in IG (P = 0.04) **Funding:** supported by public funding (MURST), the Associacione Italiana per la Ricerca sul Cancro (AIRC) and Serono, Italy

Gebbia 1994

Methods	**Design:** 4-arm parallel trial with placebo control **No. of centres:** 1 **Recruitment and setting:** University of Palermo, Italy **Recruitment period:** unclear **Observation period:** unclear **Ethical approval:** unclear
Participants	**No. of patients:** 100 randomised, 96 evaluated (51 relevant to this review) **Condition:** advanced breast cancer (26), advanced head and neck cancer (12), advanced gastric cancer (2), inoperable ovarian cancer (4), recurrent or metastatic endometrium cancer (4), SCLC (6) **Demographics:** women: 64, men: 36; mean age (range): 58.6 (40-75) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymopentin; dose/schedule: 50 mg i.m. every other day starting two days after application of chemotherapy until the beginning of the next cycle **Control treatment:** placebo (sodium chloride solution) **Basic treatment:** breast cancer: 5-FU 400 mg/m² (d1-3), FA 100 mg/m² (d1-3), mitoxantrone 24 mg/m² (d3) or 5-FU 400 mg/m² (d1-3), FA 100 mg/m² (d1-3), cyclophosphamide 500 mg/m² (d1), epidoxorubicin 120 mg/m² (d1); SCLC, head and neck cancer, endometrium cancer: cisplatin 80 mg/m²(d1), vinorelbine 25-30 mg/m² (d1, d8); gastric cancer: according to EAP regime; ovarian cancer: carboplatin 300 mg/m² (d1), cyclophosphamide 500 mg/m² (d1), epidoxorubicin 90 mg/m² (d1)

Gebbia 1994 (*Continued*)

Outcomes	**Outcome measures:** toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides)
Notes	

Gish 2009

Methods	**Design:** 2-arm open-label trial with a no-treatment control group **No. of centres:** 4 **Recruitment and setting:** California Pacific Medical Center, San Francisco; Henry Ford Health System, Detroit; University of Florida College of Medicine, Gainesville; Metropolitan Liver and Gastroenterology Center Fairfax **Recruitment period:** unclear **Observation period:** 72 weeks (24 weeks treatment and 48 weeks post-treatment monitoring); 30 months for survival **Ethical approval:** unclear
Participants	**No. of patients:** 28 randomised, 25 evaluated **Condition:** unresectable HCC, stage I-III (Okuda), **Demographics:** women: 6, men: 22; mean age (SD): IG: 59 (±9.1), CG: 60 (±6.7) **Informed consent:** unclear
Interventions	**Interventional treatment:** thymosin α_1; dose/schedule: 1.6 mg s.c., 5x/week for 24 weeks **Control treatment:** no treatment **Basic treatment:** TACE with doxorubicin or cisplatin (according to participating site´ s guidelines)
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	**Method:** small pilot study, sample size calculation was performed based on tumour response, accordingly 18 patients would have been required in each arm **Outcomes:** side effects of chemotherapy were not scored using standardized criteria **Funding:** supported by SciClone Pharmaceuticals

GISOT 1987

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 153 **Recruitment and setting:** inpatients of 153 hospitals, Italy **Recruitment period:** unclear **Observation period:** 3 months **Ethical approval:** unclear
Participants	**No. of patients:** 650 randomised, 609 evaluated **Condition:** solid tumors **Demographics:** unclear **Informed consent:** unclear
Interventions	**Interventional treatment:** thymopentin; dose/schedule: 50 mg s.c. 3x/week; for 4 weeks **Control treatment:** no treatment

GISOT 1987 (*Continued*)

	Basic treatment: chemotherapy or radiotherapy (not further specified by the author)
Outcomes	**Outcome measures:** survival, toxicity (AEs of chemo-/radiotherapy)
Notes	**Participants:** the trial included in total three groups of patients at risk of infections: elderly people (> 65 years) affected by chronic bronchitis (n=519), patients with solid tumours undergoing chemo- or radiotherapy (n=650), patients with HIV infection and lymphoadenopathy syndrome (LAS) (n=250) **Outcomes:** side effects of chemotherapy were not scored using standardized criteria

Gonnelli 1995

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** Institute of Internal Medicine and Division of Medical Oncology, University of Siena, Italy **Recruitment period:** unclear **Observation period**: 6 months **Ethical approval:** yes
Participants	**No. of patients:** 40 randomised, 36 evaluated **Condition:** breast cancer, patients with bone metastasis and at least one measurable osteolytic lesion **Demographics:** median age (range): IG: 59 (47-71), CG: 61 (43-70) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 50 mg i.m. daily for 6 months **Control treatment:** no treatment **Basic treatment:** 5-fluoruracil 500 mg/m² (d1), epirubicin 50 mg/m² (d1), cyclophosphamide 500 mg/m² (d1), or: 5-fluoruracil 400 mg/m² (d1-5), folinic acid 200 mg/m² (d1-5); mitomycin C 5 mg/m² (d3-5); every 3 weeks
Outcomes	**Outcome measures:** response, toxicity (AEs of chemo-/radiotherapy), other
Notes	**Method:** according to a sample size calculation 60 patients would have been required, but accrual was finished earlier due to loss of funding **Funding:** thymostimulin was supplied by Serono, Italy

Guzman 1988

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** unclear **Recruitment and setting:** Medical Institute Oncology Service and Guernes Center, Buenos Aires, Argentina **Recruitment period:** 12/83-12/85 **Observation period:** up to 42 months **Ethical approval:** unclear
Participants	**No. of patients:** 32 randomised, 32 evaluated **Condition:** colorectal cancer, Dukes B2, C1, C2 after surgery; colon cancer (29), rectal cancer (4) **Demographics:** women: 15, men: 17; mean age: women: 58.8, men: 61.8 years

Guzman 1988 (*Continued*)

	Informed consent: unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 25 mg/m² i.m. every chemotherapy cycle (d9-13,17,19, 24, 26) **Control treatment:** no treatment **Basic treatment :** 5-fluoruracil 600 mg/m² i.v. (d1,d8), lomustine 60 mg/m² p.o. (d1); every 3 weeks; for 6 months
Outcomes	**Outcome measures:** survival, toxicity (AEs of chemo-/radiotherapy), other
Notes	**Participants:** no reporting of distribution of risk factors between groups **Outcomes:** side effects of chemotherapy were not scored using standardized criteria

Iaffaioli 1994

Methods	**Design:** 2-arm parallel with placebo control **No. of centers:** unclear **Recruitment and setting:** unclear **Recruitment period:** 04/89-02/92 **Observation period:** approximately 5 months **Ethical approval:** yes
Participants	**No. of patients:** 69 randomised, 69 evaluated **Condition:** NSCLC, stage IIIA and B **Demographics:** men: 51, women: 18; age: patients under or 65 years: 39, patients over 65 years: 30 **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg; daily; after 2nd cycle: 3x/week, until end of treatment **Control treatment:** placebo (not further described) **Basic treatment:** radiochemotherapy: 24 fractions of 1.60 Gy 2x/day up to 38.4 G, followed within 14 days by one cycle of chemotherapy: carboplatin 250 mg/m² (d1), etoposide 100 mg/m² (d1), mitomycin C 8 mg/m² (d1-3), followed within 14 days by radiotherapy: 12 fractions of 1.6 Gy 2x/day up to 19.2 Gy, thereafter 5 cycles of chemotherapy
Outcomes	**Outcome measures:** toxicity (AEs of chemo-/radiotherapy), other
Notes	

Luzi 1984

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** unclear **Recruitment period:** unclear **Observation period:** 2 years **Ethical approval:** unclear
Participants	**No. of patients:** 50 randomised, 47 evaluated **Condition:** unresectable NSCLC, stage II or III **Demographics:** men: 45, women: 5; mean age (range): 59 (35-70) years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 0.5 mg/kg/day i.m. daily (starting 5 days before radiotherapy); thereafter 1x/week for 6 months **Control treatment:** no treatment **Basic treatment:** 3 Gy on alternate days for 5 weeks; bleomycin 8 mg/m² 2x/week during radiotherapy, after 18 days: doxorubicin 40 mg/m² (d1, 28), vincristine 1.4 mg/m² (d1, 28), lomustine 65 mg/m² (d2, 57)
Outcomes	**Outcome measures:** survival; response, other
Notes	**Funding:** the trial was supported by a grant of the national research institute (Consiglio Nazionale delle Ricerche); thymostimulin was supplied by Serono, Rome

Macchiarini 1989

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** unclear **Recruitment and setting:** unclear **Recruitment period:** 01/86-05/87 **Observation period:** up to 32 months; median 26.5 months **Ethical approval:** unclear
Participants	**No. of patients:** 28 randomised, 26 evaluated **Condition:** SCLC limited (20) or extensive (6) disease **Demographics:** men: 25, women: 1, median age: 61 years **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg/day i.m.; every chemotherapy cycle (d7-14); thereafter in pats. with complete remission, 2x/week **Control treatment:** no treatment **Basic treatment :** cyclophosphamide 1 g/m² (d1), epidoxorubicin 60 mg/m² (d1), etoposide 120 mg/m² (d1-4), or: cisplatin 60 mg/m² (d1), etoposide 120 mg/m² (d1-4); every 3-4 weeks, alternating the two regimes; for 6 cycles
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), other
Notes	

Maio 2010

Methods	**Design:** open label 5-arm parallel, patients stratified by site of distant metastasis (M1a,b,c) and lactate dehydrogenase (LDH) level **No of centres:** 64 **Recruitment and setting:** multi-centre study across 8 European countries **Recruitment period:** 08/02-01/06 **Observation period:** 14.9-56.5 months **Ethical approval:** yes
Participants	**No. of patients:** 488 patients evaluated (389 relevant to this review) **Condition:** melanoma, stage IV without brain metastasis **Demographics:** men: 250, women: 238 **Informed consent:** yes
Interventions	**Interventional treatment:** thymosin α_1; dose/schedule: IG1: 1.6 mg s.c.; IG2: 3.2 mg s.c. or IG3: 6.4 mg s.c. (d8-11 and d15-18) of every chemotherapy cycle **Control treatment:** no treatment **Basic treatment:** dacarbazine 800 mg/m² i.v. every 4 weeks for a maximum of six cycles; interferon α (IFNα) 3 MIU s.c. (d11,18) of every chemotherapy cycle
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	**Method:** sample size calculation was performed, accordingly 95 patients would be required in each arm; the original study design scheduled a four arm trial, but after preliminary analysis, which suggested a dose-response relation the protocol was extended to integrate a fifth arm with a dose of thymosin α_1 dose of 6.4 mg; sample size calculation was performed, accordingly 95 patients would be required in each arm **Participants:** only 4 of the 5 arms had a control group in accordance with the selection criteria of the review (the other arm was controlled by IFNα) **Outcomes:** AEs of thymic peptides not reported differentially; side effects of chemotherapy were not scored using standardized criteria **Funding:** supported by sigma-tau and SciClone Pharmaceuticals

Mantovani 1988

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 2 **Recruitment and setting:** university hospital and regional hospital, Cagliari, Italy **Recruitment period:** unclear **Observation period:** 1 (20 patients) or 2 years (16 patients) **Ethical approval:** unclear
Participants	**No. of patients:** 37 randomised, 37 evaluated **Condition:** breast cancer, patients with positive axillary lymph nodes, after radical or modified radical mastectomy **Demographics:** mean/median age (range): IG: 47.8/47.5 (31-60), CG: 45.8/47 (32-57) years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 60 mg/m²/day i.m or s.c. starting within 1 month after termination of chemotherapy: 7x/week (d1-15), 2x/week (d16-30), 1x/week (d31-60), repetition until d180 with a pause of 30 days in-between **Control treatment:** no treatment

Mantovani 1988 (*Continued*)

	Basic treatment : CMF regime; for 6 cycles
Outcomes	**Outcome measures:** survival, toxicity (AEs of chemo-/radiotherapy), other
Notes	**Funding:** supported by the National Research Council C.N.R.

Mustacchi 1994

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** multicentre **Recruitment and setting:** various hospitals in Italy (Trieste, Pavia, Cagliari, Napoli, Sassari, Vigevano, Pinerolo, Savona, Rome, Turin) **Recruitment period:** 02/90-12/92 **Observation period:** unclear **Ethical approval:** unclear
Participants	**No. of patients:** 235 randomised, 211 evaluated **Condition:** colorectal cancer stage IV **Demographics:** men: 107, women: 128; median age: IG: 61, CG: 60 years **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg i.m.; daily during chemotherapy treatment, 3x/week between cycles **Control treatment:** no treatment **Basic treatment:** 5-fluoruracil 375 mg/m² i.v. (60 min. infusion) (d1-5), folinic acid 200 mg/m² i.v. (60 min. infusion) (d1-5); every 3 weeks
Outcomes	**Outcome measures:** survival, response, safety (AEs of thymic peptides), other
Notes	**Method:** sample size calculation was performed for incidence of side effects and tumour response and resulted in the requirement of 130 patients per group **Outcomes:** side effects of chemotherapy were not scored using standardized criteria

Pavesi 1993

Methods	**Design:** 4-arm parallel (2 chemotherapy regimes) with no treatment control **No. of centres:** 13 **Recruitment and setting:** 13 centres all over Italy **Recruitment period:** 01/90-12/92 **Observation period:** unclear **Ethical approval:** unclear
Participants	**No. of patients:** 296 randomised, 245 evaluated **Condition:** metastatic breast cancer (presumably stage IV) **Demographics:** unclear **Informed consent:** unclear

Pavesi 1993 (*Continued*)

Interventions	**Interventional treatment:** thymostimulin; dose/schedule: IG1/IG2: 1 mg/kg i.m. daily (during chemotherapy treatment), thereafter 3x/week (until progression or withdrawal) **Control treatment:** no additional treatment **Basic treatment:** 5-fluoruracil 500 mg/m² i.v. (d1), epidoxorubicin 75 mg/m² i.v. (d1), cyclophosphamide 500 mg/m² i.v. (d1); every three weeks or: folinic acid 200 mg/m² (d1-5), 5-fluoruracil 370 mg/m² (d1-5), epidoxorubicin 75 mg/m² (d1), cyclophosphamide 500 mg/m² (d1); every three weeks
Outcomes	**Outcome measures:** survival; response, other
Notes	This study has not been published in full text (February 2010) and was performed by the Italian Cooperative Trials Group **Participants:** unclear how many patients were allocated to which arm

Salvati 1984

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 or 2 **Recruitment and setting:** Hospital C. Forlanini and Clinic of Respiratory Diseases, University of Rome, Italy **Recruitment period:** unclear **Observation period:** 6 months **Ethical approval:** unclear
Participants	**No. of patients:** 46 randomised, 40 evaluated **Condition:** SCLC, limited (34) or extensive (12) disease **Demographics:** men: 42, women: 4; median age (range): 57 (46-71) years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 1 mg/kg/day; 1st cycle (d4-10), 2nd-4th cycle (d4-6), 5th-9th cycle (d4, 5) **Control treatment:** no treatment **Basic treatment:** methotrexate 40 mg/m² i.v. (d1), doxorubicin 40 mg/m² i.v. (d1), cyclophosphamide 400 mg/m² i.v. (d1), nitrosourea 30 mg/m² i.v., (d1); every 3 weeks; for 6 months or until progression
Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), other
Notes	**Participants:** distribution of risk factors between groups not reported **Funding:** thymostimulin supplied by Serono, Rome

Sanchiz 1996

Methods	**Design:** 2-arm parallel trial with a no-treatment control group **No. of centres:** 1 **Recruitment and setting:** Department of Radiotherapy and Oncology, Clinica Platon, Barcelona, Spain **Recruitment period:** 06/92-12/93 **Observation period:** one cycle of chemotherapy **Ethical approval:** unclear
Participants	**No. of patients:** 54 randomised, 54 evaluated **Condition:** metastatic breast cancer **Demographics:** median age (range): IG: 46 (38-54), CG: 46 (32-54) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymostimulin; dose/schedule: 50 mg/day i.m.; every cycle (d2-16) **Control treatment:** no treatment **Basic treatment:** mitoxantrone 28 mg/m² i.v., supportive treatment: G-CSF 5 µg/kg s.c. (d2-16)
Outcomes	**Outcome measures:** response, toxicity (AEs of chemo-/radiotherapy)
Notes	

Scher 1988

Methods	**Design:** 2-arm parallel trial with a no-treatment control group; patients stratified by performance status and disease extent **No. of centres:** 2 **Recruitment and setting:** Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, USA **Recruitment period:** 05/79- 05/82 **Observation period:** approximately 25 to 60 months **Ethical approval:** unclear
Participants	**No. of patients:** 91 randomised, 80 evaluated **Condition:** SCLC limited (32) or and extensive disease (48) **Demographics:** men: 59, women: 32; median age (range): IG: 59 (35-73), CG: 53 (32-72) years **Informed consent:** unclear
Interventions	**Interventional treatment:** thymosin fraction 5; dose/schedule: 60 mg/m² s.c.; 2x/week from the start of induction therapy through the completion of radiotherapy **Control treatment:** no treatment **Basic treatment:** induction therapy: 1st and 3rd cycle: cyclophosphamide 1200 mg/m² (d1), doxorubicin 50 mg/m² (d1), vincristine 1.2 mg/m² (d1, 8); 2nd and 4th cycle: cisplatin 60 mg/m² (d1) and etoposide 120 mg/m² (d4, 6, 8); consolidation therapy: cyclophosphamide 500 mg/m² (d1,14), vincristine 1,4 mg/m² (d1,14) along with radiation therapy in patients with limited disease; maintenance therapy was started 10 weeks after completion of radiotherapy in patients who had achieved complete remission, others started after hematologic recovery: 1st cycle: lomustine 60 mg/m² p.o. (d1), methotrexate 30 mg/week for 4 weeks, procarbazine 100 mg/m² p.o. (d1-14); 2nd cycle cyclophosphamide 1000 mg/m² (d42) and doxorubicin 30 mg/m²(d42); 3rd cycle: vincristine 1,2 mg/m² d63, cisplatin 50 mg/m² d63 and etoposide 120 mg/m² (d67, 69, 71); radiotherapy with 2.5 Gy/day up to 45 Gy to primary site and anterior mediastinum (patients with LD); 3 Gy/day up to 30 Gy whole brain radiation (all patients)

Scher 1988 (*Continued*)

Outcomes	**Outcome measures:** survival, response, toxicity (AEs of chemo-/radiotherapy), safety (AEs of thymic peptides), other
Notes	**Method:** sample size calculation was performed, accordingly 80 patients would be required in order to detect a 25% increase in complete remission rate **Funding:** supported in part by the American Cancer Society and the National Institutes of Health (NIH); thymosin fraction 5 was supplied by Hoffmann-La Roche

Schulof 1985

Methods	**Design:** double blind 3-arm parallel with placebo control **No. of centres:** 1 **Recruitment and setting:** Washington University Medical Center, Washington D.C., USA **Recruitment period:** 11/80-01/83 **Observation period:** 1 year for relapse; all patients were followed up until death; median 40 weeks (8-108) **Ethical approval:** unclear
Participants	**No. of patients:** 42 randomised, 41 evaluated **Condition:** locally advanced NSCLC, patients who had received radiotherapy because of either an unresectable tumour or incomplete resection (R1 or R2); patients with progression under radiotherapy were not included **Demographics:** men: 26, women: 15; mean age (SD): IG1: 57.3 (± 9.2), IG2: 52.8 (± 8.5), CG: 55.6 (± 10.5) years **Informed consent:** yes
Interventions	**Interventional treatment:** thymosin α_1; dose/schedule: IG1: placebo daily for 14 days; thereafter 900 µg/m²/day s.c., 2x/week as maintenance therapy; IG2: 900µg/m²/day, for 14 days as loading dose, thereafter placebo 2x/week as maintenance therapy; administration was initiated one week after completion of radiotherapy for a period of up to 1 year or until relapse **Control treatment:** placebo (mannitol powder reconstituted in bicarbonate diluent, provided in same coded vials as thymosin α_1): daily for 14 days; maintenance therapy: 2x/week **Basic treatment:** radiotherapy: 2 Gy/day 5x/week for 6-8 weeks to mediastinum and primary lesion, patients with prior resection of tumour received irradiation only to mediastinum
Outcomes	**Outcome measures:** survival, safety (AEs of thymic peptides), other
Notes	**Participants:** imbalance in gender distribution and proportion of patients with resection of primary (IGs 11/28, CG 1/13) which was also discussed by the authors **Funding:** supported by the National Cancer Institute (NCI) and Hoffmann-La Roche

Wara 1981

Methods	**Design:** open label 2-arm parallel **No. of centres:** 1 **Recruitment and setting:** Department of Radiation Oncology and Pediatrics, University of California, San Francisco, USA **Recruitment period:** 4 years before publication **Observation period:** min. 8 months, median 2 years. **Ethical approval:** unclear
Participants	**No. of patients:** 76 randomised, 75 evaluated **Condition:** squamous cell cancer of head and neck, stage II-IV **Demographics:** unclear **Informed consent:** unclear
Interventions	**Interventional treatment:** thymosin fraction 5; dose/schedule: 60 mg/m²: daily for 10 days; thereafter 2x/week for 50 weeks **Control treatment:** no treatment **Basic treatment:** radiotherapy with 50-60 Gy
Outcomes	**Outcome measures:** survival, other
Notes	**Interventions:** thymosin fraction 5 was supplied by Hoffmann-La Roche

Outcomes which were not relevant to this review are indicated as 'other'. This includes immunologic parameters, dose modifications of chemotherapy or radiotherapy

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

Study	Reason for exclusion
Azizi 1984	Patients received neither chemotherapy nor radiotherapy
Bernengo 1983	No sufficient outcome data reported
Cartia 1990	No sufficient outcome data reported
Chen 2000	Outcome assessment not according to eligibility criteria of the review
De Maria 1993	Only immune parameters reported
Denaro 1994	Only immune parameters reported
Holowiecki 1984	Not randomised for purified thymic extract
Iaffaioli 1988	Outcome assessment not according to eligibility criteria of the review

(*Continued*)

Kreuser 1998	Registered randomised controlled trial, yet unpublished; manufacturer contacted, but no data provided
Liberati 1998	Only immune parameters reported
Mantovani 1995	Only immune parameters reported
Migeod 1985	Only immune parameters reported
Munno 1995	Only immune parameters reported
Quang-Xing 2001	Outcome assessment not according to eligibility criteria of the review
Shoham 1988	No concomitant chemotherapy or radiotherapy
Surico 1992	Outcome assessment not according to eligibility criteria of the review
Tetti 1987	Outcome assessment not according to eligibility criteria of the review

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

Dollinger 2010

Methods	Prospective randomised, placebo-controlled, double blind, multicentre clinical phase III trial
Participants	135 patients with locally advanced or metastasised HCC (Karnofsky >=60% - Child-Pugh <=12)
Interventions	Thymostimulin 75mg s.c. 5x per week or placebo
Outcomes	Primary endpoint was 12-month survival, secondary endpoints overall survival (OS), time to progression (TTP), tumour response, safety and quality of life
Notes	Current Controlled Trials ISRCTN64487365

DATA AND ANALYSES

Comparison 1. Purified thymus extracts versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8	705	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.79, 1.25]
1.1 Thymostimulin	5	469	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.85, 1.35]
1.2 Thymosin fraction 5	3	236	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.49, 1.45]
2 Disease free survival	6	511	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.16]
2.1 Thymostimulin	3	385	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.19]
2.2 Thymosin fraction 5	3	126	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.60]
3 Tumour response	11	778	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.25]
3.1 Thymostimulin	8	553	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.96, 1.62]
3.2 Thymosin fraction 5	3	225	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.19]
4 Toxicity (patients with grade 3/4 infectious complications)	4	214	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.38, 0.78]
4.1 Thymostimulin	3	134	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.19, 0.75]
4.2 Thymosin fraction 5	1	80	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.41, 0.95]
5 Toxicity (patients with grade 3/4 neutropenia)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Thymostimulin	3	149	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.25, 1.23]

Comparison 2. Synthetic thymic peptides versus no treatment or placebo

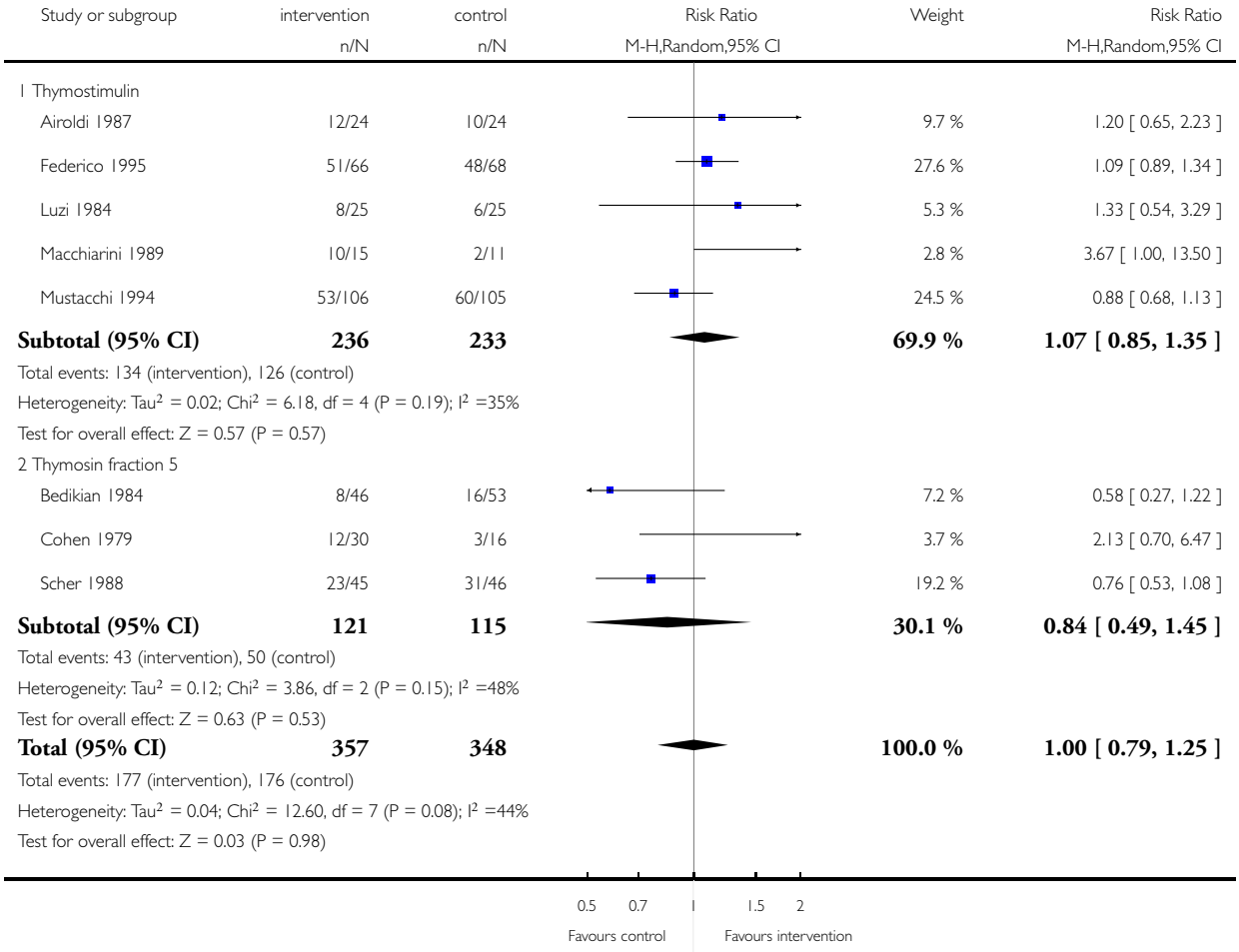
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	496	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.94, 1.56]
1.1 Thymosin α_1	4	496	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.94, 1.56]
2 Disease free survival	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Thymosin α_1	3	471	Risk Ratio (M-H, Random, 95% CI)	3.37 [0.66, 17.30]
3 Tumour response	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Purified thymus extracts versus no treatment or placebo, Outcome 1 Overall survival.

Review: Thymic peptides for treatment of cancer patients

Comparison: 1 Purified thymus extracts versus no treatment or placebo

Outcome: 1 Overall survival



Analysis 1.2. Comparison 1 Purified thymus extracts versus no treatment or placebo, Outcome 2 Disease free survival.

Review: Thymic peptides for treatment of cancer patients

Comparison: 1 Purified thymus extracts versus no treatment or placebo

Outcome: 2 Disease free survival

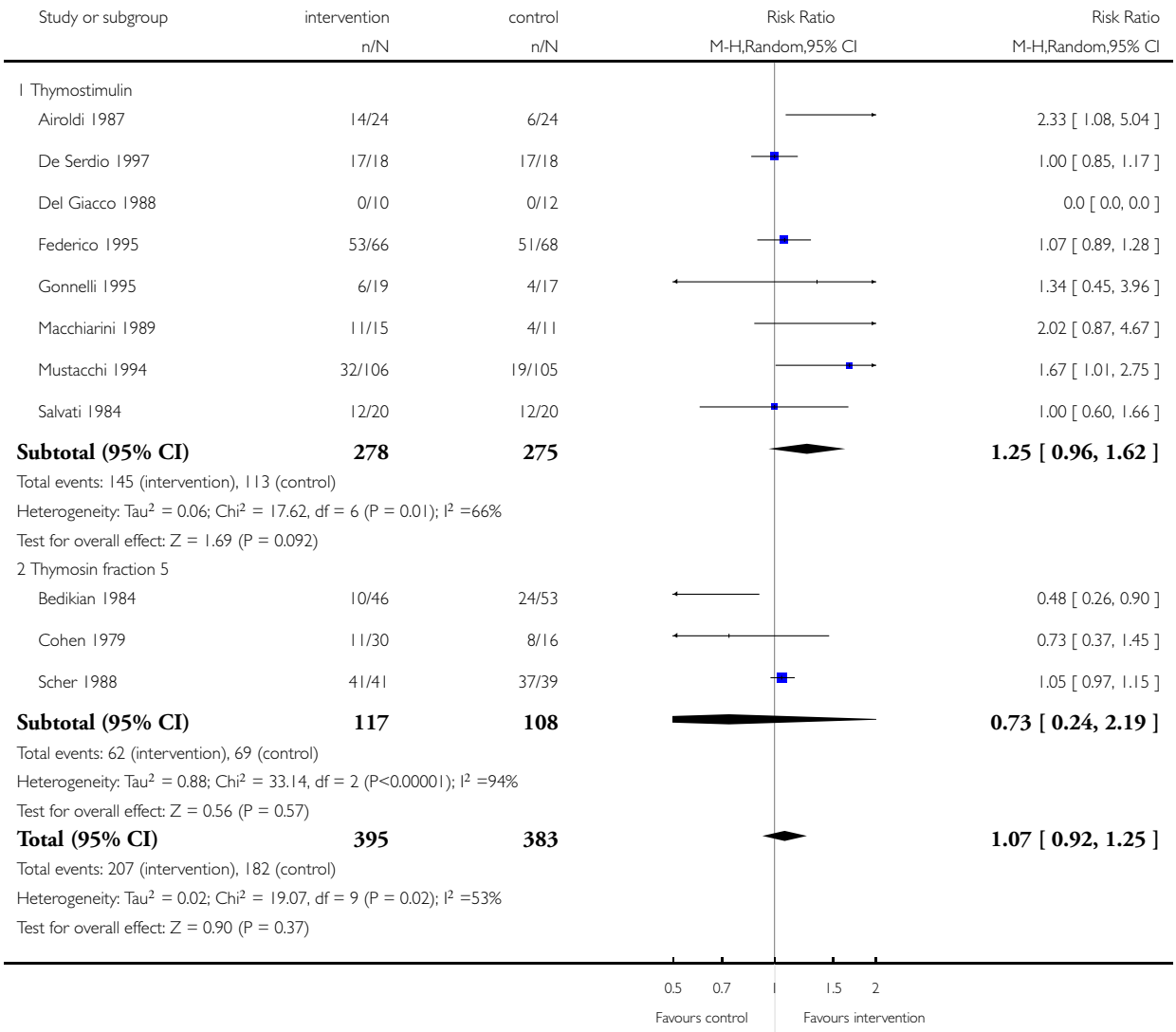
Study or subgroup	intervention n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Thymostimulin					
Federico 1995	35/39	24/29		33.9 %	1.08 [0.89, 1.32]
Mantovani 1988	5/11	7/10		4.8 %	0.65 [0.30, 1.39]
Pavesi 1993	74/148	86/148		31.8 %	0.86 [0.70, 1.06]
Subtotal (95% CI)	**198**	**187**		**70.5 %**	**0.93 [0.73, 1.19]**
Total events: 114 (intervention), 117 (control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.35, df = 2 (P = 0.11); I^2 =54%					
Test for overall effect: Z = 0.54 (P = 0.59)					
2 Thymosin fraction 5					
Cohen 1979	7/11	2/8		1.8 %	2.55 [0.71, 9.16]
Scher 1988	10/17	11/15		10.0 %	0.80 [0.49, 1.32]
Wara 1981	22/33	25/42		17.7 %	1.12 [0.79, 1.58]
Subtotal (95% CI)	**61**	**65**		**29.5 %**	**1.06 [0.71, 1.60]**
Total events: 39 (intervention), 38 (control)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 3.22, df = 2 (P = 0.20); I^2 =38%					
Test for overall effect: Z = 0.30 (P = 0.76)					
Total (95% CI)	**259**	**252**		**100.0 %**	**0.97 [0.82, 1.16]**
Total events: 153 (intervention), 155 (control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.15, df = 5 (P = 0.21); I^2 =30%					
Test for overall effect: Z = 0.30 (P = 0.77)					

Analysis 1.3. Comparison 1 Purified thymus extracts versus no treatment or placebo, Outcome 3 Tumour response.

Review: Thymic peptides for treatment of cancer patients

Comparison: 1 Purified thymus extracts versus no treatment or placebo

Outcome: 3 Tumour response



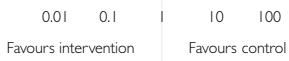
Analysis 1.4. Comparison 1 Purified thymus extracts versus no treatment or placebo, Outcome 4 Toxicity (patients with grade 3/4 infectious complications).

Review: Thymic peptides for treatment of cancer patients

Comparison: 1 Purified thymus extracts versus no treatment or placebo

Outcome: 4 Toxicity (patients with grade 3/4 infectious complications)

Study or subgroup	intervention n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Thymostimulin					
Canovas 1991	2/16	4/16		5.4 %	0.50 [0.11, 2.35]
Del Giacco 1988	0/25	2/23		1.5 %	0.18 [0.01, 3.65]
Sanchiz 1996	6/27	16/27		21.8 %	0.38 [0.17, 0.81]
Subtotal (95% CI)	**68**	**66**		**28.6 %**	**0.38 [0.19, 0.75]**
Total events: 8 (intervention), 22 (control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.35$, df = 2 (P = 0.84); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.80 (P = 0.0051)					
2 Thymosin fraction 5					
Scher 1988	17/41	26/39		71.4 %	0.62 [0.41, 0.95]
Subtotal (95% CI)	**41**	**39**		**71.4 %**	**0.62 [0.41, 0.95]**
Total events: 17 (intervention), 26 (control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.18 (P = 0.029)					
Total (95% CI)	**109**	**105**		**100.0 %**	**0.54 [0.38, 0.78]**
Total events: 25 (intervention), 48 (control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 3 (P = 0.59); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.34 (P = 0.00082)					



Analysis 1.5. Comparison 1 Purified thymus extracts versus no treatment or placebo, Outcome 5 Toxicity (patients with grade 3/4 neutropenia).

Review: Thymic peptides for treatment of cancer patients

Comparison: 1 Purified thymus extracts versus no treatment or placebo

Outcome: 5 Toxicity (patients with grade 3/4 neutropenia)

Study or subgroup	intervention n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Thymostimulin					
Iaffaioli 1994	7/37	12/32		36.9 %	0.50 [0.23, 1.13]
Macchiarini 1989	0/15	4/11		7.1 %	0.08 [0.00, 1.40]
Sanchiz 1996	20/27	27/27		56.0 %	0.75 [0.59, 0.94]

Analysis 2.1. Comparison 2 Synthetic thymic peptides versus no treatment or placebo, Outcome 1 Overall survival.

Review: Thymic peptides for treatment of cancer patients

Comparison: 2 Synthetic thymic peptides versus no treatment or placebo

Outcome: 1 Overall survival

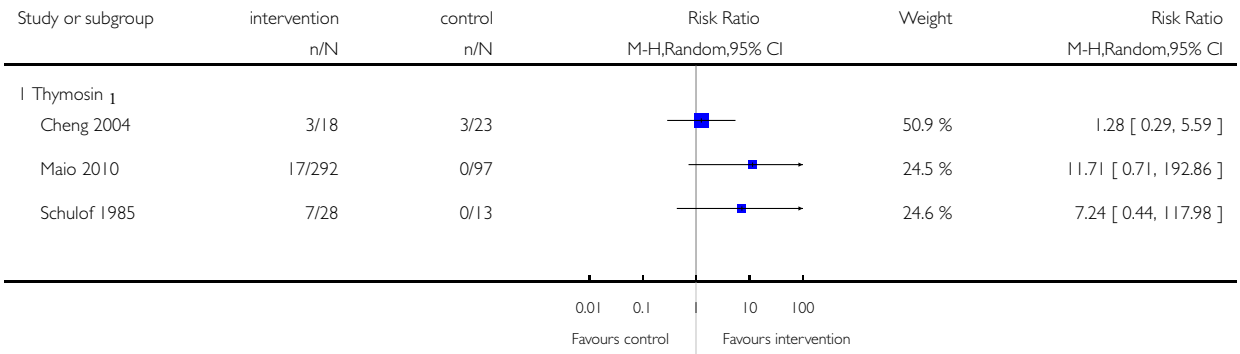
Study or subgroup	intervention n/N	control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Thymosin 1					
Cheng 2004	9/18	9/23		13.5 %	1.28 [0.64, 2.54]
Gish 2009	9/14	7/11		18.1 %	1.01 [0.56, 1.83]
Maio 2010	120/292	33/97		66.7 %	1.21 [0.89, 1.65]
Schulof 1985	12/28	1/13		1.7 %	5.57 [0.81, 38.42]
Total (95% CI)	**352**	**144**		**100.0 %**	**1.21 [0.94, 1.56]**
Total events: 150 (intervention), 50 (control)					
Heterogeneity: Tau² = 0.0; Chi² = 2.99, df = 3 (P = 0.39); I² =0.0%					
Test for overall effect: Z = 1.48 (P = 0.14)					

Analysis 2.2. Comparison 2 Synthetic thymic peptides versus no treatment or placebo, Outcome 2 Disease free survival.

Review: Thymic peptides for treatment of cancer patients

Comparison: 2 Synthetic thymic peptides versus no treatment or placebo

Outcome: 2 Disease free survival

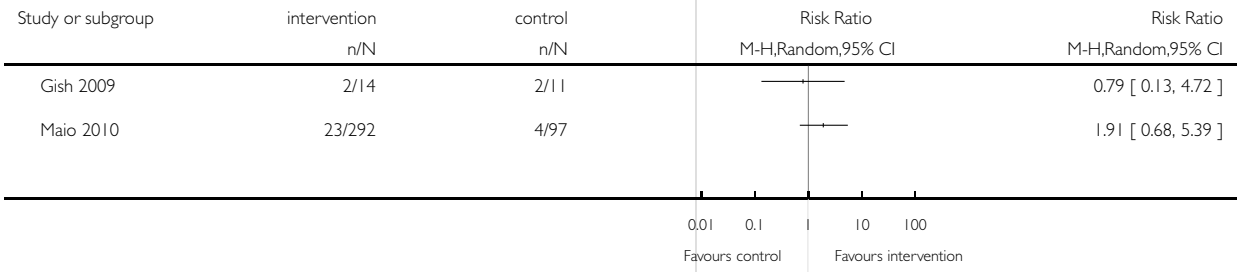


Analysis 2.3. Comparison 2 Synthetic thymic peptides versus no treatment or placebo, Outcome 3 Tumour response.

Review: Thymic peptides for treatment of cancer patients

Comparison: 2 Synthetic thymic peptides versus no treatment or placebo

Outcome: 3 Tumour response



APPENDICES

Appendix 1. Glossary of terms

EORTC	European Organization for Research and Treatment of Cancer
Breslow thickness	Measuring of the depth of penetration of a melanoma into the skin in mm
Dukes	Staging score for Colorectal cancer
WHO	World Health Organization
RECIST	Response Evaluation Criteria In Solid Tumors: a set of published rules that define when malignant tumours respond ("respond"), stay the same ("stable") or worsen ("progression") during treatments
OS	Overall survival: denotes the chances of staying alive for a group of individuals suffering from a cancer. It denotes the percentage of individuals in the group who are likely to be alive after a particular duration of time
DFS	Disease-free survival: denotes the chances of staying free of disease after a particular treatment for a group of individuals suffering from a cancer. It is the percentage of individuals in the group who are likely to be free of disease after a specified duration of time.
pTE	Purified extracts from animal thymus glands containing peptide mixtures
sTP	Synthetically produced single thymic peptides.

Appendix 2. Search strategies

PubMed - CENTRAL - MEDLINE

These databases were searched with 37 terms that referred to Thymyc/Peptide extracts.

Search terms used to identify interventions were:

1. Thymostimulin or thymoxtimulin
2. TF5
3. Thymosin
4. Thymosin fraction 5
5. Tα1 or Talpha1 or Thymosin alfa one or thymalfasin or zadaxin
6. Thymic serum factors
7. Tβ4 or thymosin beta four
8. Tγ or thymosin gamma
9. TFX or thymomodulin or thymic factor x or TFX-Polfa
10. TFX-Jelfa
11. TP-1
12. Thym-uvocal or Thymuvocal
13. Thymoject/thymojekt
14. Biosin
15. Thymex-L or thymex l
16. Thymophisin/Thymophysin

17. Zellmedin-thymus or THX
18. Neytumourin Sol
19. NeyThymun
20. Thymuskin
21. Thymushydrolysate
22. Solcothymosin
23. Thymowied
24. Leucotrofina
25. *FTS-Zn*
26. Thymulin
27. Thymic serum factor
28. *THFγ*
29. Thymic humoral factor
30. HTH or Homeostatic thymic hormone
31. Thymopoietin (I and II) or TP5 or Thymopentin
32. Prothymosin α
33. Thymus peptide
34. LSH
35. Lymphocytopoietic factor
36. Wobe-Mugos
37. t-activin or tactivin

PubMed limits to identify the type of study:

- Humans
- Type of Article: Clinical Trial OR Meta-Analysis OR Randomized Controlled Trial OR Review
- More Publication Types: Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Controlled Clinical Trial OR Multicenter Study
- Topics: Cancer OR Complementary Medicine OR Systematic Reviews OR Toxicology
- Age : All Adult: 19+ years OR Young Adult: 19-24 years OR Adult: 19-44 years OR Middle Aged: 45-64 years OR Middle Aged + Aged: 45+ years OR Aged: 65+ years80 and over: 80+ years

Example of search:

("thymostimulin"[Substance Name] **OR** "thymostimulin"[All Fields])

AND

("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])

AND

("humans"[MeSH Terms])

AND

(Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])

AND

(cancer[sb] OR cam[sb] OR systematic[sb] OR tox[sb] OR medline[sb] OR pubmed pmc local[sb]) AND ("adult"[MeSH Terms] OR "young adult"[MeSH Terms] OR "adult"[MeSH Terms:noexp] OR "middle aged"[MeSH Terms] OR ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms]) OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms]))

EMBASE SEARCH:

The same 37 above mentioned PubMed terms were also searched in EMBASE.

EMBASE limits to identify the type of study:

- human
- article or "review"
- adult <18 to 64 years> or aged <65+ years>
- intramuscular or subcutaneous

Example of search:

Thymic extracts **OR** Thymus extracts **OR** Thymos* **OR** Thym*

AND
Cancer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
OTHER DATABASE SEARCHES
The other databases were searched using the following specific terms as text words combined by the Boolean operator "OR":
thymus therapy; thymic peptide; thymic hormone; Thymustherapie; thymosin; thymosin fraction 5: thymosin fraction V; thymulin; thymusfactor; thymopentin; thymostimulin; thymic extracts; Ney-Tumorin; Neythymun; Solcothymosin; Thymex; Thymowied; Thym-Uvocal; Thymoject; thymophysin; Zellmedin-Thymus; THX; TF5; TP-1;THF;TFX;TP5.
These following terms were used to identify the study design:
"therapy"; "treatment"; clinical trial; randomised clinical trial as MeSH terms.
These following terms were used to identify cancer patients:
"cancer"; "tumours"; "neoplasms" as MeSH terms.
Date of last search 10.3.2010
All databases were searched from their inception until March 2010

Appendix 3. Kirkwood formulae

Survival Time (t)=S(t)=exp(-Êt). This transforms for the median survival time to T_{med} = - ln (0.5) / Ê. The number E_{CG} of events in the control group given N_{CG} patients in the control group at median survival time of the intervention group $T_{med}(M_{IG})$ can now be calculated via $E_{CG} = N_{CG} * (1-EXP(-T_{med}(M_{IG})*ln(2)/ T_{med}(M_{CG}))$. Obviously, the number of events in the intervention group is $E_{IG=} 0.5*N_{IG}$. Of note, these calculations assume no censoring of patients up to median follow-up time. With these numbers a relative risk with an approximate 95% CI can be calculated as implemented in standard meta-analysis software.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 2, 2011

Date	Event	Description
1 October 2008	New citation required and major changes	Authors: Reviewer team has changed Objectives: Text was rephrased and the population under study was restricted to cancer patients with thymus extracts during chemo- or radiotherapy Types of interventions: Interventional treatment under study was restricted to thymus extracts given during chemo- or radiotherapy and interventions in the control group were restricted to no treatment, or placebo treatment. Types of outcome measures: Text was rephrased Acknowledgments/Contributions of authors: the review team has changed and the text were rephrased/amended accordingly
16 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MH and EW had full access to all data in the review and takes responsibility for the integrity of the data and the accuracy of the analysis.

Study concept and design: KB, MH, SM, EW.

Inclusion and exclusion of studies: KB, MH, SM, EW.

Acquisition of data: KB, MH, SM, EW.

Data entry and plausibility check: EW, MH.

Analysis and interpretation of data: MH, SM, EW.

Drafting of the manuscript: MH, EW with contributions from all other review authors.

Statistical analysis: MH, SM, EW, MZ.

Study supervision: MH.

DECLARATIONS OF INTEREST

None known.

It is certified that there are no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (for example employment, consultancy, stock ownership, honoraria).

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

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- Cochrane Gynecologic Cancer Group, Bath, UK.