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van Dalen EC, Raphaël MF, Caron HN, Kremer LCM

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[Intervention Review]

Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer

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ABSTRACT

Background

One of the most important adverse effects of anthracyclines is cardiotoxicity. A well-informed decision on the use of anthracyclines in the treatment of childhood cancers should be based on evidence regarding both antitumour efficacy and cardiotoxicity. This review is the second update of a previously published Cochrane review.

Objectives

To compare antitumour efficacy (survival and tumour response) and cardiotoxicity of treatment including or not including anthracyclines in children with childhood cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 6), MEDLINE (1966 to July 2013) and EMBASE (1980 to July 2013). In addition, we searched reference lists of relevant articles and conference proceedings, the International Society for Paediatric Oncology (SIOP) (from 2002 to 2012) and American Society of Clinical Oncology (ASCO) (from 2002 to 2013). We have searched for ongoing trials in the ISRCTN register and the National Institute of Health register (both screened August 2013) (http://www.controlled-trials.com).

Selection criteria

Randomised controlled trials (RCTs) comparing treatment of any type of childhood cancer with and without anthracyclines and reporting outcomes concerning antitumour efficacy or cardiotoxicity.

Data collection and analysis

Two review authors independently performed the study selection, risk of bias assessment and data extraction. Analyses were performed according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

We identified RCTs for seven types of tumour, acute lymphoblastic leukaemia (ALL) (three trials; 912 children), Wilms' tumour (one trial; 316 children), rhabdomyosarcoma and undifferentiated sarcoma (one trial; 413 children), Ewing's sarcoma (one trial; 94 children), non-Hodgkin lymphoma (one trial; 284 children), hepatoblastoma (one trial; 255 children) and acute myeloid leukaemia (AML) (one trial; 394 children). All studies had methodological limitations. For ALL no evidence of a significant difference in antitumour efficacy was

identified in the meta-analyses, but in most individual studies there was a suggestion of better antitumour efficacy in patients treated with anthracyclines. For both Wilms' tumour and Ewing's sarcoma a significant difference in event-free and overall survival in favour of treatment with anthracyclines was identified, although for Wilms' tumour the significant difference in overall survival disappeared with long-term follow-up. For rhabdomyosarcoma and undifferentiated sarcoma, non-Hodgkin lymphoma and hepatoblastoma no difference in antitumour efficacy between the treatment groups was identified. The same was true for AML, with the exception of overall survival in a post hoc analysis in a subgroup of patients with relapsed core binding factor (CBF)-AML in which patients treated with anthracyclines did better. Clinical cardiotoxicity was evaluated in four RCTs; no significant difference between the treatment groups was identified, but in all individual studies there was a suggestion of a lower rate of clinical cardiotoxicity in patients who did not receive anthracyclines. None of the studies evaluated asymptomatic cardiac dysfunction. No RCTs were identified for other childhood cancers.

Authors' conclusions

At the moment no evidence from RCTs is available which underscores the use of anthracyclines in ALL. However, 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. For Wilms' tumour, rhabdomyosarcoma and undifferentiated sarcoma, Ewing's sarcoma, non-Hodgkin lymphoma, hepatoblastoma and AML only one RCT was available for each type and, therefore, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in these tumours. For other childhood cancers no RCTs were identified and therefore no conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in these tumours.

PLAIN LANGUAGE SUMMARY

Treatment with or without anthracycline chemotherapy for childhood cancer

Anthracyclines are used in the treatment of different types of childhood cancer. Unfortunately, one of the most important adverse effects of anthracyclines is damage to the heart. This can become manifest not only during treatment but also years after the end of treatment. A well-informed decision on the use of anthracyclines in the treatment of different types of childhood cancer should be based on the available evidence on both the antitumour effects of anthracyclines and the risk of damage to the heart.

This systematic review focused on randomised studies evaluating the antitumour effects of anthracycline therapy. The authors found that at the moment no high quality evidence is available which shows that the use of anthracyclines has an increased antitumour effect in acute lymphoblastic leukaemia (ALL) as compared to treatment without anthracyclines, but there was some suggestion that this might be the case. Further high quality studies are needed to provide a definitive conclusion. For Wilms' tumour, rhabdomyosarcoma and undifferentiated sarcoma, Ewing's sarcoma, non-Hodgkin lymphoma, hepatoblastoma and acute myeloid leukaemia (AML) the review authors found only limited data and were unable to draw conclusions. Also, there were no data for other childhood cancers. More high quality research is needed. At the moment there are five ongoing or unpublished randomised studies evaluating the use of anthracyclines in the following types of childhood cancer, hepatoblastoma, ALL (two studies), rhabdomyosarcoma, and Wilms' tumour.

BACKGROUND

Anthracyclines, like doxorubicin, daunorubicin and epirubicin, have gained widespread use in the treatment of numerous childhood cancers, both solid tumours and haematological malignancies. Nearly 60% of children diagnosed with a malignancy receive anthracyclines as part of their treatment.

Unfortunately, one of the most important side effects of anthracyclines is cardiotoxicity (that is damage to the heart), which has been known since their introduction (Lefrak 1973). The damage can become manifest in patients as either clinical heart failure (Von Hoff 1979) or asymptomatic cardiac dysfunction (Lipshultz 2005). Asymptomatic cardiac dysfunction includes various cardiac abnormalities diagnosed with different diagnostic methods, like echocardiography, nuclear angiography, cardiac biopsy or cardiac markers, in asymptomatic patients. Anthracycline-induced cardiotoxicity is a widely prevalent problem in children; the incidence of clinical heart failure has been reported to be as high as 16% 0.9 to 4.8 years after treatment (Kremer 2002a) and the prevalence of asymptomatic cardiac dysfunction has been reported to be more than 57% at a median of 6.4 years after treatment (Kremer 2002b). The risk of anthracycline-induced cardiotoxicity is dose-dependent. In a cohort study of 830 children a cumulative anthracycline dose of 300 mg/m^2 or more produced an eight-fold higher risk of clinical heart failure as compared to lower doses (less than 300 mg/m^2) (Van Dalen 2006). The consequences of anthracycline-induced cardiotoxicity are extensive. It can lead to long-term side effects, causing severe morbidity and reduced quality of life. The cardiotoxicity involves long-term treatment and thus high medical costs and it causes premature death. The excess mortality due to cardiac disease is eight-fold higher than expected for long-term survivors of childhood cancer compared to the normal population (Mertens 2001).

If anthracycline therapy does not have an added value with regard to tumour response and survival compared to treatment without anthracyclines, it should not be used in treatment protocols for childhood cancer. As a result, anthracycline-induced cardiotoxicity would not be an issue. Although ample evidence supports the antileukaemic activity of anthracyclines administered as a single drug, data supporting anthracycline use in modern multi-drug combinations, which now constitute the mainstay of current acute lymphoblastic leukaemia (ALL) treatments, are lacking. It is unclear if the use of anthracyclines improves the outcome (Messinger 1999). Also, in a randomised controlled trial (RCT) in children with advanced stage non-lymphoblastic non-Hodgkin's lymphoma, the addition of daunorubicin to treatment with COMP (intrathecal arabinofuranosyl cytidine (ARA-C), cyclophosphamide, vincristine, methotrexate and prednisone) did not improve the prognosis; children treated with daunorubicin had an event-free survival of 57%, whereas in children treated without daunorubicin the event-free survival was 55% (no significant difference) (Sposto 2001).

This is the second update of the first systematic review evaluating the state of the evidence on the use of anthracyclines in the treatment of childhood cancer.

OBJECTIVES

Primary objective:

- to compare survival in children with any type of malignancy receiving anthracyclines as part of their treatment with survival in children not receiving anthracyclines as part of their treatment.

Secondary objectives:

- to compare tumour response in both treatment groups;
- to compare cardiotoxicity in both treatment groups.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing treatment of childhood cancer with and without anthracyclines.

Types of participants

Children (aged 0 to 18 years at diagnosis) with any type of malignancy at any stage. RCTs including both children and adults were only eligible for inclusion in this review if the majority of participants were children and the maximal age of the participants did not exceed 30 years.

Types of interventions

Treatment with and without anthracyclines. Therapy other than anthracyclines (that is chemotherapy, cardioprotective interventions, radiotherapy or surgery, or a combination) should have been the same in both treatment groups. Timing of different aspects of the treatment may have differed between the study groups, but the cumulative doses of therapy other than anthracyclines should not have differed more than 25% between the study groups. Furthermore, prior treatment should have been comparable in both treatment groups.

Types of outcome measures

Primary outcomes

- Survival (overall survival and event-free survival as defined by the authors of the original study)

Secondary outcomes

- Tumour response (as defined by the authors of the original study)
- Anthracycline-induced cardiotoxicity (i.e. clinical heart failure (as defined by the authors of the original study) or asymptomatic cardiac dysfunction (defined as either histological abnormalities according to the Billingham score (Billingham 1978) on myocardial biopsies or abnormalities in cardiac function measured by echocardiography or radionuclide ventriculography))

Search methods for identification of studies

The following electronic databases have been searched:
The Cochrane Central Library of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 6), MEDLINE in PubMed (from 1966 to July 2013), and EMBASE in Ovid (from 1980 to July 2013). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are detailed in the appendices (Appendix 1, Appendix 2, Appendix 3).

Information about trials not registered in CENTRAL, MEDLINE or EMBASE, either published or unpublished, was located by searching the reference lists of relevant articles and review articles. We also scanned the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2002 to 2012) and American Society of Clinical Oncology (ASCO) (from 2002 to 2013), if available electronically and otherwise by handsearching. We have searched for ongoing trials in the ISRCTN register and the National Institute of Health register (both screened August 2013) (http://www.controlled-trials.com). Language restrictions were not imposed.

Data collection and analysis

Selection of studies

For the original version of the review, after employing the search strategy described previously, initial screening of identified references was performed by one review author. Case reports, studies only including adults, studies in which all patients received anthracyclines, and review articles were excluded. Identification of studies meeting the inclusion criteria from the remaining references was undertaken by two review authors working independently. Any study which seemed to meet the inclusion criteria on the grounds of the title or abstract, or both, was obtained in full for closer inspection. Again, for the original version of the review, initial screening was performed by one review author who excluded case reports, studies only including adults, studies in which all patients received anthracyclines, and review articles. The remaining full text articles were evaluated by two independent review authors. For both updates of the review, two independent review authors performed all steps of the study identification process (that is no initial screening by one review author). Details of the reasons for exclusion of any study considered for the review were clearly stated. Discrepancies between review authors were resolved by consensus or if that was not possible by third party arbitration.

Data extraction and management

Two review authors independently performed the data extraction using standardised forms. Data on the following items were extracted:

(1) Study design.

(2) Risk of bias items.

(3) Participants, including:
a. age;
b. sex;
c. type of tumour;
d. stage of disease;
e. primary tumour or recurrence;
f. prior treatment;
g. number of patients entering the trial;
h. number of patients randomised;
i. number of patients excluded (with reasons);
j. number of patients evaluable (for each outcome).

(4) Interventions, including:
a. type of anthracycline;
b. cumulative anthracycline dose;
c. anthracycline peak dose (defined as the maximal dose received in one week);
d. anthracycline infusion duration;
e. other treatment, including:
i. chemotherapy (agent and cumulative dose),
ii. radiotherapy (location and cumulative dose),
iii. surgery (location and procedure),
iv. cardioprotective interventions (method).

(5) Outcome measures.

(6) Length of follow-up.

Discrepancies between review authors were resolved by consensus. No third party arbitration was needed.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included RCTs. For this second update we used the most recent recommendations of the Childhood Cancer Group (that is selection bias, performance bias, detection bias (for each outcome separately), attrition bias (for each outcome separately), reporting bias (where 'all expected outcomes' was defined as reporting on both overall survival and cardiotoxicity and at least one of the following outcomes: event-free survival or tumour response) and other bias). We used the 'risk of bias' items and definitions of low risk, unclear risk and high risk as described in the module of the Cochrane Childhood Cancer Group (Kremer 2008), which is based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). All RCTs (including those already included in earlier versions of the review) were scored using the new 'risk of bias' items. Discrepancies between authors were resolved by discussion. No third party arbitration was needed. The risk of bias in the included studies was taken into account in the interpretation of the review's results.

Data synthesis

Data were entered into RevMan and analysed according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). Dichotomous variables were related to risk using the relative risk or risk ratio (RR). If possible, data were extracted by allocation intervention, irrespective of compliance with the allocated intervention, in order to allow an 'intention-to-treat' (ITT) analysis. If this was not possible, this was stated and we performed an 'as treated' analysis. We assessed heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is the I^2 statistic. If there was evidence of substantial heterogeneity (I^2 > 50%) (Higgins 2009) this was reported. Studies for which pooling of results was not possible were summarised descriptively. We used a random-effects model for the estimation of treatment effects throughout the review. All results were presented with the corresponding 95% confidence interval (CI). For the assessment of survival, we used the generic inverse variance function of RevMan to combine logs of the hazard ratios (HRs). We used Parmar's method if HRs had not been explicitly presented in the study (Parmar 1998). Data were analysed separately for different types of tumour and, if possible, also for different stages of disease and different histological subtypes. When a particular outcome was not evaluated in more than 50% of the patients of a study, due to the associated high risk of attrition bias we did not report the results of this outcome measure. For all outcomes for which pooled analyses were possible we

performed sensitivity analyses for all risk of bias criteria separately. We excluded studies with a high risk of bias and studies for which the risk of bias was unclear and compared the results of the studies with a low risk of bias with the results of all available studies. The risk of bias in the studies included in the analyses was taken into account in the interpretation of the results of the review. We were not able to construct a funnel plot to graphically ascertain the existence of publication bias. As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in a meta-analysis. When there are fewer studies the power of the test is too low to distinguish chance from real asymmetry (Higgins 2009). Since only a maximum of three trials could be included in the separate meta-analyses, we did not construct funnel plots. For outcomes where only one study was available, we were unable to calculate a RR if one of the treatment groups experienced no events and the Fischer's exact test was used instead; this option is not available in Revman and therefore we used http://graphpad.com/quickcalcs/contingency2/.

RESULTS

Description of studies

Running the searches in the electronic databases of CENTRAL, MEDLINE in PubMed and EMBASE in Ovid (in January 2007) yielded a total of 3277 references. Initial screening excluded 987 references based on them being case reports, review articles, studies only including adults, or studies in which all patients received anthracyclines. Of the 2290 remaining references 135 studies were assessed in full. Of the 67 articles remaining after initial screening, we included a total of seven articles which fulfilled all the criteria for this review. A total of 128 articles were excluded after assessing the full text articles, for reasons described in the Characteristics of excluded studies table. The remaining 2155 references were excluded based on the title or abstract, or both, since they were not a RCT, were laboratory studies, were animal studies, did not include children with cancer, or there was a difference in treatment other than anthracyclines between the treatment groups.

Running the searches for the update in CENTRAL, MEDLINE in PubMed and EMBASE in Ovid (in March 2010) yielded a total of 1032 new references. Following screening of the titles, abstracts, or both, 1000 references which clearly did not meet all criteria for considering studies for this review were excluded. We obtained 32 articles in full, of which a single article fulfilled all the criteria for considering studies for this review (Perilongo 2009). The other 31 articles were excluded for reasons described in the Characteristics of excluded studies table.

Running the searches for the second update in CENTRAL, MEDLINE in PubMed and EMBASE in Ovid (in July 2013) yielded a total of 1167 new references. Following screening of the titles, abstracts, or both, 1151 references which clearly did not meet all criteria for considering studies for this review were excluded. We obtained 16 articles in full (five of these were only available as a conference proceeding), of which a single article fulfilled all the criteria for considering studies for this review (Kaspers 2013). Thirteen articles were excluded for reasons described in the Characteristics of excluded studies table; two studies have not been published in full yet (see Characteristics of studies awaiting classification table).

Scanning the reference lists of relevant articles and reviews did not identify any additional eligible studies. We did identify three ongoing trials during the original review. At the time of the first update one ongoing trial identified in the original version of this review was published in full text and identified in the update of the electronic database searches (Perilongo 2009); this trial was thus removed from the Characteristics of ongoing studies table. At the time of the second update it became clear that the SIOP-2001 trial was closed and preliminary results had been presented as a conference proceeding (identified in the second update of the electronic database searches as described above); this trial was thus removed from the Characteristics of ongoing studies table. Eleven other studies (nine from the original version and two from the first update) were added to the Characteristics of excluded studies table.

By scanning the conference proceedings of SIOP and ASCO for the original version, we identified one study (described in two abstracts) that had not been published in full yet and was awaiting further assessment during the original search. At the time of the updates this study is still not published in full (see the Characteristics of studies awaiting classification table); no other additional eligible studies were identified during the updates.

By scanning the ongoing trials databases for the original version we identified three additional ongoing trials (see the Characteristics of ongoing studies table); no other additional eligible studies were identified during the updates but it became clear that the ISRCTN94206677 and the NCT00186966 trials were in fact the same study and that the study was published in full text and identified in the second update of the electronic database searches (Kaspers 2013); these publications were thus removed from the Characteristics of ongoing studies table.

Finally, during the first update an expert in the field provided us with long-term follow-up data (Green 2004) of one of the included studies (D'Angio 1981).

In summary, after the second update the total number of included RCTs was nine. We also identified two ongoing studies and three studies that have not been published in full yet and are awaiting further assessment.

Characteristics of the included studies are summarised below; for more information we refer to the Characteristics of included studies table.

The total number of patients included in the nine identified RCTs was 2668: 1318 children received no anthracyclines, whereas 1350 did receive anthracyclines. In three studies children were diagnosed with ALL (Eden 1991; Van der Does 1975; Van der Does 1989); and in one with acute myeloid leukemia (AML) (Kaspers 2013). In the other five studies they were diagnosed with a solid tumour: Wilms' tumour (D'Angio 1981), rhabdomyosarcoma or undifferentiated sarcoma (Maurer 1988), Ewing's sarcoma (Nesbit 1990), non-Hodgkin lymphoma (Sposto 2001) or hepatoblastoma (Perilongo 2009). In four studies patients were treated with daunorubicin (Eden 1991; Sposto 2001; Van der Does 1975; Van der Does 1989). In all these studies the cumulative daunorubicin dose actually received by the patients was not mentioned, but according to protocol patients should have received 90 to 350 mg/m^2. The peak anthracycline dose (that is the maximal dose received in one week) ranged from 25 to 90 mg/m^2. Infusion durations were not

mentioned. In four studies patients were treated with doxorubicin (D'Angio 1981; Maurer 1988; Nesbit 1990; Perilongo 2009). In all these studies the cumulative doxorubicin dose actually received by the patients was not mentioned, but according to protocol patients should have received either (maximal) 300 or 420 mg/m^2. The peak anthracycline dose (that is the maximal dose received in one week) was either 25 or 60 mg/m^2. Infusion durations were not mentioned in three studies, in the other study it was 30 mg/m^2/24 hours. In the final study patients were treated with daunoxome, that is liposomally entrapped daunorubicin (Kaspers 2013). The cumulative daunoxome dose actually received by the patients was not mentioned, but according to protocol patients should have received 180 mg/m^2. The peak anthracycline dose (that is the maximal dose received in one week) was 180 mg/m^2. The infusion duration was not mentioned.

Risk of bias in included studies

See the risk of bias section of the Characteristics of included studies table and Figure 1 for the exact scores per included study.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

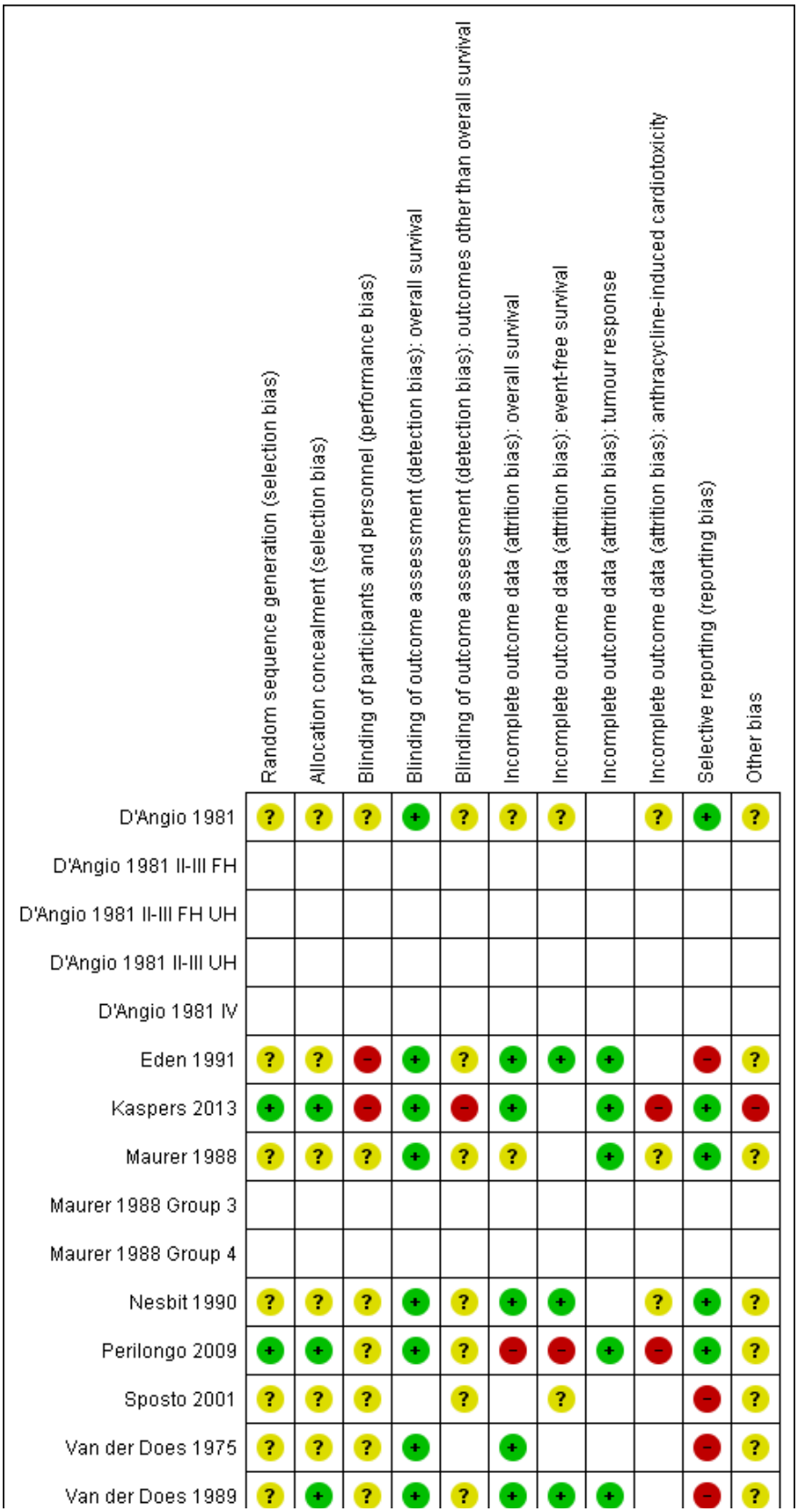


Figure 1. (Continued)

Allocation

For evaluating selection bias we have assessed the random sequence generation and the allocation concealment. The risk of selection bias was low in two studies (22%) (Kaspers 2013; Perilongo 2009), while in seven studies (78%) it was unclear (D'Angio 1981; Eden 1991; Maurer 1988; Nesbit 1990; Sposto 2001; Van der Does 1975; Van der Does 1989). For the latter study only the random sequence generation was unclear and the allocation concealment was adequate; for the other six studies both items were unclear.

Blinding

For evaluating performance bias we have assessed the blinding of participants and personnel. In two studies (22%) there was a high risk of bias (Eden 1991; Kaspers 2013), while in seven studies (78%) it was unclear (D'Angio 1981; Maurer 1988; Nesbit 1990; Perilongo 2009; Sposto 2001; Van der Does 1975; Van der Does 1989).

For evaluating detection bias we have evaluated the blinding of outcome assessors for all separate outcomes, with the exception of overall survival since for that outcome blinding is not relevant and the risk of detection bias was thus automatically judged as low for all eight studies (100%) evaluating this outcome (Eden 1991; Kaspers 2013; Maurer 1988; Nesbit 1990; Perilongo 2009; Van der Does 1975; Van der Does 1989). Six studies evaluated event-free survival; in all studies (100%) the risk of detection bias was unclear (D'Angio 1981; Eden 1991; Nesbit 1990; Sposto 2001; Perilongo 2009; Van der Does 1989). Five studies evaluated tumour response; in four studies (80%) the risk of detection bias was unclear (Eden 1991; Maurer 1988; Perilongo 2009; Van der Does 1989) while in one study (20%) the risk was judged to be high (Kaspers 2013). Five studies evaluated cardiotoxicity; in four studies (80%) the risk of detection bias was unclear (D'Angio 1981; Maurer 1988; Nesbit 1990; Perilongo 2009) while in one study (20%) the risk was judged to be high (Kaspers 2013).

Incomplete outcome data

For evaluating attrition bias we have assessed incomplete outcome data for all separate outcomes. Eight studies evaluated overall survival; in five studies (63%) there was a low risk of attrition bias (Eden 1991; Kaspers 2013; Nesbit 1990; Van der Does 1975; Van der Does 1989), in one study (12%) there was a high risk of attrition bias (Perilongo 2009) and in two studies (25%) the risk of attrition bias was unclear (D'Angio 1981; Maurer 1988). Six studies evaluated event-free survival; in three studies (50%) there was a low risk of attrition bias (Eden 1991; Nesbit 1990; Van der Does 1989), in one study (17%) there was a high risk of attrition bias (Perilongo 2009) and in two studies (33%) the risk of attrition bias was unclear (D'Angio 1981; Sposto 2001). Five studies evaluated tumour response; in all studies (100%) the risk of attrition bias was low (Eden 1991; Kaspers 2013; Maurer 1988; Perilongo 2009; Van der Does 1989). Five studies evaluated cardiotoxicity; in two studies (40%) the risk of attrition bias was high (Kaspers 2013; Perilongo 2009) while in three studies (60%) it was unclear (D'Angio 1981; Maurer 1988; Nesbit 1990).

Selective reporting

For evaluating reporting bias we have assessed selective reporting. We defined 'all expected outcomes' as reporting on both overall survival and cardiotoxicity and at least one of the following outcomes: event-free survival or tumour response. In five studies (56%) we judged the risk of reporting bias to be low (D'Angio 1981; Kaspers 2013; Maurer 1988; Nesbit 1990; Perilongo 2009) while in four studies (44%) it was judged to be high (Eden 1991; Sposto 2001; Van der Does 1975; Van der Does 1989).

Other potential sources of bias

For evaluating other potential sources of bias we have assessed the following items: block randomisation in unblinded trials, baseline imbalance between treatment groups related to outcome (prior cardiotoxic treatment, age, sex, prior cardiac dysfunction), difference in length of follow-up between treatment arms, and inappropriate influence of funders. In one study (11%) there was a high risk of other bias (Kaspers 2013) while in the other eight studies (89%) the risk was unclear (D'Angio 1981; Eden 1991; Maurer 1988; Nesbit 1990; Perilongo 2009; Sposto 2001; Van der Does 1975; Van der Does 1989). For a more detailed description of all the different items see the risk of bias section of the Characteristics of included studies table.

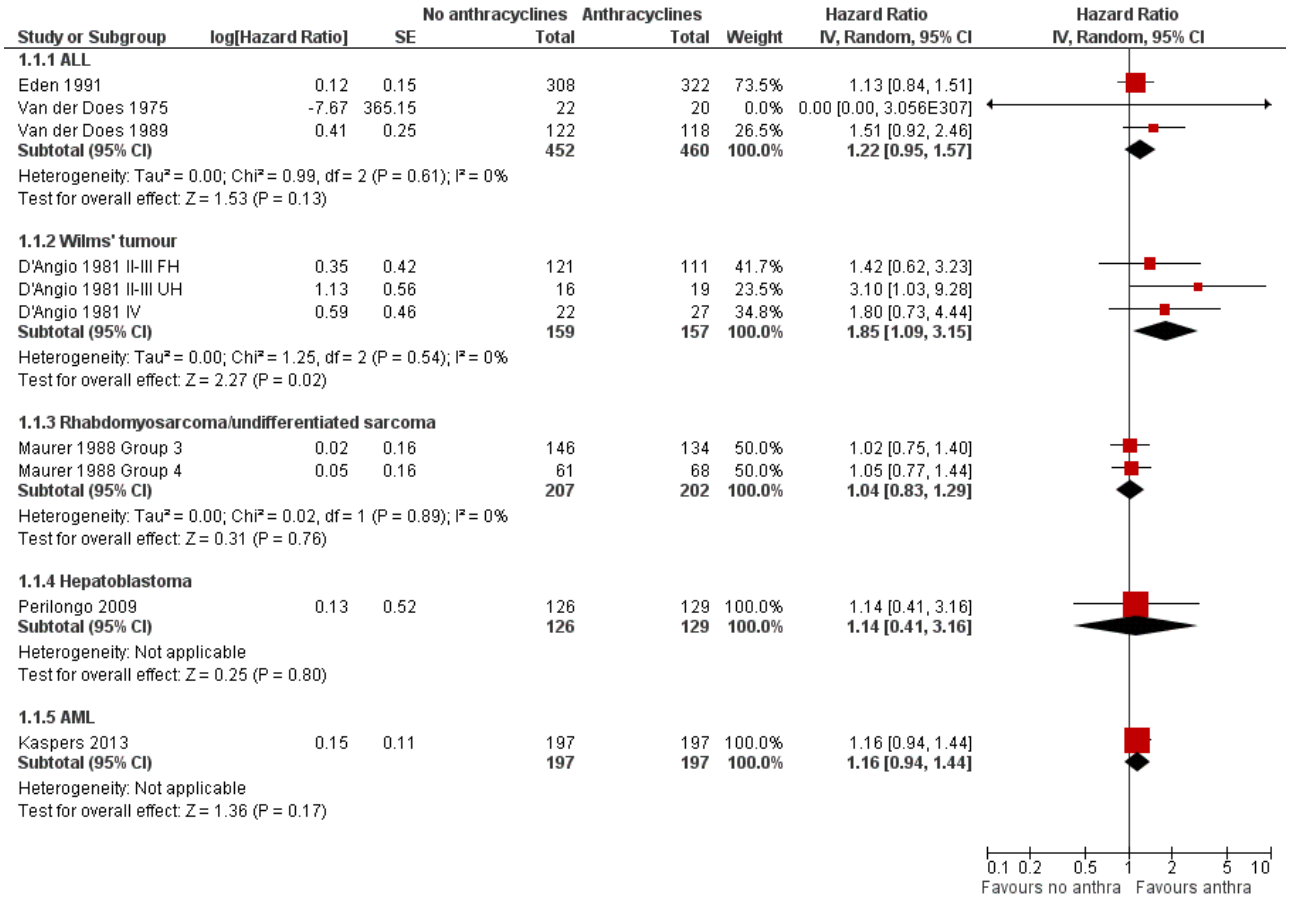
Effects of interventions

Not all articles allowed data extraction for all endpoints (see the Characteristics of included studies table for a more detailed description of the extractable endpoints of each article).

Overall survival

(See Figure 2)

Figure 2. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.1 Overall survival (Parmar's method was used to obtain the necessary data for the meta-analyses).



ALL

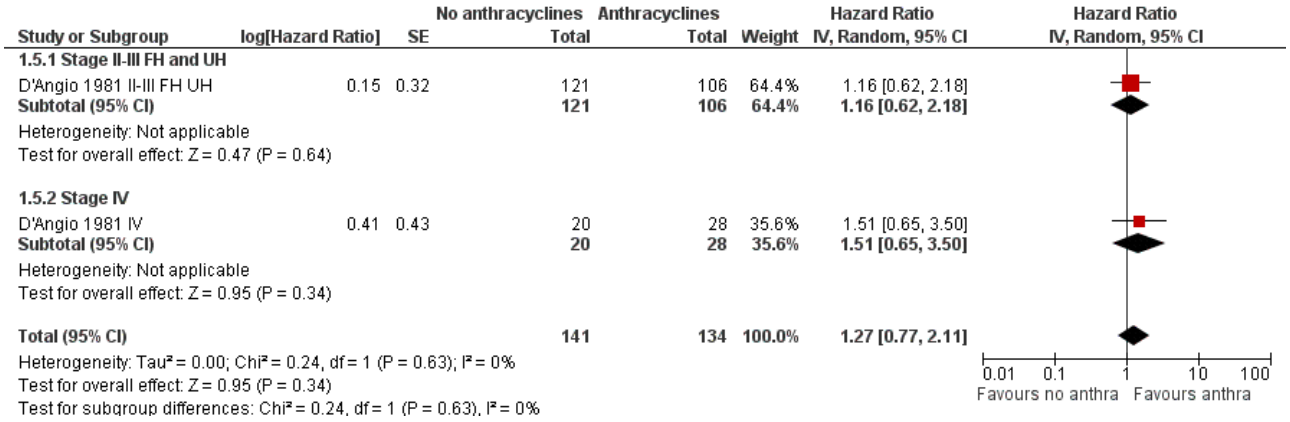
Data on overall survival could be extracted from three trials with a total of 912 patients (Eden 1991; Van der Does 1975; Van der Does 1989). Parmar's method was used to obtain the necessary data for the meta-analysis. The HR showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.22, 95% CI 0.95 to 1.57, P = 0.13). No heterogeneity was detected (I^2 = 0%).

Wilms' tumour

Data on overall survival could be extracted from one trial with a total of 316 patients (D'Angio 1981). Data were presented separately for patients with stage II or III disease with favourable histology, stage II or III with unfavourable histology, and stage IV disease. Parmar's method was used to obtain the necessary data for the analysis. The combination of all patients showed a significant difference in favour of treatment including anthracyclines (HR 1.85, 95% CI 1.09 to 3.15, P = 0.02). No heterogeneity was detected (I^2 = 0%). For patients with stage II or III disease with favourable histology and patients with stage IV disease the analyses showed no significant difference between treatment not including and treatment including anthracyclines. However, the analysis of patients with stage II or III with unfavourable histology showed a significant difference in favour of treatment including anthracyclines (HR 3.10, 95% CI 1.03 to 9.28, P = 0.04).

Long-term follow-up data of this study have been published (Green 2004; D'Angio 1981 II-III FH UH; D'Angio 1981 IV) on 275 of 316 patients: 227 patients with stage II or III disease with favourable or unfavourable histology (as opposed to D'Angio 1981 in which data were presented separately for favourable and unfavourable histology) and 48 patients with stage IV disease. The length of follow-up was not mentioned but at least some of the patients had a follow-up of 16 years. See Figure 3 for the long-term follow-up data. In contrast to the earlier results, the long-term follow-up data showed no significant difference between treatment groups (HR 1.27, 95% CI 0.77 to 2.11, P = 0.34). No heterogeneity was detected (I^2 = 0%). The long-term follow-up data also showed no significant difference between treatment groups for patients with stage II or III disease with favourable or unfavourable histology and for patients with stage IV disease. These results are in line with the earlier data; in D'Angio 1981 the overall survival of patients with stage II or III disease with favourable or unfavourable histology combined was not significantly different between treatment groups (HR 1.92, 95% CI 0.91 to 4.04, P = 0.09, I^2 = 19%; data not shown in the figures). Please note that it was not possible to perform an ITT analysis: in the stage IV group 20 patients were included in the no anthracycline group and 28 in the anthracycline group, as opposed to the original data where 22 patients were randomised to the anthracycline group and 27 to the non-anthracycline group.

Figure 3. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.5 Overall survival Wilms' tumour long-term follow-up (Parmar's method was used to obtain the necessary data for the analyses).



Rhabdomyosarcoma and undifferentiated sarcoma

Data on overall survival could be extracted from one trial with a total of 413 patients (Maurer 1988). Data were presented for patients in clinical groups III and IV separately. Parmar's method was used to obtain the necessary data for the analysis. The combination of both clinical groups showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.04, 95% CI 0.83 to 1.29, P = 0.76). The same was true for each clinical group separately. No heterogeneity was detected (I^2 = 0%).

Ewing's sarcoma

Overall survival was evaluated in one trial (Nesbit 1990). Only some of the patients included in this trial were eligible for inclusion in this review (N = 94) and, unfortunately, not all data needed for a correct analysis of overall survival in only the eligible patients were provided in the article. Therefore, we provided descriptive results of overall survival in only the eligible patients. There was evidence of a significant advantage in overall survival for patients treated with anthracyclines as compared to patients treated without anthracyclines (P = 0.02).

Non-Hodgkin lymphoma

Overall survival could not be evaluated since we were not able to reliably extract the data needed to use Parmar's method for the assessment of this outcome from this study (Sposto 2001).

Hepatoblastoma

Overall survival was evaluated in one trial with a total of 255 patients (Perilongo 2009). Parmar's method was used to obtain the necessary data for the analysis. The HR showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.14, 95% CI 0.41 to 3.16, P = 0.80). Please note that it was not possible to perform an ITT analysis: 12 randomised patients were excluded (seven lacked proper documentation, five had wrong diagnosis; it was unclear to which treatment group these patients were randomised).

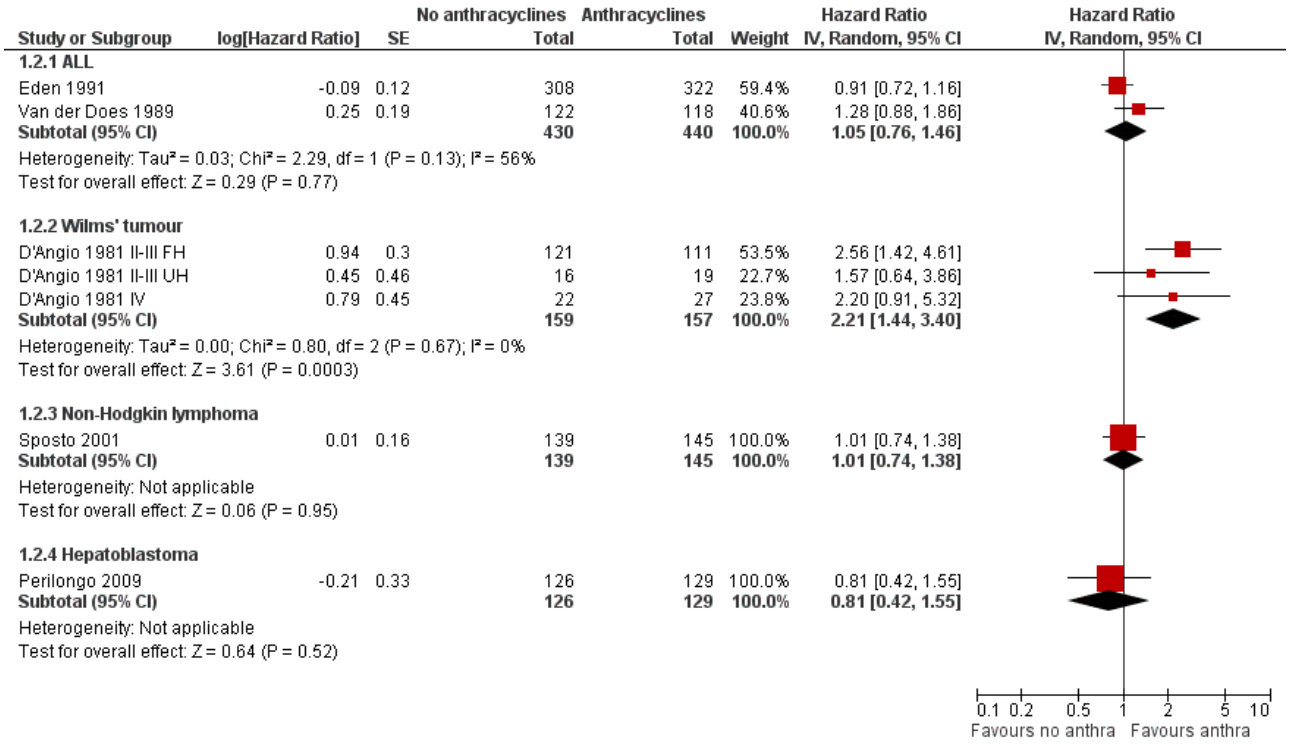
AML

Overall survival was evaluated in one trial with a total of 394 patients (Kaspers 2013). Parmar's method was used to obtain the necessary data for the analysis. The HR showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.16, 95% CI 0.94 to 1.44, P = 0.17).

Event-free survival

(See Figure 4)

Figure 4. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.2 Event-free survival (Parmar's method was used to obtain the necessary data for the meta-analyses).



ALL

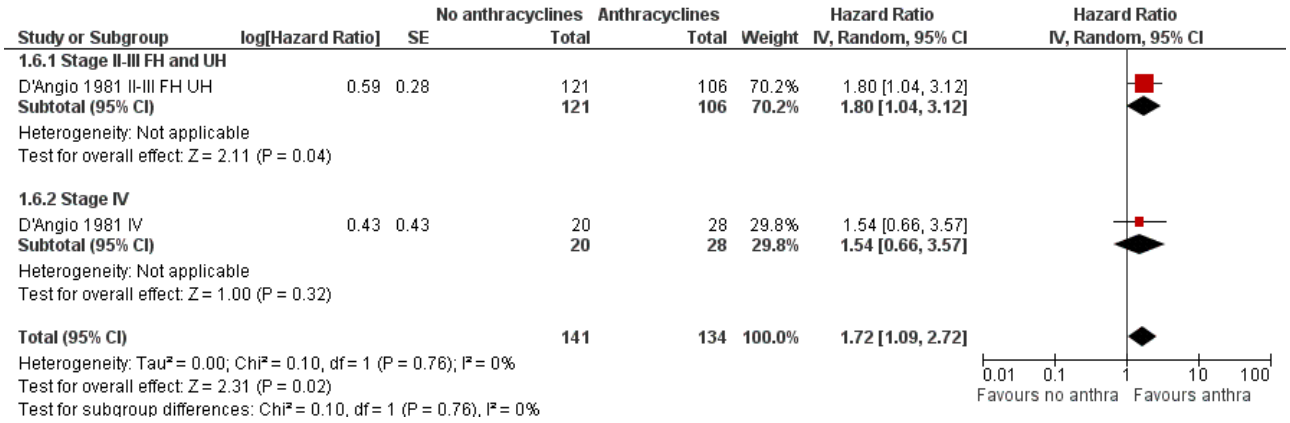
Data on event-free survival could be extracted from two trials with a total of 870 patients (Eden 1991; Van der Does 1989). Parmar's method was used to obtain the necessary data for the meta-analysis. The HR showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.05, 95% CI 0.76 to 1.46, P = 0.77). However, unexplained heterogeneity was detected (I^2 = 56%). In the study of Van der Does 1975 no information on event-free survival was provided.

Wilms' tumour

Data on event-free survival could be extracted from one trial with a total of 316 patients (D'Angio 1981). Data were presented separately for patients with stage II or III disease with favourable histology, stage II or III with unfavourable histology, and stage IV disease. Parmar's method was used to obtain the necessary data for the analysis. The combination of all patients showed a significant difference in favour of treatment including anthracyclines (HR 2.21, 95% CI 1.44 to 3.40, P = 0.0003). No heterogeneity was detected (I^2 = 0%). The analysis of patients with stage II or III disease with favourable histology also showed a significant difference in favour of treatment including anthracyclines (HR 2.56, 95% CI 1.42 to 4.61, P = 0.002). However, for patients with stage II or III disease with unfavourable histology and patients with stage IV disease the analyses showed no significant difference between treatment not including and treatment including anthracyclines.

Long-term follow-up data of this study have been published (Green 2004; D'Angio 1981 II-III FH UH; D'Angio 1981 IV) on 275 of 316 patients: 227 patients with stage II or III disease with favourable or unfavourable histology (as opposed to D'Angio 1981, data were not presented separately for favourable and unfavourable histology) and 48 patients with stage IV disease. The length of follow-up was not mentioned but at least some of the patients had a follow-up of 16 years. See Figure 5 for the long-term follow-up data, which also showed a significant difference in favour of treatment including anthracyclines (HR 1.72, 95% CI 1.09 to 2.72, P = 0.02). No heterogeneity was detected (I^2 = 0%). For the different stages or histologies the results of the long-term follow-up data were also in line with the earlier data, that is a significant difference in favour of treatment including anthracyclines for patients with stage II or III disease with favourable or unfavourable histology (for the long-term follow-up: HR 1.80, 95% CI 1.04 to 3.12, P = 0.04; for the earlier follow-up: HR 2.21, 95% CI 1.35 to 3.62, P = 0.002, I^2 = 0%; data not shown in the figures); and no significant difference between treatment groups for patients with stage IV disease. Please note that it was not possible to perform an ITT analysis: in the stage IV group 20 patients were included in the no anthracycline group and 28 in the anthracycline group, as opposed to the original data where 22 patients were randomised to the anthracycline group and 27 to the non-anthracycline group.

Figure 5. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.6 Event-free survival Wilms' tumour long-term follow-up (Parmar's method was used to obtain the necessary data for the analyses).



Rhabdomyosarcoma and undifferentiated sarcoma

Event-free survival could not be evaluated since we were not able to reliably extract the data needed to use Parmar's method for the assessment of this outcome from this study (Maurer 1988).

Ewing's sarcoma

Event-free survival was evaluated in one trial (Nesbit 1990). Only some of the patients included in this trial were eligible for inclusion in this review and, unfortunately, not all data needed for a correct analysis of event-free survival in only these patients were provided in the article. Therefore, we provide descriptive results of event-free survival in only the eligible patients. There was evidence of a significant advantage in event-free survival for patients treated with anthracyclines as compared to patients treated without anthracyclines (P = 0.01).

Non-Hodgkin lymphoma

Data on event-free survival could be extracted from one trial with a total of 284 patients (Sposto 2001). Parmar's method was used to obtain the necessary data for the analysis. The HR showed no significant difference between treatment not including and treatment including anthracyclines (HR 1.01, 95% CI 0.74 to 1.38, P = 0.95).

Hepatoblastoma

Event-free survival was evaluated in one trial with a total of 255 patients (Perilongo 2009). Parmar's method was used to obtain the necessary data for the analysis. The data showed no significant difference between treatment not including and treatment including anthracyclines (HR 0.81, 95% CI 0.42 to 1.55, P = 0.52). Please note that it was not possible to perform an ITT analysis: 12 randomised patients were excluded (seven lacked proper documentation, five had wrong diagnosis; it was unclear to which treatment group these patients were randomised).

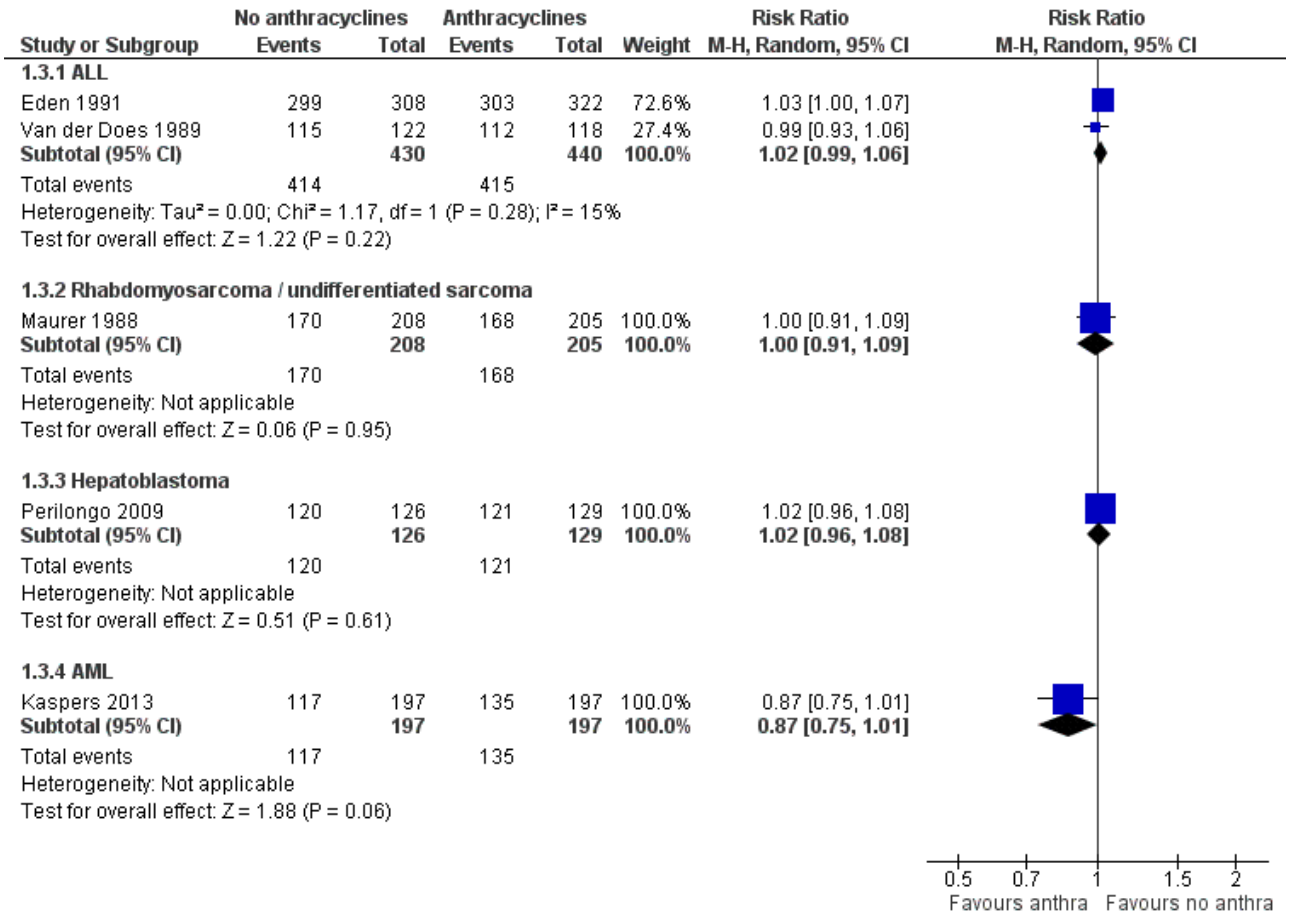
AML

No information on event-free survival was provided (Kaspers 2013).

Tumour response

(See Figure 6)

Figure 6. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.3 Tumour response.



Please note that due to the nature of this outcome (that is the number of patients with a remission) a high event rate is favourable. Therefore, in the figures of the analyses, 'favours anthracyclines' is on the left and 'favours no anthracyclines' is on the right, as opposed to the figures of the other analyses.

ALL

Data on tumour response (defined as the number of patients in complete remission) could be extracted from two studies with a total of 870 patients (Eden 1991; Van der Does 1989). The meta-analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 1.02, 95% CI 0.99 to 1.06, P = 0.22). No substantial heterogeneity was detected (I^2 = 15%).

We excluded the study of Van der Does 1975 from this analysis since no data on tumour response was provided separately in either treatment group.

Wilms' tumour

No information on tumour response was provided (D'Angio 1981).

Rhabdomyosarcoma and undifferentiated sarcoma

Data on tumour response (defined as the number of patients in complete or partial remission) could be extracted from one trial with a total of 413 patients (Maurer 1988). The analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 1.00, 95% CI 0.91 to 1.09, P = 0.95).

Ewing's sarcoma

No information on tumour response was provided (Nesbit 1990).

Non-Hodgkin lymphoma

No information on tumour response was provided (Sposto 2001).

Hepatoblastoma

Tumour response (defined as complete surgical resection, that is resection of all tumour sites on the basis of surgical findings and on postsurgical imaging) was evaluated in one trial with a total of 255 patients (Perilongo 2009). The analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 1.02, 95% CI 0.96 to 1.08, P = 0.61). Please note that it was not possible to perform an ITT analysis: 12 randomised patients were excluded (seven lacked proper documentation, five had wrong diagnosis; it was unclear to which treatment group these patients were randomised).

AML

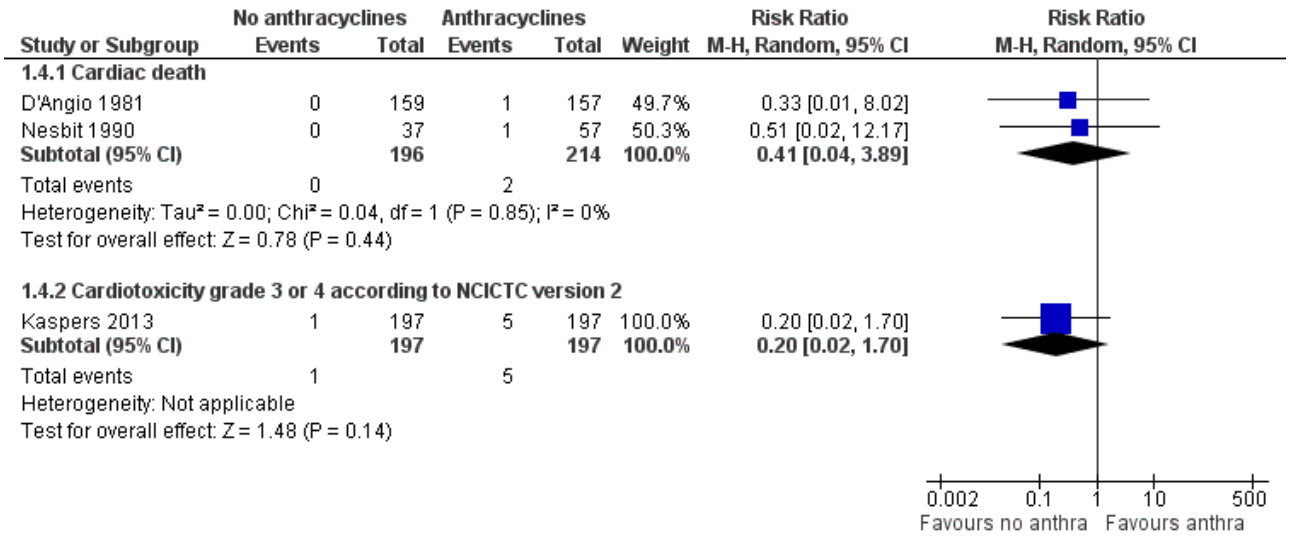
Tumour response (that is complete response after two courses defined as 5% or fewer leukaemic blasts in bone marrow with signs of normal haematopoiesis and of regeneration of normal

peripheral blood cell production (platelets > 50 x 10^9/L without transfusions, neutrophils > 1.0 x 10^9/L) and no leukaemic cells in the peripheral blood or anywhere else) was evaluated in one trial with a total of 394 patients (Kaspers 2013). The analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 0.87, 95% CI 0.75 to 1.01, P = 0.06).

Cardiotoxicity

(See Figure 7)

Figure 7. Forest plot of comparison: 1 No anthracyclines versus anthracyclines, outcome: 1.4 Clinical cardiotoxicity.



Cardiac death

Data on cardiac death could be extracted from two trials with a total of 410 patients with Wilms' tumour or Ewing's sarcoma (D'Angio 1981; Nesbit 1990). The meta-analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 0.41, 95% CI 0.04 to 3.89, P = 0.44). No heterogeneity was detected (I^2 = 0%).

Congestive heart failure

Data on congestive heart failure could be extracted from one trial with a total of 413 patients with rhabdomyosarcoma and undifferentiated sarcoma (Maurer 1988). Since in one of the treatment groups there were no events (0 out of 208 children in the group without anthracyclines experienced congestive heart failure as opposed to 1 out of 205 children in the group with anthracyclines) we were unable to calculate a RR, so we used the Fischer's exact test instead. The analysis showed no significant difference between treatment not including and treatment including anthracyclines (Fischer's exact P = 0.50).

Asymptomatic cardiac dysfunction

We could collect data on asymptomatic cardiac dysfunction from one trial with a total of 255 patients with hepatoblastoma (Perilongo 2009). However, due to the high risk of attrition bias (this outcome was evaluated in only 49% of the patients), results of this study were not reported.

Grade 3 or 4 acute cardiotoxicity according to National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2

Data on grade 3 or 4 acute cardiotoxicity according to the NCI CTC Criteria version 2 could be extracted from one trial with a total of 394 patients with AML (Kaspers 2013). The analysis showed no significant difference between treatment not including and treatment including anthracyclines (RR 0.20, 95% CI 0.02 to 1.70, P = 0.14).

In the studies of Eden 1991; Sposto 2001; Van der Does 1975 and Van der Does 1989 no (reliable) information on cardiotoxicity was provided.

Sensitivity analyses for the used quality criteria

The results of the sensitivity analyses were consistent among the trials and did not differ from the overall analyses.

DISCUSSION

Anthracycline-induced cardiotoxicity is a considerable and serious problem, causing severe morbidity and mortality. With the current improved cancer survival rates, the problem of late-onset cardiotoxicity is increasing. The risk of developing heart failure remains a lifelong threat, especially to children who have a long life-expectancy after successful antineoplastic treatment. If anthracycline therapy does not have an added value with regard to tumour response and survival compared to treatment without anthracyclines, it should not be used in treatment protocols for childhood cancer. As a result anthracycline-induced cardiotoxicity would not be an issue. This is the second update of the first systematic review evaluating the current state of evidence on the use of anthracyclines in the treatment of childhood cancer. Only RCTs were included since it is widely recognized that a RCT is the only study design which can be used to obtain unbiased evidence on the use of anthracyclines, provided that the design and execution are adequate.

We could identify RCTs for seven types of tumour, ALL, Wilms' tumour, rhabdomyosarcoma and undifferentiated sarcoma,

Ewing's sarcoma, non-Hodgkin lymphoma, hepatoblastoma, and AML. Either the use of doxorubicin or (liposomally entrapped) daunorubicin was evaluated.

For ALL three trials were identified, all evaluating the use of daunorubicin. Our meta-analysis of these three trials showed no evidence of a significant difference in overall survival between the treatment groups. Our meta-analysis of two trials also showed no evidence of a significant difference in event-free survival between the treatment groups (unexplained heterogeneity was detected). However, a long-term cardiac follow-up study of one of these studies (Van der Does 1989) mentioned that the five-year and 10-year event-free survival of patients treated with anthracyclines were significantly better than for patients treated without anthracyclines (P = 0.047 and P = 0.038, respectively) (Rammeloo 2000). Our meta-analysis of two trials showed no evidence of a significant difference in tumour response (defined as the number of patients in complete remission) between the treatment groups. Please note that the reason that no significant difference between the treatment groups was identified could be due to the fact that the numbers of patients included in these studies were too small to detect a difference between the treatment groups (that is low power). Also, the length of follow-up could be too short to detect a significant difference between the treatment groups. In most individual studies there is some suggestion of better survival in patients treated with anthracyclines. It should be noted that all these RCTs are performed in a different treatment era and not all RCTs stated the risk group(s) of included children. Nowadays most children with ALL are cured (Pieters 2008), while in the studies included in this review approximately 70% of the children survived.

For Wilms' tumour one trial was identified, evaluating the use of doxorubicin. Our analysis of all patients included in this trial showed a significant difference in overall survival in favour of treatment including anthracyclines as compared to treatment without anthracyclines (HR 1.85, 95% CI 1.09 to 3.15, P = 0.02). However, when patients with different stages of disease and different tumour histologies were analysed separately, this result was confirmed only in patients with stage II or III disease with unfavourable histology (HR 3.10, 95% CI 1.03 to 9.28, P = 0.04). For patients with stage II or III disease with favourable histology and patients with stage IV disease there was no evidence of a significant difference in overall survival between the treatment groups. However, with long-term follow-up (that is the exact length of follow-up was unclear, but at least some of the patients had a follow-up of 16 years), the overall result changed from a significant difference in favour of treatment with anthracyclines into no significant difference between the treatment groups. A possible explanation could be the mortality caused by different late effects (Mertens 2001; Reulen 2010). Our analysis of all patients included in this trial showed a significant difference in event-free survival in favour of treatment including anthracyclines as compared to treatment without anthracyclines (HR 2.21, 95% CI 1.44 to 3.40, P = 0.0003). However, when patients with different stages of disease and different tumour histologies were analysed separately, this result was confirmed only in patients with stage II or III disease with favourable histology (HR 2.56, 95% CI 1.42 to 4.61, P = 0.002). For patients with stage II or III disease with unfavourable histology and patients with stage IV disease there was no evidence of a significant difference in event-free survival between the treatment groups. The results of event-free survival did not change with long-term follow-up (HR 1.72, 95% CI 1.09 to 2.72, P = 0.02). No information on tumour response was provided and, therefore, no conclusions can be made regarding this outcome. Please note that the reason that a significant difference between the treatment groups was not found for all stages of disease and tumour histologies could be due to the fact that the numbers of patients included in these studies were too small to detect a difference between the treatment groups (that is low power). The direction of the results of the different stages of disease and different tumour histologies were the same as the overall result.

For rhabdomyosarcoma and undifferentiated sarcoma one trial was identified, evaluating the use of doxorubicin. Our analysis of all patients included in this trial showed no evidence of a significant difference in overall survival between the treatment groups. When patients in different clinical groups (that is clinical groups III and IV) were analysed separately, again no evidence of a significant difference between the treatment groups was identified. It was not possible to evaluate event-free survival in this study and, therefore, no conclusions can be made regarding this outcome. Our analysis showed no significant difference in tumour response (defined as the number of patients in complete or partial remission) between the treatment groups.

For Ewing's sarcoma one trial was identified, evaluating the use of doxorubicin. Descriptive results of overall survival and event-free survival identified evidence of a significant advantage for patients treated with anthracyclines as compared to patients treated without anthracyclines (P = 0.02 and P = 0.01, respectively). No information on tumour response was provided and, therefore, no conclusions can be made regarding this outcome.

For non-Hodgkin lymphoma one trial was identified, evaluating the use of daunorubicin. It was not possible to evaluate overall survival in this study and, therefore, no conclusions can be made regarding this outcome. Our analysis of event-free survival showed no evidence of a significant difference between the treatment groups. No information on tumour response was provided and, therefore, no conclusions can be made regarding this outcome.

For hepatoblastoma one trial was identified, evaluating the use of doxorubicin. No significant difference in overall survival, event-free survival and tumour response (defined as complete surgical resection, that is resection of all tumour sites on the basis of surgical findings and on postsurgical imaging) was identified between treatment including and treatment not including anthracyclines.

For AML one trial was identified, evaluating the use of daunoxome, that is liposomally entrapped daunorubicin. No significant difference in overall survival and tumour response (defined as complete response after two courses) was identified between treatment including and treatment not including anthracyclines. No information on event-free survival was provided and, therefore, no conclusions can be made regarding this outcome. In addition to overall survival for all randomised patients, this study reported overall survival in a subgroup of patients with relapsed core binding factor (CBF)-AML (that is t(8:21) or inv(16)). In patients randomised to treatment without anthracyclines (n = 34) overall survival at seven years was 58%, while in patients randomised to treatment with anthracyclines (n = 36) it was 82%. Since this was a post hoc analysis it was not included in the results of this review. The authors clearly stated that since this was a post hoc analysis this finding needs to be confirmed.

Please note that the reason that no significant difference between treatment groups was identified in patients with rhabdomyosarcoma and undifferentiated sarcoma, non-Hodgkin lymphoma, hepatoblastoma and AML could be due to the fact that the numbers of patients included in these studies were too small to detect a difference between the treatment groups (that is low power). Also, the length of follow-up could be too short to detect a significant difference between the treatment groups.

As mentioned earlier, one of the most serious adverse effects of anthracycline treatment is cardiotoxicity. Therefore, we did not only evaluate the antitumour efficacy of treatment with and without anthracyclines but also the occurrence of cardiotoxicity in both treatment groups. Our meta-analysis of two trials evaluating cardiac death showed no significant difference between the treatment groups. The same was true for our analysis of one trial evaluating congestive heart failure and our analysis of one trial evaluating acute grade 3 or 4 cardiotoxicity (according to the NCI CTC version 2). One study provided information on asymptomatic cardiac dysfunction but due to the high risk of attrition bias (this outcome was evaluated in only 49% of the patients) results of this study were not included in this systematic review. Please note that the reason that no significant difference between the treatment groups was identified could be due to the fact that the numbers of patients included in these studies were too small to detect a difference between the treatment groups (that is low power). Also, the length of follow-up could be too short to detect a significant difference between the treatment groups. There is some suggestion of a lower rate of clinical cardiotoxicity in patients who were not treated with anthracyclines.

Although there is only a small amount of data on the occurrence of anthracycline-induced cardiotoxicity available from RCTs, both clinical and asymptomatic anthracycline-induced cardiac damage has been evaluated in many non-randomised studies. These studies show that anthracycline-induced cardiotoxicity is a widely prevalent problem in children. The incidence of clinical heart failure has been reported to be as high as 16% at 0.9 to 4.8 years after treatment (Kremer 2002a) and the prevalence of asymptomatic cardiac dysfunction has been reported to be more than 57% at a median of 6.4 years after treatment (Kremer 2002b). The incidence of anthracycline-induced cardiotoxicity, both clinical and asymptomatic, seems to increase with a longer follow-up period (Green 2001; Kremer 2002b; Van Dalen 2006). For example, in a cohort study of 830 children with different types of tumour the estimated risk of anthracycline-induced clinical heart failure increased with time from 2% at two years after the first dose of anthracyclines to 5.5% at 15 years after the first dose of anthracyclines (Van Dalen 2006). In three of the four studies included in this review that adequately evaluated cardiotoxicity the length of follow-up was not mentioned, but it is likely that in all studies the follow-up was relatively short. In the other study the median follow-up was four years, but only acute cardiotoxicity was assessed. We did not include data on long-term cardiac follow-up from the included RCTs in this review because they included only data on some of the randomised patients and as a result the presence of selection bias could not be ruled out in these studies. Furthermore, in most long-term follow-up studies data for patients eligible for inclusion in our review could not be separated from results of patients ineligible for our review. However, in the study of Rammeloo 2000, which was a long-term cardiac follow-up study of Van der Does 1989, no late cardiac damage was demonstrated in 90 of the 136 eligible ALL survivors. The minimal follow-up was 11 years after the last dose of anthracycline therapy. The age at diagnosis ranged from 1.2 to 14.9 years; at the time of the study their age ranged from 14.7 to 31.3 years. It should be noted that in this RCT patients who were randomised to treatment with anthracyclines received a relatively low cumulative anthracycline dose (that is according to the protocol 100 mg/m^2 of daunorubicin) and that the occurrence of anthracycline-induced cardiotoxicity is dose-dependent (Green 2001; Kremer 2002a; Van Dalen 2006; Von Hoff 1979). However, it is important not to forget that although the risk of anthracycline-induced clinical heart failure is significantly increased with a cumulative anthracycline dose of 300 mg/m^2 or more (Van Dalen 2006), both clinical and asymptomatic cardiac dysfunction can occur with a lower cumulative anthracycline dose (Lipshultz 2005; Van Dalen 2006). The fact that the patients in the study of Rammeloo 2000 did not develop cardiac damage at the time of the study does not exclude the possibility that anthracycline-induced cardiotoxicity will become visible as they become older.

Just as the occurrence of anthracycline-induced cardiotoxicity is dose-dependent, it is possible that the cumulative anthracycline dose patients received influenced the antitumour efficacy of treatment. The exact cumulative anthracycline dose was not mentioned in any of the studies, but according to the different protocols the cumulative anthracycline dose ranged from 90 to 420 mg/m^2. It should be noted that in the AML study and two of the three ALL studies patients received a relatively low cumulative anthracycline dose, that is either 180 mg/m^2 (Kaspers 2013), 90 mg/m^2 (Eden 1991) or 100 mg/m^2 (Van der Does 1989). However, despite these low cumulative doses, in all studies there was still a suggestion of better antitumour efficacy with anthracycline therapy.

Patient age can be an important prognostic factor for the antitumour efficacy of treatments for different types of tumour (Biondi 2000; Gratias 2008; Pieters 2008). For example, in ALL infants aged less than one year or children aged 10 years or older have a worse outcome than children aged between one and nine years at diagnosis (Biondi 2000; Pieters 2008). Patient's age can also be a prognostic factor for the occurrence of cardiotoxicity (Kremer 2002a; Kremer 2002b). Unfortunately, due to a lack of useful data, these factors could not be evaluated in this review and, therefore, no conclusions can be made regarding age as a prognostic factor for these outcomes.

The risk of bias in the included studies varied. In most studies bias could not be ruled out due to lack of reporting. However, at the moment this is the best available evidence from RCTs evaluating treatment with and without anthracyclines in children with cancer. With regard to performance bias it should be noted that due to the nature of the interventions, blinding of care providers and patients was virtually impossible.

In this review we tried to only perform intention-to-treat (ITT) analyses, since they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000; Lee 1991). However, for the long-term results of D'Angio 1981 (Green 2004) and for Perilongo 2009 an ITT analysis was not possible and, therefore, we performed an as-treated analysis.

Eligible RCTs were identified for only seven types of tumour. No appropriate studies were found for other childhood cancers and, therefore, no conclusions can be made regarding the use of anthracyclines in the treatment of these tumours. It should be noted that in this review RCTs including both children and adults were only eligible for inclusion if the majority of participants were children, and the maximal age of the participants did not exceed 30 years. It is possible that there might be evidence on antitumour efficacy and cardiotoxicity of treatment with and without anthracyclines from studies including both children and adults (for examples see the Characteristics of excluded studies table).

We are awaiting the results of the currently ongoing studies and studies presented as abstracts during a conference on the use of anthracyclines for the following childhood cancers: hepatoblastoma (N = 1), ALL (N = 2), rhabdomyosarcoma (N = 1) and Wilms' tumour (N = 1).

AUTHORS' CONCLUSIONS

Implications for practice

Anthracycline-induced cardiotoxicity is a serious and widely prevalent problem in children treated for childhood cancer. Therefore, if anthracycline therapy does not have an added value with regard to antitumour efficacy and adverse effects compared to treatment without anthracyclines, it should not be used in treatment protocols for childhood cancer.

ALL

At the moment no evidence from RCTs is available which underscores the use of anthracyclines in ALL. However, it should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'; the fact that no significant difference in favour of treatment with anthracyclines was identified in this review can be the result of low power, a too short follow-up period, or the use of low cumulative anthracycline doses. Based on the currently available evidence, we are not able to favour treatment with or without anthracyclines in patients with ALL.

Wilms' tumour

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with a Wilms' tumour. A significant difference in survival in favour of the use of anthracyclines was identified in this study (especially for patients with stage II and III disease) but this finding should be confirmed in other RCTs. Also, it should be kept in mind that with long-term follow-up the result of the analysis of all available patients changed from a significant difference in overall survival in favour of treatment with anthracyclines into no significant difference between the treatment groups.

Rhabdomyosarcoma*and* undifferentiated sarcoma

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with a rhabdomyosarcoma and undifferentiated sarcoma. No difference in antitumour efficacy between treatment with and treatment without anthracyclines was identified, but this finding should be confirmed in other RCTs.

Ewing's sarcoma

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with Ewing's sarcoma. A significant difference in survival in favour of the use of anthracyclines was identified in this study, but this finding should be confirmed in other RCTs.

Non-Hodgkin lymphoma

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with a non-Hodgkin lymphoma. No difference in antitumour efficacy was identified between treatment with and without anthracyclines, but this finding should be confirmed in other RCTs.

Hepatoblastoma

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with a hepatoblastoma. No difference in antitumour efficacy between treatment with and without anthracyclines was identified, but this finding should be confirmed in other RCTs.

AML

Since only one RCT was identified, no definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients with AML. No difference in antitumour efficacy between treatment with and treatment without anthracyclines was identified (with the exception of overall survival in a post hoc analysis in a subgroup of patients with relapsed CBF-AML in which patients treated with anthracyclines had a better survival) but this finding should be confirmed in other RCTs.

Other childhood cancers

For other childhood cancers no RCTs were identified and, therefore, no conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients diagnosed with these malignancies.

Implications for research

ALL, Wilms' tumour, rhabdomyosarcoma and undifferentiated sarcoma, Ewing's sarcoma, non-Hodgkin lymphoma, hepatoblastoma, and AML

Future trials on the use of anthracyclines in patients with these types of tumour should be performed in homogeneous study populations with a long-term follow-up using valid outcome definitions (including antitumour efficacy and cardiotoxicity). Different risk groups, different cumulative anthracycline doses, and the age of the patients should be taken into account. It might be feasible to start these RCTs in children with unfavourable prognostic factors. The number of included patients should be sufficient to obtain the power needed for the results to be reliable. We are awaiting the results of the ongoing studies and the studies presented as abstracts during a conference, for patients with ALL, Wilms' tumour, hepatoblastoma and rhabdomyosarcoma. Also, it will be very interesting to examine long-term survival data from the already performed RCTs. The performance of an individual patient

data (IPD) analysis is another possibility to assess the antitumour efficacy of treatment with and without anthracyclines for these childhood cancers.

Other childhood cancers

No RCTs were identified for other childhood cancers. Therefore, before definitive conclusions can be made about the antitumour efficacy of treatment with or without anthracyclines in patients diagnosed with other malignancies, high quality RCTs need to be undertaken. Again, it might be feasible to start these RCTs in children with unfavourable prognostic factors. Also, these RCTs should be performed in homogeneous study populations with a long-term follow-up using valid outcome definitions (including antitumour efficacy and cardiotoxicity). Different risk groups, different cumulative anthracycline doses, and the age of the patients should be taken into account. The number of included patients should be sufficient to obtain the power needed for the results to be reliable. The performance of an IPD analysis is another possibility to assess the antitumour efficacy of treatment with and without anthracyclines for these childhood cancers.

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CHARACTERISTICS OF STUDIES

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

D'Angio 1981

Methods	Method of randomisation not clear (patients were stratified by institution, age and risk group)
Participants	316 children (age nm; 151 boys and 165 girls) with Wilms' tumour (stage II, III or IV; primary disease) No prior treatment Prior cardiac dysfunction nm
Interventions	Chemotherapy without doxorubicin (N = 159) versus chemotherapy including doxorubicin (N = 157) Cumulative doxorubicin dose nm (according to protocol 300 mg/m^2); peak dose (i.e. the maximal dose received in one week) 60 mg/m^2; infusion duration nm All patients underwent radiotherapy (dose adjusted to age; location adjusted to stage of disease) All patients underwent surgery (radical nephrectomy) No cardioprotective interventions
Outcomes	*Overall survival* (defined as time from surgery to death without regard to cause) *Event-free survival* (defined as the length of time between initial surgery and the earliest detection of abdominal recurrence, distant metastasis or death (whether or not tumour related)) *Cardiotoxicity* (clinical heart failure defined as cardiac death)
Notes	Length of follow-up nm Age in treatment and control group nm Long-term follow-up data of this study have been published (Green 2004) on 275 of 316 patients: 227 patients with stage II or III disease with favourable or unfavourable histology (as opposed to D'Angio 1981 where data were presented for favourable and unfavourable histology separately) and 48 patients with stage IV disease. The length of follow-up was nm but at least part of the patients had a follow-up of 16 years. Since in the stage IV group 20 patients were included in the no anthracycline group and 28 in the anthracycline group, as opposed to the original data where 22 patients were randomised to the anthracycline group and 27 to the non-anthracycline group, intention-to-treat analyses were not possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias

D'Angio 1981 *(Continued)*

Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival and cardiotoxicity
Incomplete outcome data (attrition bias): overall survival	Unclear risk	It was not clear if all participants were included in the analyses
Incomplete outcome data (attrition bias): event-free survival	Unclear risk	It was not clear if all participants were included in the analyses
Incomplete outcome data (attrition bias): anthracycline-induced cardiotoxicity	Unclear risk	It was not clear if all participants were included in the analyses
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (unclear if age, sex and prior cardiac dysfunction were balanced between treatment arms; no prior cardiotoxic treatment) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (the study was supported by a US Public Health Service Grant and by the National Institutes of Health, but no information on the influence of funders was provided)

D'Angio 1981 II-III FH

Methods	See D'Angio 1981
Participants	Subgroup of patients from D'Angio 1981: 232 children with stage II or III disease with favourable histology (age and sex nm). For further information: see D'Angio 1981
Interventions	Chemotherapy without doxorubicin (N = 121) versus chemotherapy including doxorubicin (N = 111). For further information: see D'Angio 1981
Outcomes	*Overall survival* (defined as time from surgery to death without regard to cause) *Event-free survival* (defined as the length of time between initial surgery and the earliest detection of abdominal recurrence, distant metastasis or death (whether or not tumour related))
Notes	See D'Angio 1981

D'Angio 1981 II-III FH UH

Methods	See D'Angio 1981.
Participants	Subgroup of patients from D'Angio 1981 with stage II or III disease with favourable (N = 232) or unfavourable histology (N = 35) (age and sex nm). For further information: see D'Angio 1981 II-III FH and D'Angio 1981 II-III UH
Interventions	Chemotherapy without doxorubicin (N = 137) versus chemotherapy including doxorubicin (N = 130). For further information: See D'Angio 1981
Outcomes	*Overall survival* (defined as time from surgery to death without regard to cause) *Event-free survival* (defined as the length of time between initial surgery and the earliest detection of abdominal recurrence, distant metastasis or death (whether or not tumour related))
Notes	See D'Angio 1981

D'Angio 1981 II-III UH

Methods	See D'Angio 1981
Participants	Subgroup of patients from D'Angio 1981: 35 children with stage II or III disease with unfavourable histology (age and sex nm). For further information: see D'Angio 1981
Interventions	Chemotherapy without doxorubicin (N = 16) versus chemotherapy including doxorubicin (N = 19). For further information: see D'Angio 1981
Outcomes	*Overall survival* (defined as time from surgery to death without regard to cause) *Event-free survival* (defined as the length of time between initial surgery and the earliest detection of abdominal recurrence, distant metastasis or death (whether or not tumour related))
Notes	See D'Angio 1981

D'Angio 1981 IV

Methods	See D'Angio 1981
Participants	Subgroup of patients from D'Angio 1981: 49 children with stage IV disease (age and sex nm). For further information: see D'Angio 1981
Interventions	Chemotherapy without doxorubicin (N = 22) versus chemotherapy including doxorubicin (N = 27). For further information: see D'Angio 1981
Outcomes	*Overall survival* (defined as time from surgery to death without regard to cause) *Event-free survival* (defined as the length of time between initial surgery and the earliest detection of abdominal recurrence, distant metastasis or death (whether or not tumour related))
Notes	See D'Angio 1981

Eden 1991

Methods	Method of randomisation not clear
Participants	630 children (age nm: an inclusion criterion for this study was age between 0 and 14 years; 337 boys and 293 girls) with acute lymphoblastic leukaemia (stage nm; nm if primary disease or relapse) Prior treatment nm Prior cardiac dysfunction nm
Interventions	Chemotherapy without daunorubicin (N = 308) versus chemotherapy including daunorubicin (N = 322) Cumulative daunorubicin dose nm (according to protocol 90 mg/m^2); peak dose (i.e. the maximal dose received in one week) 90 mg/m^2; infusion duration nm. Patients received cranial irradiation No surgery No cardioprotective interventions
Outcomes	*Overall survival* (definition nm) *Event-free survival* (defined as time to relapse or death; patients who died without going into remission were counted as having an event on day 1) *Tumour response* (definition nm; we assumed that the number of total remitters provided in the article was the number of complete remissions)
Notes	Length of follow-up nm Age in treatment and control group nm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Blinding of participants and personnel (performance bias)	High risk	Clinicians were "bound to record therapy given" and were thus not blinded to treatment. No information on blinding of participants was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias
Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival and tumour response
Incomplete outcome data (attrition bias): overall survival	Low risk	It was stated that all patients were included in the analyses

Eden 1991 *(Continued)*

Incomplete outcome data (attrition bias): event-free survival	Low risk	It was stated that all patients were included in the analyses
Incomplete outcome data (attrition bias): tumour response	Low risk	It was stated that all patients were included in the analyses
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it), but not all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (for all four items it was unclear if balanced between treatment arms) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (no information provided)

Kaspers 2013

Methods	Block randomisation (block size 4) with a central interactive computerized system (stratified by study group and time to relapse on a 1:1 basis)
Participants	394 children (age 0-19 years; 231 boys and 163 girls) with acute myeloid leukaemia (non-FAB type M3; stage nm; first relapse or primary refractory disease). Prior treatment yes (heterogenous first-line treatment, but all groups applied cytarabine-based treatment combined with an anthracycline and allogeneic stem cell transplant was used in a limited number of patients; no further information provided) No prior cardiac dysfunction (patients with symptomatic cardiac disease and/or left ventricular shortening fraction < 29% were excluded)
Interventions	Re-induction chemotherapy without daunoxome (=liposomally entrapped daunorubicin; N = 197) versus chemotherapy including daunoxome (N = 197) Cumulative daunoxome dose nm (according to protocol 180 mg/m^2); peak dose (i.e. the maximal dose received in one week) 180 mg/m^2; infusion duration nm Cranial irradiation was not recommended No surgery No cardioprotective interventions
Outcomes	*Overall survival* (defined as time from study enrolment untill last follow-up or death from any cause) *Tumour response* (complete response (after 2 courses) defined as 5% or less leukemic blasts in bone marrow with signs of normal haematopoiesis and of regeneration of normal peripheral blood cell production (platelets > 50x109/L without transfusions, neutrophils > 1.0x109/L) and no leukaemic cells in the peripheral blood or anywhere else)

Kaspers 2013 *(Continued)*

	Cardiotoxicity (grade 3 or 4 acute toxicity according to National Cancer Institute Common Toxicity Criteria version 2)
Notes	Median length of follow-up 4 years Age in treatment group ranged from 0 to 19 years (median 10 years); age in the control group ranged from 0 to 19 years (median 9 years) Re-induction chemotherapy was followed by allogeneic stem cell transplant if available (different conditioning regimens); otherwise patients received consolidation chemotherapy (different schedules). An inclusion criterium for this systematic review was that therapy other than anthracyclines should have been the same in both treatment groups; timing of different aspects of the treatment could differ between the treatment groups, but the cumulative doses of therapy other than anthracyclines should not differ more than 25% between the treatment groups. Although this was not completely clear for this study, it was stated that treatment was well-balanced between the treatment groups and therefore we gave this study the benefit of the doubt and judged it to be eligible for inclusion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation was performed using a central interactive computerised system
Allocation concealment (selection bias)	Low risk	Block randomisation was performed using a central interactive computerised system
Blinding of participants and personnel (performance bias)	High risk	It was an open label study
Blinding of outcome assessment (detection bias): overall survival	Low risk	Since this was an open label study, outcome assessors were not blinded. However, blinding of outcome assessors is not applicable for overall survival, so we judged this as a low risk of bias
Blinding of outcome assessment (detection bias): outcomes other than overall survival	High risk	It was an open label study
Incomplete outcome data (attrition bias): overall survival	Low risk	Intention-to-treat analyses were performed
Incomplete outcome data (attrition bias): tumour response	Low risk	Intention-to-treat analyses were performed
Incomplete outcome data (attrition bias): anthracycline-induced cardiotoxicity	High risk	7% of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	High risk	*Block randomisation in unblinded trials:* yes (see information provided at earlier associated risk of bias items)

Kaspers 2013 *(Continued)*

	Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction): unclear (age and sex were balanced between treatment arms; no prior cardiac dysfunction; unclear if prior cardiotoxic treatment was balaned between the treatment arms) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (there was no outside funding for the trial and daunoxome was not provided free of charge, but two authors had a consultant/advisory role at the pharmaceutical company which delivered daunoxome and where compensated for this)

Maurer 1988

Methods	Method of randomisation not clear (patients randomised within each clinical group)
Participants	413 children (age nm: an inclusion criterion for this study was age < 21 years; 240 males and 173 females) with rhabdomyosarcoma or undifferentiated sarcoma (clinical group III or IV; primary disease) No prior treatment Prior cardiac dysfunction nm
Interventions	Chemotherapy without doxorubicin (N = 208) versus chemotherapy including doxorubicin (N = 205) Cumulative doxorubicin dose nm (according to protocol 300 mg/m^2); peak dose (i.e. the maximal dose received in one week) 60 mg/m^2; infusion duration nm All patients received radiotherapy to the primary lesion (dose adjusted to age); in case of pulmonary metastases patients received pulmonary irradiation No surgery No cardioprotective interventions
Outcomes	*Overall survival* (defined as time from start of treatment to death) *Tumour response* (complete remission defined as complete disappearance of all signs and symptoms of disease; partial remission defined as at least 50% reduction in gross disease in widest diameter) *Cardiotoxicity* (clinical heart failure defined as congestive heart failure).
Notes	Length of follow-up nm Exact age in treatment and control group nm, but it was balanced between treatment groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided

Maurer 1988 *(Continued)*

Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias
Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for tumour response and cardiotoxicity
Incomplete outcome data (attrition bias): overall survival	Unclear risk	It was not clear if all participants were included in the analyses
Incomplete outcome data (attrition bias): tumour response	Low risk	Only 1% of participants were not evaluable for this outcome
Incomplete outcome data (attrition bias): anthracycline-induced cardiotoxicity	Unclear risk	It was not clear if all participants were included in the analyses
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (unclear if prior cardiotoxic treatment was balanced between treatment arms; age, sex, prior cardiac dysfunction were balanced between treatment arms) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (the study was supported by US Public Health Service Grants, but no information on the influence of funders was provided)

Maurer 1988 Group 3

Methods	See Maurer 1988
Participants	Subgroup of patients from Maurer 1988: 280 children in clinical group III (age and sex nm). The exact number of patients randomised to this subgroup is unclear. For further information: see Maurer 1988
Interventions	Chemotherapy without doxorubicin (N = 146) versus chemotherapy including doxorubicin (N = 134). For further information: see Maurer 1988
Outcomes	*Overall survival* (defined as time from start of treatment to death)

Maurer 1988 Group 3 *(Continued)*

Notes	See Maurer 1988

Maurer 1988 Group 4

Methods	See Maurer 1988
Participants	Subgroup of patients from Maurer 1988: 129 children in clinical group IV (age and sex nm). The exact number of patients randomised to this subgroup is unclear. For further information: see Maurer 1988
Interventions	Chemotherapy without doxorubicin (N = 61) versus chemotherapy including doxorubicin (N = 68). For further information: see Maurer 1988
Outcomes	*Overall survival* (defined as time from start of treatment to death)
Notes	See Maurer 1988

Nesbit 1990

Methods	Method of randomisation not clear (patients were randomised on a 2 to 3 patient basis to intervention and control group)
Participants	94 children (age nm; 56 boys and 38 girls) with non-metastatic Ewing's sarcoma of the bone (primary disease) No prior treatment Prior cardiac dysfunction nm
Interventions	Chemotherapy without doxorubicin (N = 37) versus chemotherapy including doxorubicin (N = 57) Cumulative doxorubicin dose nm (according to protocol maximal 420 mg/m^2); peak dose (i.e. the maximal dose received in one week) 60 mg/m^2; infusion duration nm Radiotherapy to primary lesion (dose adjusted to age) Part of the patients underwent surgical resection of the lesion: 3 in the intervention group and 19 in the control group No cardioprotective interventions
Outcomes	*Overall survival* (defined as time from start of treatment to death) *Event-free survival* (defined as time from start of treatment to first evidence of local recurrence or metastatic disease; patients dying before evidence of relapse were counted as failures) *Cardiotoxicity* (clinical heart failure defined as death of irreversible cardiac failure)
Notes	Length of follow-up nm Age in treatment and control group nm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Nesbit 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias
Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival and cardiotoxicity
Incomplete outcome data (attrition bias): overall survival	Low risk	All patients were included in the analyses
Incomplete outcome data (attrition bias): event-free survival	Low risk	All patients were included in the analyses
Incomplete outcome data (attrition bias): anthracycline-induced cardiotoxicity	Unclear risk	It was unclear if outcome data were available for all patients
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items and methods of the study) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (unclear if age and prior cardiac dysfunction were balanced between treatment arms; no prior cardiotoxic treatment; sex distribution was rather similar in both treatment arms) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (the study was supported by a Public Health Service Grant awarded by the National Cancer Institute, department of Health and Human Services, but no information on the influence of funders was provided)

Perilongo 2009

Methods	Randomisation by the United Kingdom Children's Cancer Study Group Data Centre (using the minimization method)

Perilongo 2009 *(Continued)*

Participants	255 patients (age 0 to 11.2 years; 155 males and 100 females) with standard risk hepatoblastoma (standard risk was defined as a PRETEXT classification I, II or III with no evidence of extra-hepatic disease; during the trial the protocol was amended to exclude patients with an alpha-fetoprotein level of less than 100 ng/mL, in view of mounting evidence of a poor outcome in these patients; primary disease) No prior treatment Prior cardiac dysfunction nm
Interventions	Chemotherapy without doxorubicin (N = 126) versus chemotherapy including doxorubicin (N = 129) Cumulative doxorubicin dose nm (according to protocol maximal 300 mg/m^2); peak dose (i.e. the maximal dose received in one week) 60 mg/m^2; infusion duration 30 mg/m^2/24 hours No radiotherapy Radical surgery of the tumour was attempted in all patients No cardioprotective interventions
Outcomes	*Overall survival* (defined as the interval between diagnosis and death from any cause or last contact) *Event-free survival* (defined as the interval between diagnosis and disease progression, relapse or death, whichever occurred first) *Tumour response* (defined as complete surgical resection, i.e. resection of all tumour sites on the basis of surgical findings and on postsurgical imaging) *Cardiotoxicity* (asymptomatic cardiac dysfunction defined as a left ventricular shortening fraction of < 30%; test to determine left ventricular shortening fraction nm)
Notes	Length of follow-up nm Age in treatment group ranged from 0 to 11.2 years (median 1 year); age in the control group ranged from 0.02 to 11.1 years (median 1.3 years) A total of 267 patients were randomized, but 12 patients were excluded (7 lacked proper documentation; 5 had wrong diagnosis; it was unclear to which treatment group these patients were randomized). As a result, intention-to-treat analyses were not possible

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using the minimization method
Allocation concealment (selection bias)	Low risk	Randomisation was performed by the United Kingdom Children's Cancer Study Group Data Centre
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias
Blinding of outcome assessment (detection bias):	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival, tumour response and cardiotoxicity

Perilongo 2009 *(Continued)*

outcomes other than overall survival		
Incomplete outcome data (attrition bias): overall survival	High risk	38% of participants lost to follow-up
Incomplete outcome data (attrition bias): event-free survival	High risk	36% of participants lost to follow-up
Incomplete outcome data (attrition bias): tumour response	Low risk	Only 1.6% of participants lost to follow-up
Incomplete outcome data (attrition bias): anthracycline-induced cardiotoxicity	High risk	51% of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* not applicable (block randomization was not used) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (age, sex and prior cardiotoxic treatment were balanced between treatment arms; for prior cardiac dysfunction this was unclear) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (no information provided)

Sposto 2001

Methods	Method of randomisation not clear (patients were stratified according to histology (large cell versus non-large cell) and principal disease site (abdomen versus other)
Participants	284 patients (age nm: an inclusion criterion for this study was age < 21 years; 197 males and 87 females) with non-lymphoblastic Non-Hodgkin lymphoma (stage I to IV; nm if primary disease or relapse) Prior treatment nm Prior cardiac dysfunction nm
Interventions	Chemotherapy without daunorubicin (N = 139) versus chemotherapy including daunorubicin (N = 145) Cumulative daunorubicin dose nm (according to protocol 350 mg/m^2); peak dose (i.e. the maximal dose received in one week) 50 mg/m^2; infusion duration nm Craniospinal radiotherapy if CNS disease at diagnosis, parameningeal disease, or isolated CNS relapse (dose depending on reason to give radiotherapy) No surgery

Sposto 2001 *(Continued)*

	No cardioprotective interventions
Outcomes	*Event-free survival* (defined as the minimal time from study entry to failure to induce remission, disease progression, disease relapse, the occurrence of secondary malignant disease or death from any cause; isolated CNS relapses as first event for which treatment was specified in the protocol are not counted as events in this definition although subsequent CNS relapses or persistent CNS disease were counted as events)
Notes	Length of follow-up nm Exact age in treatment and control group nm, but it was balanced between treatment groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival
Incomplete outcome data (attrition bias): event-free survival	Unclear risk	Unclear if all patients were included in the analyses
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it), but not all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (age and sex were balanced between treatment arms; for prior cardiotoxic treatment and prior cardiac dysfunction this was unclear) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (the study was supported by the Division of Cancer Treatment, National Cancer Institution, National Institutes of Health and the Department of Health and Human Services, but no information on the influence of funders was provided)

Van der Does 1975

Methods	Method of randomisation not clear

Van der Does 1975 *(Continued)*

Participants	42 children (age nm: an inclusion criterion for this study was age between 1 and 14 years; sex nm) with acute lymphocytic leukaemia (stage nm; primary disease) No prior treatment Prior cardiac dysfunction unclear
Interventions	Chemotherapy without daunorubicin (N = 22) versus chemotherapy including daunorubicin (N = 20) Cumulative daunorubicin dose nm (according to protocol maximal 300 mg/m^2); peak dose (i.e. the maximal dose received in one week) 30 mg/m^2; infusion duration nm No radiotherapy or surgery No cardioprotective interventions
Outcomes	*Overall survival* (definition nm)
Notes	Length of follow-up for all patients maximal 18 months Age in treatment and control group nm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that this was a randomised study, but no further information on the methods of randomisation was provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias
Incomplete outcome data (attrition bias): overall survival	Low risk	All patients were included in the analyses
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it), but not all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (unclear if age, sex and prior cardiac dysfunction were balanced between treatment arms; no prior cardiotoxic treatment) *Difference in length of follow-up between treatment arms:* unclear (not reported)

Van der Does 1975 *(Continued)*

	Inappropriate influence of funders: unclear (the study was supported by Ministerie van Volksgezondheid en Milieuhygiëne, but no information on the influence of funders was provided)

Van der Does 1989

Methods	Randomisation by the DCLSG Central Office (patients were stratified by institution and sex)
Participants	240 children (age 0 to 15 years; 119 boys and 121 girls) with standard risk acute lymphocytic leukaemia (nm if primary disease or relapse) Prior treatment nm Prior cardiac dysfunction nm
Interventions	Chemotherapy without daunorubicin (N = 122) versus chemotherapy including daunorubicin (N = 118) Cumulative daunorubicin dose nm (according to protocol 100 mg/m^2); peak dose (i.e. the maximal dose received in one week) 25 mg/m^2; infusion duration nm. Patients achieving complete remission within 6 weeks of the start of induction chemotherapy underwent cranial irradiation (dose adjusted to age) in combination with intrathecal methotrexate and prednisone No surgery No cardioprotective interventions
Outcomes	*Overall survival* (defined as time from diagnosis to time of death) *Event-free survival* (defined as time from diagnosis to induction failure, relapse, death in remission, or the occurrence of a second tumour) *Tumour response* (complete remission defined as < 5% blast cells and normal hematopoiesis in the bone marrow without evidence of disease at any other site)
Notes	Median follow-up for all patients 64 months (range 34 to 87 months) Age in treatment group ranged from 0 to 15 years; age in the control group ranged from 1 to 15 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that randomisation was peformed by the DCLSG Central Office, but no further information on the methods of randomization was provided
Allocation concealment (selection bias)	Low risk	Randomisation was performed by the DCLSG Central Office
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias): overall survival	Low risk	No information on blinding of outcome assessors was provided, but since this is not applicable for overall survival we judged this as a low risk of bias

Van der Does 1989 *(Continued)*

Blinding of outcome assessment (detection bias): outcomes other than overall survival	Unclear risk	No information on blinding of outcome assessors was provided for event-free survival and tumour response
Incomplete outcome data (attrition bias): overall survival	Low risk	All patients were included in the analyses
Incomplete outcome data (attrition bias): event-free survival	Low risk	All patients were included in the analyses
Incomplete outcome data (attrition bias): tumour response	Low risk	All patients were included in the analyses
Selective reporting (reporting bias)	High risk	There was no protocol mentioned in the manuscript (and we did not search for it), but not all expected outcomes were reported
Other bias	Unclear risk	*Block randomisation in unblinded trials:* unclear (see information provided at earlier associated risk of bias items) *Baseline imbalance between treatment arms related to outcome (prior cardiotoxic treatment, age, sex and/or prior cardiac dysfunction)*: unclear (age and sex were balanced between treatment arms; this was unclear for prior cardiotoxic treatment and prior cardiac dysfunction) *Difference in length of follow-up between treatment arms:* unclear (not reported) *Inappropriate influence of funders:* unclear (no information provided)

nm: not mentioned; DCLSG: Dutch Childhood Leukemia Study Group; CNS: central nervous system; FH: favourable histology; UH: unfavourable histology; FAB: French-American-British

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

Study	Reason for exclusion
Alvegard 1989a	Including adults aged 30 years or more
Alvegard 1989b	Double publication of Alvegard 1989a
Alvegard 1990	Including adults aged 30 years or more
Anonymous 1987	Adults aged 30 years or more
Antillon 2008	No RCT (2 different protocols)
Antman 1984a	Including adults aged 30 years or more
Antman 1984b	Including adults aged 30 years or more
Antman 1985	Double publication of Antman 1984a

Study	Reason for exclusion
Antman 1987	Including adults aged 30 years or more
Antman 1990	Review (no eligible studies)
Aur 1972	No RCT; all patients received anthracyclines
Bacci 1989	No RCT; including adults aged 30 years or more
Balwierz 2013	No randomization to treatment with and without anthracyclines; consecutive trials; all patients received anthracyclines
Barr 1992	No RCTs; all patients received anthracyclines
Bellani 1978	No RCT; all patients received anthracyclines; including adults aged 30 years or more
Berman 1989	Comparison of two types of anthracycline analogues; adults aged 30 years or more
Bernthal 2012	Difference in treatment other than anthracyclines between study groups; possibly all patients received anthracyclines; possibly including adults aged 30 years or more
Bessho 1994	No RCT
Biondi 2006	No RCT
Birch 1986	Including adults aged 30 years or more
Blakely 2003	Subgroup of patients from different RCTs; comparison of chemotherapy and surgery versus only surgery
Bradford 1998	No RCT
Breslow 2004	Subgroup of patients from different RCTs
Brouwer 2007	Follow-up study of Van der Does 1989, but only 23/240 patients (9.5%) included; no survival data presented
Burnett 2006	All patients received anthracyclines
Caceres 1978	No RCT; preliminary results of Zaharia 1986
Canter 2007	No RCT; including adults aged 30 years or more
Carlsen 1989	No RCT
Castellino 2008	All patients received anthracyclines
Chau 2003	No RCT; adults aged 30 years or more
Chessells 1992	All patients received anthracyclines
Chessells 2002	No randomisation between treatment with and without anthracyclines
Craft 1993	Review (no eligible studies)
Creutzig 2005	Review (no eligible studies)

Study	Reason for exclusion
Creutzig 2006	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines
Crist 1995	No data provided for only randomised patients
Culbert 1991	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines
D'Angio 1989	More than a 25% difference in cumulative doses of agents other than anthracyclines between study groups
De Bernardi 2003	No RCTs; all patients received anthracyclines
De Bernardi 2009	No RCT; treatment with and without anthracyclines not evaluated
Dluzniewska 2003	No RCT; all patients received anthracyclines
Dobashi 2006	Unclear if RCT; including adults aged 30 years or more; all patients received anthracyclines
Dunst 1998	Commentary on ineligible study
Eilber 1988	All patients received anthracyclines; including adults aged 30 years or more
Einhorn 1981	Including adults aged 30 years or more
Elomaa 1993	Review (no eligible studies)
Etcubanas 1984	No RCT
Evans 1985	Subgroup of patients from different RCT
Evans 1991	Subgroup of patients from different RCTs
Fink 1990	No RCT; all patients received anthracyclines
Frappaz 2002	No randomisation between treatment with and without anthracyclines; only poor responders received anthracyclines
Fukuoka 1994	Adults aged 30 years or more; all patients received anthracyclines
Gallegos-Castorena 2009	No RCTs (3 different protocols); all patients received anthracyclines
Garbes 1987	Most likely no RCT; including adults aged 30 years or more
Gaynon 1993	Difference in treatment other than anthracyclines between study groups
Gelderblom 2011	All patients received anthracyclines
Glanzmann 1998	No RCT; difference in treatment other than anthracyclines between study groups; including adults aged 30 years or more
Green 1994	Subgroup of patients from different RCTs
Green 1996	Subgroup of patients from different RCTs

Study	Reason for exclusion
Green 1999	Subgroup of patients from different RCTs
Grier 1990	Most likely no RCT; all patients received anthracyclines
Grundy 2012	No RCT
Gururangan 2000	Review (one study eligible for inclusion: published full text as Sposto 2001)
Hainsworth 1985	Unclear if RCT; including adults aged 30 years or more
Halazun 1974	Unclear if treatment other than anthracyclines was the same in both treatment groups; no survival data presented
Harms 2000	No RCT; review (no eligible studies)
Hayashi 2008	Unclear if RCT; including adults aged 30 years or more; results treatment with and without anthracyclines were not presented
Hays 1988	Subgroup of patients from different RCT
Henze 1989	Review (no eligible studies)
Hitchcock-Bryan 1986	After the initial randomisation to treatment with and without anthracyclines all patients received anthracyclines; outcomes were measured at the time all patients received anthracyclines; update of Sallan 1977
Hodgson 2003	No RCT; including adults aged 30 years or more
Holland 1971	Difference in treatment other than anthracyclines between study groups
Humphrey 1975	No data on any of the eligible outcomes provided
Iarussi 2003	No RCT
Ihde 1977	No RCT; including adults aged 30 years or more
Isu 1992	No RCT
Iwenofu 2008	No RCT; including adults aged 30 years or more
Jaffe 1981	No RCT
Janka-Schaub 1988	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines
Kalapurakal 2010	Included patients from different studies; no randomisation between treatment with and without anthracyclines
Karachunskii 2007	Double publication of Karachunskiy 2008
Karachunskiy 2008	All patients received anthracyclines
Kaspers 2010	Conference proceeding of Kaspers 2013
Kazanowska 2006	No RCT; all patients received anthracyclines

Study	Reason for exclusion
Khattab 2008	No RCT; all patients received anthracyclines
Kinsella 1991	No RCT; including adults aged 30 years or more
Kobe 2008	Including adults aged 30 years or more; all patients received anthracyclines
Komp 1976	Some patients were randomised to treatment with and without anthracyclines; unclear if treatment other than anthracyclines was the same in that subgroup; results treatment with and without anthracyclines were not presented
Konopka 1989	Most likely no RCT; difference in treatment other than anthracyclines between study groups; including adults aged 30 years or more
Kuleva 2008	No RCT
Kurrle 1988	All patients received anthracyclines; including adults aged 30 years or more
Lager 2006	Review (no eligible studies)
Li 2006	No RCT; all patients received anthracyclines
Lilleyman 1997	No RCT
Lindberg 1977	Review (no eligible studies)
Link 1986	Difference in treatment other than anthracyclines between study groups
Madej 1987	Most likely no RCT; including adults aged 30 years or more
Madon 1985	Review (no eligible studies)
Mahajan 2008	No RCT; including adults aged 30 years or more; all patients received anthracyclines
Mahmoud 1993	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines
Maiakova 1986	No RCT
Malpas 1974	Unclear if RCT; including adults aged 30 years or more
Marcus 1987	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines; including adults aged 30 years or more
Matsuzaki 2001	No RCT
Maurer 1981	Preliminary report of Maurer 1988
Meisel 1999	Subgroup of patients from different RCTs
Meza 2006	No data on patients randomised to treatment with and without anthracyclines presented; subgroup of patients included in Crist 1995
Miser 1993	Review (no eligible studies)
Moricke 2008	All patients received anthracyclines

Study	Reason for exclusion
Muus 1993	No RCT; including adults aged 30 years or more
Nachman 1993	Review (no eligible studies)
Nishimura 1983	Unclear if RCT; including adults aged 30 years or more
Ochiai 1993	Review
Oh 2006	No RCT; including adults aged 30 years or more
Okamura 1987	No RCT
Omura 1985	Adults aged 30 years or more
Ortega 1991	Subgroup of patients from different RCTs; data not presented for patients receiving or not receiving anthracyclines
Paulino 1996	Probably no RCT; difference in treatment other than anthracyclines between study groups
Paulino 2003	No RCT; including adults aged 30 years or more
Pavlovsky 1981	No RCT; including adults aged 30 years or more
Pawson 2001	No RCT; including adults aged 30 years or more
Peeters 2009	No RCT
Perez 1981	Including adults aged 30 years or more
Pfreundschuh 2008	Including adults aged 30 years or more; all patients received anthracyclines
Picci 1997	No RCT; including adults aged 30 years or more
Pontz 1981	Most likely no RCT; difference in treatment other than anthracyclines between study groups
Pratt 1981	No RCT
Pratt 1993	Review (no eligible studies)
Pritchard-Jones 2011	Double publication of SIOP2001
Pritchard-Jones 2012	No randomisation to treatment with and without anthracyclines
Quattrin 1975	Review (no eligible studies)
Rai 1981	No randomisation to treatment with and without anthracyclines; all patients received anthracyclines; including adults aged 30 years or more
Rammeloo 2000	Subgroup of patients from Van der Does 1989
Raney 1983	Subgroup of patients from different RCT
Raney 1987	No randomisation to treatment with and without anthracyclines
Raney 1988	Subgroup of patients from different RCT

Study	Reason for exclusion
Raney 1990	Subgroup of patients from different RCTs
Raza 2008	No RCT; including adults aged 30 years or more
Rees 1990	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines; including adults aged 30 years or more
Ritchey 1994	Subgroup of patients from different RCT
Ritter 1990	No RCT; all patients received anthracyclines
Roy 2005	No randomisation between treatment with and without anthracyclines
Sakic 2006	All patients received anthracyclines
Sallan 1977	After the initial randomisation to treatment with and without anthracyclines all patients received anthracyclines; preliminary results of Hitchcock-Bryan 1986
Salodof MacNeil 2010	No original research; commentary (no eligible studies)
Schaison 1992	Review (no eligible studies)
Scherrer 1994	Probably no RCT; all patients received anthracyclines; including adults aged 30 years or more
Schmits 2001	Review (no eligible studies)
Seibel 2008	All patients received anthracyclines
Silverman 2000	Review (no eligible studies)
Skoczen 2006	No RCT
Smithson 1982	No RCT; case report
Sotnikov 1989	Most likely no RCT; difference in treatment other than anthracyclines between study groups; including adults aged 30 years or more
Spears 1992	No RCT
Spreafico 2008	No RCT
Sramkova 2013	No RCT; historical controls
Stary 2003	No randomisation between treatment with and without anthracyclines
Steinherz 1993	All patients received the same agents; only the order and mode of administration were different between study groups
Steinherz 1996	Double publication of Gaynon 1993
Steinherz 1998	No RCT; difference in treatment other than anthracyclines between study groups
Tarella 2001	No RCT; difference in treatment other than anthracyclines between study groups; including adults aged 30 years or more

Study	Reason for exclusion
Taylor 2006	Including adults aged 30 years or more
Tefft 1978	Preliminary report of Evans 1985
Thirugnanam 2009	No RCT; including adults aged 30 years or more
Thomas 1988	Subgroup of patients from different RCT; no data on survival presented
Toft 2013	No RCT; all patients received anthracyclines
Tournade 1993	More than a 25% difference in cumulative doses of agents other than anthracyclines between study groups
Tsuchiya 1998	No RCT; difference in treatment other than anthracyclines between study groups; including adults aged 30 years or more
Van der Does 1988	Double publication of Van der Does 1989
Vinogradova 2008	Unclear if RCT; including adults aged 30 years or more (Russian article, no further information sought)
Virchis 2004	No RCT; including adults aged 30 years or more
Vora 2010	No randomisation to treatment with and without anthracyclines
Vose 1994	Probably no RCT; all patients received anthracyclines; including adults aged 30 years or more
Watts 2002	No RCT
Weinstein 1992	Review (no eligible studies)
Wilimas 1988	No RCT
Willemze 1982	No RCT; all patients received anthracyclines; including adults aged 30 years or more
Willnow 1986	No RCT; all patients received anthracyclines
Zaharia 1986	No RCT; update of Caceres 1978
Zdrahalova 2011	Double publication of Kaspers 2013
Zimmermann 2012	No randomisation to treatment with and without anthracyclines
Zintl 1987	No randomisation between treatment with and without anthracyclines; all patients received anthracyclines
Zittoun 1992	Difference in treatment other than anthracyclines between study groups; all patients received anthracyclines; including adults aged 30 years or more

RCT: randomised controlled trial; SIOP: International Society for Paediatric Oncology

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

FRALLE 2000-A

Methods	Method of randomisation not clear
Participants	524 children (aged 1 to 9 years; sex nm) with standard-risk B-cell precursor acute lymphoblastic leukaemia with a good marrow response at day 21 (M1). Prior therapy not mentioned; prior cardiac dysfunction not mentioned
Interventions	Treatment including (N = 247) or not including (N = 248) daunorubicin
Outcomes	No difference in efficacy and toxicity between the study groups at a follow-up of 31 months (unclear if this is a mean or median; range 3 to 59 months)
Notes	This study has not been published in full text (October 2013), but has been presented at the SIOP conference 2006

SIOP2001

Methods	Method of randomisation not clear (stratified by participating group and tumour stage)
Participants	583 children with intermediate risk stage II or III Wilms' tumour (aged 6 months to 18 years)
Interventions	Postoperative chemotherapy including (N=291) or not including (N=292) doxorubicin (total dose 250 mg/m^2)
Outcomes	No difference in 2 year EFS and 5 year OS between the study groups at a median follow-up of 39 months
Notes	This study has not been published in full text (October 2013), but has been presented at the SIOP conference 2011

Von Stackelberg 2011

Methods	Method of randomisation not clear
Participants	420 children with relapsed acute lymphoblastic leukaemia (aged 18 years or less)
Interventions	Unclear from the current information: patients might have received anthracyclines in both treatment groups (N=210 in each group) and if not, there might be a difference in treatment other than anthracyclines between study groups
Outcomes	No difference in 5 year EFS, 5 year OS and treatent related mortality between the treatment groups, significantly less relapses and mucositis, but significantly more hematological toxicity in the patients who definitely received anthracyclines (idarubicin)
Notes	This study has not been published in full text (October 2013), but has been presented at the ASH conference 2011 It is not yet clear if this study is eligible for inclusion in this review

EFS: event-free survival; OS: overall survival; SIOP: International Society for Paediatric Oncology; ASH: America Society of Hematology

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

COG AHEP0531

Trial name or title	Not mentioned
Methods	Method of randomisation not clear
Participants	Children with intermediate risk hepatoblastoma
Interventions	Cisplatin, vincristine, 5-fluorouracil with and without doxorubicin
Outcomes	Not mentioned
Starting date	Not mentioned
Contact information	Not mentioned
Notes	-

NCT00379457

Trial name or title	A protocol for nonmetastatic rhabdomyosarcoma [RMS-2005]
Methods	Method of randomisation not clear (patients are stratified according to risk group and participating country)
Participants	Children with high-risk rhabdomyosarcoma (maximal age 20 years)
Interventions	Ifosfamide, vincristine, dactinomycin with or without doxorubicin
Outcomes	Response rate, survival and toxicity
Starting date	June 2006
Contact information	Study chairs Gianni Bisogno, Meriel Jenney, Joern Treuner and Hans Merks
Notes	It is unclear from the current information if the cumulative doses of agents other than anthracyclines differ less than 25% between study groups.

DATA AND ANALYSES

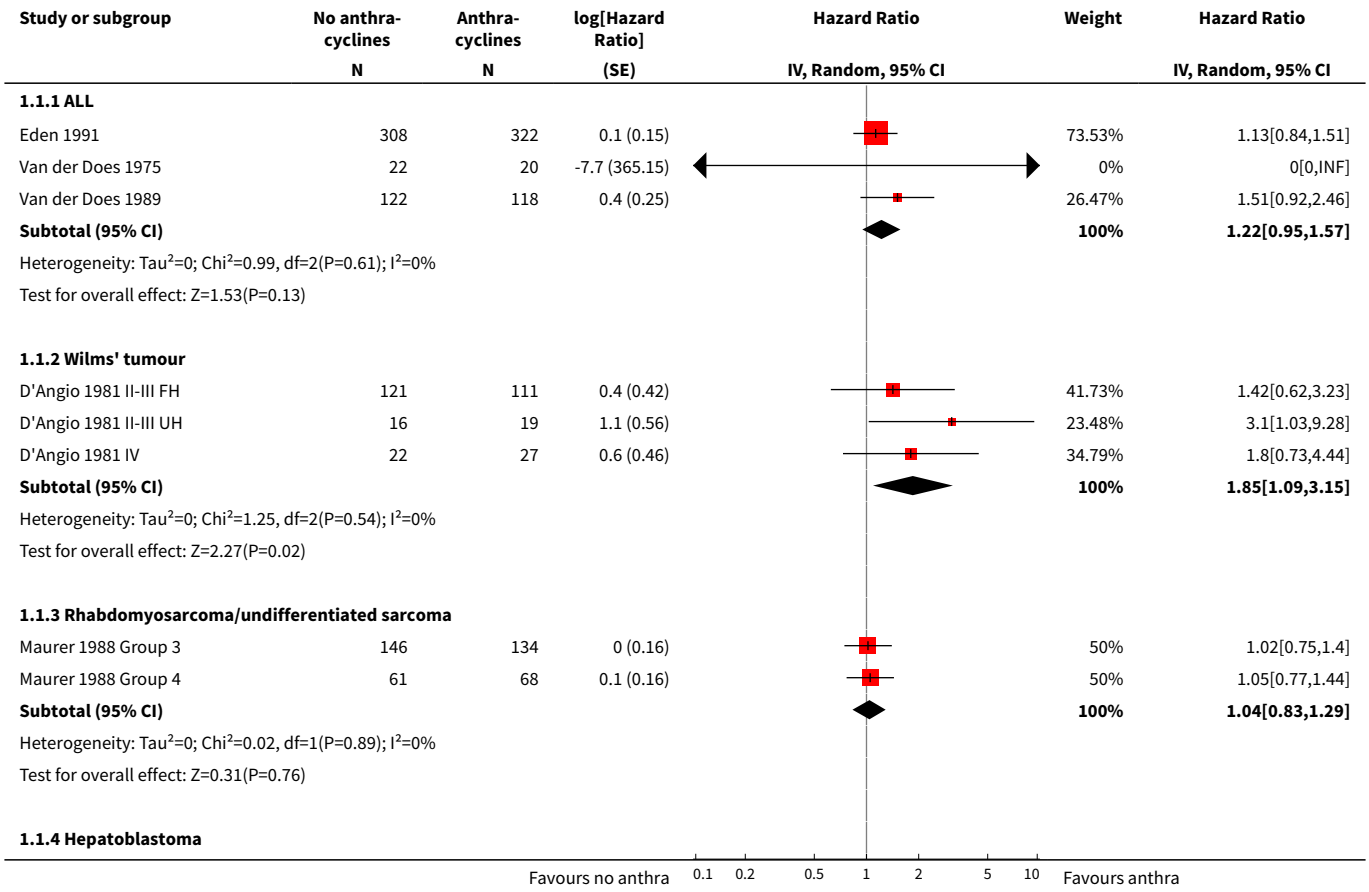
Comparison 1. No anthracyclines versus anthracyclines

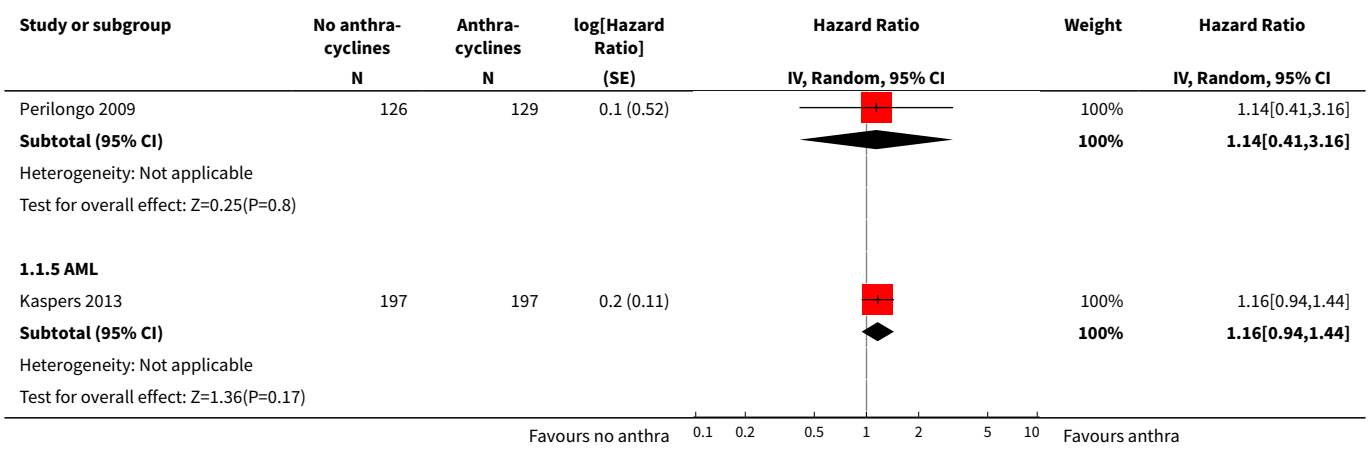
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (Parmar's method was used to obtain the necessary data for the meta-analysis)	10		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 ALL	3	912	Hazard Ratio (Random, 95% CI)	1.22 [0.95, 1.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Wilms' tumour	3	316	Hazard Ratio (Random, 95% CI)	1.85 [1.09, 3.15]
1.3 Rhabdomyosarcoma/undifferentiated sarcoma	2	409	Hazard Ratio (Random, 95% CI)	1.04 [0.83, 1.29]
1.4 Hepatoblastoma	1	255	Hazard Ratio (Random, 95% CI)	1.14 [0.41, 3.16]
1.5 AML	1	394	Hazard Ratio (Random, 95% CI)	1.16 [0.94, 1.44]
2 Event-free survival (Parmar's method was used to obtain the necessary data for the meta-analysis)	7		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 ALL	2	870	Hazard Ratio (Random, 95% CI)	1.05 [0.76, 1.46]
2.2 Wilms' tumour	3	316	Hazard Ratio (Random, 95% CI)	2.21 [1.44, 3.40]
2.3 Non-Hodgkin lymphoma	1	284	Hazard Ratio (Random, 95% CI)	1.01 [0.74, 1.38]
2.4 Hepatoblastoma	1	255	Hazard Ratio (Random, 95% CI)	0.81 [0.42, 1.55]
3 Tumour response	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ALL	2	870	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
3.2 Rhabdomyosarcoma / undifferentiated sarcoma	1	413	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.09]
3.3 Hepatoblastoma	1	255	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
3.4 AML	1	394	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
4 Clinical cardiotoxicity	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Cardiac death	2	410	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.04, 3.89]
4.2 Cardiotoxicity grade 3 or 4 according to NCICTC version 2	1	394	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.02, 1.70]
5 Overall survival Wilms' tumour long-term follow-up (Parmar's	2	275	Hazard Ratio (Random, 95% CI)	1.27 [0.77, 2.11]

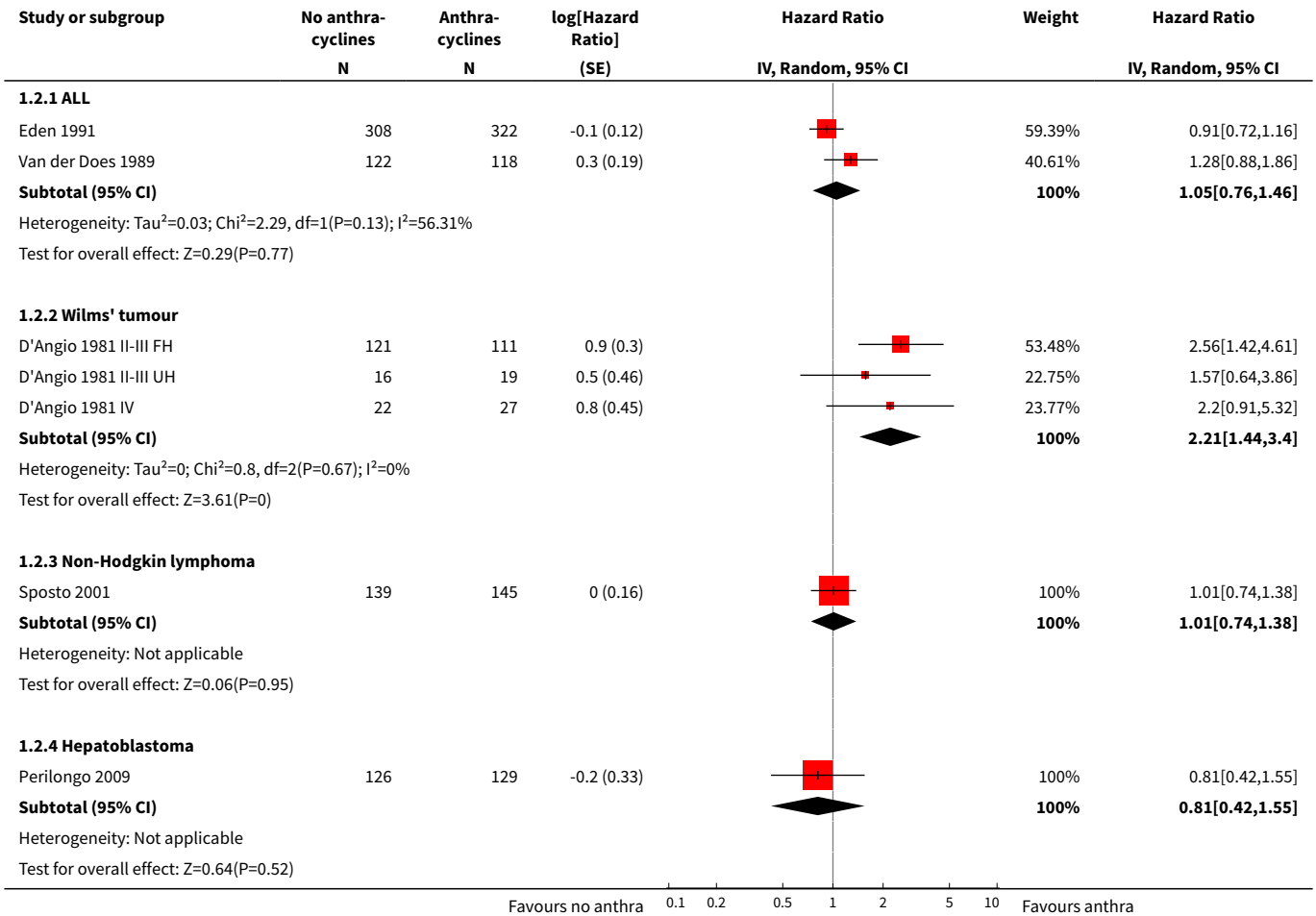
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
method was used to obtain the necessary data for the meta-analysis)				
5.1 Stage II-III FH and UH	1	227	Hazard Ratio (Random, 95% CI)	1.16 [0.62, 2.18]
5.2 Stage IV	1	48	Hazard Ratio (Random, 95% CI)	1.51 [0.65, 3.50]
6 Event-free survival Wilms' tumour long-term follow-up (Parmar's method was used to obtain the necessary data for the meta-analysis)	2	275	Hazard Ratio (Random, 95% CI)	1.72 [1.09, 2.72]
6.1 Stage II-III FH and UH	1	227	Hazard Ratio (Random, 95% CI)	1.80 [1.04, 3.12]
6.2 Stage IV	1	48	Hazard Ratio (Random, 95% CI)	1.54 [0.66, 3.57]

Analysis 1.1. Comparison 1 No anthracyclines versus anthracyclines, Outcome 1 Overall survival (Parmar's method was used to obtain the necessary data for the meta-analysis).



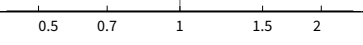


Analysis 1.2. Comparison 1 No anthracyclines versus anthracyclines, Outcome 2 Event-free survival (Parmar's method was used to obtain the necessary data for the meta-analysis).



Analysis 1.3. Comparison 1 No anthracyclines versus anthracyclines, Outcome 3 Tumour response.

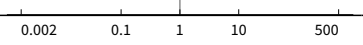
Study or subgroup	No anthracyclines n/N	Anthracyclines n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 ALL					
Eden 1991	299/308	303/322		72.6%	1.03[1,1.07]
Van der Does 1989	115/122	112/118		27.4%	0.99[0.93,1.06]
Subtotal (95% CI)	**430**	**440**		**100%**	**1.02[0.99,1.06]**
Total events: 414 (No anthracyclines), 415 (Anthracyclines)					
Heterogeneity: Tau^2=0; Chi^2=1.17, df=1(P=0.28); I^2=14.77%					
Test for overall effect: Z=1.22(P=0.22)					
1.3.2 Rhabdomyosarcoma / undifferentiated sarcoma					
Maurer 1988	170/208	168/205		100%	1[0.91,1.09]
Subtotal (95% CI)	**208**	**205**		**100%**	**1[0.91,1.09]**
Total events: 170 (No anthracyclines), 168 (Anthracyclines)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
1.3.3 Hepatoblastoma					
Perilongo 2009	120/126	121/129		100%	1.02[0.96,1.08]
Subtotal (95% CI)	**126**	**129**		**100%**	**1.02[0.96,1.08]**
Total events: 120 (No anthracyclines), 121 (Anthracyclines)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
1.3.4 AML					
Kaspers 2013	117/197	135/197		100%	0.87[0.75,1.01]
Subtotal (95% CI)	**197**	**197**		**100%**	**0.87[0.75,1.01]**
Total events: 117 (No anthracyclines), 135 (Anthracyclines)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					



Favours anthra — Favours no anthra

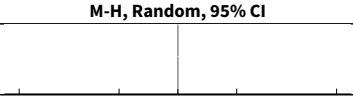
Analysis 1.4. Comparison 1 No anthracyclines versus anthracyclines, Outcome 4 Clinical cardiotoxicity.

Study or subgroup	No anthracyclines n/N	Anthracyclines n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Cardiac death					
D'Angio 1981	0/159	1/157		49.71%	0.33[0.01,8.02]
Nesbit 1990	0/37	1/57		50.29%	0.51[0.02,12.17]
Subtotal (95% CI)	**196**	**214**		**100%**	**0.41[0.04,3.89]**
Total events: 0 (No anthracyclines), 2 (Anthracyclines)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.78(P=0.44)					
1.4.2 Cardiotoxicity grade 3 or 4 according to NCICTC version 2					
Kaspers 2013	1/197	5/197		100%	0.2[0.02,1.7]
Subtotal (95% CI)	**197**	**197**		**100%**	**0.2[0.02,1.7]**
Total events: 1 (No anthracyclines), 5 (Anthracyclines)					



Favours no anthra — Favours anthra

Study or subgroup	No anthracyclines	Anthracyclines	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



Favours no anthra — Favours anthra

Analysis 1.5. Comparison 1 No anthracyclines versus anthracyclines, Outcome 5 Overall survival Wilms' tumour long-term follow-up (Parmar's method was used to obtain the necessary data for the meta-analysis).

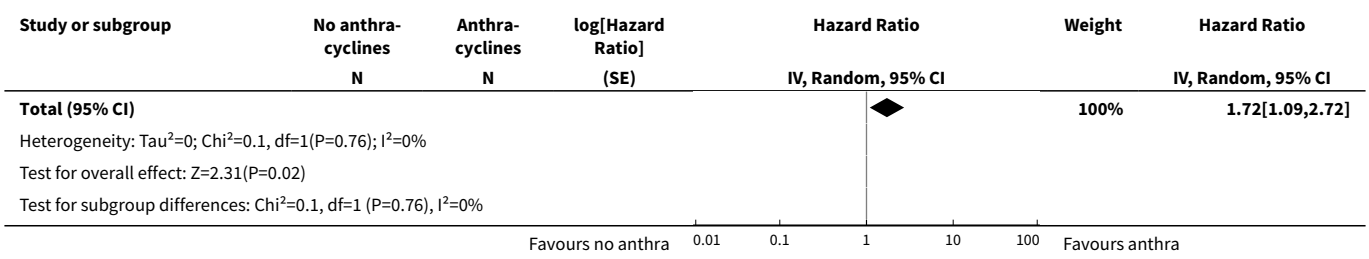
Study or subgroup	No anthracyclines	Anthracyclines	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
1.5.1 Stage II-III FH and UH						
D'Angio 1981 II-III FH UH	121	106	0.2 (0.32)		64.36%	1.16[0.62,2.18]
Subtotal (95% CI)					**64.36%**	**1.16[0.62,2.18]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.47(P=0.64)						
1.5.2 Stage IV						
D'Angio 1981 IV	20	28	0.4 (0.43)		35.64%	1.51[0.65,3.5]
Subtotal (95% CI)					**35.64%**	**1.51[0.65,3.5]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=0.95(P=0.34)						
Total (95% CI)					**100%**	**1.27[0.77,2.11]**
Heterogeneity: Tau^2=0; Chi^2=0.24, df=1(P=0.63); I^2=0%						
Test for overall effect: Z=0.95(P=0.34)						
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.63), I^2=0%						

Favours no anthra — Favours anthra

Analysis 1.6. Comparison 1 No anthracyclines versus anthracyclines, Outcome 6 Event-free survival Wilms' tumour long-term follow-up (Parmar's method was used to obtain the necessary data for the meta-analysis).

Study or subgroup	No anthracyclines	Anthracyclines	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
1.6.1 Stage II-III FH and UH						
D'Angio 1981 II-III FH UH	121	106	0.6 (0.28)		70.22%	1.8[1.04,3.12]
Subtotal (95% CI)					**70.22%**	**1.8[1.04,3.12]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.11(P=0.04)						
1.6.2 Stage IV						
D'Angio 1981 IV	20	28	0.4 (0.43)		29.78%	1.54[0.66,3.57]
Subtotal (95% CI)					**29.78%**	**1.54[0.66,3.57]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1(P=0.32)						

Favours no anthra — Favours anthra



APPENDICES

Appendix 1. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

(1) For **anthracyclines** the following text words have been used:

Anthracyclines OR anthracycline antibiotics OR doxorubicin OR adriamycin OR epirubicin OR idarubicin OR daunorubicin OR rubidomycin OR daunoxome OR myocet OR caelyx OR doxil

(2) For **children** the following text words have been used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

(3) For **survival** the following text words have been used:

survival OR survival rate OR survival rates OR cumulative survival rate OR cumulative survival rates OR survivorship OR mean survival time OR mean survival times OR survival time OR surviv* OR median survival time OR median survival times OR overall survival OR survival analysis OR survival analyses OR disease-free survival OR disease free survival OR event-free survival OR event-free survivals OR event free survival OR progression-free survival OR progression free survival OR progression-free survivals OR event-free OR event free OR progression free OR progression-free OR time to progression OR treatment outcome OR treatment effectiveness OR treatment efficacy OR neoplasm recurrence OR neoplasm recurrences OR disease-free survivals OR disease free survivals OR event free survivals OR progression free survivals OR treatment failure

Final search: 1 AND 2 AND 3

The search was performed in All Text.

[*=1 or more characters]

Appendix 2. Search strategy for MEDLINE

(1) For **anthracyclines** the following MeSH headings and text words have been used:
anthracyclines OR anthracyclin* OR anthracycline antibiotics OR antibiotics, anthracycline OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI30 OR IMI-30 OR idarubicin hydrochloride OR hydrochloride, idarubicin OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4' epidoxorubicin OR 4'-epi-doxorubicin OR 4' epi doxorubicin 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR hydrochloride, epirubicin OR farmorubicin OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR hydrochloride doxorubicin OR doxorubic* OR adriamyc* OR dauno-rubidomycine OR dauno rubidomycin OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR doxorubicin, liposomal OR myocet OR doxorubicin OR daunorubicin

(2) For **children** the following MeSH headings and text words have been used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

(3) For **survival** the following MeSH headings and text words have been used:
survival OR survival rate OR rate, survival OR rates, survival OR survival rates OR cumulative survival rate OR cumulative survival rates OR rate, cumulative survival OR rates, cumulative survival OR survival rate, cumulative OR survival rates, cumulative OR survivorship OR mean survival time OR mean survival times OR survival time, mean OR survival times, mean OR time, mean survival OR times, mean survival OR survival time OR surviv* OR median survival time OR median survival times OR survival time, median OR survival times, median OR time, median survival OR times, median survival OR overall survival OR analysis, survival OR analyses, survival OR survival analysis OR survival analyses OR disease-free survival OR disease free survival OR survival, disease-free OR disease-free survivals OR survival, disease free OR survivals, disease-free OR event-free survival OR event-free survivals OR event free survival OR survival, event-free OR survivals, event-free OR progression-free survival OR progression free survival OR progression-free survivals OR survival, progression-free OR survivals, progression-free OR event-free OR event free OR progression free OR progression-free OR time to progression OR treatment outcome OR treatment effectiveness OR treatment efficacy OR neoplasm recurrence OR neoplasm recurrences

(4) For **randomized controlled trials** the following MeSH headings and text words have been used:

In the original version of the review: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:NoExp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh]) (Higgins 2005).

For the updates of the review: randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh] (Higgins 2009).

Final search: 1 AND 2 AND 3 AND 4

[*=1 or more characters; tiab= title or abstract; pt=publication type; sh=subheading; mh= mesh heading; mh:NoExp=mesh heading without explosion; tw= text word]

Appendix 3. Search strategy for EMBASE

(1) For **anthracyclines** the following Emtree terms and text words have been used:

1. exp ANTHRACYCLINE ANTIBIOTIC AGENT/ or exp ANTHRACYCLINE/ or exp ANTHRACYCLINE DERIVATIVE/
2. (anthracycline or anthracyclines).mp.
3. anthracyclin$.mp.
4. doxorubicin.mp. or exp DOXORUBICIN DERIVATIVE/ or exp DOXORUBICIN/
5. adriamycin.mp.
6. exp DAUNORUBICIN DERIVATIVE/ or daunorubicin.mp. or exp DAUNORUBICIN/
7. rubidomycin.mp.
8. epirubicin.mp. or exp EPIRUBICIN/
9. exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or idarubicin.mp.
10. (doxorubic$ or adriamyc$ or daunorubic$ or rubidomyc$ or epirubic$ or idarubic$).mp.
11. (daunoxome or doxil or caelyx or myocet).mp.
12. or/1-10

(2) For **children** the following Emtree terms and text words have been used:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant$ or newborn$ or (new adj born$) or baby or baby$ or babies or neonate$ or perinat$ or postnat$).mp.
6. (child$ or (school adj child$) or schoolchild$ or (school adj age$) or schoolage$ or (pre adj school$) or preschool$).mp.
7. (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp.
8. (minors$ or (under adj ag$) or underage$ or juvenil$ or youth$).mp.
9. (puber$ or pubescen$ or prepubescen$ or prepubert$).mp.
10. (pediatric$ or paediatric$ or peadiatric$).mp.

11. (school or schools or (high adj school$) or highschool$ or (primary adj school$) or (nursery adj school$) or (elementary adj school) or (secondary adj school$) or kindergar$).mp.
12. or/5-11
13. 4 or 12

(3) For **survival** the following Emtree terms and text words have been used:

1. (survival or survival rate or survival rates).mp.
2. (cumulative survival rate or cumulative survival rates).mp.
3. survivorship.mp.
4. (mean survival time or mean survival times).mp.
5. (survival time or surviv$).mp.
6. (median survival time or median survival times).mp.
7. overall survival.mp.
8. (survival analysis or survival analyses).mp.
9. (disease-free survival or disease free survival).mp.
10. (disease-free survivals or disease free survivals).mp.
11. (event-free survival or event-free survivals or event free survival or event free survivals).mp.
12. (progression-free survival or progression free survival or progression-free survivals or progression free survivals).mp.
13. (survival period or survival probability).mp.
14. (event-free or event free or progression free or progression-free).mp.
15. (time to progression or treatment outcome or treatment effectiveness or treatment efficacy).mp.
16. (neoplasm recurrence or neoplasm recurrences).mp.
17. (cancer recurrence or cancer recurrences or cancer recidive or cancer remission).mp.
18. (therapy outcome or therapeutic efficacy).mp.
19. or/1-18
20. SURVIVAL RATE/ or SURVIVAL/ or SURVIVAL TIME/
21. Treatment Outcome/
22. Cancer survival/ or Cancer Recurrence/
23. or/19-22
24. 19 or 23

(4) For **randomized controlled trials** the following Emtree terms and text words have been used:

In the original version of the review (based on Higgins 2005*):*

1. Clinical Trial/
2. Controlled Study/
3. Randomized Controlled Trial/
4. Double Blind Procedure/
5. Single Blind Procedure/
6. Comparative Study/
7. RANDOMIZATION/
8. Prospective Study/
9. PLACEBO/
10. Phase 2 Clinical Trial/
11. phase 3 clinical study.mp.
12. phase 4 clinical study.mp.
13. Phase 3 Clinical Trial/
14. Phase 4 Clinical Trial/
15. or/1-14
16. allocat$.mp.
17. blind$.mp.
18. control$.mp.
19. placebo$.mp.
20. prospectiv$.mp.
21. random$.mp.
22. ((singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$)).mp.
23. (versus or vs).mp.
24. (randomized controlled trial$ or randomised controlled trial$).mp.
25. controlled clinical trial$.mp.
26. clinical trial$.mp.
27. or/16-26

28. Human/
29. Nonhuman/
30. ANIMAL/
31. Animal Experiment/
32. or/29-31
33. 32 not 28
34. (15 or 27) not 33

For the updates of the review (based on Higgins 2009*):*

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8

Final search: 1 AND 2 AND 3 AND 4

[mp= title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; $=1 or more characters; ti,ab=title or abstract; sh=subheading; /=Emtree term]

WHAT'S NEW

Date	Event	Description
11 June 2014	New citation required and conclusions have changed	Summary of most important changes in the update: The search for eligible studies was updated to July 2013. One new randomised controlled trial (RCT) addressing children with acute myeloid leukemia was included (this type of tumour was not addressed in the earlier versions of this review). For the risk of bias assessment we used the most recent recommendations of the Childhood Cancer Group. All RCTs (including those already included in earlier versions of the review) were scored using the new risk of bias criteria.
11 June 2014	New search has been performed	The search for eligible studies was updated to July 2013.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 1, 2009

Date	Event	Description
30 August 2010	New citation required and conclusions have changed	Summary of most important changes in the update: The search for eligible studies was updated to March 2010. One new randomized controlled trial addressing children with hepatoblastoma was included (this type of tumour was not addressed in the original version of the review).

Date	Event	Description
		Furthermore, long-term follow-up data of the RCT addressing children with Wilms' tumour were included in the update. For overall survival the results changed from a significant difference in favour of treatment with anthracyclines into no significant difference between the treatment groups.
30 August 2010	New search has been performed	The search for eligible studies was updated to March 2010.

CONTRIBUTIONS OF AUTHORS

Elvira van Dalen designed the study and wrote the protocol. She developed the search strategy. She identified the studies meeting the inclusion criteria (both by initial screening and thereafter). She searched for unpublished and ongoing studies. She performed the data extraction and risk of bias assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the manuscript.

Martine Raphaël identified the studies meeting the inclusion criteria and performed the data extraction and risk of bias assessment of the included studies. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Leontien Kremer critically reviewed the protocol. She acted as third party arbitrator. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Huib Caron critically reviewed the protocol. He contributed to the interpretation of the results. He critically reviewed the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Foundation of Paediatric Cancer Research (SKK), Netherlands.
- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the second update we used the most recent recommendations of the Childhood Cancer Group for the assessment of risk of bias in the included studies. All RCTs (including those already included in earlier versions of the review) were scored using the new 'risk of bias' items. Also, since performing the original review and the first update of this review, the Childhood Cancer Group has adjusted some of its recommendations regarding analyses: when for a particular outcome only one study is available and there are no events in one of the treatment groups, it is impossible to calculate an adequate risk ratio using the RevMan software, instead the Fischer's exact test should be used. We have adjusted this where necessary.

INDEX TERMS

Medical Subject Headings (MeSH)

Anthracyclines [adverse effects] [*therapeutic use]; Antibiotics, Antineoplastic [adverse effects] [*therapeutic use]; Bone Neoplasms [drug therapy]; Heart Diseases [chemically induced]; Hepatoblastoma [drug therapy]; Kidney Neoplasms [drug therapy]; Leukemia, Myeloid, Acute [drug therapy]; Liver Neoplasms [drug therapy]; Lymphoma, Non-Hodgkin [drug therapy]; Neoplasms [*drug therapy]; Precursor Cell Lymphoblastic Leukemia-Lymphoma [drug therapy]; Randomized Controlled Trials as Topic; Sarcoma [drug therapy]; Wilms Tumor [drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn