Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma (Review)

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[Intervention Review]

Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

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ABSTRACT

Background

Combined modality treatment (CMT) consisting of chemotherapy followed by localised radiotherapy is standard treatment for patients with early stage Hodgkin lymphoma (HL). However, due to long term adverse effects such as secondary malignancies, the role of radiotherapy has been questioned recently and some clinical study groups advocate chemotherapy only for this indication.

Objectives

We performed a systematic review with meta-analysis of randomised controlled trials (RCTs) comparing chemotherapy alone with CMT in patients with early stage Hodgkin lymphoma with respect to response rate, progression-free survival (alternatively tumour control) and overall survival (OS).

Search strategy

We searched MEDLINE, EMBASE and CENTRAL as well as conference proceedings from January 1980 to November 2010 for randomised controlled trials comparing chemotherapy alone to the same chemotherapy regimen plus radiotherapy.

Selection criteria

Randomised controlled trials comparing chemotherapy alone with CMT in patients with early stage HL. Trials in which the chemotherapy differed between treatment arms were excluded. Trials with more than 20% of patients in advanced stage were also excluded.

Data collection and analysis

Effect measures used were hazard ratios (HR) for tumour control and OS as well as relative risks for response rates. Two review authors independently extracted data and assessed quality of trials. We contacted study authors to obtain missing information. Since none of the trials reported progression-free survival according to our definitions, all similar outcomes were evaluated as tumour control.

Main results

Five RCTs involving 1245 patients were included. The HR was 0.41 (95% confidence interval (CI) 0.25 to 0.66) for tumour control and 0.40 (95% CI 0.27 to 0.61) for OS for patients receiving CMT compared to chemotherapy alone. Complete response rates were similar between treatment groups. In sensitivity analyses another six trials were included that did not fulfil the inclusion criteria of our protocol but were considered relevant to the topic. These trials underlined the results of the main analysis.

Authors' conclusions

Adding radiotherapy to chemotherapy improves tumour control and overall survival in patients with early stage Hodgkin lymphoma.

PLAIN LANGUAGE SUMMARY

Treatment of early stage Hodgkin lymphoma

Hodgkin lymphoma is a malignancy of the lymphatic system, first described by Thomas Hodgkin. It can occur in children and adults, but it is more common in the third decade of life. It is one of the most curable forms of cancer. Clinically speaking, there are four stages of Hodgkin lymphoma. Generally, stages I and II are considered as early stage Hodgkin lymphoma and stages III and IV as advanced stage Hodgkin lymphoma. Using risk factors such as presence or absence of bulky disease, age, erythrocyte sedimentation rate and presence or absence of B symptoms, such as night sweats or fever, early stage Hodgkin lymphoma is further classified into early favourable and early unfavourable stages. Treatment options for Hodgkin lymphoma are chemotherapy, radiotherapy or chemotherapy plus radiotherapy. Nowadays chemotherapy plus radiotherapy to involved areas is considered as standard treatment for patients with early stage Hodgkin lymphoma. Radiotherapy has comparatively more treatment related late side effects than chemotherapy, including second malignancies. Perhaps, patients with early stage Hodgkin lymphoma can benefit more by avoiding radiotherapy and can be treated with chemotherapy alone as effectively as with same chemotherapy plus radiotherapy. With this assumption we assess the role of radiotherapy in the treatment of patients with early stage Hodgkin lymphoma. This systematic review compares chance of dying (overall survival) and chance of tumour control in patients with early stage Hodgkin lymphoma after receiving chemotherapy alone or chemotherapy plus radiotherapy. This review includes 1245 patients from five trials in the main analyses. The result of this review is that the addition of radiotherapy to six cycles of chemotherapy is a better treatment option than six cycles of same chemotherapy alone in patients with early stage Hodgkin lymphoma. In terms of five-year tumour control, approximately 5 patients would be needed to treat with chemotherapy plus radiotherapy to prevent one additional relapse or progression in five years. For survival, 11 to 55 patients (depending on the risk of death) require treatment with additional radiotherapy to prevent one death in five years. Therefore chemotherapy plus radiotherapy (combined modality treatment) is superior to the identical chemotherapy alone in patients with early stage Hodgkin lymphoma.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Chemotherapy plus radiotherapy compared to chemotherapy alone for early stage Hodgkin lymphoma

Patient or population: Early stage Hodgkin lymphoma
Intervention: Chemotherapy plus radiotherapy
Comparison: Chemotherapy

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk (95% CI)				
	Chemotherapy	**Chemotherapy plus radiotherapy**				
Overall survival Hazard Ratio (follow-up: median 5 years)	**Low risk population**[1]		**HR 0.40** (0.27 to 0.6)	1245 (5)	⊕⊕⊕ **moderate**[2]	
	30 deaths per 1000	**12 per 1000** (8 to 18)				
	High risk population[1]					
	150 deaths per 1000	**63 per 1000** (43 to 93)				
Tumour control (follow-up: median 5 years)	**Low risk population**[1]		**HR 0.41** (0.25 to 0.66)	1202 (4)	⊕⊕⊕ **moderate**[3]	
	100 progresses or relapses per 1000	**42 per 1000** (26 to 67)				
	High risk population[1]					
	300 progresses or relapses per 1000	**136 per 1000** (85 to 210)				

Complete Response Rate	**Low risk population**[4]		**RR 1.07** (0.98 to 1.17)	653 (4)	⊕⊕⊕ **moderate**[5]	
	960 complete responses per 1000	**1027 per 1000** (941 to 1123)				
	High risk population[4]					
	650 complete responses per 1000	**696 per 1000** (637 to 760)				
Long term secondary malignancies	See comment	See comment	Not estimable	-	See comment	As most of the trials had a median observation time of less than 10 years, long term information on secondary malignancies cannot be expected.[6]
Acute adverse effects	See comment	See comment	Not estimable	-	See comment	Acute adverse effects were reported differently in the studies and are similar in both groups.[7]
Long term toxicities	See comment	See comment	Not estimable	-	See comment	Long term toxicities other than secondary malignancies are not reported.[8]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The risk for the low risk population (of patients with early stage Hodgkin lymphoma) was taken from the trial with the lowest rates of tumour control at 5 years the EORTC-GELA H9-F trial. The high risk rate is approximately the risk in the GATLA 9-H-77.

2 The supplemental analyses shifted the effect estimate (see results section). For this reason, the outcome overall survival was downgraded to moderate.

[3] The definitions of tumour control varied between trials. In some trials the choice of tumour control outcome to be reported may have been guided by strength of the effect. These heterogeneous definitions also lead to an imprecise estimate of the effect or may be considered a publication bias. The effect of these heterogeneous definitions is downgraded here. The same cause is not downgraded in another section again.

[4] The complete response rate for the low risk population is the highest CR rate reported in an included trial in this review (MSKCC #90-44). The rate for the low risk population is the lowest CR rate reported in this review (CALGB 7751). This estimate of high risk may no longer be relevant today, as ABVD produces much higher rates of CR than CVPP:

[5] Note that for trials using only ABVD the RR is 1.02 (0.95 to 1.09).

[6] A non-systematic search of cohorts of Hodgkin lymphoma survivors did not reveal any cohorts that presented 20-year secondary malignancy rates for early stage patients treated with chemotherapy alone versus chemotherapy plus radiotherapy. Cohorts of all patients suggest a higher risk of secondary malignancies for patients receiving any type of radiotherapy. The question of secondary malignancies is addressed in another Cochrane review of individual patient data (Franklin 2005). This review reports 4% versus 5% cumulative incidence of secondary malignancies at 20 years. This rate is much lower than the rates for patients with advanced stages (~20%).

[7] Due to diversity in reporting, adverse effects were not meta-analysed. Common diverse effects reported are nausea and vomiting, alopecia, grade III neutropenia and grade I-II thrombopenia. Rare (<2%) are bleomycin induced lung disease, infection-related mortality or high grade neurotoxicity.

[8] In cohorts of patients with Hodgkin lymphoma infertility and chronic cardiac disease are relatively common. However information on how frequent these effects are in early stage patients treated with the treatments discussed in this review was not reported.

BACKGROUND

Description of the condition

Hodgkin lymphoma (HL) is one of the most common malignancies in young adults (Swerdlow 2003; Thomas 2002). It is a malignancy of the lymph nodes and lymphatic system with possible involvement of other organs. The disease is rare with an annual incidence of approximately two to three per 100,000 in most countries (DeVita 1997; Diehl 2005; Mauch 1999) and occurs mostly in young people, the incidence being greatest in the third decade of life (Mueller 1999). Factors associated with Hodgkin lymphoma include family history, viral exposures, and immune suppression (Glaser 1996).

Staging of HL is based on the Ann Arbor system (Carbone 1971), with the addition of a definition of bulky disease (largest tumour diameter > 10 cm), often referred to as the Cotswold modification (Lister 1989). Information about prognostic factors such as mediastinal mass, other bulky nodal disease, and extent of subdiaphragmatic disease is included in this classification. Generally, HL is differentiated into early stage HL and advanced stage HL. On the basis of clinical staging and risk factors, patients are usually assigned to early favourable, early unfavourable and advanced stages (Engert 2007; Klimm 2005). However, there are still small differences in the definition of risk factors used and in the classification of certain subgroups of patients among the different study groups in Europe and the USA.

Description of the intervention

Usually patients with early stage Hodgkin lymphoma receive two to six cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) in combination with involved-field radiotherapy (IF-RT) (Diehl 2005; Engert 2007; Meyer 2005; MSKCC trial #90-44). Depending on the intensity and dose of treatment given, long term complications such as secondary malignancies (Franklin 2005), cardiac disease (Adams 2004) and infertility are common in Hodgkin survivors. For patients with early stage disease, the 20 year cumulative secondary malignancy rate is estimated to be between four percent and 20 percent (Franklin 2005; Ng 2002a). Risk factors for secondary malignancies (and cardiac disease) are the choice and dose of radiotherapy and chemotherapy (Aleman 2003; Bhatia 2003; Dores 2002; Franklin 2005; Green 2000; Ng 2002a; Ng 2002b; Swerdlow 2000; van Leeuwen 2000). Unfortunately, no long-term comparison of combined modality treatment (CMT), consisting of chemotherapy plus radiotherapy, with chemotherapy alone was possible in cohorts of Hodgkin survivors, in part due to the changes in treatment regimens over time (Ng 2002a). Nonetheless, to avoid additional radiation-induced toxicity, chemotherapy-only treatment for patients with early stage Hodgkin lymphoma has been advocated (Canellos 2005; Meyer 2005a). This notion was supported by two clinical trials comparing combined modality treatment with chemotherapy alone in which no significant survival disadvantage was observed in patients receiving chemotherapy alone (Meyer 2005; MSKCC trial #90-44). However, one of these trials compared two cycles of chemotherapy plus radiotherapy with four to six cycles of chemotherapy.

How the intervention might work

Chemotherpay (CT) and radiotherapy (RT) act on differentiating cells, prone to damage, and stop their growth and ultimately damage them, as result tumour mass shrinks. Along with tumour cure normal body cells are also affected after treatment resulting in treatment related side effects.

Biologic basis of chemotherapy

The most commonly used chemotherapeutic drugs in the treatment of early stage HL are classified as follows.

- Alkylating agents: cyclophospahamide, mechlorethamine, procarbazine, dacarbazine, cisplatine.
- Anti-tumour antibiotics: bleomycine, doxorubicine (adriamycin), epirubicine, etoposide.
- Anti-mitotic agents: vincristine, vinblastine.
- Steroid hormones: prednisone.

Alkylating agents and anti-tumour antibiotics are phase-nonspecific chemotherapeutic drugs, which can injure DNA at any phase of cell cycle but appear to then block in S-phase or G2 at a check point in a cell cycle before cell division (Sausville 2005). Anti-mitotic agents and steroid hormones are phase-specific chemotherapeutic drugs. Anti-mitotic agents act in M-phase and prevent tumour cell division by destroying mitotic spindle and anti-metabolites act in S-phase and prevent replication of tumour cell's DNA, stopping tumour cell proliferation. Steroid hormones act in M-phase by suppressing the mitosis in lymphocytes (Chaber 2006).

Biologic basis of radiotherapy

In the target tumour tissue (lymph nodes), RT directly damages the DNA of tumour cells and prevents further cell differentiation of tumour cells and shrinks the tumour mass. Indirectly, it generates free radicals from cell water that are capable of damaging DNA, cell membranes, proteins and organelles. Although radiation can interfere with many cellular processes, many experts feel that cell must undergo a double stranded DNA break from radiation in order to be killed (Hahn 2005). RT is effective when it exerts greater cytotoxic effects on tumour cells than on normal tissues and/or the cells of the normal tissues are more capable of repairing the radiation damage than the tumour cells.

Why it is important to do this review

In recent years, a concept of minimal curative therapy with greatest efficacy and least toxicity has emerged in the treatment of early stage HL (Connors 2001; Connors 2005). This concept is based on the assumption that avoidance of RT would result in fewer deaths from late-effects and the long-term survival would be at least comparable and possibly better for patients treated with CT alone in early stage HL. To test this assumption, we performed a systematic review with meta-analysis of randomised controlled trials comparing chemotherapy alone with chemotherapy plus radiotherapy in patients with early stage Hodgkin lymphoma with respect to adverse events, response rate, progression-free survival or similar outcomes and overall survival (OS).

OBJECTIVES

The objective of the review was to analyse the efficacy of CT-alone compared to CMT in patients with early favourable and early unfavourable stage HL (clinical stage (CS) I and CS II), with respect to OS as primary outcome measure and progression-free survival (PFS) or similar, response rate and adverse events as secondary outcome measures. Outcomes similar to progression-free survival are called "tumour control" in this review.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs comparing CT-alone with combined modality treatment (CMT) consisting of chemotherapy plus radiotherapy in newly diagnosed patients with CS I and CS II HL (early favourable and early unfavourable stages of HL). We excluded RCTs comparing CT-alone with CMT in patients with all stages of HL if more than 20% of patients had advanced disease. We used the risk factor definitions as described in the individual trials. The terms "early stage" and "limited-stage" were considered equivalent. We excluded quasi randomised trials. Trials including fewer than 10 participants per arm were also excluded according to the protocol. No such trials were found.

Types of participants

We included both male and female patients of all ages, with newly confirmed diagnosis of early stage HL (CS I and II) without any prior treatment for HL. If there were more than 20% of the participants with advanced stage, the trial was excluded. Post hoc, we included such trials in sensitivity analyses. If possible we used subgroup data of early stages.

Types of interventions

We compared CT (single agent or multiple agent, regardless of dose, number of cycles and intervention time) and both CT plus RT (regardless of dose, field used and intervention time) as primary treatment for patients with CS I and CS II HL (early favourable and early unfavourable stages of HL). We excluded trials if the CT regimen was not identical in both study arms. Post hoc, we included such trials in sensitivity analyses of overall survival and tumour control.

Types of outcome measures

Primary outcomes

We evaluated overall survival as the primary endpoint. The preferred definition of OS was "time from entry onto the clinical trial until death as a result of any cause" (Cheson 2007).

Secondary outcomes

Overall response rate (ORR) and complete response (CR) were evaluated as secondary endpoints. The definitions of overall response and complete response were used as given in the publication. If only complete response and partial response were given, the overall response rate was calculated as complete response plus partial response. Further, we also planned to compare progression-free survival (PFS) between CT-alone and CMT for patients with early stage HL. Because no trials reported PFS according to our definition (time to tumour progression, relapse or death), we accepted other tumour control outcomes and evaluated these. Finally we evaluated all reported adverse events.

Search methods for identification of studies

We used search methods as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and by the Cochrane Haematological Malignancies Group (CHMG). No language restriction was applied to reduce the language bias, especially English language bias, as studies showing an intervention to be effective are more likely to be published in English (Dickersin 1993; Egger 1997; Juni 2002). We designed a search strategy with the assistance of the Trials Search Co-ordinator of CHMG for health-related bibliographic databases.

Electronic searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL) (see Appendix 1) and MEDLINE (see Appendix 2) for the years January 1977 until November 2010. We searched EMBASE (see Appendix 3) for the years January 1977 until February 2009.

Searching other resources

We hand-searched the proceedings of the American Society of Hematology for the years 1977 to 2009, except for the year 1979. We searched abstracts of the American Society of Clinical Oncology (ASCO) from 1977 to 2010, except for the year 1990. Proceedings of the International Symposium on Hodgkin Lymphoma (IHSL) were searched from 2004 on. Additionally, two authors performed a cross reference search (screening) of references in primary studies and review articles and checked databases of ongoing clinical trials.

Data collection and analysis

Two authors independently extracted data from full text publications or from abstract publication and assessed the quality of trials.

Selection of studies

Two authors independently screened the titles and abstracts of potentially relevant RCTs comparing CT-alone with CMT (with identical CT regimen in both arms) in newly diagnosed patients with CS I and CS II (favourable and early unfavourable stages of HL) according to predefined criteria. Both authors identified eligible trials using a "study eligibility form" which included the following eligibility criteria:

1. Is the study described as randomised?
2. Did $\geq$ 80% of the included participants have early stage HL?
3. Were comparison arms treated with CT-alone in one arm and CMT in other arm or arms?
4. Was the same CT regimen used in the comparison arms?
5. Did the study document OS, tumour control (progression-free survival or similar) or response rate as outcome measure?

Studies that met the above mentioned inclusion criteria from screening titles and abstracts were retrieved as full text publications for detailed evaluation. We referred any disagreement between authors to a third author and a decision was made by consensus.

Data extraction and management

We obtained the full text versions of the publications and abstracts of selected trials for data extraction.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias (quality) in included trials. Please note that this assessment differed from the one proposed in the protocol in order to comply with the new Cochrane Handbook for Systematic Reviews of Interventions. We assessed the following domains:

1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Was knowledge of allocated intervention adequately prevented during trial from outcome assessors?
4. Were incomplete outcome data adequately addressed?
5. Are reports of the trial free of suggestion of selective outcome reporting?
6. Was the trial apparently free of other problems that could put it at risk of bias (e.g. similarity of patients' characteristics at baseline)

We referred any disagreement between reviewers to a third reviewer and a decision was made by consensus. Trials were not assessed blind, since the review authors knew the study author's name, institution, source of publication and results of publication.

Measures of treatment effect

Time-to-event data

Treatment effect measures of individual trials were estimated as hazard ratios (HRs) for OS and tumour control from survival analysis, using methods described by Parmar 1998 and Tierney 2007. As no hazard ratios were reported, the HRs for OS and tumour control were estimated indirectly, using logrank statistics through reported P values and number of events in comparison arms. If P values were not reported, we estimated HRs for OS and tumour control using survival curves data. Finally, log HRs with standard errors (SEs) were calculated and entered in RevMan 5 for analysis.

In sensitivity analyses, we included additional trials. For some of these trials there were insufficient data (Nachman 2002; Picardi 2007) for tumour control for the calculation of HRs. These HR estimates were improper as they were calculated from the RR and without any time-to-event information. The analysis was repeated without the improper estimates.

Dichotomous data

The treatment effect measures of individual trials for ORR and CR were calculated as relative risks (RRs).

Dealing with missing data

Missing outcome data

Each trial was assessed for missing patients after randomisation due to drop outs, participants lost to follow-up or protocol violations and number of patients not included in the primary (OS) and secondary outcomes (tumour control and response rates) analyses were calculated. Trials excluding more than 10% of the randomised patients from outcomes analyses were included in the review and a sensitivity analysis was performed to check the robustness of the results.

Missing information

To obtain missing information, we contacted study authors and checked previous trial reports of the same investigators.

Assessment of heterogeneity

A P value of the homogeneity test (Chi^2 test) was used to identify the statistical heterogeneity between trials with the significance level being set at $P < 0.1$. The extent of inconsistency (heterogeneity) across the trials was quantified by performing I^2 statistics in the meta-analyses (Higgins 2002; Higgins 2003). A value of $I^2 \geq 50\%$ was considered as substantial heterogeneity across the trials in the meta-analysis.

Assessment of reporting biases

We drew a funnel plot to detect the reporting (publication) and related biases in the meta-analyses that contained at least four included trials. Due to the small number of trials, no linear regression test (Egger 1997a) was performed.

Data synthesis

We pooled estimated HRs for OS of individual trials using the "Generic Inverse Variance method" using a random-effects model. We pooled estimated relative risks (RRs) for complete response and overall response rate using Der Simonian-Laird method.
We calculated the number needed to treat to benefit with 95% confidence intervals for five-year overall survival or five-year tumour control for hazard ratios as described by Altman 1999.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses to investigate the potential causes of heterogeneity with different treatment effects in different groups:

1. Proportion of patients with early favourable stage HL versus early unfavourable stage HL.
2. CS I HL versus CS II HL.
3. Bulky versus non-bulky disease e.g. i) with mediastinal mass versus without mediastinal mass ii) with > 3 involved nodal areas versus < 3 involved nodal areas.
4. Different age groups e.g. < 18 years versus 18 to 50 years versus > 50 years.
5. Male versus female patients.
6. Different sequence of interventions e.g. CT + RT versus RT + CT versus CT-RT-CT.
7. Different RT treatment regimens e.g. IF-RT versus extended field radiotherapy (EF-RT).
8. Different CT regimens e.g. ABVD versus CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone) versus EBVP (epirubicin, bleomycin, vinblastine, prednisone).
9. Median length of follow-up (six years or less, more than 6 years)
10. 4-year survival in the CT-alone group (> 90%, 80% to 90%)

Of these planed subgroups, numbers 2, 4, and 5 could not be performed due to lack of data. Post hoc, we performed subgroup analyses including trials that did not fulfil the inclusion criteria of the protocol, but were considered to give information relevant to the review (for a description of these trials see the Results section). We assessed subgroup differences using the test for subgroup differences in RevMan5.

Sensitivity analysis

We performed a sensitivity analysis to assess the robustness of the overall result with respect to quality and trial design. Using sensitivity analysis we explored:

1. Measures of study quality (ITT-analysis, > 10% of patients not evaluated vs. ≤ 10% not evaluated, allocation concealment).
2. The influence of a single large study on the overall result.

RESULTS

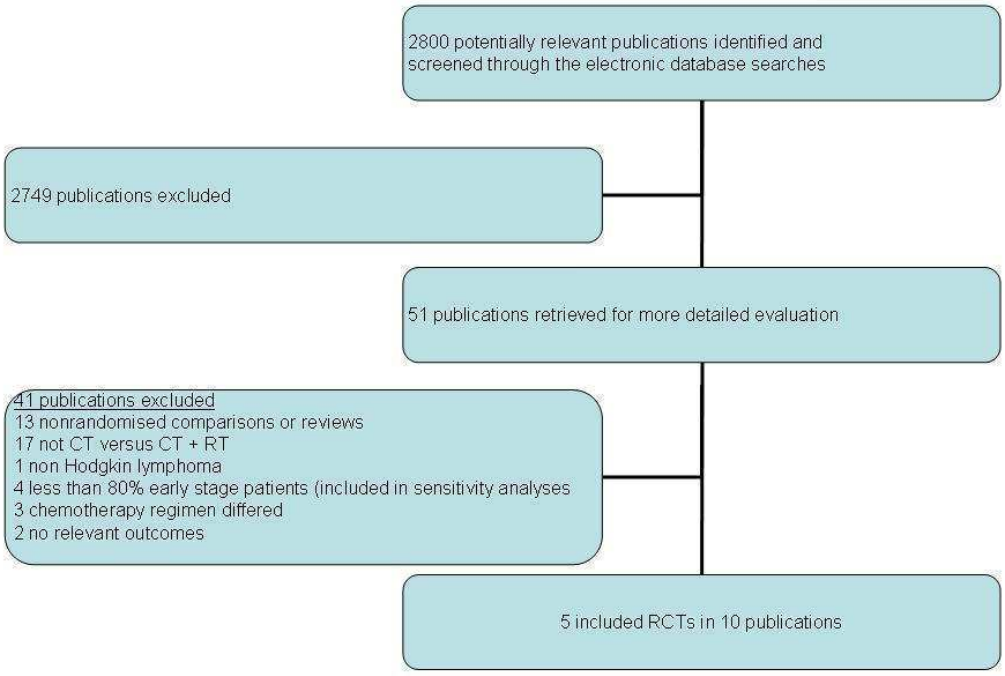
Description of studies

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

Results of the search

Our literature search produced 2800 potentially relevant references related to the treatment of patients with early stage HL. Of these, 2749 were excluded at the initial stage of screening because they did not fulfil our predefined inclusion criteria. The remaining 51 publications were retrieved as full text publications or abstract publications for detailed evaluation. Of these 51 trials, we excluded 41 and finally 5 trials (10 publications) with 1245 patients were formally included in the main analyses of this review. The overall number of trials screened, identified, selected, excluded and included was documented with reasons according to QUOROM flow diagram (Moher 1999) (Figure 1).

Figure 1. QUOROM-DIAGRAM: Note that the reasons for exclusion are hierarchical, i.e. reasons higher in the list were considered before those lower down.



Among the excluded trials (according to our review protocol) six trials were included in sensitivity analyses post hoc, as they yielded relevant information to the underlying clinical question. Five trials included more than 20% of patients in advanced stages (Kung 2006; Laskar 2004; Nachman 2002; O'Dwyer 1985; Picardi 2007). We identified two trials (Kung 2006; Meyer 2005) in which the patients in the chemotherapy alone group received more cycles of chemotherapy than the patients in the chemotherapy plus radiotherapy group, one of which also included patients of all stages of HL. Characteristics and main results of these trials are described in Table 1.

Table 1. Characteristics of selected excluded trials

Trial	Patients	Time of randomisation	Chemotherapy and radiotherapy	Subgroup of early stage patients?	Length of observation	Overall survival	Progression-free survival (or event-free survival)

Table 1. Characteristics of selected excluded trials (*Continued*)

Laskar 2004	All stages, age < 70 years	in CR	6 X ABVD + (mainly) IF-RT vs. 6 X ABVD	yes; stage I-II: CMT: 55 CT: 44	8 years	CMT: 100% CT: 98%	CMT: 97% CT: 94%
Nachman 2002	Children with any stage of HL	in CR	Early stage: 4X COPP/ABV + low dose IF-RT vs. 4X COPP/ABV	yes; early stage (I-II) patients: CMT: 189 CT: 173	3 years	100% in both groups	CMT: 97% +/- 1.7 (SE) CT: 91% +/- 2.8 (SE)
O'Dwyer 1985;	stages IB to IIIA	Before CT	MOPP +RT vs. MOPP	no; CMT : 16 CT: 17	6 years	CMT: 3 deaths CT: 2 deaths	CMT: 3 progression or relapse CT: 4 progression or relapse
Picardi 2007	bulky HL with residual masses in CT that were PET negative at restaging after CT	In CR	6 X VEBEP + RT vs. 6 X VEBEP	yes; CMT: 53 CT: 52	5 years	100% in both groups	# of patients who relapsed: CMT: 0/53 CT: 6/52
Trials in which the number of cycles varied between the chemotherapy alone and the chemotherapy plus radiotherapy group							
Kung 2006	Children, PS I-IIIA	In CR or PR	***4*** X MOPP/ABVD + IF-RT vs. ***6*** X MOPP/ABVD	no (31% IIIA)	8 years	CMT: 96.8% +/- 2.7% CT: 93.6% +/- 3.9% P = 0.79	CMT: 91.1% +/- 4.5% CT: 82.6% +/- 5.9% P = 0.15
Meyer 2005	Early stage (I-IIA); absence of bulky disease	Before trial	***2*** X ABVD + subtotal nodal irradiation vs. ***4-6*** X ABVD	only early stage	5 years	HR = 1.82 [0.58 to 5.68]	HR = 0.33 [0.14 to 0.80]

Included studies

The characteristics of included studies are also summarized in Table 2.

Table 2. Characteristics of included trials

Trial	*Inclusion criteria*	*Number of patients analysed*	*Treatment*	*Median follow-up in years (range)*	*ITT- analysis*	*Not evaluated or lost to follow-up (%)*
Mexico B2H031	CS I to II Supradiaphragmatic disease and Bulky disease	99	6xABVD	11.4 (6.3 to 16.5)	No	6
		102	6xABVD+ IF-RT			
CALGB 7751 Interim results	"poor prognosis" PS I or II	18	6xCVPP.	2 (0 to ?)	No	32
		19	6xCVPP+ IF-RT			
EORTC-GELA H9-F Interim results	CS I - II Supradiaphragmatic disease All of the favourable features (age < 50 years, ESR < 50 mm/h or B symptoms and ESR < 30 mm/h, mediastinal-thoracic ratio < 0.35) CR after 6 cycles EBVP	130	6xEBVP	4.3 years (1.2 to 6.8)	Yes	0
		448	6x/EBVP + 36 Gy IF-RT or 20 Gy IF-RT			
GATLA 9-H-77	CS I and II, 173 patients with favourable and 104 patients with unfavourable characteristics (age > 45, sites > 2, bulky tumour)	142	6xCVPP	4 years (not reported)	No	6
		135	6xCVPP + IF-RT			
MSKCC trial #90-44	CS I to IIIA without bulky disease, 13% with CS IIIA ~ 30 to 50% unfavourable disease.	76	6xABVD	5.6 (0.1 to 10.4)	Yes (OS)	0 (OS) 9 (CR, tumour control)

Table 2. Characteristics of included trials (*Continued*)

		76	6xABVD + IF-RT or EF-RT			

Five trials (CALGB 7751; EORTC-GELA H9-F; GATLA 9-H-77; Mexico B2H031; MSKCC trial #90-44) were included in the review. The earliest trial recruited in the 1970s and the latest in 1998 to 2004. The data were extracted from full text publications for four trials and for one trial (EORTC-GELA H9-F) data were extracted from the abstract.

Design

Of the five included trials, three were two-armed randomised controlled trials and two were three-armed randomised controlled trials. Mexico B2H031 randomised to radiotherapy alone, CMT or CT-alone. The radiotherapy arm was not included in this systematic review. EORTC-GELA H9-F randomised to chemotherapy alone, CMT with 36 Gy or CMT with 20 Gy. The two radiotherapy dosages were evaluated together in this review.There were three multi-centre trials and for two of them (CALGB 7751; GATLA 9-H-77) it was not clear whether they were single centre or multicentre.

Sample sizes

The smallest trial included 55 (37 analysed) patients (CALGB 7751) and the largest trial 578 patients (EORTC-GELA H9-F).

Location

The included trials came from a range of research groups from different countries. The trials were conducted in the following countries: one trial in USA (CALGB 7751); one trial in USA and Canada (MSKCC trial #90-44), one trial in different institutions of European countries (EORTC-GELA H9-F); one trial in Mexico (Mexico B2H031); one trial in Argentina (GATLA 9-H-77).

Participants

A total of 1245 male and female patients of all ages, with a newly confirmed diagnosis of clinical stage (CS) I and II or pathologic stage (PS) I and II HL and without previous treatment were included. For most patients, histopathologic diagnosis was made according to Rye modification of Lukes and Butler classification (Lukes 1966).

Interventions

Patients from included trials were treated with six cycles of CT-alone or six cycles of same CT plus radiotherapy (CMT). For included trials, the following CT regimens were used: adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) in two trials (Mexico B2H031; MSKCC trial #90-44); CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone) for two trials (CALGB 7751; GATLA 9-H-77); EBVP (epirubicin, bleomycin, vinblastine, prednisone) for one trial (EORTC-GELA H9-F). The size of radiation fields used for the delivery of radiotherapy were as follows: IF-RT in three trials (CALGB 7751; EORTC-GELA H9-F; GATLA 9-H-77); extended-field radiotherapy in two trials (Mexico B2H031; MSKCC trial #90-44). Two trials (GATLA 9-H-77; Mexico B2H031) administrated three cycles of CT before and after RT (sandwich technique), in the other trials CT was administered prior to RT.

Outcomes

Primary outcome measure

All included trials analysed overall survival. The median observation times for overall survival were as follows: 11 years for one trial (Mexico B2H031); seven years for one trial (GATLA 9-H-77); four to five years for two trials (EORTC-GELA H9-F; MSKCC trial #90-44); 22 months for one trial (CALGB 7751).

Secondary outcome measures

None of the included trials reported PFS data according to our definition (time to progression or death of any cause). All trials except CALGB 7751 reported some type of progression outcome (see Table 3). Four trials (CALGB 7751; GATLA 9-H-77; Mexico B2H031; MSKCC trial #90-44) reported response rate.

Table 3. Definitions of progression outcomes

Trial	Definition of progression outcome
Mexico B2H031	Contradictory definitions. In the methods section: "Disease free survival was calculated for CR patients from the beginning of treatment until clinically or radiologically and biopsy proven relapse." In the results section the percent disease free were calculated based on the full population.
EORTC-GELA H9-F	Definition of disease-free survival not reported. (Note all patients are in CR at the time of randomisation.)
GATLA 9-H-77	Patients who failed to respond were evaluated as relapsed at first month. Patients in CR were evaluated from date of CR to date of first relapse or death.
MSKCC trial #90-44	Time from enrolment until any progression of disease.

Funding

Academic funding was provided for three trials (CALGB 7751; GATLA 9-H-77; MSKCC trial #90-44). Source of funding was not described by the remaining two trials.

Conflict of interest

No trial reported information with respect to conflict of interest.

Excluded studies

Among the excluded trials (according to our review protocol) a number of trials were included in sensitivity analyses post hoc, as they yielded relevant information to the underlying clinical question. Three trials (566 patients) included patients of all stages and reported some subgroup information for early stage patients (Laskar 2004; Nachman 2002; Picardi 2007). One of these trials examined patients with bulky disease and residual masses after VEBEP chemotherapy who were PET negative (Picardi 2007). One trial included patients in stages I through IIIa which included very few patients (O'Dwyer 1985). Finally we identified two trials in which the patients in the chemotherapy alone group received more cycles of chemotherapy than the patients in the chemotherapy plus radiotherapy group (Kung 2006; Meyer 2005). The chemotherapies used in these trials were ABVD (Laskar 2004; Meyer 2005), COPP/ABV (Nachman 2002), VEBEP (Picardi 2007), MOPP/ABVD (Kung 2006) and MOPP (O'Dwyer 1985). Their characteristics and main outcomes are presented in Table 1.

For information on excluded trials see Characteristics of excluded studies, where reasons for the exclusion of important excluded trials are listed. For the publication on bleomycin toxicity, where no information for the relevant comparison was found, basic outcomes are also reported.

A total of 41 articles were excluded after detailed evaluation of full text publications. The main reasons for exclusion were:

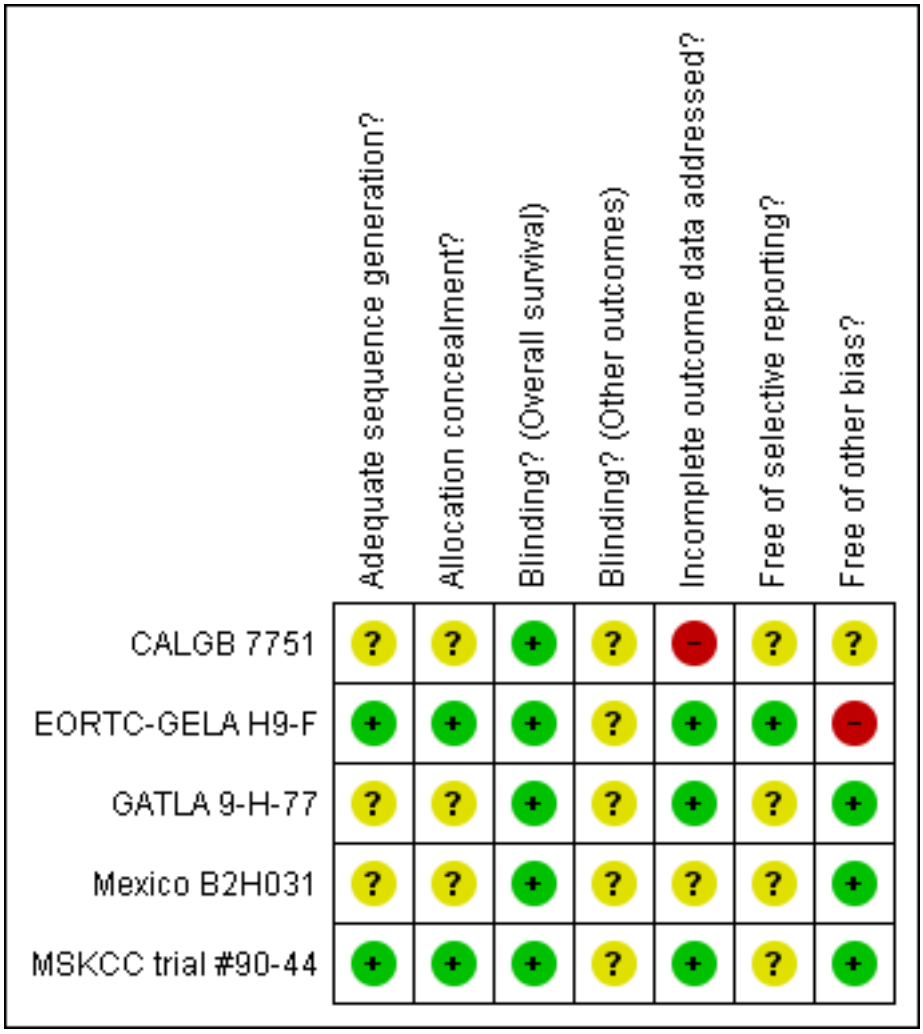
- 13 non-randomised comparisons or reviews
- 17 not CT versus CMT
- 1 not Hodgkin lymphoma
- 1 only advanced stages
- 4 < 80% early stage patients (included in sensitivity analyses)
- 3 chemotherapy regimen differed
- 2 publications of "one trial", where MSKCC patients were randomised to CT vs CMT or different CT plus differing radiotherapy schemes were followed for pulmonary function for approximately one year. The 45 patients with a relevant comparison to this review are presumably included in the MSKCC trial #90-44. For more details see Characteristics of excluded studies.

Some of these publications are described under Characteristics of excluded studies.

Risk of bias in included studies

See "risk of bias tables" of included trials and for an overview of the results please see Figure 2.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



In the EORTC-GELA H9-F trial the chemotherapy alone arm ended early due to stopping rules. Unfortunately it was not possible to receive the data on patients receiving additional radiotherapy only up to the date the chemotherapy alone arm was stopped.

Allocation

Treatment allocation of patients was performed at a central trials office for one trial (MSKCC trial #90-44); no information was available for the other trials. No trial reported the sequence generation. Sequence generation and allocation concealment was judged to probably be adequate in large multi-centre trials that have previously adequately randomised and whose allocation was previously adequately concealed (EORTC-GELA H9-F; MSKCC trial #90-44).

Blinding

As radiotherapy is difficult to blind, one does not expect the patients to be blinded. However, none of the other trials reported information about blinding of outcome assessors or statisticians. As blinding of the outcome assessors is considered important for this review, all trials were judged "unclear" for the question of blinding.

Incomplete outcome data

Overall survival

Most trials described missing outcome data in detail (GATLA 9-H-77) or included all randomised patients in the analysis without reporting any missing data for this outcome (EORTC-GELA H9-F; MSKCC trial #90-44). In the Mexico B2H031 trial 20/327 patients were missing from the analyses without further information (this information was not available only for the two arms included in this review). No trial reported imputation of results for missing data in the context of an intention-to-treat analysis. A high proportion of patients were not analysed in the CALGB 7751 trial but the trial has a low weight in the meta-analysis due to the small number of patients (36 patients evaluated). Due to the small proportion of missing data and the detailed descriptions in most trials, we do not believe that bias was introduced into the meta-analysis by missing data.

For the predefined subgroup analyses we used a strict definition of intention-to-treat analysis (Deeks 2008). Therefore trials that did not include all patients in the analysis and did not describe the method of analysis were not considered to have performed an intention-to-treat analysis (CALGB 7751; GATLA 9-H-77; Mexico B2H031).

Secondary outcomes

There were more missing data among the secondary outcomes response rate and tumour control.

Selective reporting

Little information was available about which outcomes were primary outcomes and how these were defined. The choice of progression outcome may be due to selective outcome reporting (see below).

Other potential sources of bias

None identified.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of Findings Table

Primary outcome: Overall survival (OS)

All five trials of the main analysis with 1245 patients reported OS. The addition of radiotherapy significantly improved OS (HR = 0.40; 95% CI 0.27 to 0.61) with no evidence for heterogeneity between trials (I^2 = 0%); Figure 3. In three trials the hazard ratios had to be based on the survival curves or reported dates of deaths (CALGB 7751; EORTC-GELA H9-F; Mexico B2H031). In all cases, constant censoring was assumed as described by Tierney 2007. However, this assumption is problematic for the EORTC-GELA H9-F trial because the no-radiation arm was closed early. Estimating a difference in censoring to account for the premature closure of the chemotherapy alone arm had only a minor effect on the hazard ratio calculated (Table 4 shows HR of Mexico B2H031 and EORTC-GELA H9-F with different censoring assumptions). Other uncertainties in the hazard ratio calculation arose from P values with only one significant digit. The results of the meta-analysis were dominated by the Mexico B2H031 trial, which had a weight of 50.4% (Figure 3). When excluding the Mexico B2H031 trial from the meta-analysis in a sensitivity analysis, the summary hazard ratio remained statistically significant favouring CMT (0.57; 95% CI 0.33 to 0.98, I^2 = 0%) (Figure 4). The substantial weight of the Mexico B2H031 trial was due to the higher number of observed deaths occurring with longer follow-up. Here, patients had been followed up for a median of 12 years as compared to two to seven years in the other trials. The four-year survival rate of 83% in the Mexico B2H031 trial was comparable to those of the other trials ranging from 85% (MSKCC trial #90-44) to 87% (GATLA 9-H-77). No information on the four-year survival was available from CALGB 7751. The EORTC-GELA H9-F trial included early favourable patients in CR only and as a result had a higher five-year survival rate of 97%. None of the subgroup analyses showed statistically significant differences between the subgroups examined (type of chemotherapy P = 0.14, early favourable or unfavourable disease P = 0.31, bulky or no bulky disease P = 0.98, type (P = 0.20) and timing (P = 0.76) of radiation therapy. See Figure 5, Figure 6, Figure 7, Figure 8, Figure 9. Subgroup analyses by age or sex were not possible due to the limited amount of data available. Subgroup differences in performed sensitivity and subgroup analyses were not statistically significant. The P values for subgroup differences were P = 0.12 (length of follow-up Figure 10), P = 0.82 (four-year overall survival in the chemotherapy group Figure 11), P = 0.56 (allocation concealment Figure 12), P = 0.56 (ITT-analysis Figure 13). Due to the small number of trials included in the meta-analysis true differences between subgroups may be missed in the subgroup and sensitivity analyses.

Figure 3. Forest plot of comparison: 1 Overall Survival, outcome: 1.1 All trials.

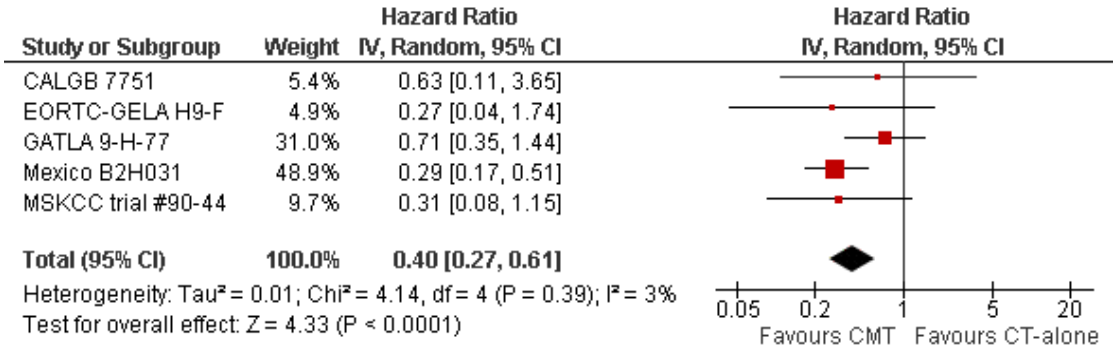


Figure 4. Forest plot of comparison: 1 Overall Survival, outcome: 1.11 Excluding the trial with highest weight (Mexico B2H031).

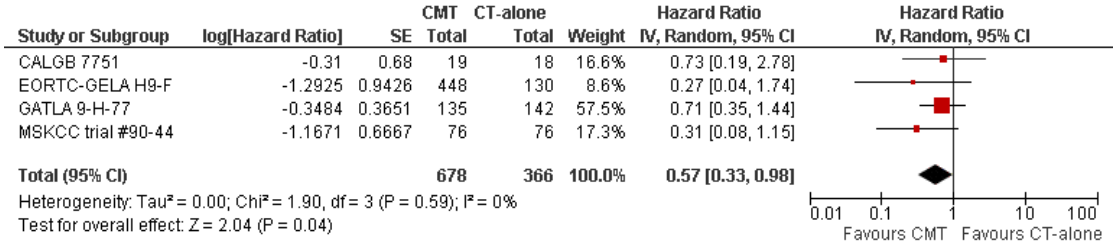


Figure 5. Forest plot of comparison: 1 Overall Survival, outcome: 1.2 Proportion of patients early favourable.

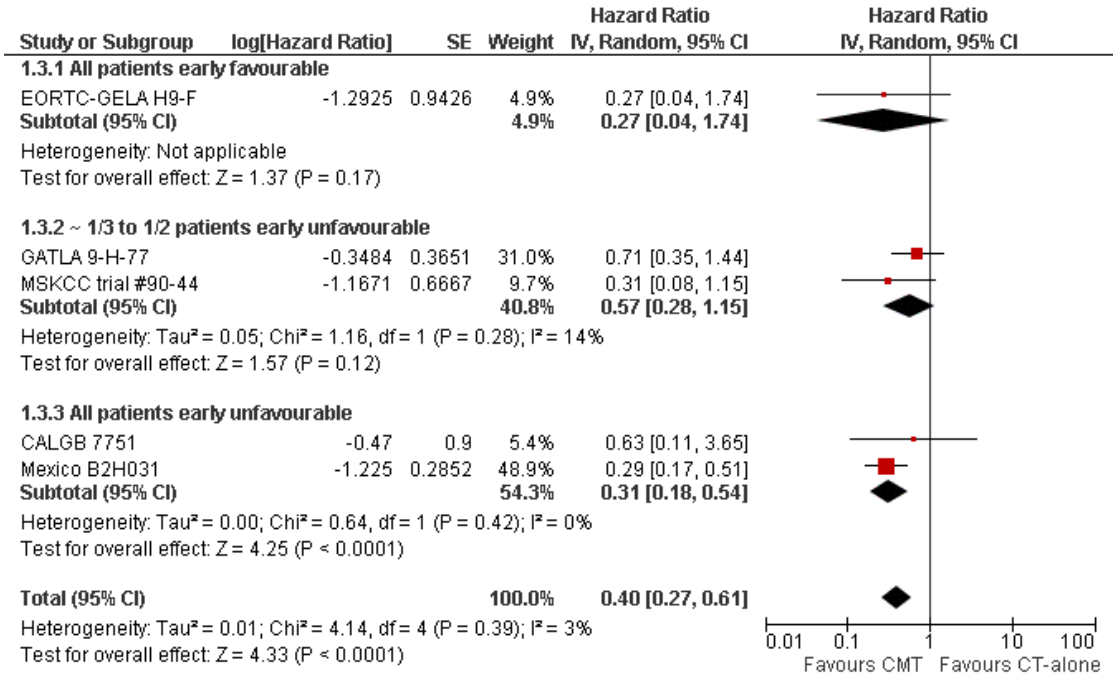


Figure 6. Forest plot of comparison: 1 Overall Survival, outcome: 1.3 Bulky vs non-bulky.

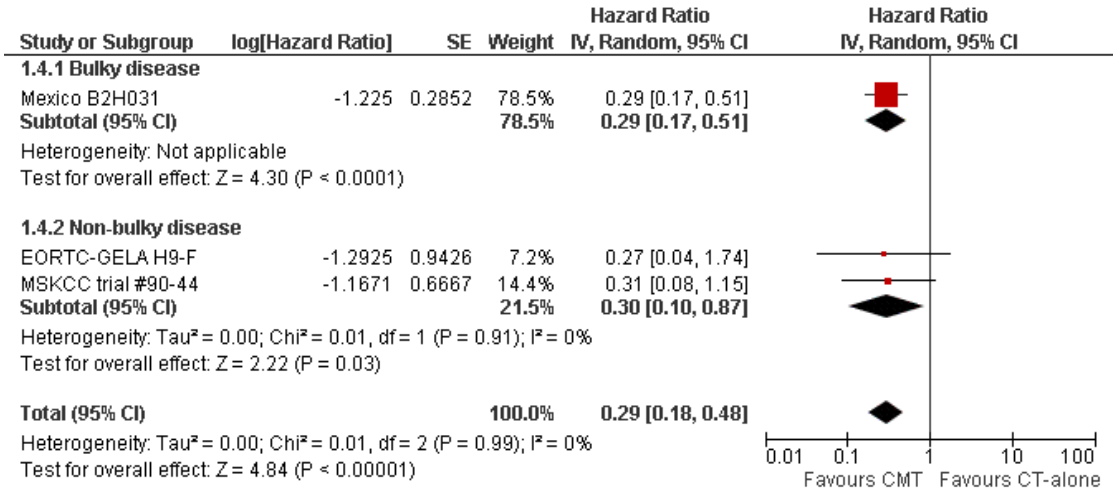


Figure 7. Forest plot of comparison: 1 Overall Survival, outcome: 1.4 Timing of radiotherapy.

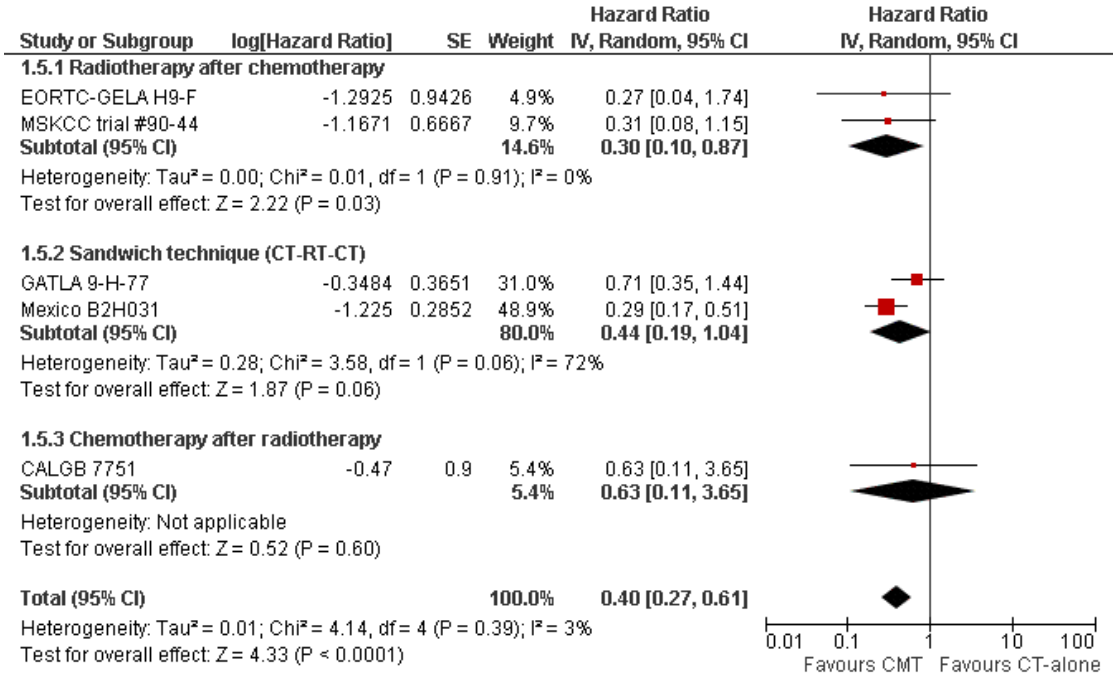


Figure 8. Forest plot of comparison: 1 Overall Survival, outcome: 1.5 Type of radiotherapy.

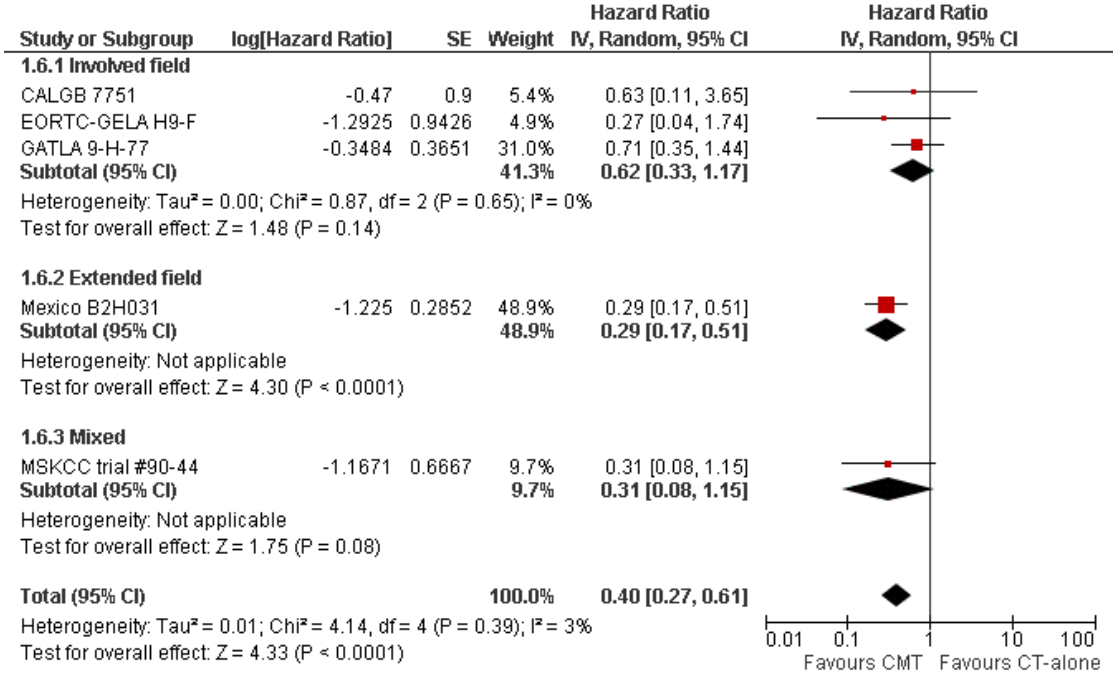


Figure 9. Forest plot of comparison: 1 Overall Survival, outcome: 1.6 Type of chemotherapy.

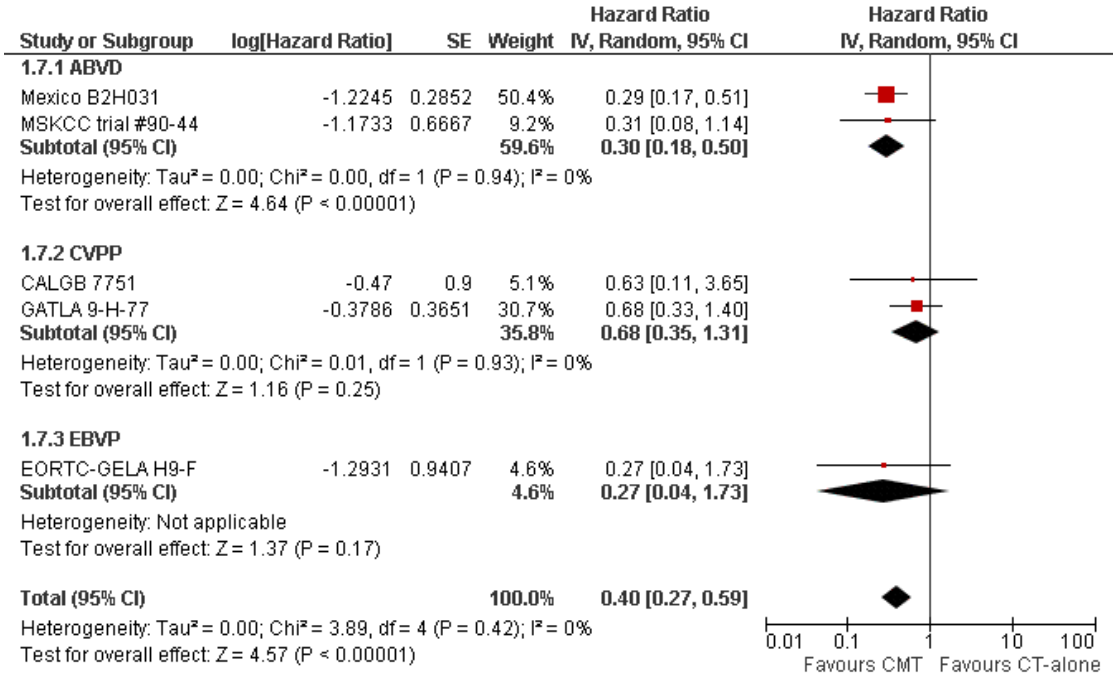


Figure 10. Forest plot of comparison: 1 Overall Survival, outcome: 1.7 Length of follow-up.

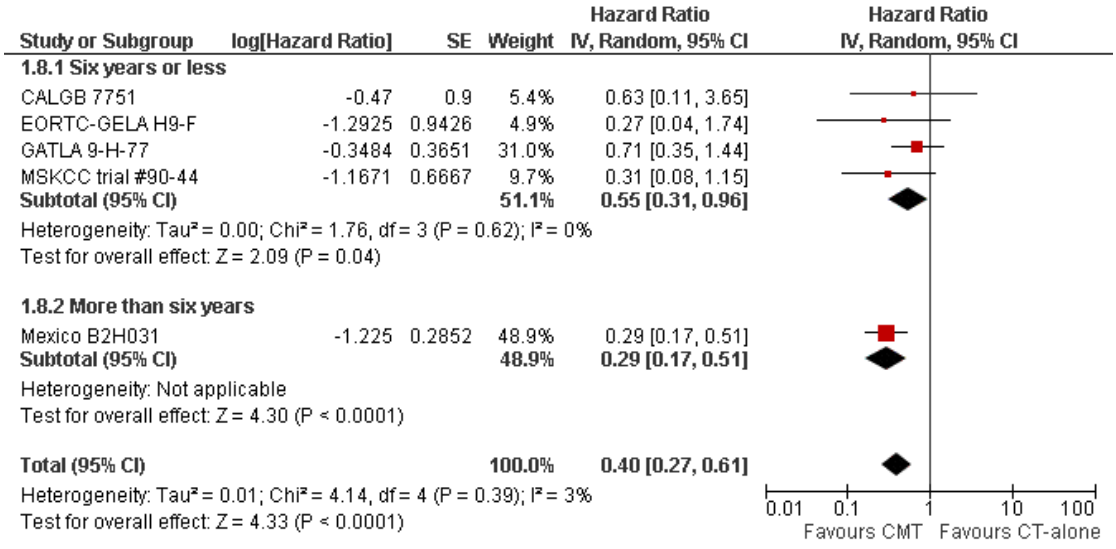


Figure 11. Forest plot of comparison: 1 Overall Survival, outcome: 1.8 4 year survival in the CT group.

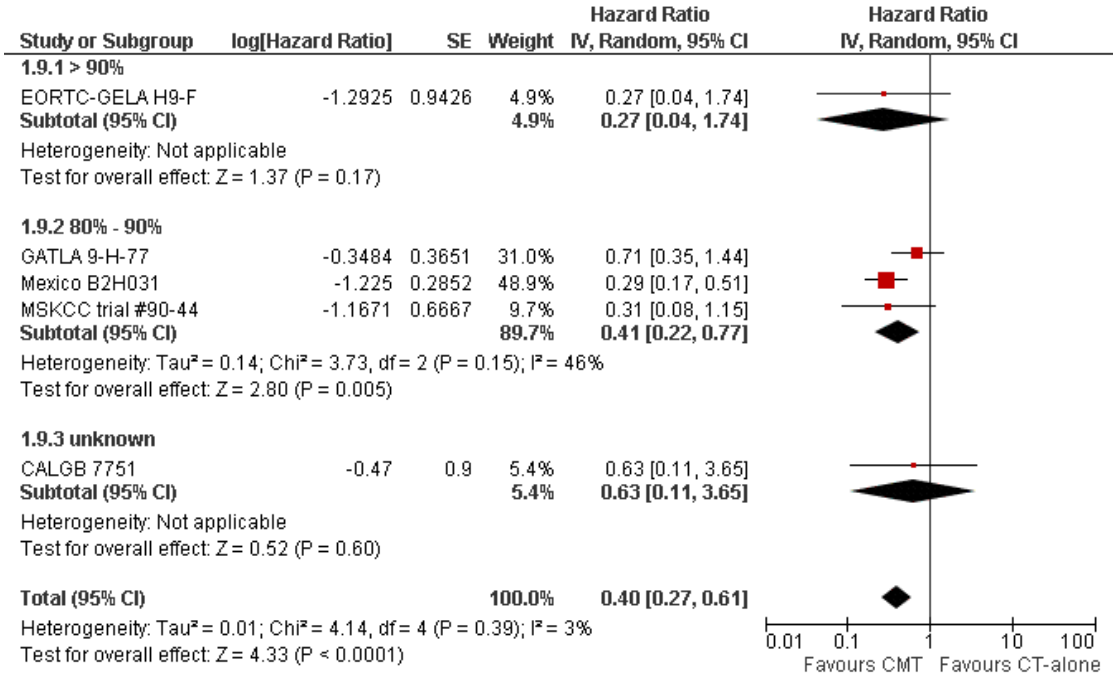


Figure 12. Forest plot of comparison: 1 Overall Survival, outcome: 1.9 Allocation concealment.

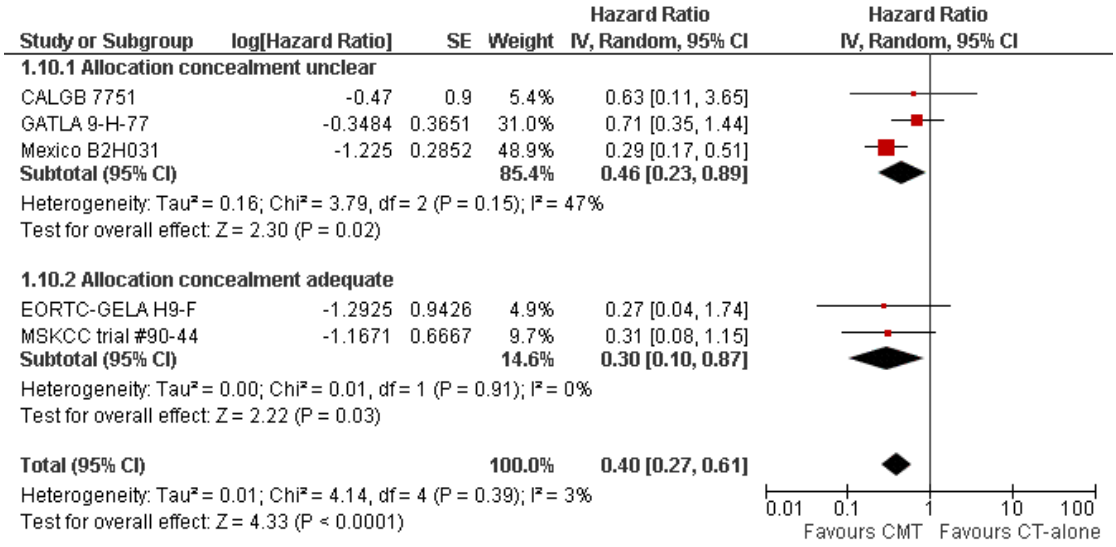


Figure 13. Forest plot of comparison: 1 Overall Survival, outcome: 1.10 ITT-analysis.

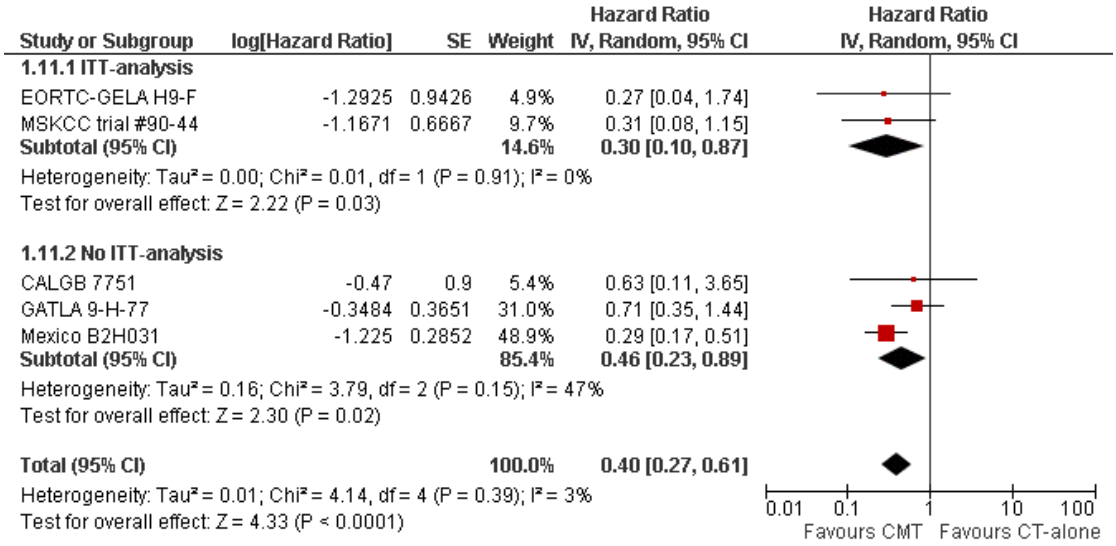


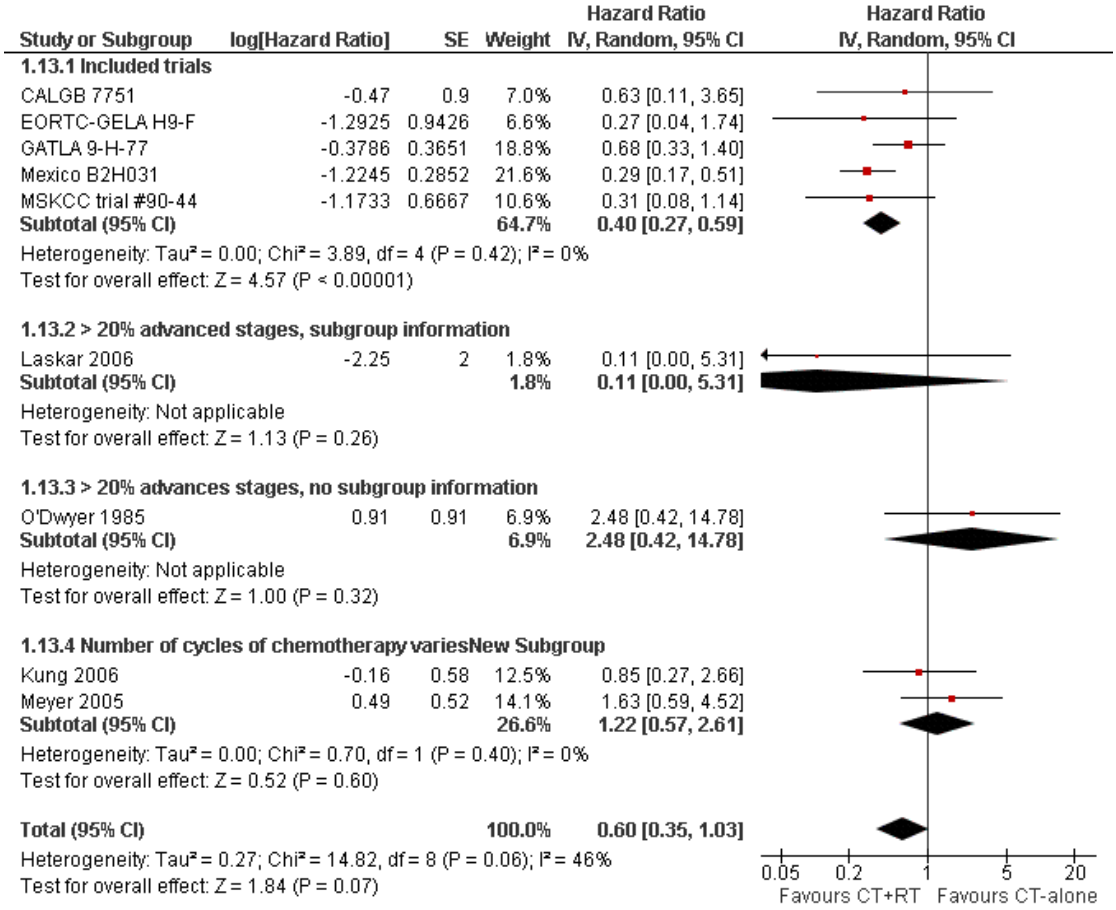
Table 4. Effects of censoring on estimates for overall survival hazard ratios calculated from survival curves

Censoring assumption	Mexico B2H031	EORTC-GELA H9-F
Parmar Method without corrections	0.29 [0.17 to 0.51]	0.27 [0.04 to 1.74]
Parmar method with censoring *2	0.27 [0.16 to 0.48]	0.16 [0.02 to 1.49]
Parmar method with censoring *4	0.27 [0.15 to 0.48]	0.09 [0.01 to 1.67]
Parmar method with censoring *4, assuming censoring began at the beginning of the trial	0.27 [0.15 to 0.50]	0.09 [0.00 to 2.21]

Please note that using these methods censoring was assumed to be non-informative and constant. For the Mexico trial, even higher censoring or assuming twice the amount of censoring in one of the groups had little effects on the HR. For the EORTC-GELA trial, differences in censoring are expected between the two arms of the trial due to the early stopping of the arm without radiotherapy. Estimating differences in median follow-up and incorporating them into the Parmar Method yielded a HR of 0.26 [0.05 to 1.72].

The sensitivity analysis that included trials not fulfilling the inclusion criteria of our review protocol and including improper estimates yields a HR of 0.60 (95% CI 0.35 to 1.03) with high heterogeneity (I^2 = 46%) Figure 14. When excluding the trials where the number of cycles varies, the HR was 0.46 (0.27 to 0.78). The two trials that examined chemotherapy plus radiotherapy versus more chemotherapy reported conflicting results among the two trials (Kung 2006; Meyer 2005). The trial by Meyer 2005 comparing two to four cycles of ABVD plus subtotal nodal irradiation with six cycles of ABVD had an (estimated) HR of 1.73 (95% CI 0.62 to 4.86), while the Kung 2006 trial comparing ***four*** MOPP/ABVD + IF-RT versus ***six*** MOPP/ABVD had an estimated HR of 0.86 (95% CI 0.29 to 2.54).

Figure 14. Overall Survival: Sensitivity analysis including additional trials. No early stage patients died in the Nachman 2002 and the Picardi 2007 trial.



Numbers needed to treat to benefit have been calculated and are presented in Table 5 based on the main analysis.

Table 5. Number Needed To Treat To Benefit

Outcome	Assumed five-year survival in the control group	NNT (95% confidence interval)
Tumour control	70%	6 (5 to 11)
Overall survival	85%	11 (9 to 18)
Overall survival	97%	55 (46 to 86)

2. Secondary outcomes

Tumour control

No trial reported progression-free survival (PFS) according to the definition in the protocol (time to progression or death from any

cause). However, four trials in the main analysis reported some progression endpoint, such as event-free survival, time to treatment failure and time to progression and were evaluated as tumour control. Exact definitions are given in Table 3. Tumour control was statistically significant in three of the four trials in which it was reported. The combination of chemotherapy and radiotherapy improved tumour control with a hazard ratio (HR) of 0.41 (95% confidence interval (CI) 0.25 to 0.66, random-effects model; Figure 15). There was clear statistical heterogeneity between trials (I^2 = 68%) which may in part be due to the different definitions used. For example, some trials examined progression or freedom from treatment failure in all patients, while others examined disease free survival which is restricted to patients who reached CR. A subgroup analysis by the type of tumour control definition was statistically significant (P = 0.01; see Figure 16). The subgroup by proportion of patients with early favourable disease was statistically significant (P = 0.01). However this result is not plausible, as the group with a mixed patient population showed less effect of the addition of radiotherapy and the two groups with only early favourable and only early unfavourable patients were similar (Figure 17). The other subgroup and sensitivity analyses showed neither statistically significant difference between subgroups nor resulted in a relevant reduction of statistical heterogeneity. Factors analysed included type of chemotherapy (P = 0.10), early favourable versus unfavourable stages (P = 0.01), type (P = 0.09) and timing (P = 0.57) of radiation, and the use of quality measures (Figure 18, Figure 19, Figure 20, Figure 21, Figure 22, Figure 23). The data extraction was hampered by discrepancies in P values MSKCC trial #90-44 or number of patients included in the analysis MSKCC trial #90-44, as well as by extraction of hazard ratios from survival curves MSKCC trial #90-44; EORTC-GELA H9-F.

Figure 15. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.1 All trials.

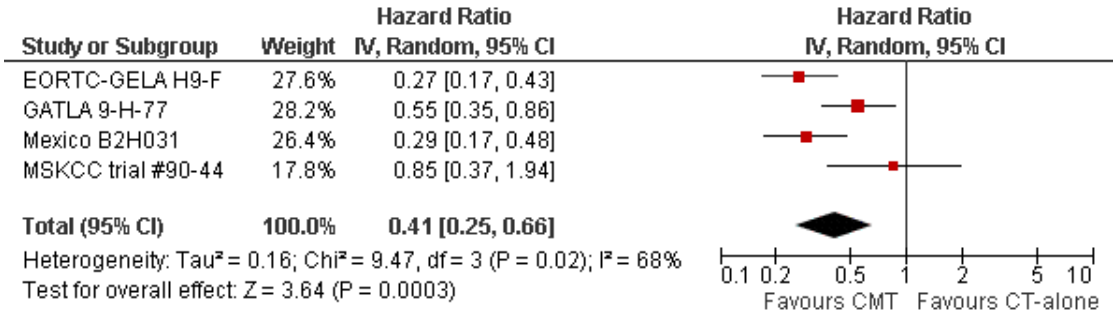


Figure 16. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.4 Definition of progression.

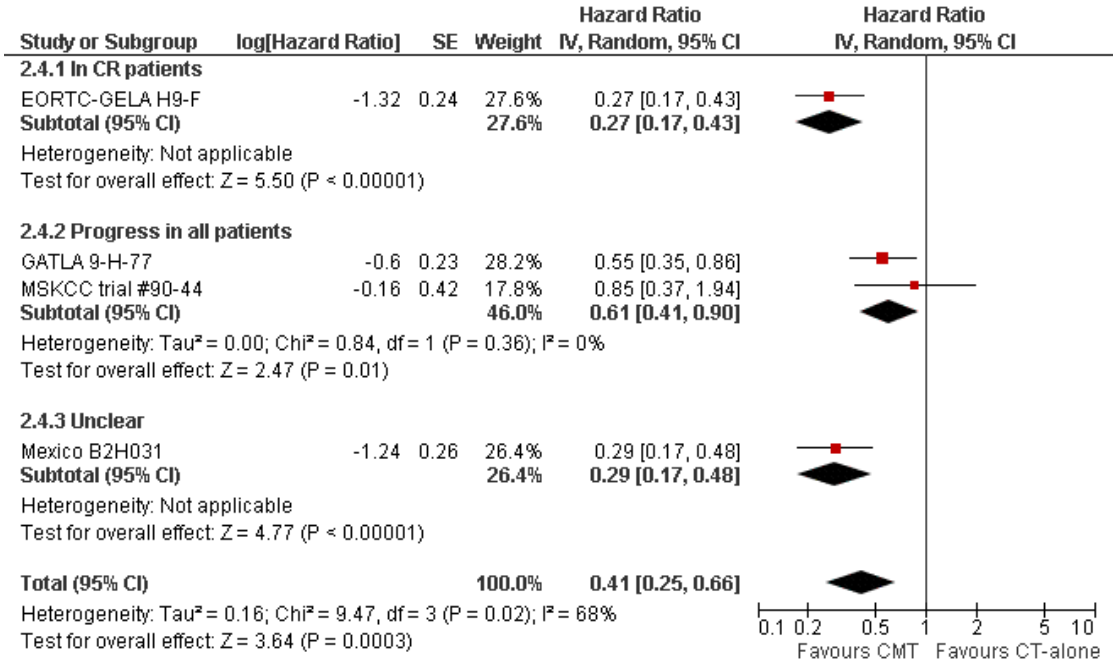


Figure 17. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.3 Proportion of patients early favourable.

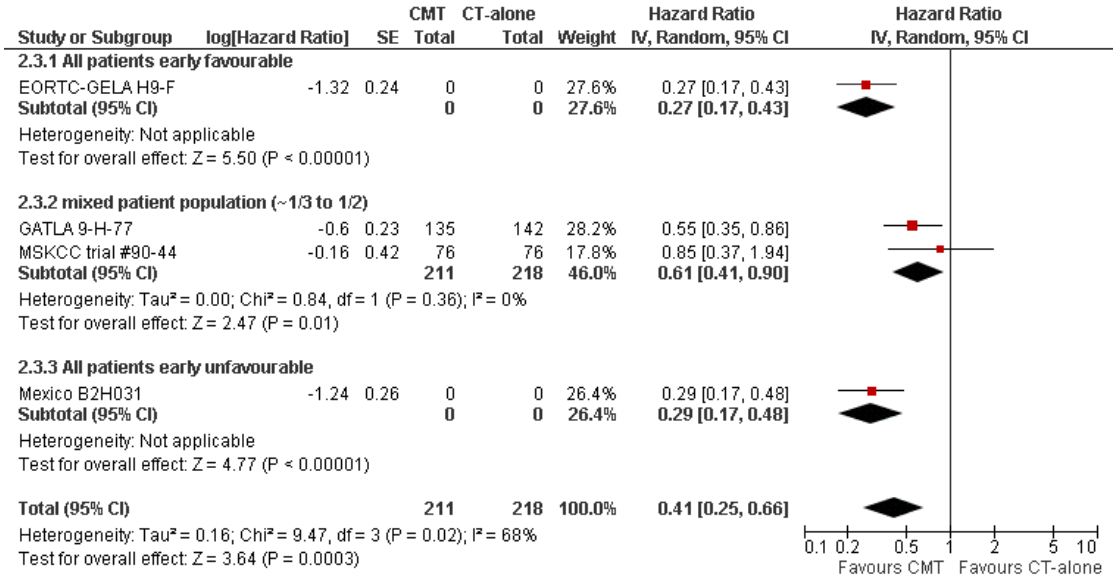


Figure 18. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.2 Type of chemotherapy.

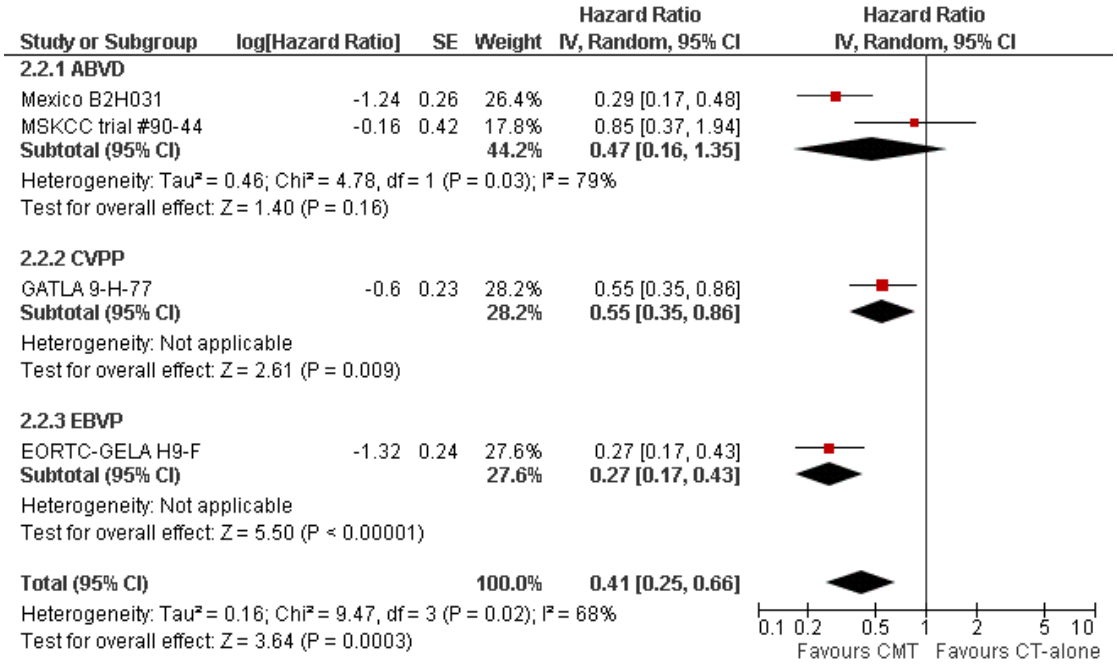


Figure 19. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.5 Timing of radiotherapy.

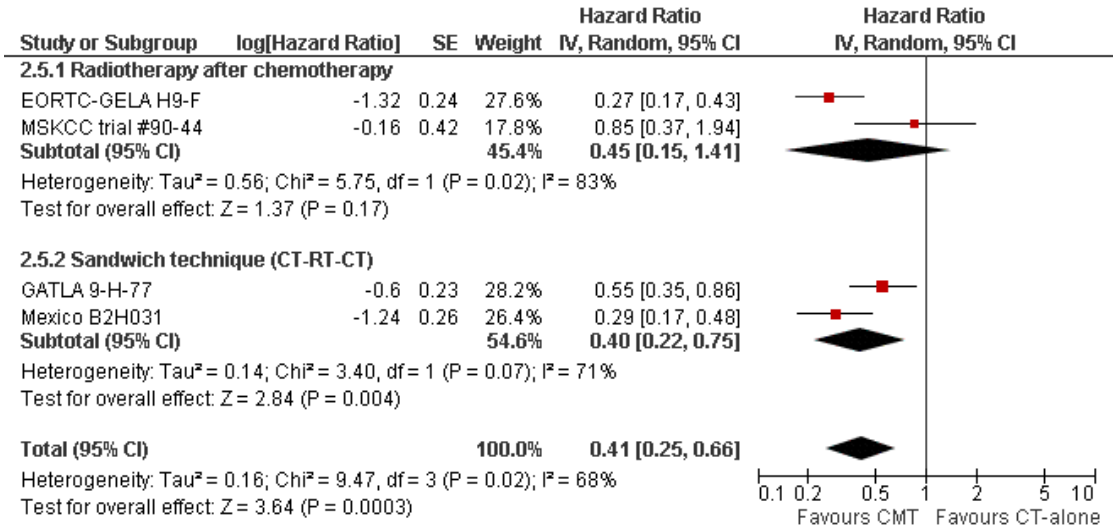


Figure 20. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.6 Type of radiotherapy.

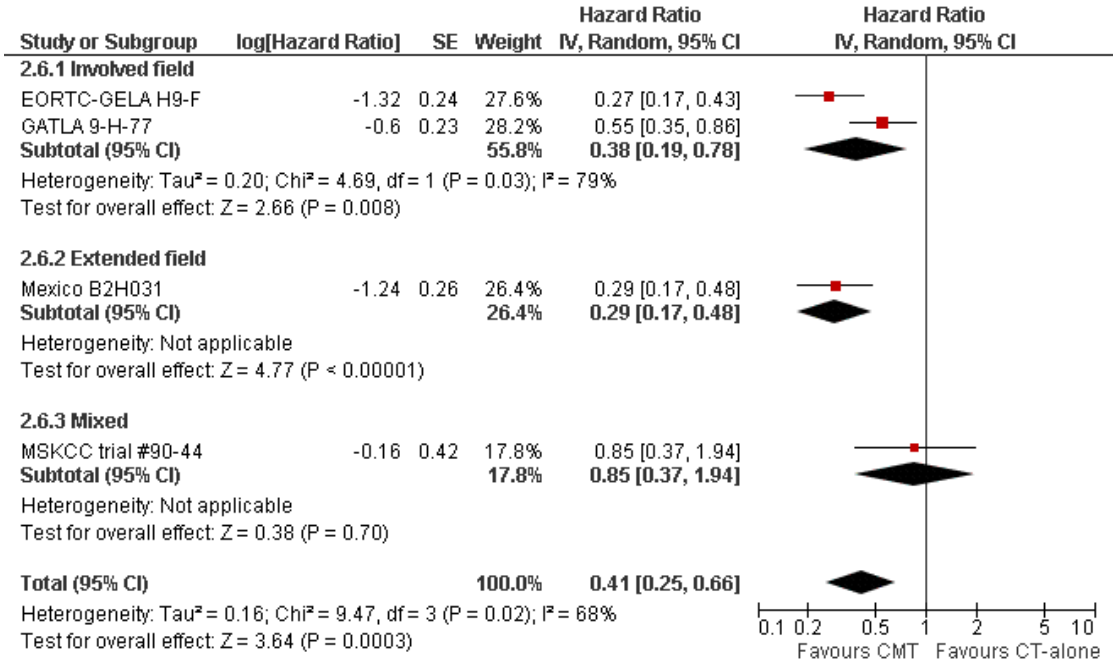


Figure 21. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.7 Length of follow-up.

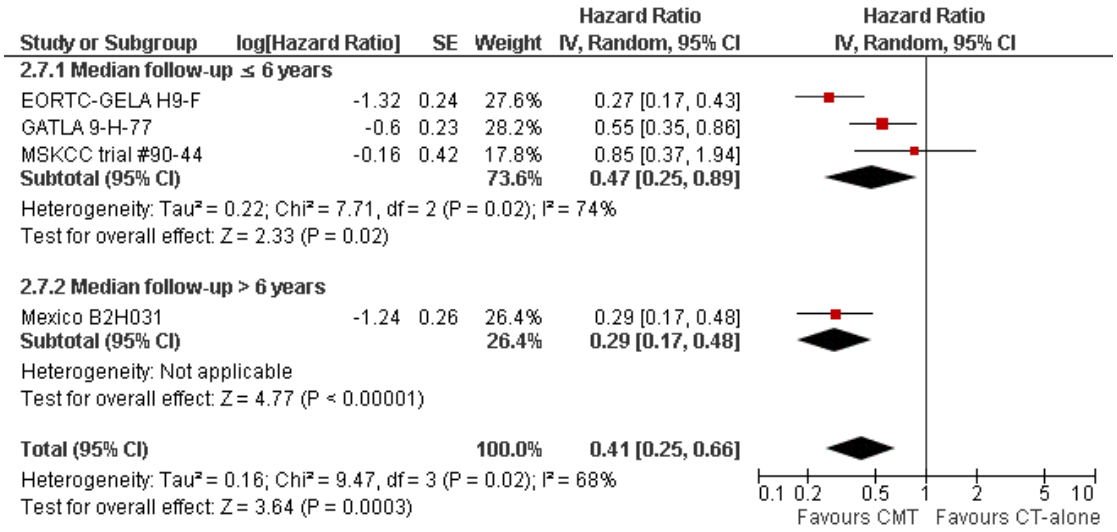


Figure 22. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.8 Allocation concealment.

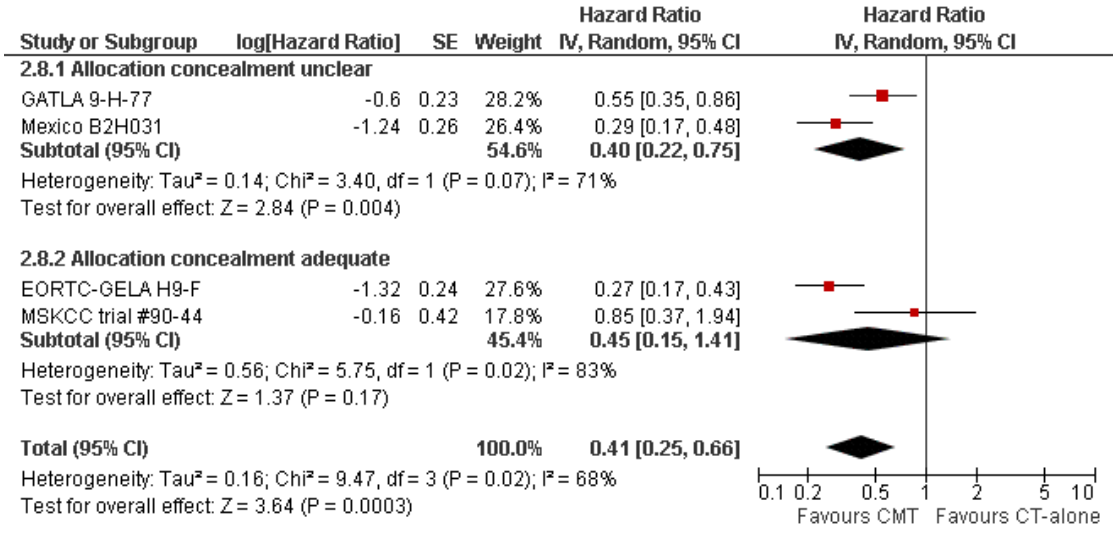
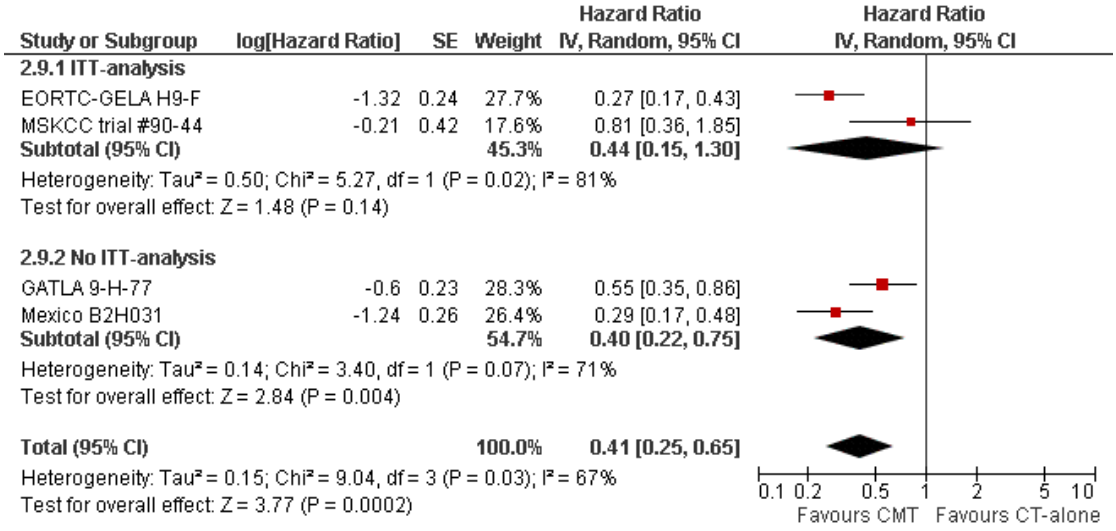


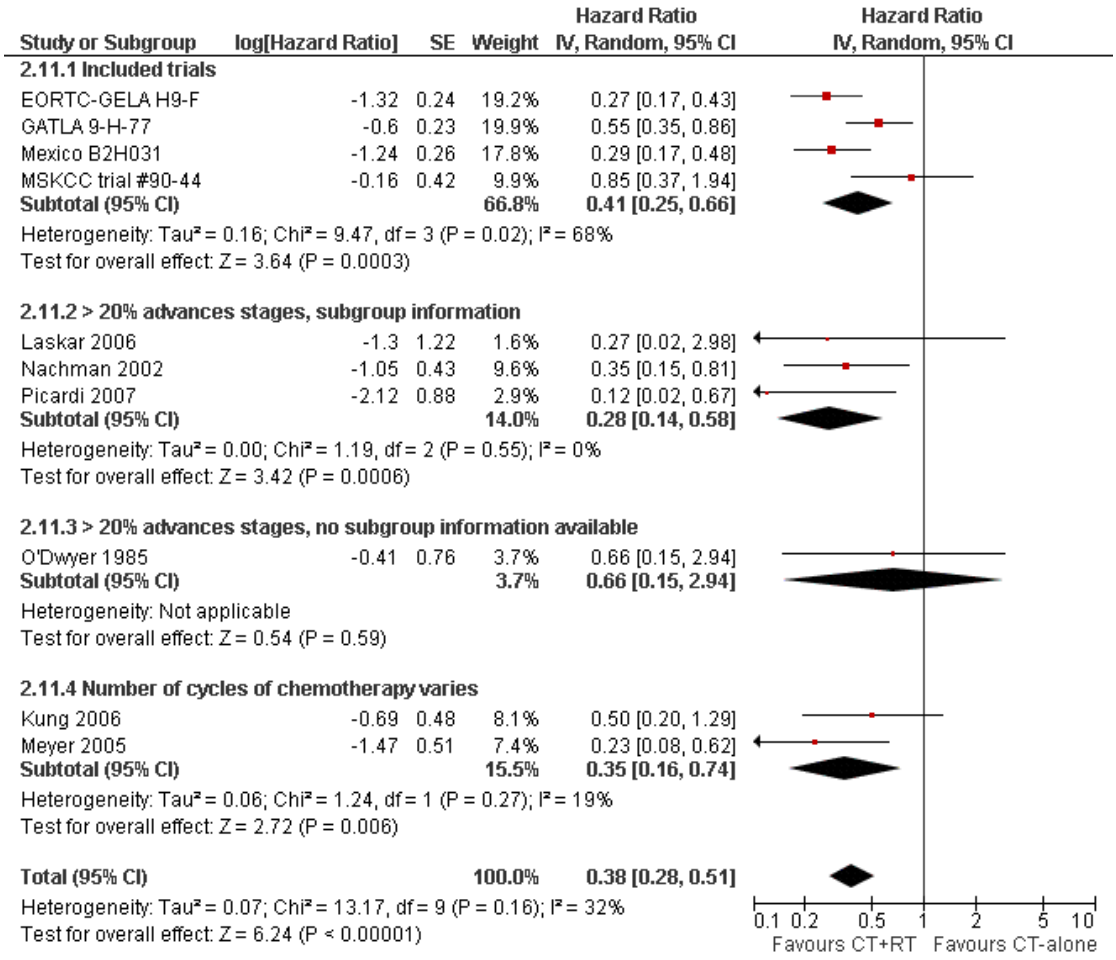
Figure 23. Forest plot of comparison: 2 Progression-Free Survival, outcome: 2.9 ITT-Analysis.



All of the trials that did not meet the strict inclusion criteria of our review protocol favoured combined modality treatment with respect to tumour control (Kung 2006; Laskar 2004; Meyer 2005; Nachman 2002; O'Dwyer 1984; Picardi 2007). When including these trials into a meta-analysis for tumour control the HR was 0.38, 95% CI 0.28 to 0.57 (Figure 24). When restricting the analysis to the trials that kept the number of cycles the same between the group that received radiotherapy and those that did not (without Kung 2006 and Meyer 2005), the HR was 0.39 (95% CI 0.27 to 0.55). Repeating these analyses without the improper estimates (without Nachman 2002 and Picardi 2007) yields a HR of 0.40

(0.28 to 0.56) for the full group and 0.42 (0.28 to 0.63) for the analysis without Kung 2006 and Meyer 2005.

Figure 24. Tumour Control: Sensitivity analysis including additional trials. Note: improper estimates based on the number of events and the number in each group were used for the estimates of the Nachman trial and the Picardi trial. The hazard ratio without the improper estimates is 0.40 (0.28 to 0.56)



Numbers needed to treat to benefit have been calculated and are presented in Table 5 based on the main analysis.

Complete response (CR)

Four trials including 653 patients reported the CR rate and were meta-analysed (CALGB 7751; GATLA 9-H-77; Mexico B2H031; MSKCC trial #90-44). No evidence of an improvement in CR in favour of CMT group was found (RR: 1.07; 95% CI 0.98 to 1.17), using a random-effects analysis due to substantial heterogeneity (P value of the homogeneity test = 0.07; I^2 = 57%) (Figure 25). Subgroup analyses by chemotherapy regimen (P for subgroup differences = 0.10), evaluable patients (P = 0.07) and ITT-analysis (P = 0.07) were performed (Figure 26, Figure 27, Figure 28). When examining only those trials with less than 10% non-evaluable patients, the result had borderline significance (HR = 1.06; 95% CI 1.00 to 1.12) with moderate heterogeneity (I^2 = 20%) (Figure 28).

For CR rates the sensitivity analysis including the additional trials was not performed.

Figure 25. Forest plot of comparison: 3 Complete Response Rate, outcome: 3.1 All trials.

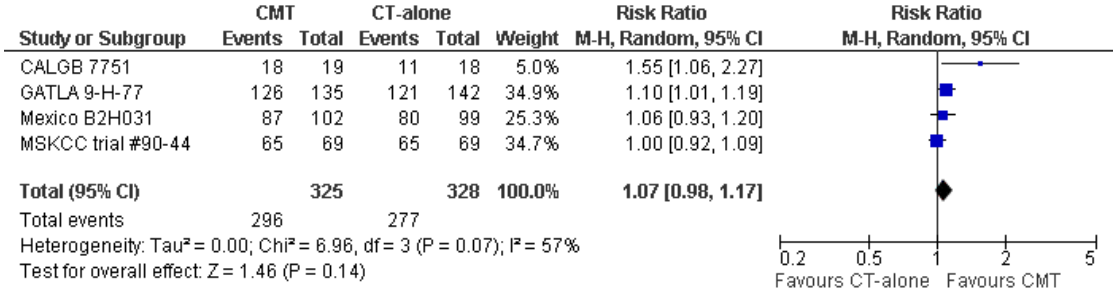


Figure 26. Forest plot of comparison: 3 Complete Response Rate, outcome: 3.2 Type of Chemotherapy.

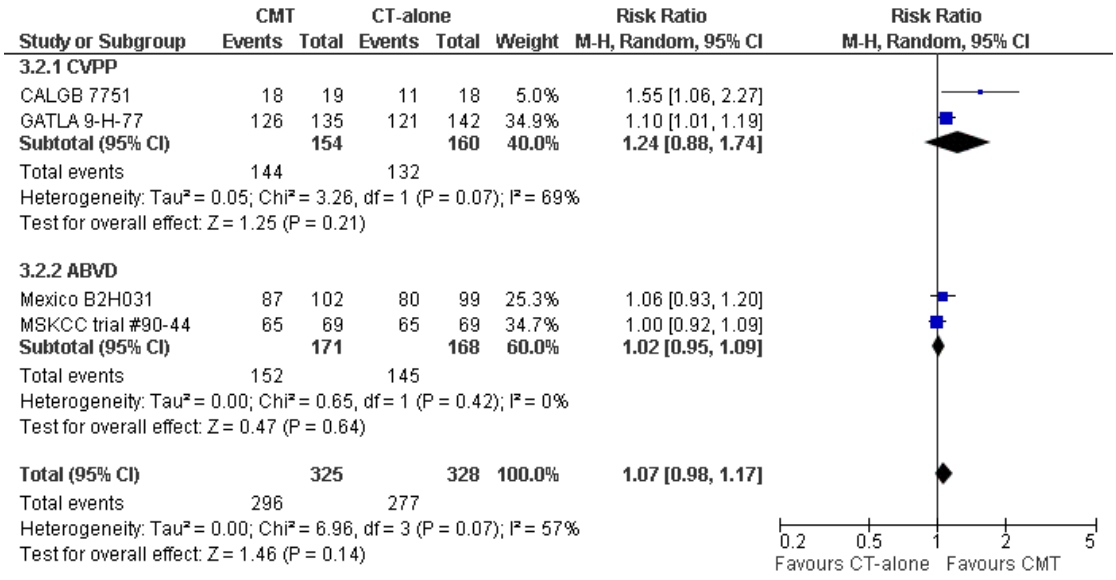


Figure 27. Forest plot of comparison: 3 Complete Response Rate, outcome: 3.3 ITT-analysis.

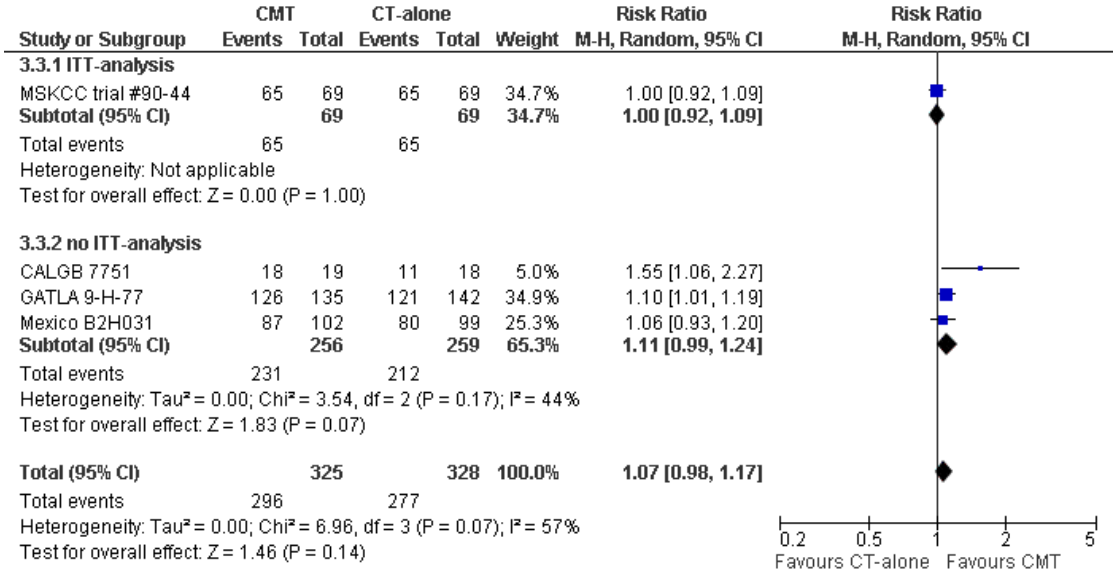
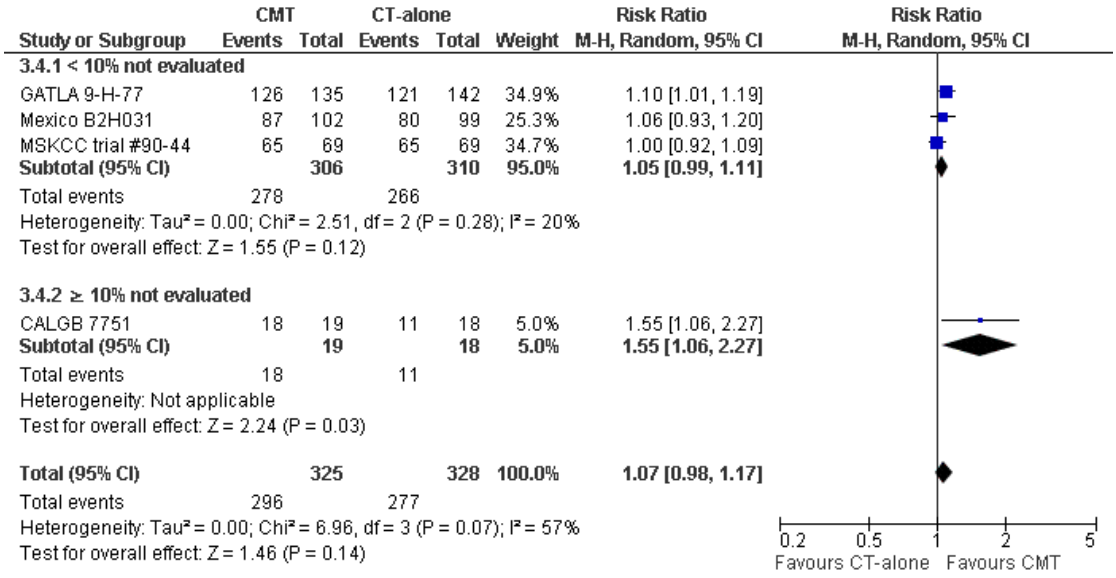


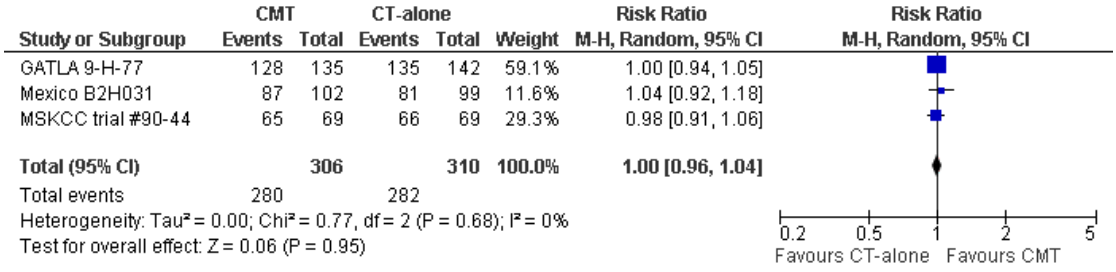
Figure 28. Forest plot of comparison: 3 Complete Response Rate, outcome: 3.4 Number of evaluable patients.



Overall response rate (ORR)

A total of 616 patients from 3 trials (GATLA 9-H-77; Mexico B2H031; MSKCC trial #90-44) were included in the meta-analysis, of which 310 patients were in the CT-alone group and 306 patients in the CMT group. We found no evidence of a statistically significant difference regarding ORR between the CMT group and the CT-alone group (RR: 1.00; 95% CI 0.96 to1.06), with a fixed-effect analysis. We found no evidence of heterogeneity across the trials in the meta-analysis (P value of the homogeneity test = 0.68; I^2 = 0%) (Figure 29).

Figure 29. Forest plot of comparison: 4 Overall Response Rate, outcome: 4.1 All Trials.



Adverse events

Adverse events, both long term toxicities and acute toxicities are tabulated in Table 6. All adverse events reported in the trials of the main analysis are in the table. Certain adverse events considered of particular interest (secondary malignancies, fertility, cardiac disease) but not reported are also listed. Most adverse events seem to be similar in both groups and are typical for the chemotherapy received (e.g. haematological effects, infections, bleomycin induced lung disease).

Table 6. Adverse Events

	CALGB 7751	EORTC-GELA H9-F	GATLA 9-H-77	Mexico B2H031	MSCKK trial #90-44
Number of patients evaluated	18: CT 19: CmT	130: CT 448: CmT	142: CT 135: CmT	99: CT 102: CMT	76: CT 76: CMT
Chemotherapy and radiotherapy	6 cycles of CVPP +/- involved-field radiotherapy (dosage unknown)	6 cycles of EBVP +/- IF RT	6 cycles of CVPP +/- IF-RT	6 cycles of ABVD +/- EF-RT	6 cycles of ABVD +/- EF or IF RT

Table 6. Adverse Events (*Continued*)

Median duration of follow-up	1.8 years	4.3 years	4 years	11.4 years	5.6 years
Leukopenia or neutropenia	NR	NR	"mild" in both groups CT: 12% CMT 14%	CT grade I-II: 31 (31%); grade III-IV: 7 (7%) CMT grade I-II: 39 (39%); grade III-IV 24 (22%)	Leukopenia: 27 (18%) developed grade II-IV leukopenia 12 patients hospitalised for neutropenia (8%) After a protocol amendment 1992 to allow the use of prophylactic filgrastim, up to 62% of patients received filgrastim
Infections and infection-related mortality	NR	NR	CT: 1 patient died of sepsis CMT: 2 patients died of sepsis	no febrile neutropenia was observed	1 patient died of sepsis and pneumonia in the context of neutropenia
Thrombopenia	NR	NR	NR	CT: 2 (2%) CMT: 5 (4%) Grades I-II	Grade 4 thrombopenia in 3 patients (2%)
Anaemia	NR	NR	NR	NR	Grade 3 decrease in haemoglobin in 5 patients (3%), grade 4 decrease in 2 patients (1%)
Neurotoxicity	NR	NR	"no severe case was reported"	CT: grade I-II 24 (24%) CMT grade I-II 36 (35%); grade III-IV 3 (3%)	NR
Alopecia	NR	NR	"mild"	CT: 34 (34%) CMT: 29 (28%) Grade III-IV CT: 13 (13%) CMT: 8 (8%)	NR
Nausea and Vomiting	NR	NR	"mild"	CT grade I-II: 46 (46%) CMT grade I-II: 63	Grade 3 nausea in 15 patients (10%) Grade 3 emesis in 7

Table 6. Adverse Events (*Continued*)

				(61%)	patients (5%)
Lung fibrosis	NR	NR	NR	0 patients	33 patients (22%) (18 patients ABVD+RT, 15 ABVD-alone) discontinued bleomycin due to an in- crease of more than 20% in the DLCO (diffusion lung capacity) test; 10 patients were treated with glycocorticoids. None developed chronic symptomatic pulmonary disease. One patient died of bleomycin induced toxicity.
Secondary malignancy	NR	1 patient died of AML (number of secondary malignancies not reported)	One patient in the CT group developed bladder cancer.	CT: 2 patients developed malignant lymphoma 3.6; 6.4 years after completion of treatment (both alive at the end of study) CMT: 2 patients had MDS and subsequent acute leukaemia. They died 3.1 and 9.5 years after completion of therapy	CT: 2 patients with secondary malignancies observed (gastric carcinoma, 2 non-fatal skin cancers in one patient) CMT: 5 secondary malignancies: 3 prior to RT: follicular thyroid carcinoma, 2 patients with follicular B-cell non-Hodgkin′ s lymphoma; 2 after RT: one papillary thyroid carcinoma, one parotid carcinoma
Infertility	NR	NR	NR	NR	NR
Cardiac disease	1 patient in the CMT group died of a heart attack during chemotherapy	NR	NR	NR	NR

DISCUSSION

The following findings emerge from this meta-analysis:

1. In patients with early stage HL, there is no evidence that the complete response rate is different in patients receiving chemotherapy alone compared to those receiving combined modality treatment (CMT) consisting of chemotherapy plus radiotherapy.

2. Tumour control is better in patients receiving CMT compared to chemotherapy alone.

3. Adding radiotherapy to chemotherapy improves overall survival in this group of patients.

To our knowledge this is the first comprehensive review focusing on patients with early stage Hodgkin lymphoma that compares chemotherapy alone with CMT consisting of chemotherapy plus additional radiotherapy. The main analysis according to the strict inclusion criteria of our review protocol included five randomised controlled trials with 1245 patients of both early favourable and early unfavourable Hodgkin lymphoma. The literature search revealed a number of trials with more than 20% of patients in advanced stages or with fewer cycles of chemotherapy in patients receiving radiotherapy. Because these trials were considered to be relevant to the underlying clinical question, these trials were included in sensitivity analyses, where subgroup information of early stage patients was used if available. These sensitivity analyses underlined the results of the main analyses.

The hazard ratio for overall survival (0.40; 95% CI 0.27 to 0.61) is similar to that of tumour control. With an assumed OS of 85% at five years as observed in the three trials included here (GATLA 9-H-77; Mexico B2H031; MSKCC trial #90-44), approximately 11 patients (95% CI 9 to 18) would require treatment with CMT for one additional patient to survive during the first five years. With better survival (97.5%) as reported in the EORTC-GELA H9-F trial, approximately 55 patients (95% CI 46 to 86) would be needed. (For other numbers needed to treat to benefit see Table 5). These potentially surprising results were robust when excluding the Mexico B2H031 trial, which had a high weight in the analysis due to the long period of follow-up and the relatively high mortality. The only concern in the overall survival analyses stems from hazard ratios estimated from survival curves (EORTC-GELA H9-F; Mexico B2H031) and the use of preliminary data from the EORTC-GELA H9-F trial. However, these are minor points, as the direction of the effect is clear and only the magnitude may vary slightly. Again, the sensitivity analysis including additional trials (Kung 2006; Laskar 2004;Meyer 2005; Nachman 2002; O'Dwyer 1985; Picardi 2007) also supported the results in favour of CMT. Two additional trials had effect estimates favouring CMT, two trials observed no deaths (Nachman 2002; Picardi 2007) and two trials observed a slight effect favouring chemotherapy alone, which was not statistically significant. One of these trials is a very small, very old trial using MOPP chemotherapy (O'Dwyer 1985). The other trial Meyer 2005, similar to the trial by Kung 2006 replaced two to four cycles of ABVD chemotherapy with subtotal nodal irradiation. They are therefore not directly comparable to the trials which used the same number of cycles in both arms of the trials, nor to trials examining smaller radiation fields.

In the present analyses we found no evidence for interaction of treatment options or patient characteristics. Two of five trials employed ABVD, and the summary hazard ratios in the subgroup analyses by chemotherapy regimen were very similar. No difference in tumour control or OS was observed between trials that examined the addition of involved field or extended field radiotherapy. This is in line with the finding that extended field radiotherapy had little or no advantage over involved field radiotherapy in Hodgkin patients when used alone or after effective chemotherapy (Engert 2003; Franklin 2005; Specht 1998). In addition, subgroup analyses gave no hint that the hazard ratios may differ depending on the proportion of patients with early favourable or early unfavourable disease or the inclusion or exclusion of patients with bulky disease. However, due to the small number of trials included, obtaining reliable information from subgroup analyses is unlikely.

Long term adverse effects such as secondary malignancies or cardiac disease are important in HL patients and can occur later than the reported observation times of the discussed trials. Radiotherapy can induce secondary malignancies while the exact increase in the risk is unclear. The absolute risk difference between chemotherapy alone and chemotherapy plus radiotherapy in a recent individual patient data meta-analysis was about 1% in early stage patients at 15 years (Franklin 2005). Some cohorts of Hodgkin patients of any stage suggest that this difference may be higher (Bhatia 2003; Dores 2002; Swerdlow 2003; van Leeuwen 2000). Unfortunately, the results of these cohorts are mixed and far from clear (see Table 7). In addition, patients who relapse have a more pronounced risk of secondary malignancies according to a cohort study by Aleman 2003. Therefore the addition of radiotherapy which reduces the number of patients with relapse (who require more aggressive therapy) may contribute to a smaller overall risk difference than suggested by the cohorts who do not distinguish between relapsed an non-relapsed patients when evaluating the risk of radiotherapy.

Table 7. Risk of secondary malignancies in cohorts of patients with Hodgkin lymphoma

Cohort	Comparison	Measure	Results	notes
Dores 2002	any radiotherapy vs. chemotherapy alone	observed divided by expected (O/E)	**1 to 9 years after treatment:** 488 RT and 221 CT pts: O/E 2.3 (RT) and 2.3 (CT); **10 to 14 years:** 206 and 48 pts; 3.2 (RT) and 2.6 (CT); **15 to 19 years:** 132 RT and 14 CT pts O/E: 3.5 (RT) and 1.7 (CT)	no stage information
van Leeuwen 2000	initial CT+ RT (first year) and initial CT alone	Relative risk compared to general population by type of cancer CT-alone: 75 pts; CT + RT: 234 pts	**breast cancer:** CT-alone: (no cases) CT + RT as initial therapy: 7.5 (2.7 to 16.3) **All solid tumours except breast:** CT-alone: 1.3 (0.03 to 7.4) CT + RT as initial therapy: 4.4 (2.0 to 8.3)	adolescence and early adulthood; no stage information; no information about the length of follow-up in each group
Swerdlow 2000	final treatment received	standardized incidence ratio (SIR) compared to the general population by age of first treatment	**Chemotherapy alone:** age 25 to 44: SIR = 4.0 (2.7 to 5.6); age 45 to 54: SIR = 2.3 (1.4 to 3.4) **CT + RT:** age 25 to 44 SIR = 4.2 (3.1 to 5.6); age 45 to 54 SIR = 3.8 (2.5 to 5.4)	no stage information
Bhatia 2003	final treatment received	% of pts with secondary malignancies	**Chemotherapy alone**: 9.4% of 106 pts; **CT + RT:** 12.7% of 960 pts.	no information on stage, nor on original therapy, nor duration of follow-up

Cardiac disease is associated with mediastinal radiation and with the cumulative dose of chemotherapy, in particular doxorubicin (Singal 1998). Radiation fields have been reduced substantially from extended field radiotherapy to involved field or even involved node radiotherapy used today. Replacing consolidation radiotherapy with chemotherapy, as evaluated by Meyer 2005, increases the dose of doxorubicin and may thus increase long term cardiac toxicity. Importantly, there was also a detrimental effect on progression-free survival in the group of patients receiving chemotherapy only.

Identifying patients at low risk of relapse might be considered an alternative to consolidation radiotherapy for all patients. Currently, however, no reliable evidence for such a strategy exists. In this

meta-analysis, the presence of conventional CR after chemotherapy such as ABVD (Mexico B2H031; MSKCC trial #90-44) or EBVP (EORTC-GELA H9-F) does not seem to accurately identify a group of patients who do not benefit from radiotherapy with regard to tumour control. PET may be an alternative. However in patients with bulky early stage disease having residual masses in CT that are PET negative, the rate of relapse after ABVD chemotherapy was much higher in patients who did not receive consolidation radiotherapy (Picardi 2007). Two other trials are planed or under way in patients with early stage Hodgkin lymphoma (clinicaltrials.gov identifiers: NCT00736320, NCT00433433).

AUTHORS' CONCLUSIONS

Implications for practice

Adding radiotherapy to a commonly used chemotherapy regimen such as ABVD increases five-year overall survival and tumour control in patients with early stage Hodgkin lymphoma.

Implications for research

Since adding radiotherapy may result in more secondary malignancies or cardiac disease and deaths thereof, long-term follow-up (more than 15 years) of clinical trials examining treatment options in early stage HL would be helpful. In addition, clear definitions of outcomes that examine tumour control would be useful in order to reduce heterogeneity. We recommend the use of progression-free survival, i.e. time to progression, relapse or death of any cause.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

CALGB 7751

Methods	• Randomised controlled trial with two arms: CT-alone arm and CMT arm. • Conducted by the Cancer and Leukemia Group B (CALGB), USA. • Recruitment period in 1970s, exact period unclear. • 55 patients allocated; exact number per arm not reported. • 37 patients evaluated: 18 patients in CT-alone arm and 19 patients in CMT arm. • Baseline patient's characteristics described. • Median follow-up time: 22 months. • Not ITT analysis; more than 10% of the enrolled patients not evaluated.
Participants	• Inclusion criteria: patients with histologically documented, previously untreated, poor prognosis pathological stage I and I; poor prognosis was defined as symptom class B, mixed cellularity or lymphocyte depleted histology, a large mediastinal mass, or age > 40 years • Exclusion criteria: not reported. • PS I, II: CT-alone: 1, 17; CMT: 6, 13. • Prognostic features: not reported. • Mean age: CT-alone: 24 years; CMT: 30 years; • Gender male, female: CT-alone: 6, 12; CMT: 14; 5. • Baseline patient's characteristics: more male patients in CMT arm; more patients with mediastinal mass in CT-alone arm. • Histopathologic diagnosis: according to Rye modification of Lukes and Butler classification.
Interventions	• CT-alone: 6 cycles of CVPP (cyclophosphamide (75 mg/m² orally, day 1), vinblastine (4mg/m² intravenous, days 1 and 8), procarbazine (100 mg/m² orally, days 1-14), prednisone (40 mg/m² orally, days 1-14)); repeated every 14 days. • CMT: same CT with involved-field radiotherapy; dose of radiotherapy (RT) not reported; RT delivered before CT. • No additional treatment.
Outcomes	• Overall survival reported. • Complete response reported. • Partial response not reported. • Progression-free survival not reported.
Notes	• Response documented after two cycles of CT. • Source of funding not reported.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"randomly allocated"
Allocation concealment?	Unclear	Not reported.

CALGB 7751 (*Continued*)

Blinding? Overall survival	Yes	Patients not blinded. No information about blinding of the assessor. This is judged not to be a source of bias for overall survival.
Blinding? Other outcomes	Unclear	Patients not blinded. No information about blinding of the assessor.
Incomplete outcome data addressed? All outcomes	No	22 months OS and response outcome: 18/55 missing from the outcome analysis; no information per study arm. This trial was considered not to have performed an ITT analysis in the subgroup analysis.
Free of selective reporting?	Unclear	Dates of relapse and deaths are given. Dates of progression not given nor information about censoring. No time to event outcomes calculated.
Free of other bias?	Unclear	Very little information in the report.

EORTC-GELA H9-F

Methods	• A randomised controlled trial with three arms: comparison of three radiation dosis; 36 Gy involved-field radiotherapy, 20 Gy involved-field radiotherapy and no radiotherapy in patients that achieved complete response (CR) after six cycles of EBVP. • Conducted by EORTC (European Organization for Research and Treatment of Cancer) and GELA (Groupe d'Etude des Lymphomes de l'Adulte); 111 institutions from 10 European countries involved. • Recruitment period from September 1998 to May 2004. • 784 patients enrolled. • 13 patients not evaluable before randomisation (6 refusals, 3 protocol violations, 4 unspecified). • 578 patients randomised to three radiation doses. • 578 patients evaluated. • Baseline patient's characteristics not reported (abstract publication). • Median follow-up 51 months (range 14 to 81). • ITT analysis.
Participants	• Inclusion criteria: adult patients with supradiaphragmatic CS I-II Hodgkin lymphoma and favourable features (age < 50, CS I-II, symptoms class A + ESR < 50 or symptoms class B + ESR < 30 and MT ratio < 0.35). • Exclusion criteria: not reported. • Age: 31 (15 to 49) • Gender: 55% male; 45% female • CS: patients with CS I-II without bulky disease. • Prognostic features: all included patients with favourable risk factors. • Histopathologic diagnosis: not reported.

EORTC-GELA H9-F (*Continued*)

Interventions	• CT-alone: 6 cycles of EBVP (epirubicin (70 mg/m² intravenous, day 1), bleomycin (10 mg/m² intravenous/intramuscular, day 1), vinblastine (6 mg/m² intravenous, day 1), prednisone (40 mg/m² orally, day 1-5)); repeated after every 21 days. • CMT: same CT before randomisation with 36 Gy involved-field radiotherapy or 20 Gy involved-field radiotherapy. • No additional treatment.
Outcomes	• Overall survival reported; observation time 4 years. • Response not reported. • Progression-free survival not reported. • Disease-free survival reported (Table 3).
Notes	• Inclusion of patients in no radiotherapy arm was stopped in May 2002 because stopping rules were met that is > 20% events occurred. • Hazard ratio estimate is based on the full group receiving additional radiotherapy and not only those patients up to the time the no radiotherapy arm was stopped. • Source of funding not reported.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Patients were randomly allocated. No further information available. However it was a large multicenter trial with presumably central allocation (older trials of the same group). We therefore assume that it was probably ok.
Allocation concealment?	Yes	No information available from the publications. However, it is a large multicenter trial with 120 centres. Older trials from this group were centrally allocated. We therefore assume that it was probably ok.
Blinding? Overall survival	Yes	Patients not blinded (not expected due to the treatment with radiotherapy). No information about blinding of the assessor. This is judged not to be a source of bias for overall survival.
Blinding? Other outcomes	Unclear	Patients and physicians not blinded (not expected due to the treatment with radiotherapy). No information about blinding of the assessor.

EORTC-GELA H9-F (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	No withdrawals and protocol violations after randomisation reported. Analysis was performed on ITT basis and all randomised patients were included in the analysis.
Free of selective reporting?	Yes	Rationale for the use of disease-free survival not described. However all patients are in CR at the time of randomisation. Disease-free survival should therefore be equivalent to progression free survival. Other progression outcomes that are more prone to bias are not used and not reported. Despite no protocol being available, we judge that the trial is free of selective outcome reporting.
Free of other bias?	No	Trial was ended early due to predefined stopping rule. This is known to increase the effect estimate of trials. In addition the data are preliminary.

GATLA 9-H-77

Methods	• A randomised controlled trial with two arms: CT-alone arm and CMT arm. • Conducted by Group Argentino de Tratamientode la Leucemia Aguda (GATLA). • Recruitment period from September 1977 to October 1986. • 293 patients randomised: CT-alone:148; CMT: 145. • 277 patents evaluated: 142 in CT-alone arm and 135 in CMT arm. • 16 patients not evaluated; 4 drop outs and 2 protocol violations in CT-alone arm; 9 drop outs and one protocol violation in CMT arm. • Baseline patient's characteristics described. • Median time on study was 43 months for CT-alone arm and 51 months for CMT arm. • Not ITT analysis; less than 10% of enrolled patients not evaluated.
Participants	• Inclusion criteria: patients with pathologically proven Hodgkin lymphoma, according to Lukes and Butler's criteria. • Exclusion criteria: patients with CS III. • CS I, II: CT-alone: 47, 95; CMT: 46, 89; overall CS I 93, CS II 184. • Prognostic features: CT-alone: 82 patients with early favourable stage; 60 patients with early unfavourable stage; CMT: 91 patients with early favourable stage; 44 patients with early unfavourable stage. • Age: patients of all ages; median age not reported; 124 patients (45%) were children < 16 years. • Gender: CT-alone: 87 males, 55 females; CMT: 88 males, 47 females. • Similar baseline patient's characteristics in comparison arms. • Histopathologic diagnosis: according to the Rye modification of the Lukes and Butler.

GATLA 9-H-77 (*Continued*)

Interventions	• CT-alone: 6 monthly cycles of CVPP (cyclophosphamide (600 mg/m² intravenous, day 1), vinblastine (6 mg/m² intravenous, day 1), procarbazine (100 mg/m² orally, days 1-14), prednisone (40 mg/m² orally, days 1-14)). • CMT: same CT with IF-RT between third and fourth cycle of CT (sandwich technique); dose of RT was 3000 rad. • No additional treatment.
Outcomes	• Overall survival reported also for prognostic groups; observation time 7 years. • Complete response reported. • Partial response reported. • Progression-free survival not reported. • "Disease-free survival" reported (see Table 3)
Notes	• Limited overall survival data for prognostic groups; estimation of HR not possible. • Academic funding.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"[...] patients [...] were randomised [...] " No further information available.
Allocation concealment?	Unclear	No information available.
Blinding? Overall survival	Yes	Patients not blinded. No information about blinding of the assessor. This is judged not to be a source of bias for overall survival.
Blinding? Other outcomes	Unclear	Patients not blinded. No information about blinding of the assessor.
Incomplete outcome data addressed? All outcomes	Yes	5 years OS and response rate: 6/142 missing from CT-alone arm and 10/135 from CMT arm; 13 lost to follow-up before completing 6 cycles and 3 protocol violations (not described in detail); Therefore for subgroup analysis this trial was considered not to have performed an ITT analysis. Despite the authors not addressing the missing outcomes in analyses, we judge that these few missing data have very little influence on the overall results.
Free of selective reporting?	Unclear	For progression outcome, disease-free survival was chosen. No other progression outcomes are reported but it is unclear why dis-

GATLA 9-H-77 (*Continued*)

		ease-free survival was chosen and not progression free survival. No protocol is available.
Free of other bias?	Yes	From the report, the trial seems free of other bias.

Mexico B2H031

Methods	• Randomised controlled trial with three arms: CT-alone arm, CMT arm and RT-alone arm. • Conducted at Oncology Hospital, National Medical Center, Mexico. • Recruitment period from 1983 to 1988. • 327 patients enrolled. • 307 patients evaluated; 99 patients in CT-alone arm; 102 patients in CMT arm and 106 patients in RT-alone arm. • 20 patients not evaluated due to advanced stage and infradiaphragmatic involvement. • Baseline patient characteristics described. • Median follow-up time 11.4 years (range 6.3 - 16.5 years). • Not ITT analysis; less than 10% of enrolled patients not evaluated.
Participants	• Inclusion criteria: both male and female adult patients with clinical stage I and II (CS I and II), supradiaphragmatic disease and the presence of bulky disease. • Exclusion criteria: patients with advanced stages and infradiaphragmatic involvement. • CS I, II: CT-alone: 21, 78; CMT: 22, 80; overall CS I 34%, CS II 66%. • Prognostic features not reported. • Mean age (range): CT-alone: 39 (20 to 70) years; CMT: 42 (18 to 71) years. • Gender: CT-alone: 40 males, 59 females; CMT: 51 males, 51 females. • Similar baseline patient's characteristics in comparison arms. • Histopathologic diagnosis: according to Rye modification of Lukes and Butler classification.
Interventions	• CT-alone: 6 monthly cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); dose not reported. • CMT: same CT with mantle-field radiotherapy (MF-RT) between third and fourth cycles of CT (sandwich technique); dose of RT: 3500-3800 cGy in fraction of 200-250 cGy four to five times a week for four to six weeks. • RT-alone: EF-RT with a dose of 3500-3800 cGy in fraction of 200-250 cGy four to five times a week over a period of four weeks; 106 patients from this arm not included in the review. • No additional treatment.
Outcomes	• Overall survival reported; observation time 12 years. • Complete response reported. • Partial response reported. • Progression-free survival not reported. • Contradictory definitions of disease-free survival (see Table 3)

Mexico B2H031 (*Continued*)

Notes	• Source of funding not reported.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"a prospective randomised trial" No further information available.
Allocation concealment?	Unclear	No information available.
Blinding? Overall survival	Yes	Patients not blinded. No information about blinding of the assessor. This is judged not to be a source of bias for overall survival.
Blinding? Other outcomes	Unclear	Patients and physicians not blinded. No information about blinding of the assessor.
Incomplete outcome data addressed? All outcomes	Unclear	12 years OS and tumour control outcome: 20/327 missing from the outcome analysis; no information per study arm. The authors do not give any further information about the method of analysis (e.g. intention-to-treat) We do not believe that these few missing patients induced large bias in the analysis, but because the information is not available by study arm and it remained unclear in which arm patients who did not receive radiotherapy were evaluated, we judged unclear. For subgroup analysis this trial was considered to have no ITT analysis.
Free of selective reporting?	Unclear	In the methods section: "Disease-free survival was calculated for CR patients from the beginning of treatment until clinical or radiological and biopsy proven relapse." No information about patients that did not achieve CR. However, the denominator in the results section is the full population, not only patients in CR. Both disease-free survival and relapse free survival were calculated but only disease free survival was reported. Due to the information given about toxic deaths, overall survival and disease-free survival, we assume that relapse free

Mexico B2H031 (*Continued*)

		survival would also have been statistically significant and possibly similar to disease-free survival, thus not resulting in any bias. In addition, disease-free survival is preferable to relapse free survival as it includes deaths. For these reasons, we choose "unclear" and not "no". There is no information about progression free survival. A study protocol was not available.
Free of other bias?	Yes	No reason to suspect other sources of bias.

MSKCC trial #90-44

Methods	• A randomised controlled with two arms: CT-alone arm and CMT arm. • Conducted by MSKCC (Memorial Sloan-Kettering Cancer Center), USA. • Recruitment period from May 1990 to June 2000. • 152 patients randomised. • 152 patients evaluated for OS; 138 patients evaluated for response rate. • 14 patients not evaluated for response outcome. • Baseline patient's characteristics described. • Median follow-up time 67 months (range 1 to 125 months). • ITT analysis for overall survival; not ITT analysis for response outcomes.
Participants	• Inclusion criteria: patients with a confirmed diagnosis of Hodgkin lymphoma, without previous treatment and with clinical or pathological stage IA, IIA, IIB or IIIA and lack of bulky nodal tumour (mediastinal mass $\leq$ 0.33, the thoracic diameter on chest x-ray measured at T11, and/or peripheral or retroperitoneal adenopathy $\leq$ 10 cm in its largest diameter). • Exclusion criteria: patients with chronic lung disease with a diffusing capacity of less than 60% and/or with cardiac disease with clinical congestive heart failure or an abnormal ventricular ejection fraction (< 50%) on echocardiogram or multiple gated acquisition scan were excluded. • CS I, II: CT-alone: 19, 46; CMT: 9, 58. • CS III: CT-alone: 11; CMT: 9. • Prognostic features not reported. • Median age: CT-alone: 33 years (range 16-68 years); CMT: 39 years (range 15-66 years). • Gender: 87 males, 65 females. • Small imbalance in the distribution of sex, stage and histology, regarding baseline patient's characteristics in comparison arms. • Histopathologic diagnosis: according to the Rye modification of the Lukes and Butler classification.
Interventions	• CT-alone: 6 cycles of ABVD (doxorubicin (25 mg/m²), bleomycin (10 units/m²), vinblastine (6 mg/m²), dacarbazine (375 mg/m² intravenously, days1 and 15)); repeated after every 28 days. • CMT: same CT with extended-field radiotherapy (EF-RT) or involved-field radiotherapy (IF-RT); dose of RT 36 Gy in 180 cGY daily fractions starting after 4-6

MSKCC trial #90-44 (*Continued*)

	weeks after completion of CT. • Additional intervention: filgrastim was used for subsequent treatment of neutropenic patients.
Outcomes	• Overall survival reported; observation time 5 years. • Complete response reported. • Partial response reported. • Progression-free survival not reported. • Time to progression reported (see Table 3).
Notes	• 13% patients with CS IIIA. • Academic funding.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Sequence generation was not reported. "Randomisation was performed after a check for eligibility. Patients were stratified according to clinical stage (IA or IIa, IIIA, I B or IIB)." Presumably the randomisation was adequate.
Allocation concealment?	Yes	"Patients were enrolled by telephone call or fax to the MSKCC Clinical Trials Office"
Blinding? Overall survival	Yes	Patients and physicians not blinded. No information about blinding of the assessor. This is judged not to be a source of bias for overall survival.
Blinding? Other outcomes	Unclear	Patients and physicians not blinded. No information about blinding of the assessor.
Incomplete outcome data addressed? All outcomes	Yes	11 patients randomised to RT never received RT: 6 refused, 4 progressed on chemotherapy prior to receiving RT, 1 never received RT because of bleomycin induced toxicity to RT. OS: all patients included in the analysis, ITT-analysis Tumour control: all patients included in the analysis, ITT-analysis Response rates: 7/76 excluded from CT-alone arm and 7/76 excluded from CMT arm; three lost to follow-up before completion of six cycles of chemotherapy and 11

MSKCC trial #90-44 (*Continued*)

		stage IA patients with no measurable disease prior to treatment.
Free of selective reporting?	Unclear	Choice of progression outcome not described - both disease-free survival and freedom from progression evaluated; freedom from progression was closer to our definition of PFS and was thus used in the analyses.
Free of other bias?	Yes	No other bias identified.

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

Study	Reason for exclusion
Andrieu 1999	Comparison arms not treated with CT-alone or CMT; all included patients received CMT. Less than 80% of the participants had early stage Hodgkin lymphoma; only 25% of the included patients had early stage Hodgkin lymphoma
Bonnet 2007	Less than 80% of the participants had early stage Hodgkin lymphoma; only 6 of the 576 included patients had Hodgkin lymphoma.
Brusamolino 1994	Comparison arms not treated with CT-alone or CMT; compared interventions RT-alone versus CMT.
Cheveresan 1998	Comparison arms not treated with CT-alone or CMT; all included patients received CMT.
Cimino 1990	Not a randomised controlled trial; a review article.
Cosset 1992	Not a randomised controlled trial; a review article.
Desablens 1999	Comparison arms not treated with CT-alone or CMT; all patients received CMT.
Dionet 1988	Comparison arms not treated with CT-alone or CMT and different CT regimens used in comparison arms.
Hirsch 1996	Evaluation of pulmonary symptoms in patients randomised to MSKCC trials 1989 to 1993. Not a report of one specific trial Relevant patients presumably analysed in MSKCC trial #90-44 (recruitment 1990-2000) Only 45 patients with the relevant comparison included 30: 6 X ABVD 15: 6 X ABVD plus EF RT No mortality data given Adverse events included only pulmonary function and included 15 patients not in the relevant randomised comparison. During CT 53% of patients had symptoms of cough or dyspnoea on exertion At the end of follow-up (~ 1 year after treatment), 18% (CT) vs. 30% (CMT) reported persistent symptoms

(*Continued*)

	(P = 0.36)
Horning 1996	Less than 80% of the participants had early stage Hodgkin lymphoma; only 42% of the included patients had early stage Hodgkin lymphoma.
Horning 2007	Comparison arms not treated with CT-alone or CMT; compared interventions RT-alone versus CMT.
Kim 2003	Not a randomised controlled trial; a retrospective data analysis of patients' records with Hodgkin lymphoma.
Koerholz 2004	Not a randomised controlled trial.
Kung 1993	Less than 80% of the participants had early stage Hodgkin lymphoma; 69% of the included patients had early stage Hodgkin lymphoma. No subgroup information available. (See also Kung 2006).
Kung 2006	Less than 80% of the participants had early stage Hodgkin lymphoma; 69% of the included patients had early stage Hodgkin lymphoma. No subgroup information available.
Laskar 2004	Less than 80% of the participants had early stage Hodgkin lymphoma; 55% of the included patients had early stage Hodgkin lymphoma.
Longo 1992	Not a randomised controlled trial; a review article about the trials (GATLA 9-H-77; O'Dwyer 1985).
Meyer 2005	Chemotherapy differed between treatment arms (2 cycles of ABVD+RT vs. 4-6 cycles of ABVD)
Nachman 2002	Less than 80% of the participants had early stage Hodgkin lymphoma; 55% of the included patients had early stage Hodgkin lymphoma.
Noordijk 2006	Comparison arms not treated with CT-alone or CMT; compared interventions RT-alone versus CMT.
O'Dwyer 1984	Less than 80% of the participants with early stage Hodgkin lymphoma; 69% of the evaluable patients with early stage Hodgkin lymphoma. Duplicate publication (see also O' Dwyer 1985).
O'Dwyer 1985	Less than 80% of the participants had early stage Hodgkin lymphoma; 69% of the evaluable patients had early stage Hodgkin lymphoma.
Pavlovsky 1997	Comparison arms not treated with CT-alone or CMT.
Picardi 2007	Less than 80% of the participants had early stage Hodgkin lymphoma; 66% of the included patients had early stage Hodgkin lymphoma. No subgroup information available.
Radford 2002	Comparison arms not treated with CT-alone or CMT; compared interventions RT-alone versus CMT.
Rüffer 1996	Comparison arms not treated with CT-alone or CMT; compared interventions RT versus RT.
Rüffer 1998	Comparison arms not treated with CT-alone or CMT; all patients received CMT.
Rüffer 1999	Comparison arms not treated with CT-alone or CMT; all patients received CMT. Duplicate publication (see also Ruffer 1998); all patients received CMT.

(*Continued*)

Specht 1992	Not a randomised controlled trial; a review article.
Straus 1989	Comparison arms not treated with CT-alone or CMT; all patients received CMT.
Thistlethwaite 2007	Comparison arms not treated with CT-alone or CMT; compared interventions RT-alone versus CMT.

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

EORTC-GELA HD 10

Trial name or title	Official title: The H10 EORTC/GELA Randomized Intergroup Trial on Early FDG-PET Scan Guided Treatment Adaptation Versus Standard Combined Modality Treatment in Patients With Supradiaphragmatic Stage I/II Hodgkin's Lymphoma
Methods	Randomised controlled trial
Participants	• 15 Years to 70 Years • DISEASE CHARACTERISTICS: ○ Histologically confirmed Hodgkin's lymphoma ○ No nodular lymphocyte-predominant subtype (nodular paragranuloma) ○ Supradiaphragmatic Ann Arbor clinical stage I or II disease ○ Must meet criteria for 1 of the following prognostic subsets: ◇ Unfavourable subset, defined as meeting 1 of the following criteria: Clinical stage II disease with > 4 nodal areas involved Mediastinum and hili are considered as 1 nodal area Age > 50 years Erythrocyte sedimentation rate (ESR) < 50 mm/hr with no B symptoms ESR < 30 mm/hr with B symptomsMediastinum/thoracic (MT) ratio < 0.35 ◇ Favourable subset, defined as meeting all of the following criteria: Clinical stage I disease OR stage II disease with < 3 involved areas Age < 50 years ESR < 50 mm/hr (no B symptoms) OR ESR < 30 mm/hr (B symptoms present) MT ratio < 0.35 ○ Previously untreated disease ○ Planning to undergo fludeoxyglucose F 18 positron emission tomography after the first 2 courses of study chemotherapy • PATIENT CHARACTERISTICS:WHO performance status 0-3 ○ Bilirubin < 2.5 times upper limit of normal (ULN) ○ Creatinine < 2.5 times ULN ○ Not pregnant or nursing ○ Negative pregnancy test ○ Fertile patients must use effective contraception ○ No severe cardiac, pulmonary, neurologic, psychiatric, or metabolic disease ○ No unstable diabetes mellitus ○ No other malignancies within the past 5 years except for basal cell skin cancer or adequately treated carcinoma in situ of the cervix ○ No known HIV infection

EORTC-GELA HD 10 (*Continued*)

	○ No psychological, familial, sociological, or geographical condition that would preclude study compliance
Interventions	• Arm I (standard): Patients receive ABVD chemotherapy comprising doxorubicin hydrochloride IV, bleomycin IV or intramuscularly (IM), vinblastine IV, and dacarbazine IV on days 1 and 15. Treatment repeats every 28 days in the absence of disease progression or unacceptable toxicity. Patients with favourable prognostic profile receive 3 courses of ABVD. Patients with unfavourable prognostic profile receive 4 courses of ABVD. Patients undergo FDG-PET scan after completion of 2 courses of ABVD. Beginning 3-4 weeks after completion of ABVD, patients undergo involved-node radiotherapy (INRT) 5 days a week for 4-6 weeks. • Arm II (experimental): Patients receive ABVD as in arm I for 2 courses and then undergo FDG-PET scan. Further treatment is adapted according to FDG-PET scan result.FDG-PET negative: Patients with favourable prognostic profile receive 2 additional courses of ABVD. Patients with unfavourable prognostic profile receive 4 additional courses of ABVD. FDG-PET positive: Patients receive escalated BEACOPP chemotherapy comprising cyclophosphamide IV and doxorubicin hydrochloride IV on day 1, vincristine IV and bleomycin IV or IM on day 8, etoposide IV on days 1-3, oral procarbazine hydrochloride on days 1-7, oral prednisone on days 1-14, and filgrastim (G-CSF) subcutaneously beginning on day 9 and continuing until blood count recover. Treatment repeats every 21 days for 2 courses in the absence of disease progression or unacceptable toxicity. Beginning 3-4 weeks after completion of BEACOPP, patients undergo INRT 5 days a week for 4-6 weeks.
Outcomes	Primary Outcome Measures: Progression-free survival Secondary Outcome Measures: Event-free survival; Overall survival; Long-term toxicity, in terms of secondary malignancies, cardiovascular events, and pulmonary events; Response Duration 10 years
Starting date	October 2006
Contact information	John Raemaekers, MD, PhD 31-24-361-4762 J.Raemaekers@hemat.umcn.nl
Notes	NCT00433433, 1600 patients planned

Friedman

Trial name or title	Official title: A phase III group-wide study of dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate risk Hodgkin disease.
Methods	A randomised controlled trials. Initial CT to all patients with 2 cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide). Patients with RER (rapid early response) that > 60% disease reduction receive 2 additional courses of ABVE-PC. Patients with complete response after 4 courses randomised to receive either RT or no further treatment. Patients with SER (slow early response) that < 60% disease reduction: Arm I: 2 courses of DECC (dexamethasone, etoposide, cytarabine, cisplatin) and 2 additional courses of ABVE-PC and RT; Arm II: Patients with SER receive 2 additional courses of ABVE-PC without DECC and RT (Arm II). These patients are not relevant for the review

Friedman (*Continued*)

Participants	Both male and female patients up to 21 years with newly diagnosed Hodgkin's lymphoma without prior therapy.
Interventions	CT-alone: 4 cycles of ABVE-PC, repeated after every 21 days. CMT: 4 cycles of ABVE-PC and RT
Outcomes	Primary outcome measure: event-free survival. Secondary outcome measures: overall survival; disease response; toxicity.
Starting date	September 2002.
Contact information	Investigator: Debra L. Friedman MD, Childrens Hospital and Regional Medical Center, Seattle. Childrens Oncology Group, National Cancer Institute (NCI).
Notes	The trial has been suspended (last accessed August 7th, 2009) Final data collection date for primary outcome measure June 2010. ClinicalTrials.gov Identifier: NCT00025259 (www.clinicaltrials.gov)

GHSG HD 16

Trial name or title	Official Title: HD16 for Early Stages - Treatment Optimization Trial in the First-Line Treatment of Early Stage Hodgkin Lymphoma; Treatment Stratification by Means of FDG-PET
Methods	Randomised controlled trial, non-inferiority design
Participants	18 Years to 75 Years Inclusion Criteria: • Hodgkin lymphoma • CS I, II without any of the following risk factors: large mediastinal mass (> 1/3 of maximum transverse thorax diameter)extranodal involvement elevated ESR3 or more involved nodal areas • Written informed consent Exclusion Criteria: • Leucocytes < 3000/µl • Platelets < 100000/µl • Hodgkin lymphoma as composite lymphoma • Activity index (WHO) > 2
Interventions	Arm 1: 2 cycles ABVD followed by 30 Gy IF-RT irrespective of FDG-PET results after chemotherapy Arm 2: 2 cycles ABVD followed by 30 Gy IF-RT if FDG-PET is positive after chemotherapy; 2 cycles ABVD and treatment stop if FDG-PET is negative after chemotherapy
Outcomes	Primary Outcome Measures: Progression Free Survival (Time Frame: 5 years) Secondary Outcome Measures: Overall survival, acute and late toxicity, CR-rate (Time Frame: 5 years)
Starting date	unclear
Contact information	Michael Fuchs; GHSG@uk-koeln.de

GHSG HD 16 (*Continued*)

Notes	clinicaltrials.gov identifier NCT00736320; 1100 patients to be enrolled

DATA AND ANALYSES

Comparison 1. Overall Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials	5	1245	Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
2 Excluding the trial with highest weight (Aviles)	4	1044	Hazard Ratio (Random, 95% CI)	0.57 [0.33, 0.98]
3 Proportion of patients early favourable	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
3.1 All patients early favourable	1		Hazard Ratio (Random, 95% CI)	0.27 [0.04, 1.74]
3.2 ~ 1/3 to 1/2 patients early unfavourable	2		Hazard Ratio (Random, 95% CI)	0.57 [0.28, 1.15]
3.3 All patients early unfavourable	2		Hazard Ratio (Random, 95% CI)	0.31 [0.18, 0.54]
4 Bulky vs non-bulky	3		Hazard Ratio (Random, 95% CI)	0.29 [0.18, 0.48]
4.1 Bulky disease	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.51]
4.2 Non-bulky disease	2		Hazard Ratio (Random, 95% CI)	0.30 [0.10, 0.87]
5 Timing of radiotherapy	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
5.1 Radiotherapy after chemotherapy	2		Hazard Ratio (Random, 95% CI)	0.30 [0.10, 0.87]
5.2 Sandwich technique (CT-RT-CT)	2		Hazard Ratio (Random, 95% CI)	0.44 [0.19, 1.04]
5.3 Chemotherapy after radiotherapy	1		Hazard Ratio (Random, 95% CI)	0.63 [0.11, 3.65]
6 Type of radiotherapy	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
6.1 Involved field	3		Hazard Ratio (Random, 95% CI)	0.62 [0.33, 1.17]
6.2 Extended field	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.51]
6.3 Mixed	1		Hazard Ratio (Random, 95% CI)	0.31 [0.08, 1.15]
7 Type of chemotherapy	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.59]
7.1 ABVD	2		Hazard Ratio (Random, 95% CI)	0.30 [0.18, 0.50]
7.2 CVPP	2		Hazard Ratio (Random, 95% CI)	0.68 [0.35, 1.31]
7.3 EBVP	1		Hazard Ratio (Random, 95% CI)	0.27 [0.04, 1.73]
8 Length of follow-up	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
8.1 Six years or less	4		Hazard Ratio (Random, 95% CI)	0.55 [0.31, 0.96]
8.2 More than six years	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.51]
9 4 year survival in the CT group	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
9.1 > 90%	1		Hazard Ratio (Random, 95% CI)	0.27 [0.04, 1.74]
9.2 80% - 90%	3		Hazard Ratio (Random, 95% CI)	0.41 [0.22, 0.77]
9.3 unknown	1		Hazard Ratio (Random, 95% CI)	0.63 [0.11, 3.65]
10 Allocation concealment	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
10.1 Allocation concealment unclear	3		Hazard Ratio (Random, 95% CI)	0.46 [0.23, 0.89]
10.2 Allocation concealment adequate	2		Hazard Ratio (Random, 95% CI)	0.30 [0.10, 0.87]
11 ITT-analysis	5		Hazard Ratio (Random, 95% CI)	0.40 [0.27, 0.61]
11.1 ITT-analysis	2		Hazard Ratio (Random, 95% CI)	0.30 [0.10, 0.87]

11.2 No ITT-analysis	3	Hazard Ratio (Random, 95% CI)	0.46 [0.23, 0.89]

Comparison 2. Progression-Free Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials	4	1208	Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
2 Type of chemotherapy	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
2.1 ABVD	2		Hazard Ratio (Random, 95% CI)	0.47 [0.16, 1.35]
2.2 CVPP	1		Hazard Ratio (Random, 95% CI)	0.55 [0.35, 0.86]
2.3 EBVP	1		Hazard Ratio (Random, 95% CI)	0.27 [0.17, 0.43]
3 Proportion of patients early favourable	4	429	Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
3.1 All patients early favourable	1	0	Hazard Ratio (Random, 95% CI)	0.27 [0.17, 0.43]
3.2 mixed patient population (~1/3 to 1/2)	2	429	Hazard Ratio (Random, 95% CI)	0.61 [0.41, 0.90]
3.3 All patients early unfavourable	1	0	Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.48]
4 Definition of progression	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
4.1 In CR patients	1		Hazard Ratio (Random, 95% CI)	0.27 [0.17, 0.43]
4.2 Progress in all patients	2		Hazard Ratio (Random, 95% CI)	0.61 [0.41, 0.90]
4.3 Unclear	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.48]
5 Timing of radiotherapy	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
5.1 Radiotherapy after chemotherapy	2		Hazard Ratio (Random, 95% CI)	0.45 [0.15, 1.41]
5.2 Sandwich technique (CT-RT-CT)	2		Hazard Ratio (Random, 95% CI)	0.40 [0.22, 0.75]
6 Type of radiotherapy	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
6.1 Involved field	2		Hazard Ratio (Random, 95% CI)	0.38 [0.19, 0.78]
6.2 Extended field	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.48]
6.3 Mixed	1		Hazard Ratio (Random, 95% CI)	0.85 [0.37, 1.94]
7 Length of follow-up	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
7.1 Median follow-up ≤ 6 years	3		Hazard Ratio (Random, 95% CI)	0.47 [0.25, 0.89]
7.2 Median follow-up > 6 years	1		Hazard Ratio (Random, 95% CI)	0.29 [0.17, 0.48]
8 Allocation concealment	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.66]
8.1 Allocation concealment unclear	2		Hazard Ratio (Random, 95% CI)	0.40 [0.22, 0.75]
8.2 Allocation concealment adequate	2		Hazard Ratio (Random, 95% CI)	0.45 [0.15, 1.41]
9 ITT-Analysis	4		Hazard Ratio (Random, 95% CI)	0.41 [0.25, 0.65]
9.1 ITT-analysis	2		Hazard Ratio (Random, 95% CI)	0.44 [0.15, 1.30]
9.2 No ITT-analysis	2		Hazard Ratio (Random, 95% CI)	0.40 [0.22, 0.75]

Comparison 3. Complete Response Rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials	4	653	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.98, 1.17]
2 Type of Chemotherapy	4	653	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.98, 1.17]
2.1 CVPP	2	314	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.88, 1.74]
2.2 ABVD	2	339	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.09]
3 ITT-analysis	4	653	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.98, 1.17]
3.1 ITT-analysis	1	138	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.92, 1.09]
3.2 no ITT-analysis	3	515	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.99, 1.24]
4 Number of evaluable patients	4	653	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.98, 1.17]
4.1 < 10% not evaluated	3	616	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]
4.2 ≥ 10% not evaluated	1	37	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.06, 2.27]

Comparison 4. Overall Response Rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All Trials	3	616	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.04]

Analysis 1.1. Comparison 1 Overall Survival, Outcome 1 All trials.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 1 All trials

Study or subgroup	CMT N	CT-alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
CALGB 7751	19	18	-0.47 (0.9)		5.4 %	0.63 [0.11, 3.65]
EORTC-GELA H9-F	448	130	-1.2925 (0.9426)		4.9 %	0.27 [0.04, 1.74]
GATLA 9-H-77	135	142	-0.3484 (0.3651)		31.0 %	0.71 [0.35, 1.44]
Mexico B2H031	102	99	-1.225 (0.2852)		48.9 %	0.29 [0.17, 0.51]
MSKCC trial #90-44	76	76	-1.1671 (0.6667)		9.7 %	0.31 [0.08, 1.15]
Total (95% CI)					**100.0 %**	**0.40 [0.27, 0.61]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.14$, df = 4 (P = 0.39); $I^2 = 3\%$

Test for overall effect: Z = 4.33 (P = 0.000015)

Analysis 1.2. Comparison 1 Overall Survival, Outcome 2 Excluding the trial with highest weight (Aviles).

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 2 Excluding the trial with highest weight (Aviles)

Study or subgroup	CMT N	CT-alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
CALGB 7751	19	18	-0.31 (0.68)		16.6 %	0.73 [0.19, 2.78]
EORTC-GELA H9-F	448	130	-1.2925 (0.9426)		8.6 %	0.27 [0.04, 1.74]
GATLA 9-H-77	135	142	-0.3484 (0.3651)		57.5 %	0.71 [0.35, 1.44]
MSKCC trial #90-44	76	76	-1.1671 (0.6667)		17.3 %	0.31 [0.08, 1.15]
Total (95% CI)					**100.0 %**	**0.57 [0.33, 0.98]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 3 (P = 0.59); $I^2 = 0.0\%$

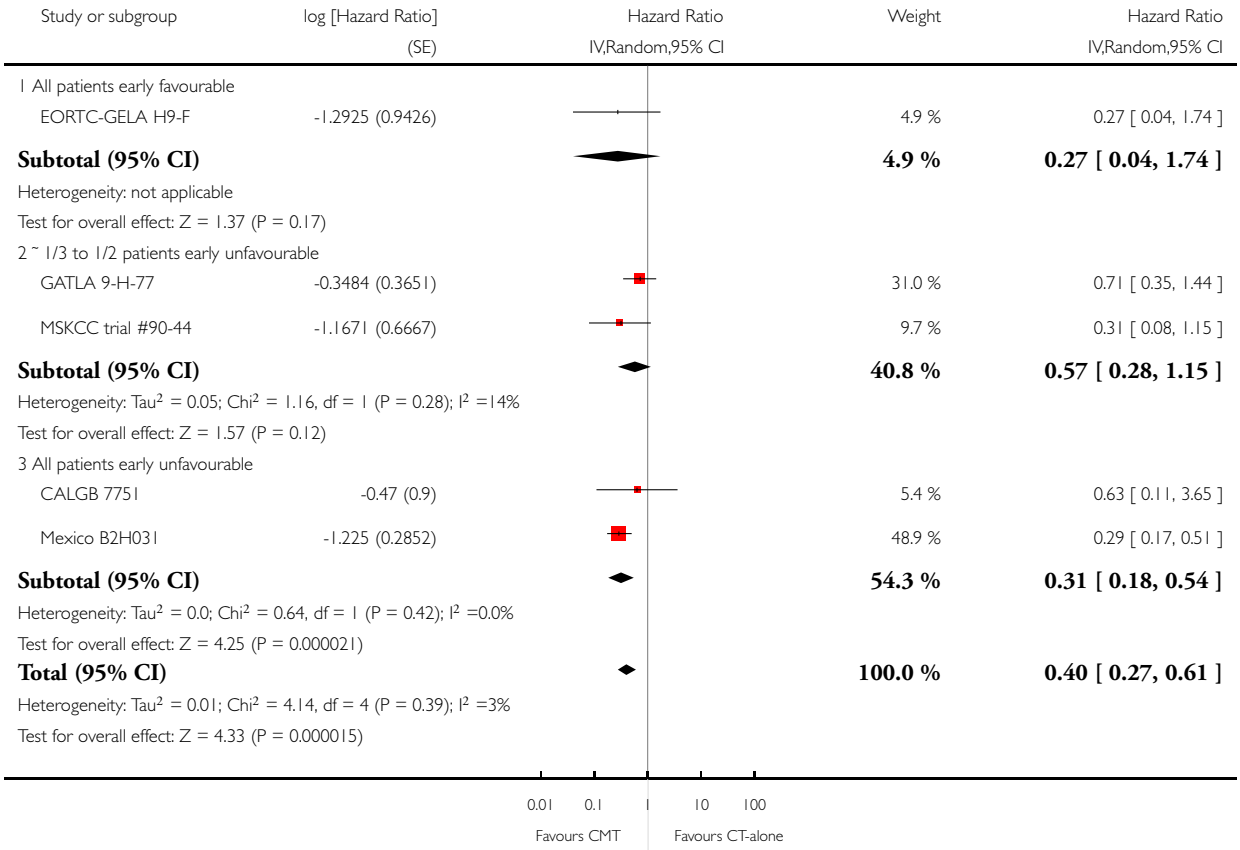
Test for overall effect: Z = 2.04 (P = 0.041)

Analysis 1.3. Comparison 1 Overall Survival, Outcome 3 Proportion of patients early favourable.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 3 Proportion of patients early favourable

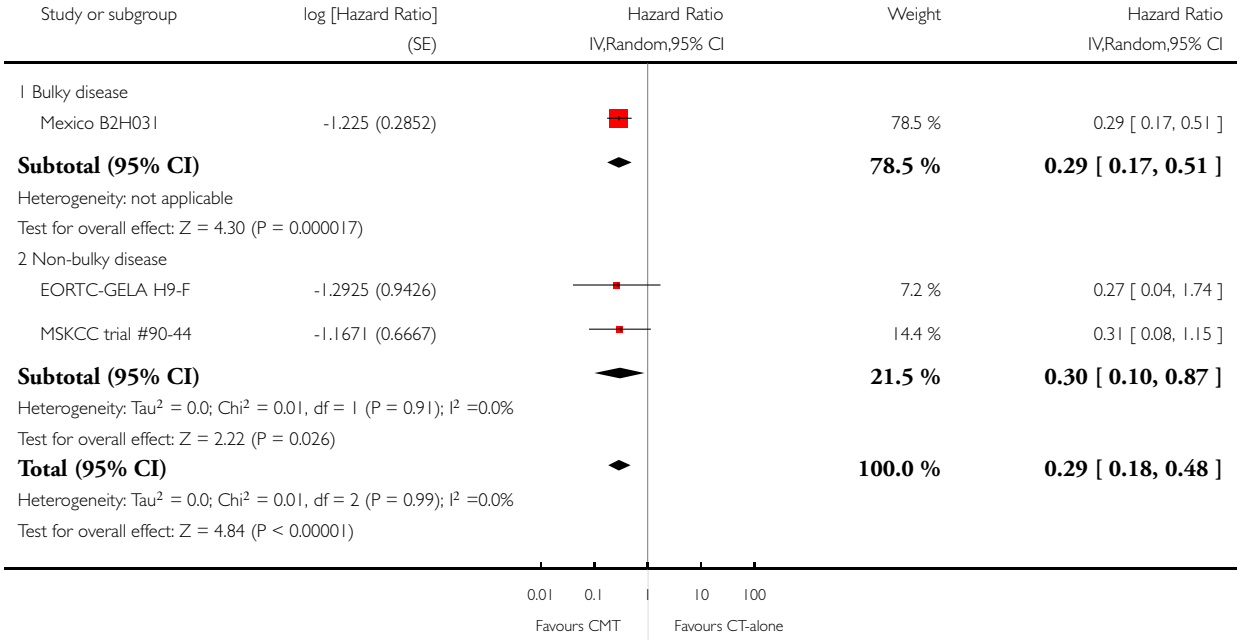


Analysis 1.4. Comparison 1 Overall Survival, Outcome 4 Bulky vs non-bulky.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 4 Bulky vs non-bulky

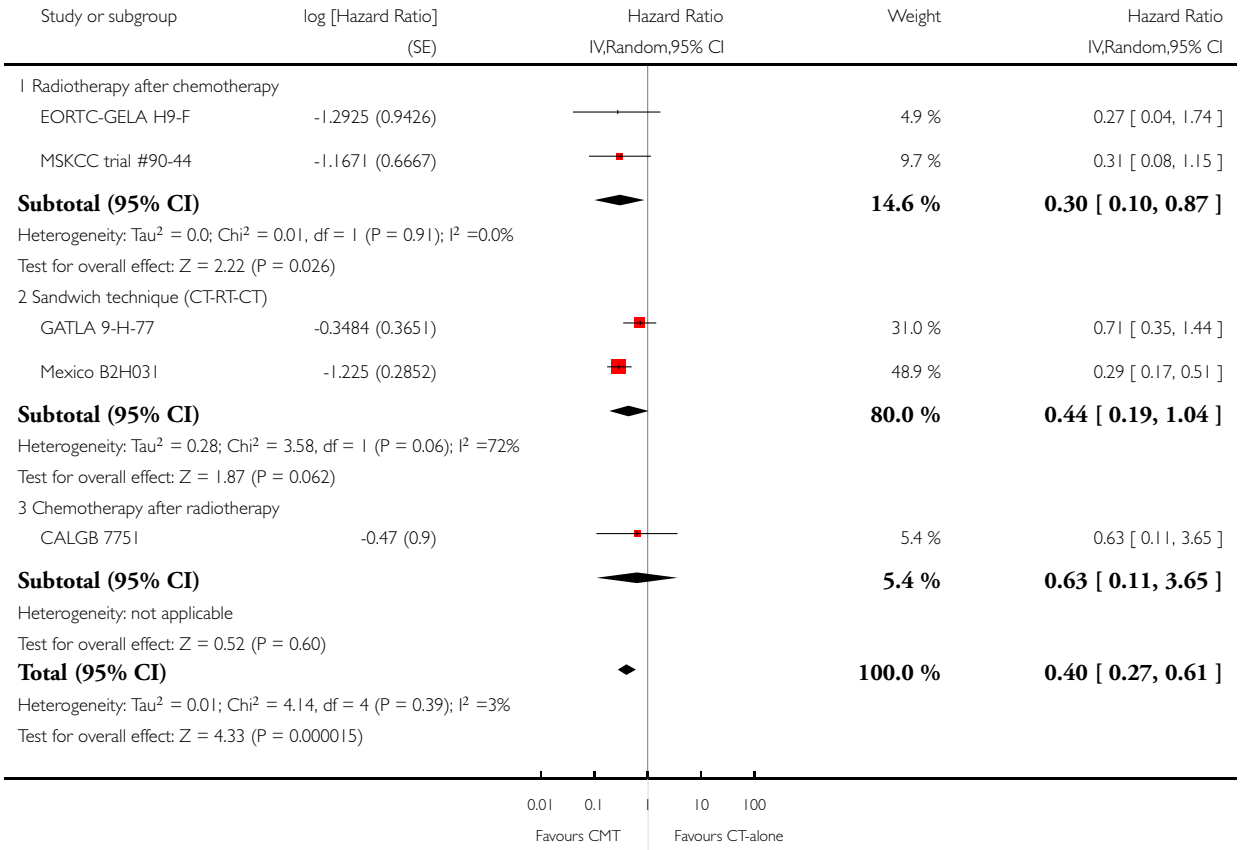


Analysis 1.5. Comparison 1 Overall Survival, Outcome 5 Timing of radiotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 5 Timing of radiotherapy

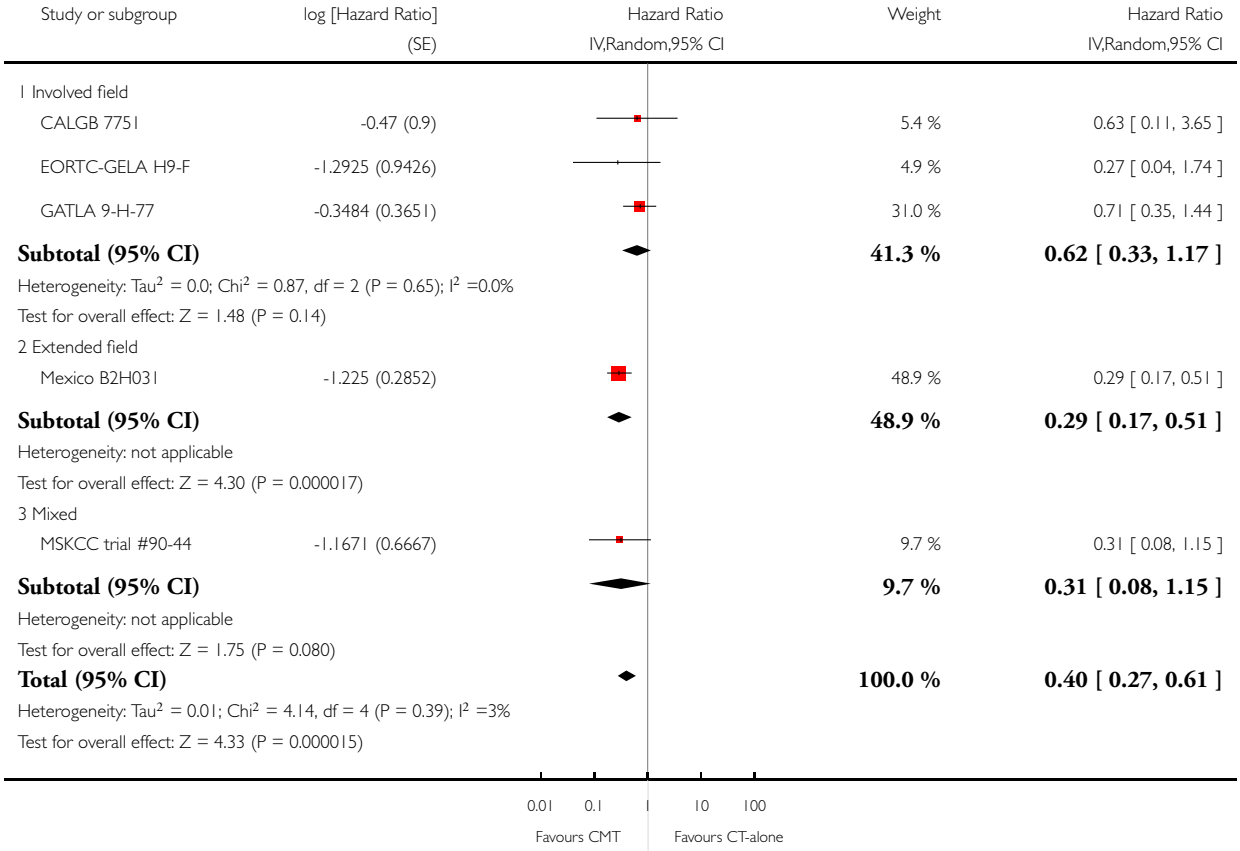


Analysis 1.6. Comparison 1 Overall Survival, Outcome 6 Type of radiotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 6 Type of radiotherapy

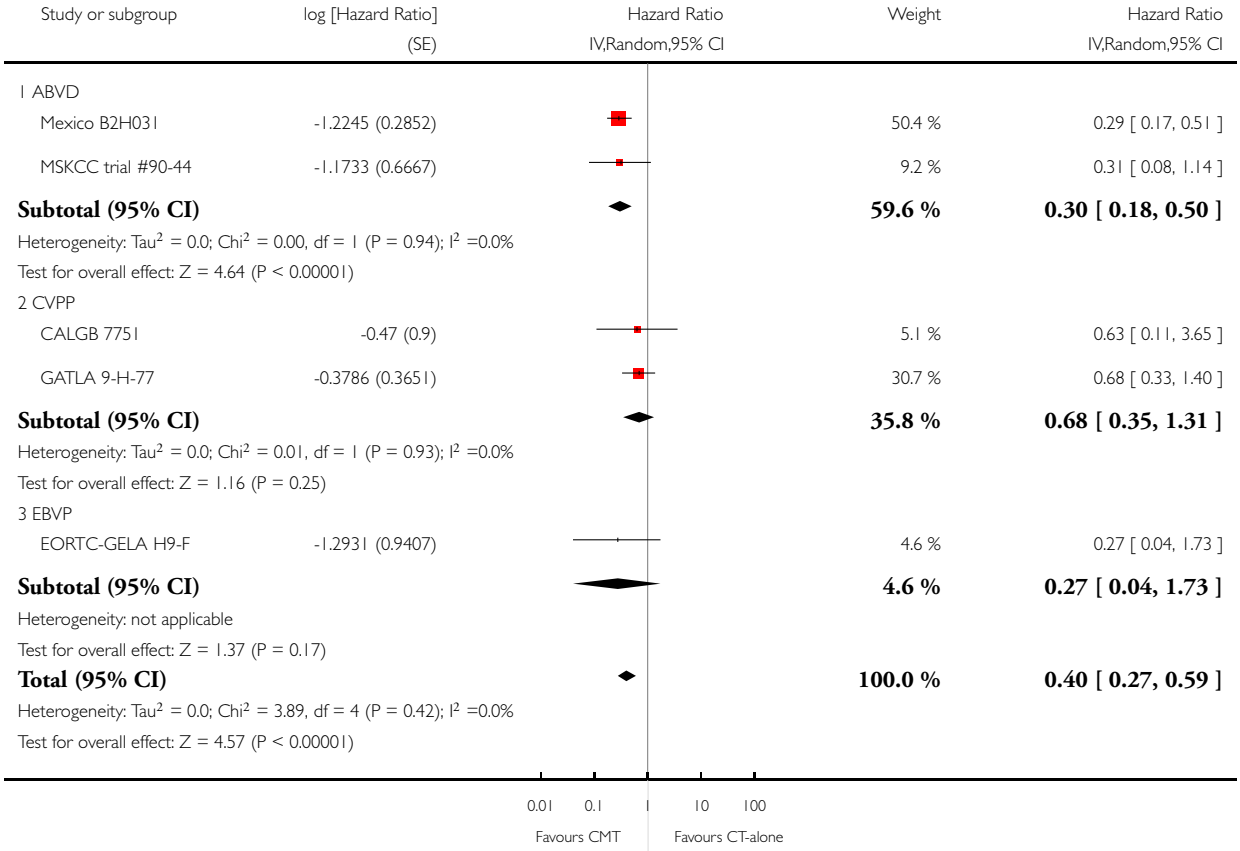


Analysis 1.7. Comparison 1 Overall Survival, Outcome 7 Type of chemotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 7 Type of chemotherapy

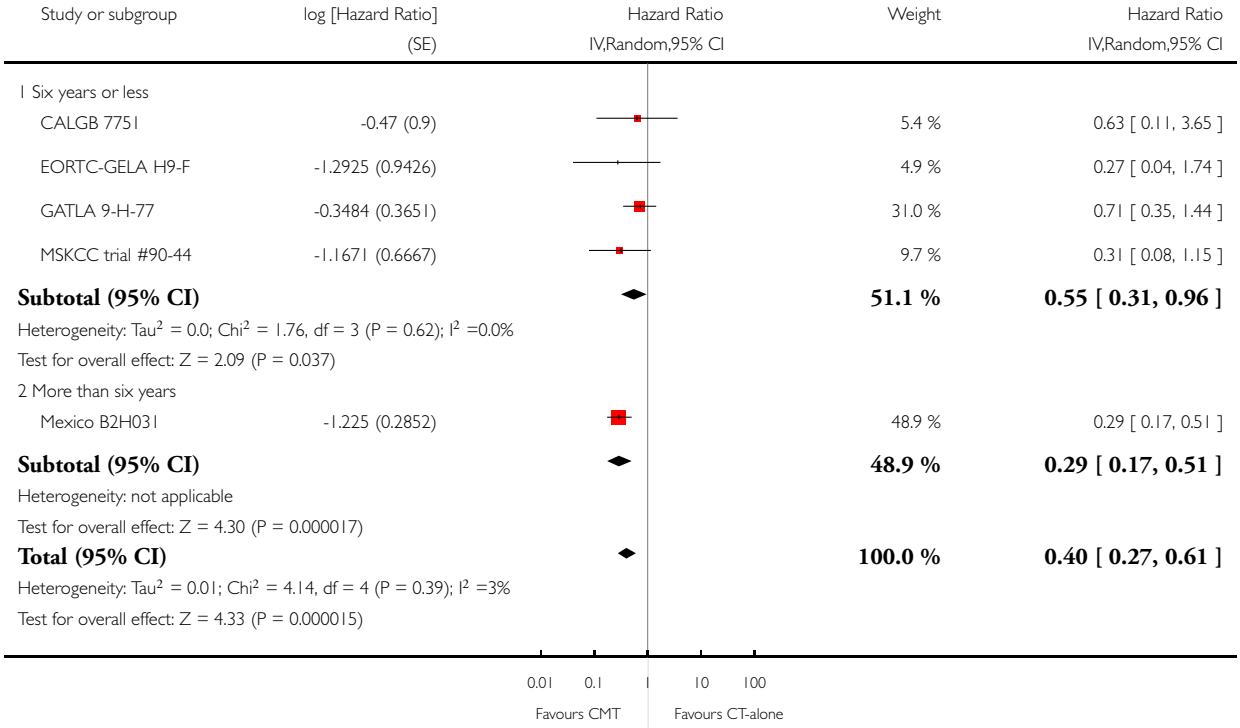


Analysis 1.8. Comparison 1 Overall Survival, Outcome 8 Length of follow-up.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 8 Length of follow-up

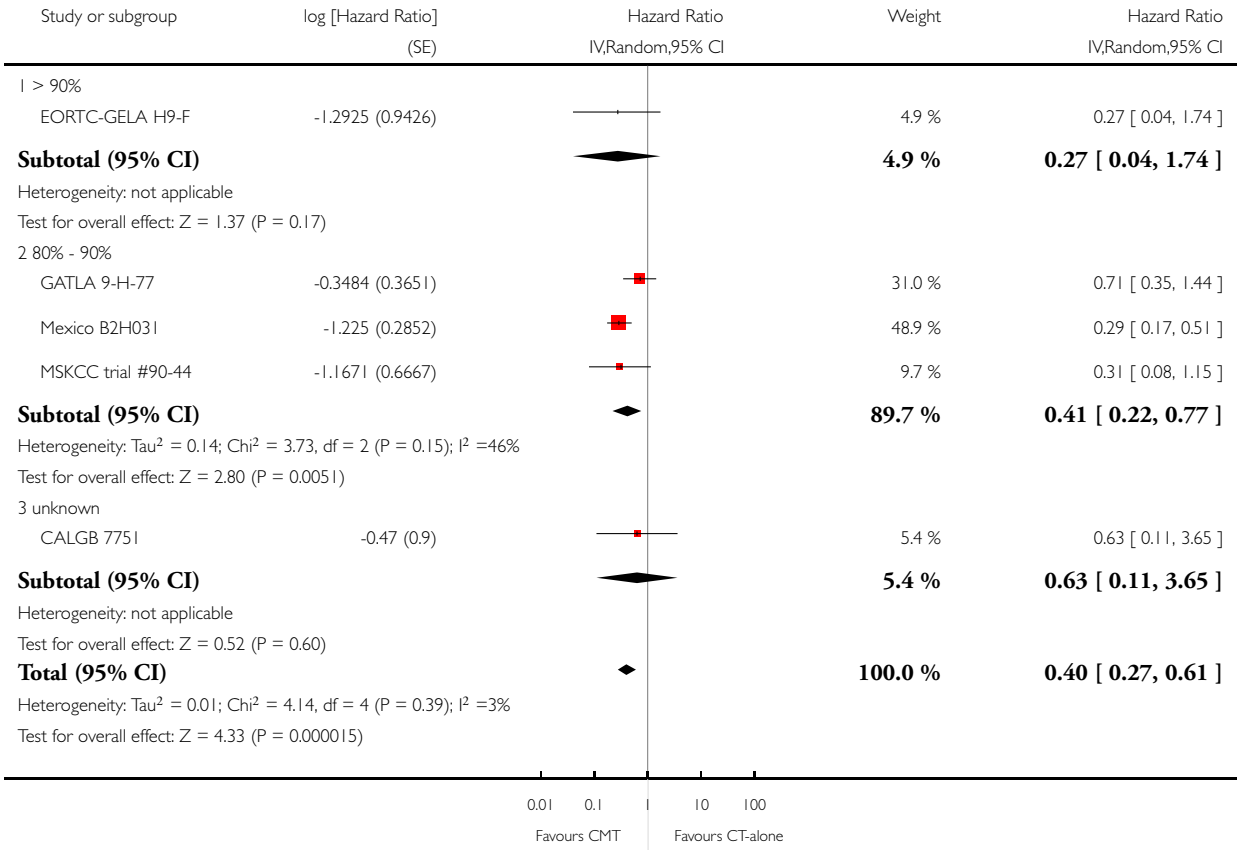


Analysis 1.9. Comparison 1 Overall Survival, Outcome 9 4 year survival in the CT group.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 9 4 year survival in the CT group



Analysis 1.10. Comparison 1 Overall Survival, Outcome 10 Allocation concealment.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 10 Allocation concealment

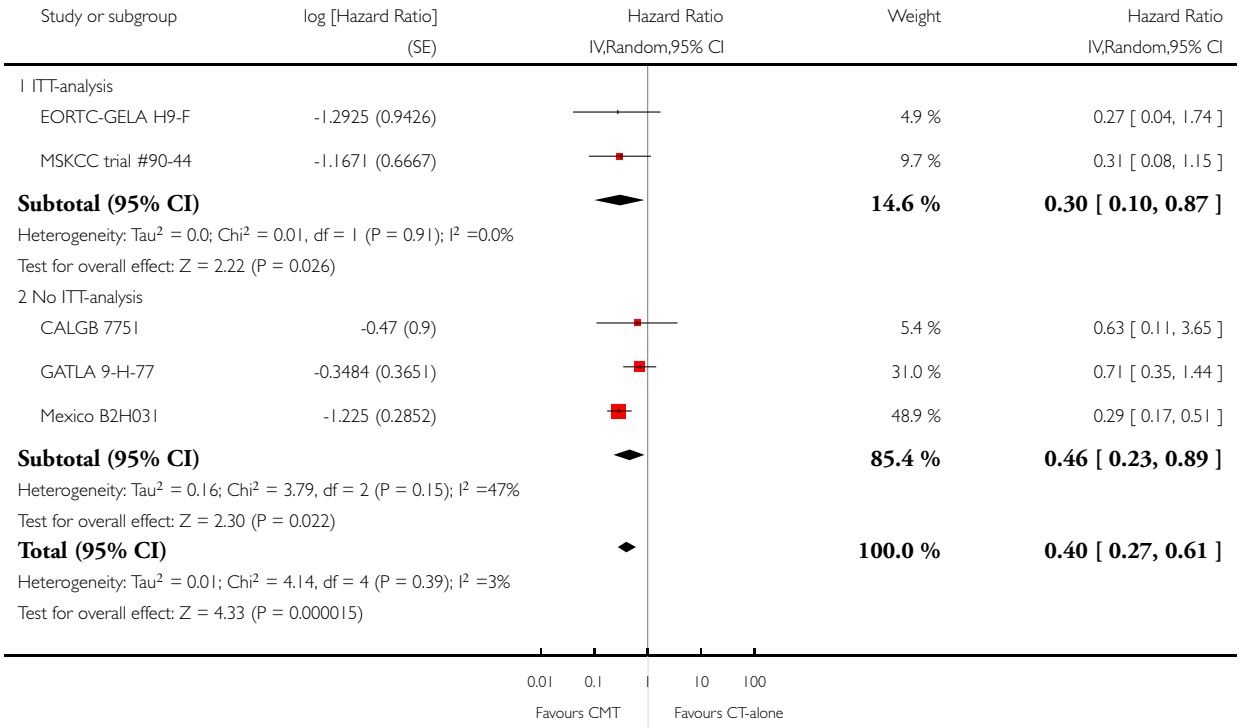
Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Allocation concealment unclear				
CALGB 7751	-0.47 (0.9)		5.4 %	0.63 [0.11, 3.65]
GATLA 9-H-77	-0.3484 (0.3651)		31.0 %	0.71 [0.35, 1.44]
Mexico B2H031	-1.225 (0.2852)		48.9 %	0.29 [0.17, 0.51]
Subtotal (95% CI)			**85.4 %**	**0.46 [0.23, 0.89]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 3.79$, df = 2 (P = 0.15); $I^2 = 47\%$				
Test for overall effect: Z = 2.30 (P = 0.022)				
2 Allocation concealment adequate				
EORTC-GELA H9-F	-1.2925 (0.9426)		4.9 %	0.27 [0.04, 1.74]
MSKCC trial #90-44	-1.1671 (0.6667)		9.7 %	0.31 [0.08, 1.15]
Subtotal (95% CI)			**14.6 %**	**0.30 [0.10, 0.87]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.22 (P = 0.026)				
Total (95% CI)			**100.0 %**	**0.40 [0.27, 0.61]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.14$, df = 4 (P = 0.39); $I^2 = 3\%$				
Test for overall effect: Z = 4.33 (P = 0.000015)				

Analysis 1.11. Comparison 1 Overall Survival, Outcome 11 ITT-analysis.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 1 Overall Survival

Outcome: 11 ITT-analysis



Analysis 2.1. Comparison 2 Progression-Free Survival, Outcome 1 All trials.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 1 All trials

Study or subgroup	CMT N	CT-alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
EORTC-GELA H9-F	448	130	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
GATLA 9-H-77	135	142	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
Mexico B2H031	102	99	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]
MSKCC trial #90-44	76	76	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Total (95% CI)					**100.0 %**	**0.41 [0.25, 0.66]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 9.47$, df = 3 (P = 0.02); $I^2 = 68\%$

Test for overall effect: Z = 3.64 (P = 0.00028)

Analysis 2.2. Comparison 2 Progression-Free Survival, Outcome 2 Type of chemotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 2 Type of chemotherapy

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 ABVD				
Mexico B2H031	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]
MSKCC trial #90-44	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Subtotal (95% CI)			**44.2 %**	**0.47 [0.16, 1.35]**
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 4.78$, df = 1 (P = 0.03); $I^2 = 79\%$				
Test for overall effect: Z = 1.40 (P = 0.16)				
2 CVPP				
GATLA 9-H-77	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
Subtotal (95% CI)			**28.2 %**	**0.55 [0.35, 0.86]**

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Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 2.61 (P = 0.0091)				
3 EBVP				
EORTC-GELA H9-F	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
Subtotal (95% CI)			**27.6 %**	**0.27 [0.17, 0.43]**
Heterogeneity: not applicable				
Test for overall effect: Z = 5.50 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**0.41 [0.25, 0.66]**
Heterogeneity: Tau² = 0.16; Chi² = 9.47, df = 3 (P = 0.02); I² =68%				
Test for overall effect: Z = 3.64 (P = 0.00028)				

Analysis 2.3. Comparison 2 Progression-Free Survival, Outcome 3 Proportion of patients early favourable.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 3 Proportion of patients early favourable

Study or subgroup	CMT N	CT-alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 All patients early favourable						
EORTC-GELA H9-F	0	0	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
Subtotal (95% CI)					**27.6 %**	**0.27 [0.17, 0.43]**
Heterogeneity: not applicable						
Test for overall effect: Z = 5.50 (P < 0.00001)						
2 mixed patient population (~1/3 to 1/2)						
GATLA 9-H-77	135	142	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
MSKCC trial #90-44	76	76	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Subtotal (95% CI)					**46.0 %**	**0.61 [0.41, 0.90]**
Heterogeneity: Tau² = 0.0; Chi² = 0.84, df = 1 (P = 0.36); I² =0.0%						
Test for overall effect: Z = 2.47 (P = 0.013)						
3 All patients early unfavourable						
Mexico B2H031	0	0	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]

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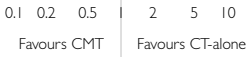
Study or subgroup	CMT N	CT-alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Subtotal (95% CI)					**26.4 %**	**0.29 [0.17, 0.48]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.77 (P < 0.00001)						
Total (95% CI)					**100.0 %**	**0.41 [0.25, 0.66]**
Heterogeneity: Tau² = 0.16; Chi² = 9.47, df = 3 (P = 0.02); I² =68%						
Test for overall effect: Z = 3.64 (P = 0.00028)						



Analysis 2.4. Comparison 2 Progression-Free Survival, Outcome 4 Definition of progression.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 4 Definition of progression

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 In CR patients				
EORTC-GELA H9-F	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
Subtotal (95% CI)			**27.6 %**	**0.27 [0.17, 0.43]**
Heterogeneity: not applicable				
Test for overall effect: Z = 5.50 (P < 0.00001)				
2 Progress in all patients				
GATLA 9-H-77	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
MSKCC trial #90-44	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Subtotal (95% CI)			**46.0 %**	**0.61 [0.41, 0.90]**
Heterogeneity: Tau² = 0.0; Chi² = 0.84, df = 1 (P = 0.36); I² =0.0%				
Test for overall effect: Z = 2.47 (P = 0.013)				
3 Unclear				
Mexico B2H031	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]
Subtotal (95% CI)			**26.4 %**	**0.29 [0.17, 0.48]**
Heterogeneity: not applicable				
Test for overall effect: Z = 4.77 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**0.41 [0.25, 0.66]**
Heterogeneity: Tau² = 0.16; Chi² = 9.47, df = 3 (P = 0.02); I² =68%				
Test for overall effect: Z = 3.64 (P = 0.00028)				

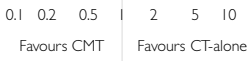
Analysis 2.5. Comparison 2 Progression-Free Survival, Outcome 5 Timing of radiotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 5 Timing of radiotherapy

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Radiotherapy after chemotherapy				
EORTC-GELA H9-F	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
MSKCC trial #90-44	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Subtotal (95% CI)			**45.4 %**	**0.45 [0.15, 1.41]**
Heterogeneity: Tau^2 = 0.56; Chi^2 = 5.75, df = 1 (P = 0.02); I^2 =83%				
Test for overall effect: Z = 1.37 (P = 0.17)				
2 Sandwich technique (CT-RT-CT)				
GATLA 9-H-77	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
Mexico B2H031	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]
Subtotal (95% CI)			**54.6 %**	**0.40 [0.22, 0.75]**
Heterogeneity: Tau^2 = 0.14; Chi^2 = 3.40, df = 1 (P = 0.07); I^2 =71%				
Test for overall effect: Z = 2.84 (P = 0.0045)				
Total (95% CI)			**100.0 %**	**0.41 [0.25, 0.66]**
Heterogeneity: Tau^2 = 0.16; Chi^2 = 9.47, df = 3 (P = 0.02); I^2 =68%				
Test for overall effect: Z = 3.64 (P = 0.00028)				

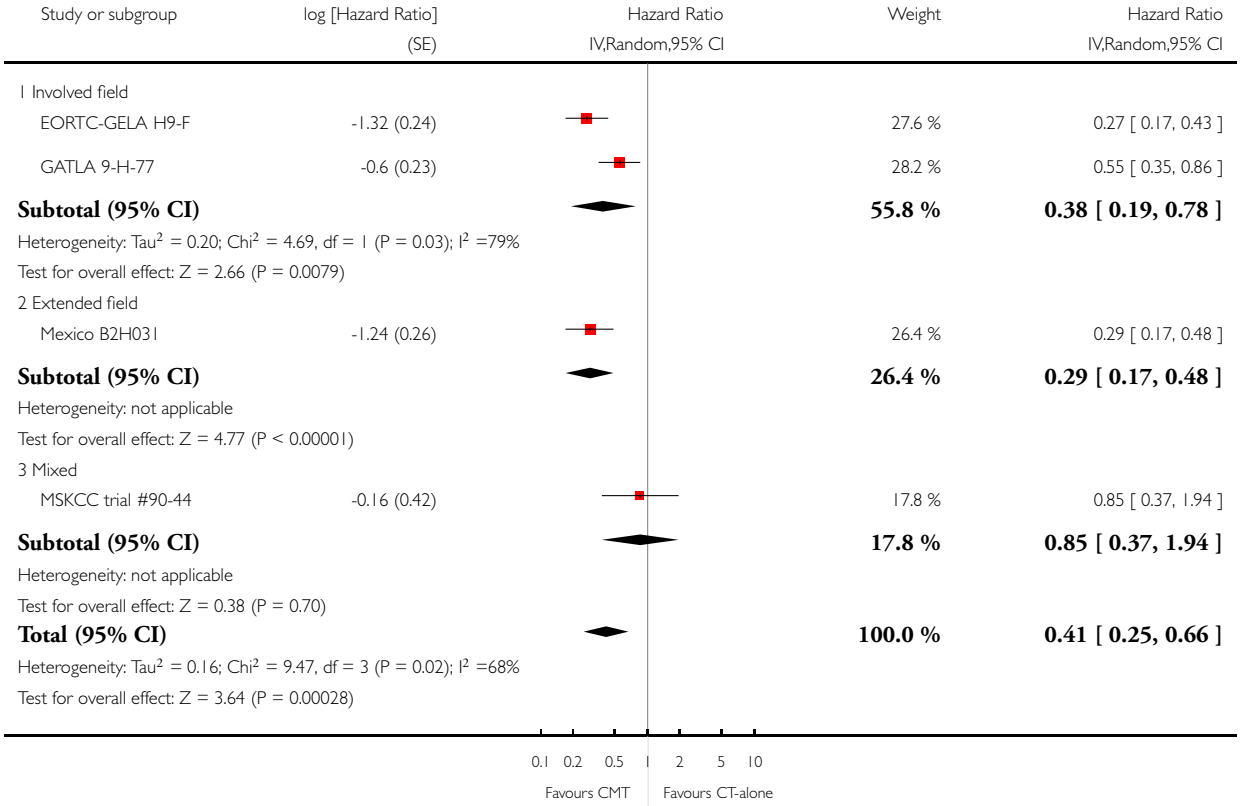


Analysis 2.6. Comparison 2 Progression-Free Survival, Outcome 6 Type of radiotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 6 Type of radiotherapy

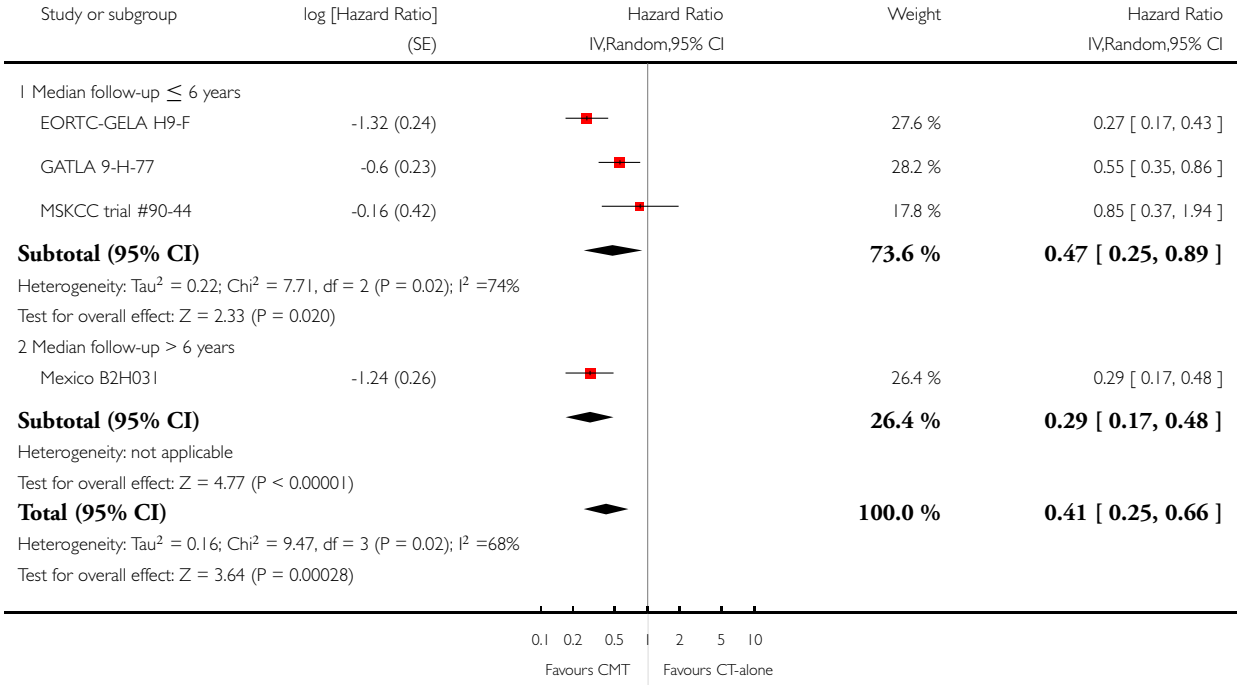


Analysis 2.7. Comparison 2 Progression-Free Survival, Outcome 7 Length of follow-up.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 7 Length of follow-up



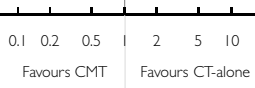
Analysis 2.8. Comparison 2 Progression-Free Survival, Outcome 8 Allocation concealment.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 8 Allocation concealment

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Allocation concealment unclear				
GATLA 9-H-77	-0.6 (0.23)		28.2 %	0.55 [0.35, 0.86]
Mexico B2H031	-1.24 (0.26)		26.4 %	0.29 [0.17, 0.48]
Subtotal (95% CI)			**54.6 %**	**0.40 [0.22, 0.75]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 3.40$, df = 1 (P = 0.07); $I^2 = 71\%$				
Test for overall effect: Z = 2.84 (P = 0.0045)				
2 Allocation concealment adequate				
EORTC-GELA H9-F	-1.32 (0.24)		27.6 %	0.27 [0.17, 0.43]
MSKCC trial #90-44	-0.16 (0.42)		17.8 %	0.85 [0.37, 1.94]
Subtotal (95% CI)			**45.4 %**	**0.45 [0.15, 1.41]**
Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 5.75$, df = 1 (P = 0.02); $I^2 = 83\%$				
Test for overall effect: Z = 1.37 (P = 0.17)				
Total (95% CI)			**100.0 %**	**0.41 [0.25, 0.66]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 9.47$, df = 3 (P = 0.02); $I^2 = 68\%$				
Test for overall effect: Z = 3.64 (P = 0.00028)				

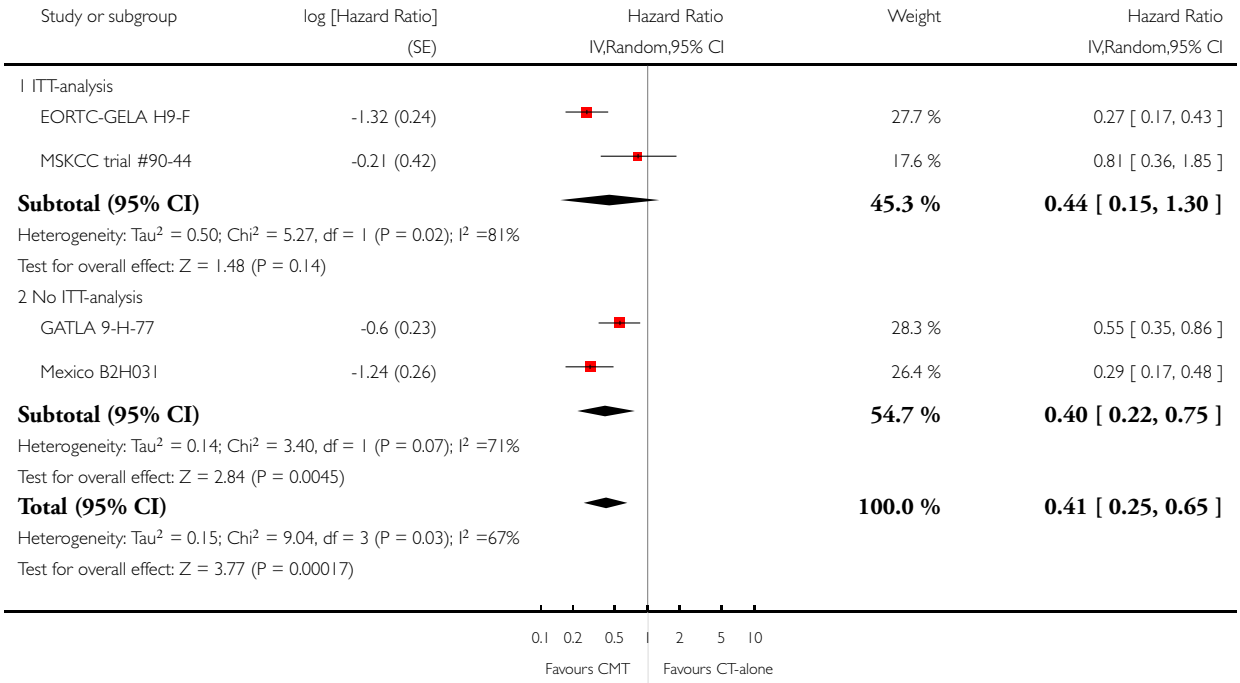


Analysis 2.9. Comparison 2 Progression-Free Survival, Outcome 9 ITT-Analysis.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 2 Progression-Free Survival

Outcome: 9 ITT-Analysis



Analysis 3.1. Comparison 3 Complete Response Rate, Outcome 1 All trials.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 3 Complete Response Rate

Outcome: 1 All trials

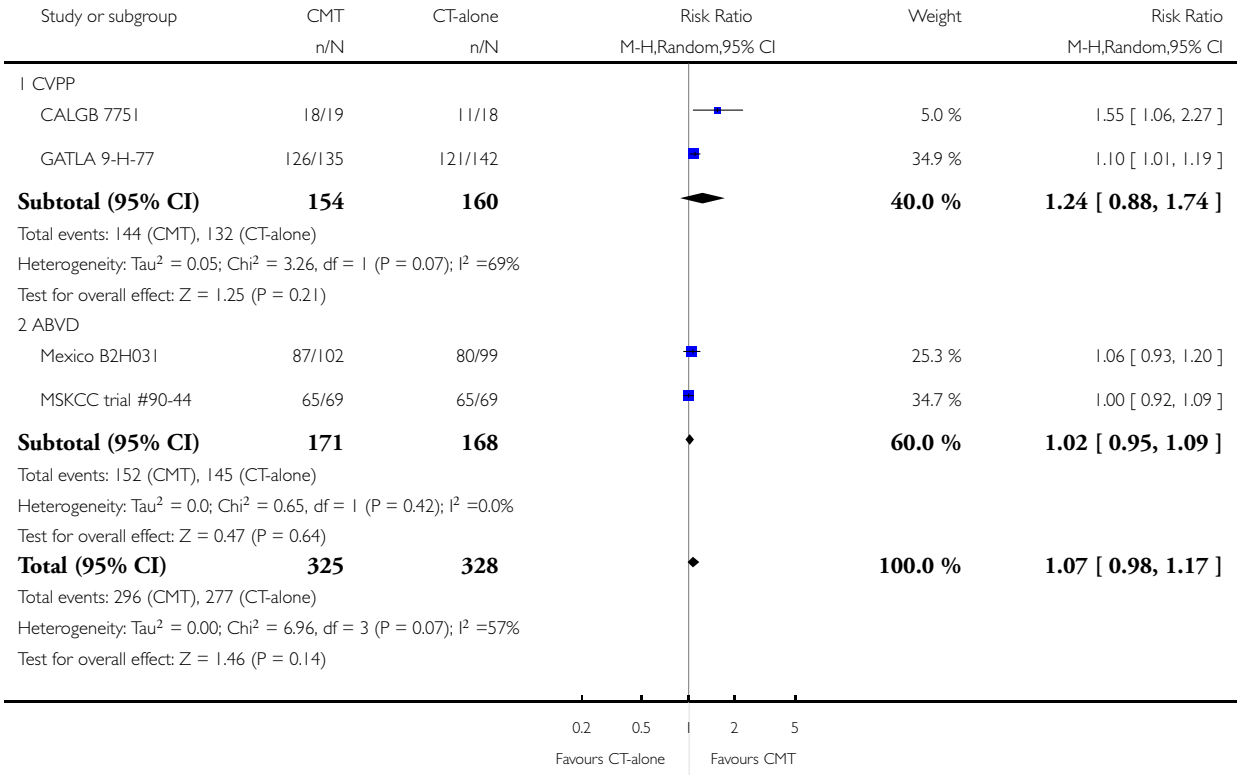
Study or subgroup	CMT n/N	CT-alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CALGB 7751	18/19	11/18		5.0 %	1.55 [1.06, 2.27]
GATLA 9-H-77	126/135	121/142		34.9 %	1.10 [1.01, 1.19]
Mexico B2H031	87/102	80/99		25.3 %	1.06 [0.93, 1.20]
MSKCC trial #90-44	65/69	65/69		34.7 %	1.00 [0.92, 1.09]
Total (95% CI)	**325**	**328**		**100.0 %**	**1.07 [0.98, 1.17]**
Total events: 296 (CMT), 277 (CT-alone)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.96$, df = 3 (P = 0.07); $I^2 = 57\%$					
Test for overall effect: Z = 1.46 (P = 0.14)					

Analysis 3.2. Comparison 3 Complete Response Rate, Outcome 2 Type of Chemotherapy.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 3 Complete Response Rate

Outcome: 2 Type of Chemotherapy



Analysis 3.3. Comparison 3 Complete Response Rate, Outcome 3 ITT-analysis.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 3 Complete Response Rate

Outcome: 3 ITT-analysis

Study or subgroup	CMT n/N	CT-alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 ITT-analysis					
MSKCC trial #90-44	65/69	65/69		34.7 %	1.00 [0.92, 1.09]
Subtotal (95% CI)	**69**	**69**		**34.7 %**	**1.00 [0.92, 1.09]**
Total events: 65 (CMT), 65 (CT-alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 no ITT-analysis					
CALGB 7751	18/19	11/18		5.0 %	1.55 [1.06, 2.27]
GATLA 9-H-77	126/135	121/142		34.9 %	1.10 [1.01, 1.19]
Mexico B2H031	87/102	80/99		25.3 %	1.06 [0.93, 1.20]
Subtotal (95% CI)	**256**	**259**		**65.3 %**	**1.11 [0.99, 1.24]**
Total events: 231 (CMT), 212 (CT-alone)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.54, df = 2 (P = 0.17); I^2 =44%					
Test for overall effect: Z = 1.83 (P = 0.067)					
Total (95% CI)	**325**	**328**		**100.0 %**	**1.07 [0.98, 1.17]**
Total events: 296 (CMT), 277 (CT-alone)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.96, df = 3 (P = 0.07); I^2 =57%					
Test for overall effect: Z = 1.46 (P = 0.14)					

Analysis 3.4. Comparison 3 Complete Response Rate, Outcome 4 Number of evaluable patients.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 3 Complete Response Rate

Outcome: 4 Number of evaluable patients

Study or subgroup	CMT n/N	CT-alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 < 10% not evaluated					
GATLA 9-H-77	126/135	121/142		34.9 %	1.10 [1.01, 1.19]
Mexico B2H031	87/102	80/99		25.3 %	1.06 [0.93, 1.20]
MSKCC trial #90-44	65/69	65/69		34.7 %	1.00 [0.92, 1.09]
Subtotal (95% CI)	**306**	**310**		**95.0 %**	**1.05 [0.99, 1.11]**
Total events: 278 (CMT), 266 (CT-alone)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.51$, df = 2 (P = 0.28); $I^2 = 20\%$					
Test for overall effect: Z = 1.55 (P = 0.12)					
2 ≥ 10% not evaluated					
CALGB 7751	18/19	11/18		5.0 %	1.55 [1.06, 2.27]
Subtotal (95% CI)	**19**	**18**		**5.0 %**	**1.55 [1.06, 2.27]**
Total events: 18 (CMT), 11 (CT-alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
Total (95% CI)	**325**	**328**		**100.0 %**	**1.07 [0.98, 1.17]**
Total events: 296 (CMT), 277 (CT-alone)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.96$, df = 3 (P = 0.07); $I^2 = 57\%$					
Test for overall effect: Z = 1.46 (P = 0.14)					

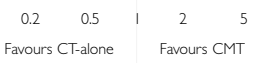
Analysis 4.1. Comparison 4 Overall Response Rate, Outcome 1 All Trials.

Review: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma

Comparison: 4 Overall Response Rate

Outcome: 1 All Trials

Study or subgroup	CMT n/N	CT-alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
GATLA 9-H-77	128/135	135/142		59.1 %	1.00 [0.94, 1.05]
Mexico B2H031	87/102	81/99		11.6 %	1.04 [0.92, 1.18]
MSKCC trial #90-44	65/69	66/69		29.3 %	0.98 [0.91, 1.06]
Total (95% CI)	**306**	**310**		**100.0 %**	**1.00 [0.96, 1.04]**
Total events: 280 (CMT), 282 (CT-alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.77, df = 2 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					



APPENDICES

Appendix 1. CENTRAL search strategy

The following search strategy was used to search CENTRAL:
1. (favourable or unfavourable)
2. ((earl* or low* or limit*) near/3 (stag* or grad*))
3. (intermediate*)
4. (bulky)
5. (#1 OR #2 OR #3 OR #4)
6. MeSH descriptor LYMPHOMA, this term only
7. MeSH descriptor HODGKIN DISEASE explode all trees
8. (hodgkin* near/2 (disease* or granulom*))
9. (reticulolymphosarcom* or germinoblastom*)
10. (malignan* near/2 (lymphogranulom* or granulom*))
11. (#6 OR #7 OR #8 OR #9 OR #10)
12. MeSH descriptor ANTINEOPLASTIC AGENTS explode all trees
13. MeSH descriptor REMISSION INDUCTION explode all trees
14. MeSH descriptor ANTINEOPLASTIC PROTOCOLS explode all trees
15. ((consolidat* or induct* or maintenance or conditioning*) and (therap* or treat* or regimen* or patient*))
16. ((therap* or induc*) near/3 remission*)
17. (chemotherap* or chemo-therap*)
18. (Antineoplast* or anti-neoplast*)
19. ((cytosta* or cytotox*) near/2 (therap* or treat* or regimen*))
20. MeSH descriptor RADIOTHERAPY explode all trees
21. (radiotherap* or radio-therap*)

22. (chemoradiotherap* or chemo-radio-therap*)
23. MeSH descriptor COMBINED MODALITY THERAPY explode all trees
24. ((multimodal* or multi-modal*) near/3 (treat* or therap*))
25. MeSH descriptor LYMPHATIC IRRADIATION explode all trees
26. (combi* near/3 modalit*)
27. (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
28. (#5 AND #11 AND #27)
The search strategy was modified the following updated search strategy was also used and will be used for further updates:

#1	(favourable or favorable or unfavourable or unfavorable)
#2	(I-II or I-III)
#3	(earl* near/3 grad*) or (earl* near/3 stag*) or (low* near/3 stag*) or (low* near/3 grad*)
#4	(limit* near/3 stag*) or (limit* near/3 grad*)
#5	(intermediate*)
#6	(bulky)
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8	MeSH descriptor Lymphoma explode all trees
#9	MeSH descriptor Hodgkin Disease explode all trees
#10	(Germinoblastom* or Reticulolymphosarcom*)
#11	(hodgkin*)
#12	(malignan* near/2 lymphogranulom*) or (malignan* near/2 granulom*)
#13	(#8 OR #9 OR #10 OR #11 OR #12)
#14	MeSH descriptor Antineoplastic Agents explode all trees
#15	MeSH descriptor Remission Induction explode all trees
#16	MeSH descriptor Antineoplastic Protocols explode all trees
#17	(consolidat* and therap*) or (consolidat* and treat*) or (consolidat* and regimen*) or (consolidat* and patient*)
#18	(induct* and therap*) or (induct* and treat*) or (induct* and regimen*) or (induct* and patient*)
#19	(maintenance* and therap*) or (maintenance* and treat*) or (maintenance* and regimen*) or (maintenance* and patient*)
#20	(conditioning* and therap*) or (conditioning* and treat*) or (conditioning* and regimen*) or (conditioning* and patient*)

(*Continued*)

#21	(therap* near/3 remission*) or (induc* near/3 remission*)
#22	(chemotherap* or chemo-therap*)
#23	(Antineoplast* or Anti-neoplast*)
#24	(cytosta* near/2 therap*) or (cytosta* near/2 treat*) or (cytosta* near/2 regimen*)
#25	(cytotox* near/2 therap*) or (cytotox* near/2 treat*) or (cytotox* near/2 regimen*)
#26	(#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27	MeSH descriptor Radiotherapy explode all trees
#28	(radiotherap* or radio-therap*)
#29	MeSH descriptor Lymphatic Irradiation explode all trees
#30	(#27 OR #28 OR #29)
#31	(#26 AND #30)
#32	(chemoradiotherap*) or (chemo-radiotherap*)
#33	MeSH descriptor Combined Modality Therapy explode all trees
#34	(multimodal* near/3 therap*) or (multimodal* near/3 treat*) or (multi-modal* near/3 therap*) or (multi-modal* near/3 treat*)
#35	(combi* near/3 modalit*)
#36	(#32 OR #33 OR #34 OR #35)
#37	(#31 OR #36)
#38	(#13 AND #37)
#39	(#7 AND #13 AND #37)
#40	(#39), from 2008 to 2009

Appendix 2. MEDLINE search strategy

The following search strategy was used to search MEDLINE:
1. (favourable or unfavourable).tw,kf,ot.
2. ((earl$ or low$ or limit$) adj3 (stag$ or grad$)).tw,kf,ot.
3. intermediate$.tw,kf,ot.
4. bulky.tw,kf,ot.
5. or/1-4
6. *LYMPHOMA/
7. exp HODGKIN DISEASE/
8. Germinoblastom$.tw,kf,ot.
9. Reticulolymphosarcom$.tw,kf,ot.
10. Hodgkin$.tw,kf,ot.
11. (malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
12. or/6-11
13. exp ANTINEOPLASTIC AGENTS/
14. REMISSION INDUCTION/
15. exp ANTINEOPLASTIC PROTOCOLS/
16. ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw,kf,ot.
17. ((therap$ or induc$) adj3 remission$).tw,kf,ot.
18. (chemotherap$ or chemo-therap$).tw,kf,ot.
19. (Antineoplast$ or anti-neoplast$).tw,kf,ot.
20. ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).tw,kf,ot.
21. exp RADIOTHERAPY/
22. (radiotherap$ or radio-therap$).tw,kf,ot.
23. (chemoradiotherap$ or chemo-radio-therap$).tw,kf,ot.
24. exp COMBINED MODALITY THERAPY/
25. ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw,kf,ot.
26. exp LYMPHATIC IRRADIATION/
27. (combi$ adj3 modalit$).tw,kf,ot.
28. or/13-27
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. RANDOMIZED CONTROLLED TRIALS/
32. RANDOM ALLOCATION/
33. DOUBLE BLIND METHOD/
34. SINGLE BLIND METHOD/
35. or/29-34
36. (ANIMALS not HUMANS).sh.
37. 35 not 36
38. clinical trial.pt.
39. exp CLINICAL TRIALS/
40. (clin$ adj25 trial$).ti,ab.
41. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
42. PLACEBOS/
43. placebo$.ti,ab.
44. random$.ti,ab.
45. RESEARCH DESIGN/
46. or/38-45
47. 46 not 36
48. 47 not 37
49. COMPARATIVE STUDY/
50. exp EVALUATION STUDIES/

51. FOLLOW UP STUDIES/
52. PROSPECTIVE STUDIES/
53. (control$ or prospectiv$ or volunteer$).ti,ab.
54. or/49-53
55. 54 not 36
56. 55 not (37 or 48)
57. 37 or 48 or 56
58. 5 and 12 and 28 and 57

The search strategy was updated during the review process and the following search strategy was used in addition the the above one. For updates the following search strategy will be used:

1	(favo?rable or unfavo?rable).tw,kf,ot.
2	(I-II or I-III).tw,kf,ot.
3	((earl$ or low$ or limit$) adj3 (stag$ or grad$)).tw,kf,ot.
4	intermediate$.tw,kf,ot.
5	bulky.tw,kf,ot.
6	or/1-4
7	*Lymphoma/
8	exp Hodgkin Disease/
9	Germinoblastom$.tw,kf,ot.
10	Reticulolymphosarcom$.tw,kf,ot.
11	Hodgkin$.tw,kf,ot.
12	(malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
13	or/7-12
14	exp Antineoplastic Agents/
15	Remission Induction/
16	exp antineoplastic protocols/
17	((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw,kf,ot.
18	((therap$ or induc$) adj3 remission$).tw,kf,ot.
19	(chemotherap$ or chemo-therap$).tw,kf,ot.

(*Continued*)

20	(Antineoplast$ or anti-neoplast$).tw,kf,ot.
21	((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).tw,kf,ot.
22	or/14-21
23	exp Radiotherapy/
24	(radiotherap$ or radio-therap$).tw,kf,ot.
25	exp Lymphatic Irradiation/
26	or/23-25
27	22 and 26
28	(chemoradiotherap$ or chemo-radio-therap$).tw,kf,ot.
29	exp Combined Modality Therapy/
30	((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw,kf,ot.
31	(combi$ adj3 modalit$).tw,kf,ot.
32	or/28-31
33	27 or 32
34	13 and 33
35	13 and 33 and 6
36	randomized controlled trial.pt.
37	controlled clinical trial.pt.
38	randomized controlled trials/
39	random allocation/
40	double blind method/
41	single blind method/
42	or/36-41
43	(ANIMALS not HUMANS).sh.

(*Continued*)

44	42 not 43
45	clinical trial.pt.
46	exp clinical trial/
47	(clin$ adj25 trial$).ti,ab.
48	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
49	placebos/
50	placebo$.ti,ab.
51	random$.ti,ab.
52	research design/
53	or/45-52
54	53 not 43
55	54 not 44
56	comparative study/
57	exp evaluation studies/
58	follow up studies/
59	prospective studies/
60	(control$ or prospectiv$ or volunteer$).ti,ab.
61	or/56-60
62	61 not 43
63	62 not (44 or 55)
64	44 or 55 or 63
65	13 and 32 and 64
66	65 and 6
67	limit 66 to ed=20080401-20090204

(*Continued*)

68	randomized controlled trial.pt.
69	controlled clinical trial.pt.
70	randomized controlled trials as topic/
71	random allocation/
72	double blind method/
73	single blind method/
74	or/68-73
75	(ANIMALS not HUMANS).sh.
76	74 not 75
77	clinical trial.pt.
78	exp clinical trial as topic/
79	(clin$ adj25 trial$).ti,ab.
80	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
81	placebos/
82	placebo$.ti,ab.
83	random$.ti,ab.
84	research design/
85	or/77-84
86	85 not 75
87	86 not 76
88	comparative study/
89	exp evaluation studies/
90	follow up studies/
91	prospective studies/

(*Continued*)

92	(control$ or prospectiv$ or volunteer$).ti,ab.
93	or/88-92
94	93 not 75
95	94 not (76 or 87)
96	76 or 87 or 95
97	35 and 96
98	from 67 keep 1-19
101	limit 66 to ed=20080101-20090204
102	from 101 keep 1-28
103	limit 97 to ed=20080101-20090204
104	from 103 keep 1-32

Appendix 3. EMBASE search strategy

The following strategy was used for EMBASE:
1. (favourable or unfavourable or favorable or unfavorable).tw,kf,ot.
2. ((earl$ or low$ or limit$) adj3 (stag$ or grad$)).tw,kf,ot.
3. intermediate$.tw,kf,ot.
4. bulky.tw,kf,ot.
5. or/1-4
6. *LYMPHOMA/
7. exp HODGKIN DISEASE/
8. Germinoblastom$.tw,kf,ot.
9. Reticulolymphosarcom$.tw,kf,ot.
10. Hodgkin$.tw,kf,ot.
11. (malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
12. or/6-11
13. exp ANTINEOPLASTIC AGENT/
14. REMISSION/
15. exp CLINICAL PROTOCOL/
16. ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw,kf,ot.
17. ((therap$ or induc$) adj3 remission$).tw,kf,ot.
18. (chemotherap$ or chemo-therap$).tw,kf,ot.
19. (Antineoplast$ or anti-neoplast$).tw,kf,ot.
20. ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).tw,kf,ot.
21. exp RADIOTHERAPY/
22. (radiotherap$ or radio-therap$).tw,kf,ot.
23. (chemoradiotherap$ or chemo-radio-therap$).tw,kf,ot.

24. exp MULTIMODALITY CANCER THERAPY/
25. ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw,kf,ot.
26. exp LYMPH NODE IRRADIATION/
27. (combi$ adj3 modalit$).tw,kf,ot.
28. or/13-27
29. CLINICAL TRIAL/
30. RANDOMIZED CONTROLLED TRIALS/
31. RANDOM ALLOCATION/
32. SINGLE-BLIND METHOD/
33. DOUBLE-BLIND METHOD/
34. CROSS-OVER STUDIES/
35. PLACEBOS/
36. Randomi?ed controlled trial$.tw.
37. RCT.tw.
38. Random allocation.tw.
39. Randomly allocated.tw.
40. Allocated randomly.tw.
41. (allocated adj2 random).tw.
42. Single blind$.tw.
43. Double blind$.tw.
44. ((treble or triple) adj blind$).tw.
45. Placebo$.tw.
46. PROSPECTIVE STUDIES/
47. or/29-46
48 CASE STUDY/
49. Case report.tw.
50. ABSTRACT REPORT/ or LETTER/
51. or/48-50
52. 47 not 51
53. ANIMAL/
54. HUMAN/
55. 53 not 54
56. 52 not 55
57. 5 and 12 and 28 and 56

WHAT'S NEW

Last assessed as up-to-date: 1 January 2011.

Date	Event	Description
8 February 2011	Amended	Typo correction

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 2, 2011

CONTRIBUTIONS OF AUTHORS

Herbst C: Abstract screening, data extraction, quality assessment (RoB), data analysis and interpretation, drafting of the review, SoF table, adverse events

Rehan F: Drafting of the protocol, abstract screening, data extraction, data entry into RevMan, drafting of the review

Skoetz N: Data checking (third author), communication between authors, proofreading, update screening

Brillant C: Data extraction, data analysis and interpretation, statistical advice

Bohlius J: Conception of the review, drafting of the protocol, methodological advice

Schulz H: Clinical expertise

Monsef I: Search strategy, electronic search, handsearching

Specht L: Clinical expertise, advice for the protocol

Engert A: Clinical expertise, content input

DECLARATIONS OF INTEREST

There is no known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Köln Fortune, Germany.

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External sources

- BMBF, Germany.

Project grant application NO 01KG0815, Federal Ministry of Education and Research (BMBF)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Assessment of risk of bias in included studies

For quality assessment we preferred to use a "domain-based evaluation" as described in The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008), since it was more compatible to the risk of bias table included in the RevMan 5. We replaced the following quality questions:

- Was treatment allocation concealed?
- Were outcome assessors blind to treatment assigned?
- Were numbers of withdraws, drop outs, lost to follow-up and protocol violations in each group stated and were less than 10% in each arm?
- Were participants included in the analyses as part of the group to which they were allocated (intention-to-treat analyses)?
- Were the baseline characteristics similar in both groups?

Progression-free survival

Because no trials reported progression-free survival (PFS) according to our definition (time to progress or relapse or death of any cause in all randomised patients), we accepted other progression outcomes and evaluated these as tumour control.

Adverse events

It was not planned to extract adverse events because the adverse events relevant for decision making were not expected to be reported in the reviews. To further underline this point, all adverse events reported in the review were summarised in a table.

Summary of Findings Table

A Summary of Findings Table using the GRADE approach was included.

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy [methods]; Hodgkin Disease [*drug therapy; pathology; *radiotherapy]; Randomized Controlled Trials as Topic; Survival Analysis

MeSH check words

Humans