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[Intervention Review]

Anthracycline-containing regimens for treatment of follicular lymphoma in adults

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ABSTRACT

Background

Anthracycline-containing regimens (ACR) are the most prevalent regimens in the management of patients with advanced follicular lymphoma (FL). However, there is no proof that they are superior to non-anthracycline-containing regimens (non-ACR).

Objectives

To compare the efficacy of ACRs to other chemotherapy regimens, in the treatment of FL.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 3), MEDLINE (January 1966 to April 2013), smaller databases, relevant conference proceedings (2004 to 2012) and the National Medical Library (April 2013).

Selection criteria

We included randomized controlled trials (RCTs) comparing ACR with non-ACR for adult patients with FL. We excluded trials in which immunotherapy, radiotherapy alone or stem-cell transplantation were used in one arm alone. Our primary outcome was overall survival (OS). Secondary outcomes included disease control, as measured by progression-free survival (PFS) or remission duration (RD).

Data collection and analysis

Two review authors assessed the quality of trials and extracted data. We contacted study authors for additional information. We analyzed trials separately according to resemblance of the chemotherapeutic regimens in study arms, other than the addition of anthracyclines ('same' versus 'different' chemotherapy). Hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI) were estimated and pooled using the fixed-effect model.

Main results

Eight RCTs, conducted between 1974 and 2011, and involving 2636 patients were included in this meta-analysis. All trials included therapy-naïve patients. Rituximab was used in one trial only. Follow-up was between three and five years in most trials (range three to 18 years). All trials were published in peer-reviewed journals.

Five trials compared similar chemotherapeutic regimens, except for the anthracycline. In three studies reporting overall survival specifically in FL patients, there was no statistically significant difference between ACR and non-ACR arms (HR 0.99; 95% CI 0.77 to 1.29; $I^2 = 0\%$). ACR significantly improved disease control (HR 0.65; 95% CI 0.52 to 0.81; four trials). Progression or relapse at three years were reduced (RR 0.73; 95% CI 0.63 to 0.85). Anthracyclines did not significantly increase rates of complete response (RR 1.05; 95% CI 0.94 to 1.18) or overall response (RR 1.06; 95% CI 1.00 to 1.12), but heterogeneity was substantial.

Overall, ACR were more often associated with cytopenias, but not with serious infections or death related to chemotherapy. Cardiotoxicity, albeit rare, was associated with anthracycline use (RR 4.55; 95% CI 0.92 to 22.49; four trials).

Three trials added anthracycline to one arm of two different regimens. None showed benefit to ACR regarding OS, yet there was a trend in favor of anthracyclines for disease control. Results were heterogeneous.

We judged the overall quality of these trials as moderate as all are unblinded, some are outdated and are not uniform in outcome definitions.

Authors' conclusions

The use of anthracyclines in patients with FL has no demonstrable benefit on overall survival, although it may have been mitigated by the more intense regimens given in the control arms of three of five trials. ACR improved disease control, as measured by PFS and RD with an increased risk for side effects, notably cardiotoxicity. The current evidence on the added value of ACR in the management of FL is limited. Further studies involving immunotherapy during induction and maintenance may change conclusion.

PLAIN LANGUAGE SUMMARY

Anthracyclines in the treatment of follicular lymphoma (FL) in adults

FL is the most common indolent non-Hodgkin's lymphoma (NHL). It is a slowly progressive disease, with a risk of transformation to a more aggressive lymphoma. Advanced disease (stage III and IV) has been considered incurable. However, in recent years, the use of combination therapy and treatment with the monoclonal anti-CD20 antibody rituximab, have prolonged survival and decreased transformation rate, and is now considered standard of care in FL patients. One of the most common chemotherapies used in the treatment of FL is the combination of rituximab with cyclophosphamide, vincristine, adriamycin, prednisone (R-CHOP), which contains an anthracycline (adriamycin). Other anthracycline-containing regimens (ACR) have also been used to treat FL patients. However, there is no proof that ACRs are better than non-anthracycline-containing regimens (non-ACRs), and there are no standard guidelines for the initial treatment of advanced FL. Importantly, anthracyclines have serious side effects, notably a decrease in blood counts and potential damage to the heart, depending on the dose.

The aim of this systematic review and meta-analysis was to examine if there is a benefit in the use of anthracyclines for patients with FL. We looked at overall survival (OS); measures of disease control; response rates; and side effects.

We found eight randomized controlled trials, of which five compared similar chemotherapy regimens in both trial arms, except for the anthracycline. Even among these five trials, three included more intense chemotherapy in the control arm. Most trials were conducted in the 1980s and 1990s. Only one of them included rituximab as part of the chemotherapy regimen. Almost all patients were treatment-naive with advanced disease. Follow-up ranged between three and five years in most trials. The main results from this set of trials are.

1. There is no evidence that OS is prolonged with the use of anthracyclines, although it may have been hampered by the more intense regimens given in the control arms of three of five trials.
2. Anthracyclines improved disease control. Concordantly, less patients progressed or relapsed within three years of treatment with ACR.
3. There is no statistically significant difference in complete or overall response rates.
4. Qualitatively, more side effects were reported with ACR, myelotoxicity and cardiotoxicity included.

This evidence is limited, mainly due to disparities in regimens between control and study arms, but also since most included trials were conducted over one to two decades ago, and only one employed rituximab. Importantly, results from this study were in agreement with pooled-outcomes from trials of the pre-rituximab era.

It is essential to find the optimal chemotherapeutic regimen in conjunction with rituximab and other novel agents, and understand the role of anthracyclines in this combination, especially with current methods that are able to reduce their toxicity. With longer follow-up periods we may better understand whether improved disease control will eventually translate to an increase in survival.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ACR compared to non-ACR for treatment of follicular lymphoma in adults

ACR compared to non-ACR for treatment of follicular lymphoma in adults

Patient or population: adults receiving treatment for follicular lymphoma

Settings:

Intervention: Anthracycline

Comparison: no anthracycline same chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No anthracycline same chemotherapy	Anthracycline				
Overall survival number of dead patients Follow-up: median 50 months	538 per 1000	535 per 1000 (449 to 631)	HR 0.99 (0.77 to 1.29)	464 (3 studies)	⊕⊕⊕⊕ moderate ¹	
Mortality at 3 years	260 per 1000	239 per 1000 (174 to 327)	RR 0.92 (0.67 to 1.26)	465 (3 studies)	⊕⊕⊕⊕ moderate ¹	
Overall response	839 per 1000	889 per 1000 (839 to 940)	RR 1.06 (1 to 1.12)	622 (3 studies)	⊕⊕⊕⊕ moderate ²	
Disease control number of patients with progression Follow-up: median 30 months	492 per 1000	356 per 1000 (297 to 423)	HR 0.65 (0.52 to 0.81)	759 (4 studies)	⊕⊕⊕⊕ high	
Progression/relapse at 3 years	544 per 1000	397 per 1000 (343 to 463)	RR 0.73 (0.63 to 0.85)	724 (4 studies)	⊕⊕⊕⊕ high	
Neutropenia grade 3-4	190 per 1000	368 per 1000 (277 to 485)	RR 1.94 (1.46 to 2.56)	533 (2 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	
Cardiotoxicity**	2 per 1000	8 per 1000 (2 to 40)	RR 4.55 (0.92 to 22.49)	1412 (3 studies)	⊕⊕⊕⊕ very low ^{4,5}	

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

**Includes all trials, irrespectively of the comparison ("same chemotherapy"; "different chemotherapy").

CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 Small number of events
- 2 Moderate heterogeneity
- 3 Different reporting methods
- 4 Not consistently reported
- 5 Wide confidence interval

BACKGROUND

Description of the condition

Follicular lymphoma (FL) is the most common indolent and the second most common non-Hodgkin lymphoma (NHL) subtype in the Western world. It constitutes up to 30% of all NHL (NHLCP 1997), and its incidence has risen in the last decades and is currently 3.3 to 3.8 cases per 100,000 patient-years, in the white US population (Morton 2006). It is defined as a group of malignancies composed of follicle center cells, usually a mixture of centrocytes (cleaved cells) and centroblasts (large non-cleaved cells) (Vitolo 2008).

The Revised European-American Classification of Lymphoid Neoplasms (REAL classification) (Harris 1994), and more recently the updated World Health Organization (WHO) classification (Harris 1999; Swerdlow 2008) propose the term follicle center lymphoma, and divide it into grades 1, 2, 3a, and 3b. The grades are distinguished by the presence of predominantly small, mixed small and large, and large cells, respectively. Pathologically, according to the 'Berard Criteria', the grades are defined by the number of centroblasts per high power field (Mann 1983). In grade 3a centrocytes are still present, while grade 3b involves centroblasts only. Grade 3 FL is biologically distinct from grades 1 and 2 in its clinical behavior and response to chemotherapy and is treated as aggressive lymphoma. Owing to imprecision in differentiating between grade 3a and 3b, its relative infrequency, and the nature of the trials involved, it is difficult to assess its natural history. Yet, some consider FL grades 1, 2, 3a as a single histologic entity, and keep it apart from grade 3b, which is treated closely to diffuse large B-cell lymphoma (Chau 2003; Ganti 2006; Vitolo 2008). FL encompasses most malignancies previously classified as nodular lymphoma in the Working Formulation, most tumors classified as follicular center cell lymphoma in the Lukes-Collins classification, and all cases in Kiel classification category of centroblastic/centrocytic (CB/CC) follicular or follicular CB lymphoma (Vitolo 2008).

The molecular hallmark of FL is the acquisition of translocation t(14;18) by pre-B cells during an abnormal immunoglobulin rearrangement in the bone marrow, and the overexpression of bcl2 protein, which protects cells from apoptosis (Bendandi 2008). However, only 70% to 95% of FL patients are t(14;18) positive (Vitolo 2008), and t(14;18)-positive cells may also be found in healthy individuals and patients with other malignancies. Staging of FL is done according to the Ann Arbor system, according to number of involved lymph-node regions, presence of extra-lymphatic involvement, and presence of B symptoms. Stages I/II are considered early disease, while stages III/IV are considered advanced. Advanced disease is present in more than 80% of FL patients, and bone marrow involvement in more than 60% (Vitolo 2008).

Contemporary scoring systems specific for FL are the Italian Lymphoma Intergroup Index (ILI) (Federico 2000) and the more widely accepted Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Celigny 2004). The FLIPI designates prognostic groups as having low, intermediate, or high risk based on the presence or absence of five adverse prognostic factors: age > 60 years, Ann Arbor stage III/IV, hemoglobin level < 12 g/dL, involvement of more than four nodal sites, and elevated serum lactate dehydrogenase (LDH) level. The risk of transformation is higher in patients with advanced stage and higher FLIPI. Another

scoring system was offered by the same group, FLIPI2, which is intended to stratify risk in the era of immunotherapy, and takes progression-free survival (PFS) as the principal outcome measure. It takes into account β_2 -microglobulin higher than the upper limit of normal, longest diameter of the largest involved node longer than 6 cm, bone marrow involvement, hemoglobin level lower than 12 g/dL, and age older than 60 years (Federico 2009). FL has had over the years a median survival of eight to 10 years. Its course is largely unpredictable, and it may undergo more aggressive histologic and clinical transformation to aggressive lymphoma at a rate of 3% per year (Bendandi 2008), which is usually poorly responsive to chemotherapy. The median survival from transformation is about one year (Vitolo 2008).

Treatment for FL is considered separately for early-stage versus advanced-stage disease and for newly diagnosed versus relapsed or resistant disease. Historically, advanced FL was considered incurable, with no difference in overall survival (OS) between early treatment and 'watch and wait' approach, and with relapse as a rule (Bendandi 2008). However, in recent years, new treatment approaches, and specifically the introduction of rituximab (a monoclonal anti-CD20 antibody), have decreased transformation rate (Montoto 2007) and improved survival (Tilly 2008). Thus, the first challenge, especially in newly diagnosed patients with FL, is distinguishing those most likely to benefit from an aggressive, curative-intent approach.

Early-stage FL is curable in 30% to 40% of patients, and is usually treated with localized radiotherapy, with even better results with combined-modality therapy (Bendandi 2008), especially in patients with high tumor burden (Vitolo 2008). In newly diagnosed advanced FL, observation is still an option, especially in high-risk patients and provided there are no high tumor burden features (Horning 1984). In this case, usual indications for treatment in advanced FL are symptomatic disease, hematopoietic impairment, bulky disease, or rapid lymphoma progression. Specific criteria have been established to guide initiation of therapy, such as the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (Solal-Celigny 1993). However, at least in principal, eradication should be the initial goal in the management of most patients. In relapsing or resistant FL, salvage therapy includes chemoimmunotherapy regimens not used in first-line therapy, radioimmunotherapy and stem-cell transplantation (SCT) (Bendandi 2008; Greb 2008; Vitolo 2008).

There are no standard guidelines for the initial treatment of advanced FL. The choice of chemotherapy largely depends on many factors such as: patient's age and performance status, comorbidity, the pace of disease, and the aim of the treatment (i.e. palliation or attempt to cure). Chemotherapy regimens may include: alkylating agents, anthracycline-based chemotherapies, purine analogs, and regimens resembling the cyclophosphamide, vincristine, prednisone (CVP)-like regimens (Vitolo 2008). The combination of rituximab with nearly any chemotherapy regimen is superior to the same chemotherapy regimen alone (Tilly 2008) as was shown in many randomized trials, and summarized in a meta-analysis published in *The Cochrane Library* (Schulz 2007). Thus, the concomitant administration of rituximab and a chemotherapy regimen has rapidly become the first-line standard of treatment in FL. It also has a role in maintenance therapy as well as in relapsed, recurrent, or resistant patients (Vidal 2009). According to the National LymphoCare Study (NLCS), most FL patients in

the US (regardless of staging) were treated by chemotherapy and rituximab combination, 55% of whom with rituximab, cyclophosphamide, vincristine, adriamycin, prednisone (R-CHOP) regimen, 23% with R-CVP, and 15% with fludarabine-based regimens (Friedberg 2009). High-dose chemotherapy followed by autologous SCT is still a controversial modality in first-line treatment of FL.

Response to therapy is monitored through history, physical examination, computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG-PET), and bone marrow biopsy in some patients. Complete response (CR) has been achieved when: there is no clinical evidence of disease or disease-related symptoms; all lymph nodes are normal sized on CT scan; spleen and liver are non-palpable and without nodules; previously involved bone marrow is negative on repeat biopsy. Partial response (PR) is defined as decrease in nodal size by at least 50% and no progression otherwise (Cheson 1999; Cheson 2007). These patients are treated as refractory disease. Molecular response, detecting minimal residual disease, by using polymerase chain reaction (PCR) for bcl-2/IgH translocation and clonally rearranged IgH genes, correlates well with outcome as shown by several prospective studies. However, it is still unclear whether eradicating the t(14;18)-bearing clone is an important goal of therapy, and is not routinely performed (Vitolo 2008).

Description of the intervention

We are going to assess the role of anthracyclines in the treatment of FL.

Anthracyclines are antibiotic drugs that are among the most important antitumor agents. They include doxorubicin (adriamycin) and daunorubicin, and the analogous idarubicin and epirubicin. Mitoxantrone is an anthracenedione, but is practically considered in this group. These drugs intercalate with deoxyribonucleic acid (DNA), directly affecting transcription and replication. Moreover, they form a tripartite complex with topoisomerase II and DNA, and inhibit the religation of broken DNA strands leading to apoptosis. They also generate free radicals that damage DNA (Goodman 2006).

The toxic manifestations of these agents include: myelotoxicity; stomatitis; alopecia; gastrointestinal (GI) disturbances; and dermatological manifestations such as 'adriamycin flare' at the site of injection, facial flushing, conjunctivitis, and lacrimation. Cardiac toxicity is a unique and the most important adverse event. Two types of cardiomyopathy may occur. An acute form, develops within 24 hours of treatment, and is characterized by abnormal electrocardiogram (ECG) findings and even transient reduction in ejection fraction, elevation of troponin, and pericardial effusion. A subacute/chronic, cumulative dose-related toxicity (usually above 550 mg/m²) is manifested as congestive heart failure. Its incidence ranges widely, but is approximately 7.5% at a cumulative dose above 550 mg/m². Elderly people, females, children and patients with a history of cardiac disease are at increased risk, as are patients treated with chest irradiation, and with the administration of high-dose cyclophosphamide or another anthracycline, and concomitant trastuzumab or paclitaxel (Outomuro 2007).

In FL, anthracycline-based regimens are the most frequently employed first-line treatment in the US, and are considerably utilized even in early-stage disease (Friedberg 2009), yet

there is no proof of their superiority over regimens without anthracyclines. Even trials comparing single-agent versus combination chemotherapy including anthracyclines have not consistently shown a benefit in response, relapse rate, or survival to combination therapy (Lister 1978). In some, a benefit was significant only in higher-grade FL (Peterson 2003) or in elderly patients (Coiffier 1999). Furthermore, it is undetermined whether the benefit may be attributed to anthracyclines, other drugs, or the combination in itself.

In a retrospective study, 633 FL patients treated with anthracycline-containing regimens (ACR) were compared to 128 comparable patients treated with combination chemotherapy not containing anthracyclines. The former group had better complete remission, five-year OS, and failure-free survival (FFS) (Rigacci 2003). This stands in contrast to previous survival data of patients with low-grade lymphoma entered into Southwest Oncology Group (SWOG) lymphoma trials, where doxorubicin-containing treatment did not prolong the median OS, in comparison to less aggressive programs (Dana 1993). Most other data come from indirect comparisons, comparing treatment arms from different trials (Brandt 2001; Bendandi 2008; Tilly 2008; Vitolo 2008; Siddhartha 2009). An analysis of five consecutive studies at MD Anderson Cancer Center, involving advanced FL patients has shown improvement in OS and FFS over a 25-year period (Liu 2006). The fact that all protocols involved anthracyclines underscores the methodologic difficulty in comparing outcome rates in one trial with previous trials or historical cohorts, with versus without anthracyclines as is often done. Previous studies suggested that ACRs are advantageous specifically among patients with grade 3 FL (Wendum 1997; Chau 2003; Ganti 2006), and show a plateau in FFS following ACR (Bartlett 1994). As a result, the recommended treatment for patients with grade 3 FL (both 3a and 3b) is now R-CHOP, even in early-stage disease (Buske 2008).

Why it is important to do this review

FL is the most common indolent NHL, yet there is no standard guideline for its management. It has been considered an incurable progressive disease, but in recent years, implementation of combination therapy and treatment with rituximab have prolonged survival and decreased transformation rate. ACRs are of the most prevalent first-line therapies, especially in advanced disease, but also in limited or relapsed cases. However, there is no proof that they are superior to other, non-ACRs, or even single-agent therapy. Observational studies show conflicting results and other data are based on indirect comparisons that are not reliable. However, the optimal design for assessment of interventions is randomized controlled trials (RCTs). Anthracycline use is often limited to younger patients with more advanced or high-grade disease, owing to concern of their adverse effects, especially cardiotoxicity, although it may be diminished in face of preventive strategies (van Dalen 2009).

In this systematic review we assessed the evidence on the role of anthracyclines in the treatment of FL. This question is still important in the rituximab era, since the preferred combination chemotherapy used with it has not been elucidated.

OBJECTIVES

To compare the efficacy of ACRs to other chemotherapy regimens, in the treatment of FL.

METHODS

Criteria for considering studies for this review

Types of studies

We considered any published or unpublished RCT eligible for inclusion in this review, without language restriction.

Types of participants

We included adult patients over 18 years of age, with a histologically confirmed diagnosis of FL, without gender or ethnicity restriction. If the trial had recruited patients with FL in addition to patients with other types of lymphoma, we included the study and extracted data for patients with FL separately. Where data were not provided separately for FL, we included the study and reported the number of patients with FL; we analyzed data only for studies with over 75% FL patients. We excluded studies that did not specify the number of FL patients enrolled.

We considered all stages and grades of FL. Classification systems for FL varied between trials, as they were conducted at different times. Considering the different classification systems, we unified various nomenclatures in the following manner:

- grade 1 equivalent to follicular small cell lymphoma or CB/CC follicular or nodular lymphocytic poorly differentiated;
- grade 2 equivalent to mixed small and large cell FL or CB/CC follicular and diffuse or nodular mixed;
- grade 3 equivalent to large cell FL or CB/CC diffuse or nodular histiocytic. No equivalents to grade 3a and 3b in previous classifications.

We included both trials assessing treatment-naïve patients and previously treated patients (with or without relapse).

Types of interventions

The main intervention was an ACR compared to a non-ACR, including any chemotherapy or immunochemotherapy.

We defined the interventions as follows:

- intervention: ACR, regardless of additional agents, with or without radiotherapy;
- control: non-ACR, as a single agent or multiple agents, regardless of dose.

Anthracyclines considered in this review included doxorubicin (adriamycin), daunorubicin, idarubicin, epirubicin, mitoxantrone, and pixantrone. We included trials involving rituximab, interferon, or other novel chemoimmunotherapy only if the same chemotherapy regimen was administered in both arms. We excluded trials in which the control arm included one of the following: watchful waiting, radiotherapy alone, high-dose chemotherapy with SCT.

We separated trials according to the similarity of chemotherapeutic regimens, other than anthracyclines, between study arms. Trials with the same chemotherapy, where the main difference was the addition of an anthracycline, were summed together. Studies with different chemotherapies were described narratively.

Types of outcome measures

We based the outcomes of this review on the revised response criteria for malignant lymphoma published in 2007 (Cheson 2007). Given that some studies were conducted before these guidelines and that data were reported heterogeneously, we allowed for deviations from these definitions and documented the study definitions.

Primary outcomes

- OS, defined as the time from entry to study until death of any cause (Cheson 2007) and assessed among all patients. In addition we assessed all-cause mortality at three, five and 10 years.

Secondary outcomes

- PFS: defined as the time from entry into the study until lymphoma progression (including relapse) or death of any cause (Cheson 2007). This outcome was analyzed for all patients. We accepted other outcome definitions (e.g. excluding non-lymphoma-related deaths) as long as all patients were accounted for. We also tried to extract the number of patients with progression (progression, relapse, or death from any cause) at three and five years out of all patients.
- CR: we accepted CR definitions as defined in study. In this category we included both documented and uncertain CR (CRu).
- Overall response rate (ORR), defined as CR + CRu + PR, as defined in study.
- RD: defined from the time when criteria for response (i.e. CR or PR) were met until the first documentation of relapse or progression (Cheson 2007). This outcome was analyzed for the subgroup of patients achieving remission. We accepted other outcome definitions counting the subgroup of patients achieving remission and defining events as progression, relapse, need for treatment, or death (e.g. relapse-free survival (RFS), event-free interval).
- Relapse: number of patients with relapse out of those achieving CR. We extracted preferentially relapse at five years, but accepted other time points and documented these.
- Disease control: a general measure including various outcome measures reported in trials (i.e. PFS, RFS, event-free survival, time to treatment failure, time to progression, or RD). These measures were often ill-defined, and were not necessarily compatible with common guidelines (Cheson 1999; Cheson 2007). The outcomes and their definitions are specified in the [Characteristics of included studies](#) table.
- Quality of life (QoL) assessed using validated questionnaires.
- Adverse events which were defined as follows:
 - cardiotoxicity - clinical: defined on the basis of symptoms failure, confirmed by an abnormal diagnostic test; subclinical: defined as either histological abnormalities according to the Billingham score (Billingham 1978) on myocardial biopsy; or abnormalities in cardiac function measured by echocardiography or radionuclide ventriculography;
 - myelosuppression defined as number of patients developing grade III/IV neutropenia (Miller 1981);
 - infections, as defined in study;
 - alopecia (Miller 1981);
 - stomatitis (Miller 1981).

Search methods for identification of studies

We conducted a comprehensive search with the purpose of identifying all eligible trials regardless of language, year of publication, or status of publication (published in peer review journal, conference proceeding, thesis, or unpublished).

Electronic searches

We searched the electronic databases of Cochrane Central Register of Controlled Trials (CENTRAL, published in *The Cochrane Library* 2013, Issue 3) and MEDLINE (January 1966 to April 2013). We have provided the different search strategies in [Appendix 1](#) and [Appendix 2](#). We also searched the *metaRegister* of Controlled Trials (*mRCT*) for ongoing or unpublished trials.

Searching other resources

We searched conference proceedings available from 2004 to 2012 of the following: the American Society of Hematology (ASH), European Hematology Association (EHA), and American Society of Clinical Oncology (ASCO). We scanned references of all included trials.

Data collection and analysis

Selection of studies

One review author (Gilad Itchaki (GI)) scanned the results of the search. Two review authors (GI, Mical Paul (MP)) independently applied inclusion and exclusion criteria for possibly relevant studies.

Data extraction and management

Two review authors independently extracted the data from included trials into an electronic table (GI, MP). We extracted the following data.

Trial characteristics

- Trial design
- Setting and dates
- Total duration of study
- Duration of study follow-up
- Exclusion criteria
- Statistical methods
- Publication status
- Funding
- Ethical committee approval and informed consent

Risk of bias

- We extracted data to assess the risk of bias, as specific below

Patient characteristics

- Mean age and sex
- Age over 60 years
- Histologic confirmation of FL
- Grade and stage (including B-symptoms and bulky disease)
- Bone marrow involvement
- IPI or FLIPI score
- Indication for initiation of therapy

- Performance status (Eastern Cooperative Oncology Group (ECOG), Karnofsky)
- Time from diagnosis to first treatment
- Previous treatment
- Other medical conditions, specifically: cardiac, hepatic, or renal dysfunction
- Fulfillment of inclusion and exclusion criteria

Interventions

- Setting
- Type of chemotherapy, dose, number of cycles, possibility of dose reduction, addition of immunotherapy (type and dose) or radiation
- Cumulative anthracycline dose, peak dose, infusion duration
- Administration and timing of granulocyte-colony stimulating factor (G-CSF)
- Compliance
- Cross-over and rate of completion

Outcomes

- As defined above. We documented and reported the definitions of time-to-event outcomes (including the population assessed, event definition, and whether all-cause or disease-related deaths were included in the outcome).

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in included studies and extracted the data into the electronic table. We used a domain-based evaluation as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Review authors were not blinded to trial authors, its publication status, or other study characteristics. We assigned each domain a low or high risk of bias, using the definitions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). When there was insufficient information about the process, we assigned the domain an unclear risk of bias. We assessed the following domains for this review:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel, and outcome assessors;
- incomplete outcome data: we assessed the number of exclusions and attrition for the primary outcomes and defined a priori high risk of bias when the number of randomized patients that were not included in outcome assessed was 30%;
- selective outcome reporting: we assessed this domain if the trial's protocol was available and predefined outcomes could be compared to those reported. In all other cases we have classified the domain as unclear, unless there was a discrepancy between the outcome results reported in the publication and those specified in its methods section (where an assignment of inadequate was be given);
- early stopping of the trial.

Measures of treatment effect

For dichotomous data (deaths, CR, adverse events) we extracted the number of patients with events and number of patients assessed, and compared study groups using risk ratios (RRs).

For survival data we extracted the summary effect measures as reported in the primary study, preferably hazard ratios (HRs) with 95% confidence intervals (CIs). If HRs were not reported, we tried to calculate them from the values reported on survival curves. We used the number of patients and events per group and P value to calculate the HR with 95% CIs, and the observed-expected with variance (the latter was used in the meta-analysis). When a P value was not reported, we manually estimated the percentage of events for several time points on the Kaplan Meier curve (at least three) and calculated the same values from these data. This was done using the excel spreadsheet developed by Sydes and Tierney (Tierney 2007), which is based on the methods described in Parmar 1998 and Williamson 2002.

Dealing with missing data

We tried to complement missing data regarding review-defined outcomes and risk of bias assessment by correspondence with trial authors. None of the authors replied or could complete missing data.

We have analyzed outcomes with missing data for some patients using available data only, since we were not able to impute missing values for time to event outcomes.

Assessment of heterogeneity

We assessed heterogeneity in each meta-analysis using a Chi² test of heterogeneity and the I² statistic of inconsistency. Given the small number of studies in each of the analyses, we based the heterogeneity assessment mainly on the I² statistic where a value greater than 50% represents substantial heterogeneity. We interpreted the importance of the observed I² value by looking at the magnitude and the direction of effects.

Assessment of reporting biases

In analyses that include at least 10 trials we planned to draw funnel plots of effect estimates against study precision, and inspect asymmetry visually and indicate publication bias or other small study effects (Higgins 2011). However, all analyses were of five trials or less.

Data synthesis

We pooled RRs with 95% CIs using the fixed-effect model. We recalculated all analyses using the random-effects model, and reported significant discrepancies between the models. HRs were

pooled according to Peto's method. Analyses were done in RevMan 5 (RevMan 2012).

Subgroup analysis and investigation of heterogeneity

As detailed above, we conducted a separate analysis for studies assessing directly the efficacy of anthracyclines by comparing the same chemotherapy regimens with or without the addition of an anthracycline. We set to investigate heterogeneity in each analysis based on the following preplanned subgroup analyses:

- FL grade 3;
- age over 60 years;
- first-line versus relapse or refractory;
- regimens with or without monoclonal antibodies;
- different anthracyclines.

However, the paucity of trials and lack of data in included studies allowed for subgroup analyses of the last count alone.

Sensitivity analysis

- Allocation concealment (see above), which has been shown to affect subjective outcomes most strongly (Wood 2008). We planned to assess the effect of blinding, but all trials were open-labelled.
- Trials that encompassed a second randomization.
- Publication status: published in a peer-reviewed journal.

Given the paucity of included trials, we were able to fulfil only the first two counts, and did not undertake any further sensitivity analyses.

RESULTS

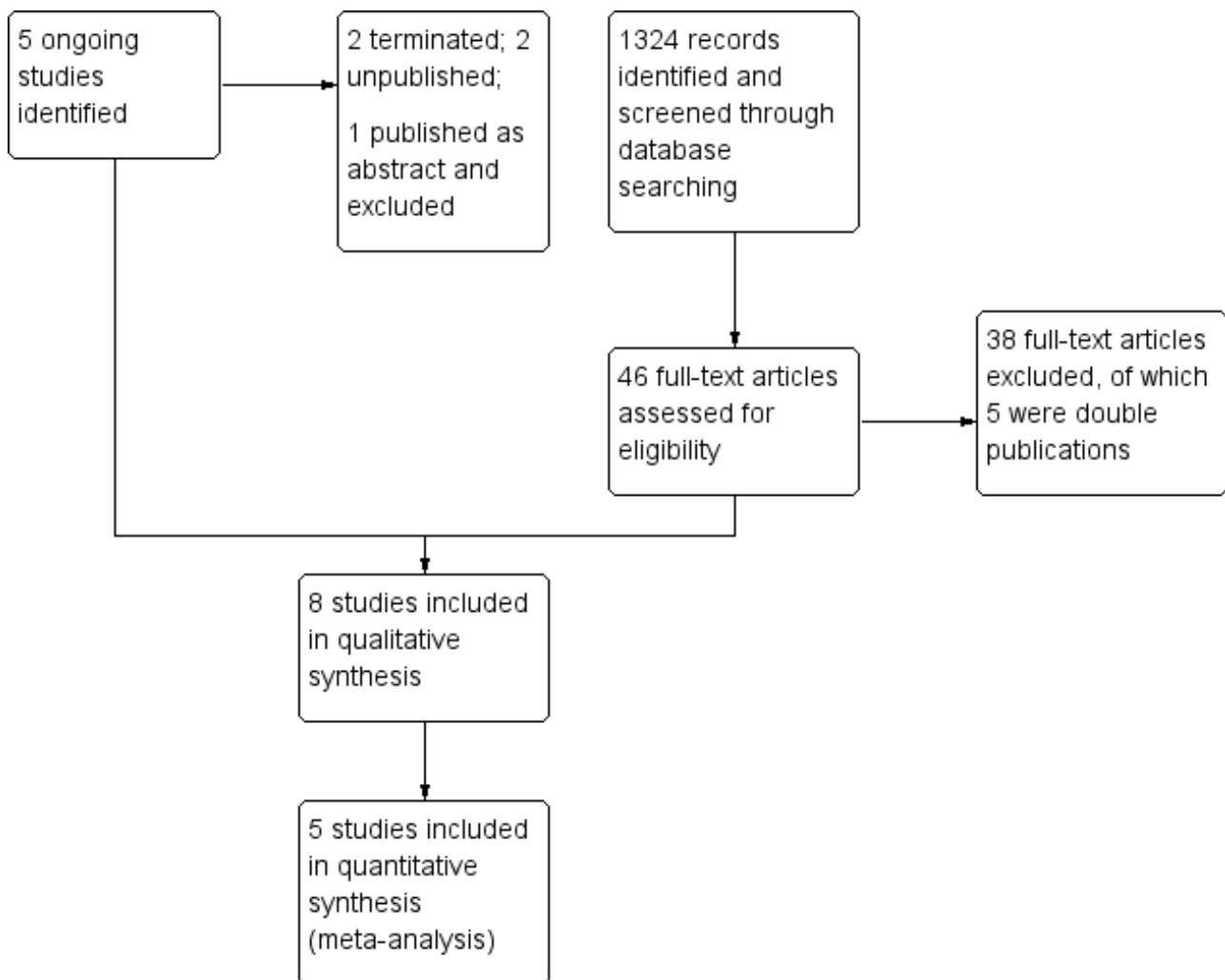
Description of studies

Results of the search

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); ; and [Characteristics of ongoing studies](#) tables.

A total of 1324 potentially relevant titles and abstracts were identified and screened for retrieval. Forty-six were evaluated in more detail. Of these, 38 were excluded. Additional five ongoing trials were identified, of which two were terminated, two are ongoing and one was published in abstract form and excluded, since no randomization was done between ACR and non-ACR (Flinn 2012). See [Figure 1](#) for a flow diagram of the search.

Figure 1. Study flow diagram.



Included studies

Eight RCTs were included in the systematic review, involving a total of 2636 randomized adult patients. Trials were conducted between 1974 and 2011, yet most were published in the 1980s and 1990s. Six studies recruited patients in Europe and two (Jones 1983; Peterson 2003) in the US. Six trials were conducted as part of a study group (Jones 1983; Kimby 1994; Unterhalt 1996; Peterson 2003; Taylor 2006; Federico 2013), and two were not (Lepage 1990; Zinzani 2000). All were multicenter trials. Time of follow-up varied between three years and 18 years. Most trials reported outcomes at three to five years, while two trials (Peterson 2003; Taylor 2006) also reported outcomes at 10 years or more.

Type of participants

All trials involved patients with low-grade NHL. Jones et al (Jones 1983) also included patients with high-grade lymphoma, yet stratification and analysis was separate for patients with FL. All trials included patients with initial, untreated indolent NHL. In these trials, no prior chemotherapy was allowed. In three trials (Jones 1983; Taylor 2006; Federico 2013) prior radiotherapy to bulky regions was allowed, but was given in very few patients (not reported in Federico 2013).

Classification systems were not identical: three trials used REAL/WHO classification; three used Kiel classification initially, but two of those eventually reported results according to REAL classification; one used Working Formulation; and one used Rappaport classification.

In all studies recruitment was based on the pathologic diagnosis of the primary institution, yet central pathology reclassification was performed. Analysis was done according to initial classification, with subgroup analysis according to central pathology, except for one trial (Jones 1983) where changes in classification were frequent and analysis was based on central pathology alone.

Four trials (Jones 1983; Kimby 1994; Unterhalt 1996; Peterson 2003) included only patients with advanced lymphoma (stage III/IV according to the Ann Arbor classification); three trials (Lepage 1990; Zinzani 2000; Federico 2013) included patients with stage II to IV NHL; and one trial (Taylor 2006) considered all patients eligible for treatment, yet only one patient with stage I disease was included. Of reported data, 96% of patients were stage III or IV.

All trials reported histology consistent with FL. They included 1520 evaluated patients with histologically confirmed FL. However, only two trials (Peterson 2003; Federico 2013) were designed

specifically for FL patients. Other common indolent lymphomas included in studies were chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and immunocytoma and mantle cell lymphoma (MCL). Grades of FL were reported in most trials, as specified in Additional Table 1. Most randomized FL patients were grade 1 or 2.

Common exclusion criteria were: severe cytopenias; significant kidney and liver disease; high ECOG score; cardiac failure contraindicating use of anthracyclines; and, where appropriate, any pulmonary dysfunction contraindicating use of bleomycin.

All patients were given first-line treatment. Usual indications for treatment, when reported, were symptomatic, progressive or bulky disease, or cytopenia. In one trial (Peterson 2003) treatment was started within 100 days of diagnosis, regardless of symptoms. FLIPI/IPI score was reported in three trials (Zinzani 2000; Taylor 2006; Federico 2013). In the Taylor 2006 and Federico 2013 trials up to 37% of patients had a high FLIPI score. In Federico 2013, 27% of patients also had a high FLIPI2 score.

Study design

In four studies (Jones 1983; Lepage 1990; Unterhalt 1996; Taylor 2006) two consecutive randomization processes were performed (patients were randomized to type of induction therapy and then randomized again to maintenance therapy or observation). Our analyses refer to the first randomization.

Two studies had a triple-arm design. Jones 1983 compared CHOP-Bleo (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) versus CVP-Bleo (cyclophosphamide, vincristine, prednisone, bleomycin) versus CHOP-BCG (cyclophosphamide, doxorubicin, vincristine, prednisone, Bacillus Calmette Guerin). Since BCG was given also as part of induction therapy, and might be considered an immunotherapy, we did not extract data from this arm. Federico 2013 compared R-CVP versus R-CHOP versus R-FM. We extracted data only for the first comparison, according to protocol.

Intervention

Five studies (Jones 1983; Lepage 1990; Zinzani 2000; Taylor 2006; Federico 2013) assessed the same chemotherapeutic regimen between study arms, yet only three trials reported OS data for FL patients specifically.

Importantly, three trials with 'same chemotherapies' were not exactly identical. Zinzani 2000 compared fludarabine with fludarabine-idarubicin combination, yet fludarabine was given for five days in the control arm and only three days in the experimental arm. In Jones 1983 (CVP-B versus CHOP-B), the administration of cyclophosphamide varied by route, rate, and total dose between study arms, and there were also minor differences in bleomycin dose and frequency of cycles. In Federico 2013 (R-CVP versus R-CHOP), eight versus six cycles were given between non-ACR and ACR arms, but the number of rituximab cycles was identical. Since regimens were basically similar, and higher doses were administered in the control arms, we have decided to pool results of these trials as 'same chemotherapy'.

Three studies (Kimby 1994; Unterhalt 1996; Peterson 2003) compared different regimens in the ACR and non-ACR arms. For baseline characteristics of interventions see Additional Table 2. For

a detailed comparison of therapeutic regimens see Additional Table 3.

Different anthracyclines were used in the studies: five used doxorubicin (Jones 1983; Lepage 1990; Kimby 1994; Peterson 2003; Federico 2013); two used idarubicin (Zinzani 2000; Taylor 2006); and one used mitoxantrone (Unterhalt 1996). Rituximab was used only in Federico 2013.

Outcome assessment

All but one trial (Unterhalt 1996) assessed OS, although not necessarily as the primary outcome. However, Federico 2013 did not eventually report OS data and Zinzani 2000 did not report OS separately in FL patients. Finally, only three trials with similar chemotherapeutic regimens were analyzed for survival (Jones 1983; Lepage 1990; Taylor 2006).

All trials assessed response rate, although definitions were not uniform across trials. Outcomes regarding disease control varied considerably across trials, and commonly were not compatible with the subsequently published criteria for reporting outcomes from clinical trials (Cheson 1999; Cheson 2007). The outcomes and their definitions are specified in the Characteristics of included studies table.

Excluded studies

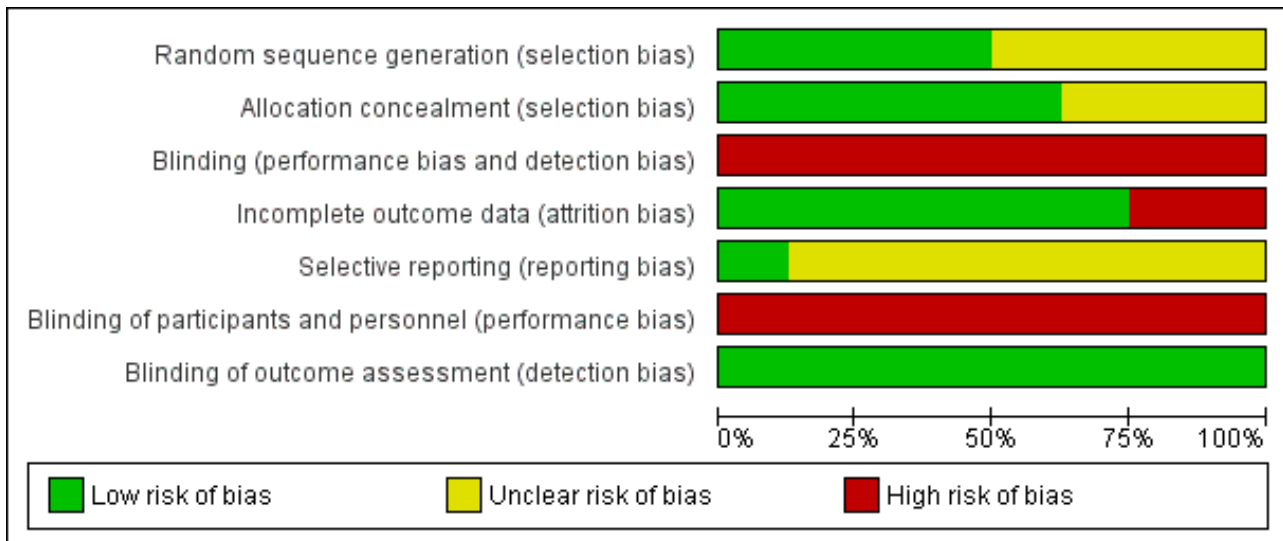
Thirty-nine trials were excluded (including one ongoing trial, Flinn 2012). Reasons for exclusion were as follows: eight were non-randomized; five did not include patients with FL; four did not include anthracyclines in study arms and two included anthracyclines in both study arms (one study with multiple combinations); three trials compared irradiation to ACR; one trial had immunotherapy (interferon) only in one study arm; one involved different chemotherapeutic regimens in conjunction with immunotherapy (rituximab); two did not randomize between ACR and non-ACR arms; one was a cross-over trial; one article emphasized comparison of different diseases rather than therapeutic arms; two were reviews; in two relevant outcome data could not be retrieved; and five were double publications, that did not add information to the main articles. Three trials reported results for indolent NHL patients, but did not specify the number of FL patients included. Al-Ismaïl 1987 randomized 47 low grade lymphoma patients between CVP and epirubicin, vincristine, prednisolone (EPV) regimen. There was no difference in response rates, response duration or OS. Prentice 1996, published only in abstract form, randomized 182 patients with low grade NHL, that were stage II or more, between chlorambucil-prednisone combination and same therapy with mitoxantrone. The results indicated benefit for ACR, with a higher rate of CR (58% versus 44%, $P = 0.02$); longer disease-free survival (2.98 years versus not reached); and longer OS (median of 3.31 years versus not reached). Lastly, Santoro 2006, also published in abstract form, compared rituximab as single agent with pixantrone and rituximab combination, in 38 relapsed and refractory indolent NHL patients. Response rates were higher in the immunochemotherapy combination, as was progression-free survival, although data are missing from abstract, and we could not retrieve any further information from authors.

Risk of bias in included studies

All included studies were described as RCTs. Generation of randomization sequence was assessed as adequate for four trials, where it was done centrally (Jones 1983; Kimby 1994; Unterhalt

1996; Federico 2013). The other studies did not describe the methods used for generation of randomization and hence were classified as unclear. Allocation concealment was assessed as adequate in five trials (Jones 1983; Lepage 1990; Kimby 1994; Unterhalt 1996; Federico 2013) and not reported in the other trials. None of the trials were blinded (Figure 2).

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Two trials were stopped early. In Jones 1983, the control arm (CVP-B) was stopped early when inferiority was suspected. Moreover, 652 patients were randomized in this trial, but only 497 were centrally reclassified and analyzed. Unterhalt 1996 enrolled 442 patients, 42 of whom were excluded owing to protocol violation and NHL subtypes not in concert with trial. However, after only 246 patients were analyzed, the authors' basic assumption of a 20% improvement in overall response could be rejected. Hence, analysis of remaining patients was abandoned, and it was not specified in two double publications (Hiddemann 1994; Unterhalt 1994).

Trials stated that analysis was done on an intention-to-treat (ITT) basis, but in most cases, the provided data could not fully support this statement. Drop-out rate was less than 10% in all but one trial (Unterhalt 1996). Incomplete outcome data could not be well assessed also for Jones 1983 where data were analyzed only for 497 patients with centrally reviewed pathologies, out of total of 636 eligible randomized patients. Thus, according to incomplete outcome data, six trials were considered as low risk for attrition bias and two as high risk.

In Peterson 2003, data were reported for 228 patients (six patients were excluded, three in each arm). Of those, a separate analysis was made for 189 patients with confirmed central pathology, in order to compare between grade 1 and grade 2 FL. In our analysis, we used data from the whole cohort, which is more elaborate and where outcomes were reported on an ITT basis.

Selective outcome reporting could not be assessed since most trials were old and trial registry or protocol were unavailable. The outcomes reported were in accordance with those specified in the methods section of the final publication.

Taylor 2006 reported a protocol violation that may have confounded results, as more patients in the experimental arm received radiotherapy, although they did not initially suffer from a bulky disease. They were included in the analysis on an ITT basis.

All trials were published in peer-reviewed journals, and all reported ethics committee approval and that informed consent was obtained from the patients.

Three trials declared their funding resources, and were not supported by the pharmaceutical industry (Jones 1983; Taylor 2006; Federico 2013). Five studies did not report funding resources (Lepage 1990; Kimby 1994; Unterhalt 1996; Zinzani 2000; Peterson 2003).

Effects of interventions

See: [Summary of findings for the main comparison ACR compared to non-ACR for treatment of follicular lymphoma in adults](#)

Studies comparing same chemotherapy

Five of the eight trials included in this review administered the same chemotherapy (other than anthracyclines). The following sections report outcome measures of these trials alone, and when possible, sum their total effect. We analyzed data specifically for FL patients, or from trials with over 75% FL patients. Three of the trials used higher doses of non-anthracycline therapies in the control arm. When possible, we examined the effect of those trials separately. In Zinzani 2000, FL patients constituted only about a half of the cohort. Results were included in analysis, only for parameters reported separately for FL patients.

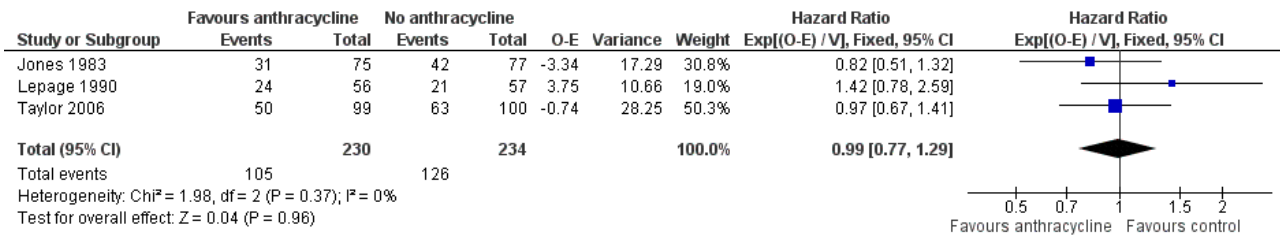
The three trials that used different chemotherapies in study arms, will be described separately. Since the regimens differ considerably between trials, we did not sum their effect, but rather summarized them in a table.

Overall survival

OS data were analyzed for 464 patients included in three studies (Jones 1983; Lepage 1990; Taylor 2006). The pooled HR for OS

was 0.99 (95% CI 0.77 to 1.29; Figure 3), indicating that there was no advantage to ACR chemotherapy compared with other chemotherapy. There was no heterogeneity among trials ($P = 0.37$; $I^2 = 0\%$). Federico 2013 did not publish mortality data, as it was under-powered to assess survival. We did not include Zinzani 2000 in the analysis, since survival data were reported for the whole cohort, and not specifically for FL. However, adding it did not change the pooled results (HR 0.97; 95% CI 0.76 to 1.23, Analysis 1.2).

Figure 3. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.1 Overall survival.

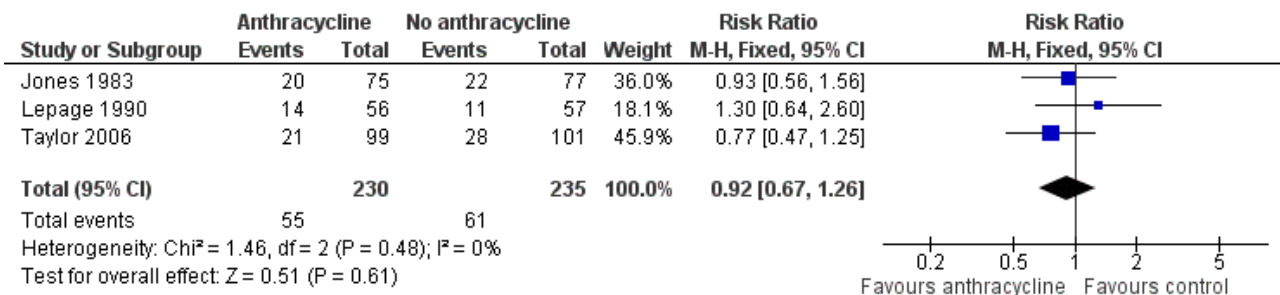


All-cause mortality

There was no difference between ACR and non-ACR chemotherapy for mortality at three years (RR 0.92; 95% CI 0.67 to 1.26; three trials; Figure 4), and no heterogeneity among trials ($P = 0.48$; $I^2 = 0\%$). We

found similar results for five-year mortality (RR 0.95; 95% CI 0.77 to 1.18; three trials; 539 patients; Analysis 1.4). Data regarding 10-year all-cause mortality were reported only in Taylor 2006, where there was no benefit to anthracyclines.

Figure 4. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.3 Mortality at 3 years.

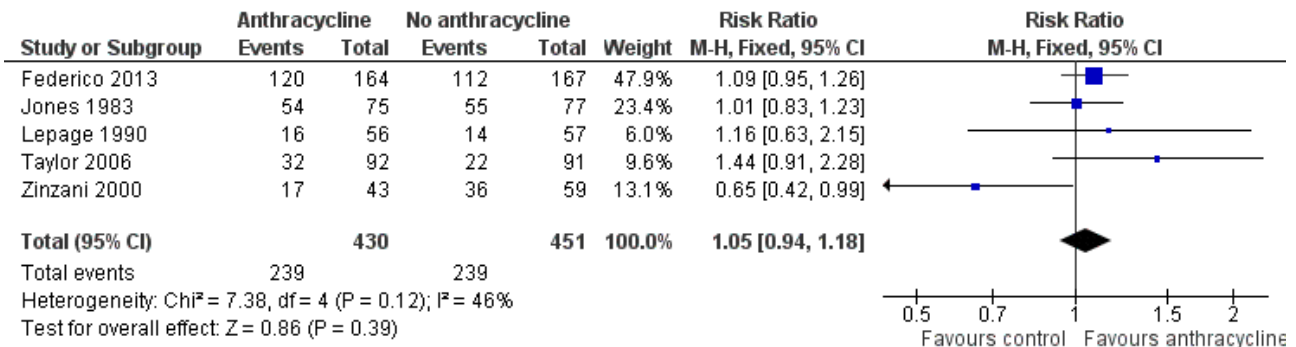


Response rate (CR and ORR)

All trials contributed to the analysis of CR, and all reported response data for FL patients separately. Use of ACR was not statistically significantly better than non-ACR (RR 1.05; 95% CI 0.94 to 1.18; Figure 5), yet there was moderate heterogeneity between trials (P

$= 0.12$; $I^2 = 46\%$). One trial, showing the opposite, contributed to the heterogeneity (Zinzani 2000). This discrepancy may arise from the higher dose of fludarabine in the control arm. Excluding Zinzani 2000 from the analysis did not change results (RR 1.11; 95% CI 0.99 to 1.25; $I^2 = 0\%$). Also, using the random-effects model did not considerably change the analysis (RR 1.03; 95% CI 0.86 to 1.23).

Figure 5. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.5 Complete response.



ORR data were available in three trials (Zinzani 2000; Taylor 2006; Federico 2013), analyzing 616 patients. The pooled RR was 1.06 (95% CI 1.00 to 1.12; I² = 12%; Analysis 1.6), with a probable effect for ACR, although not statistically significant.

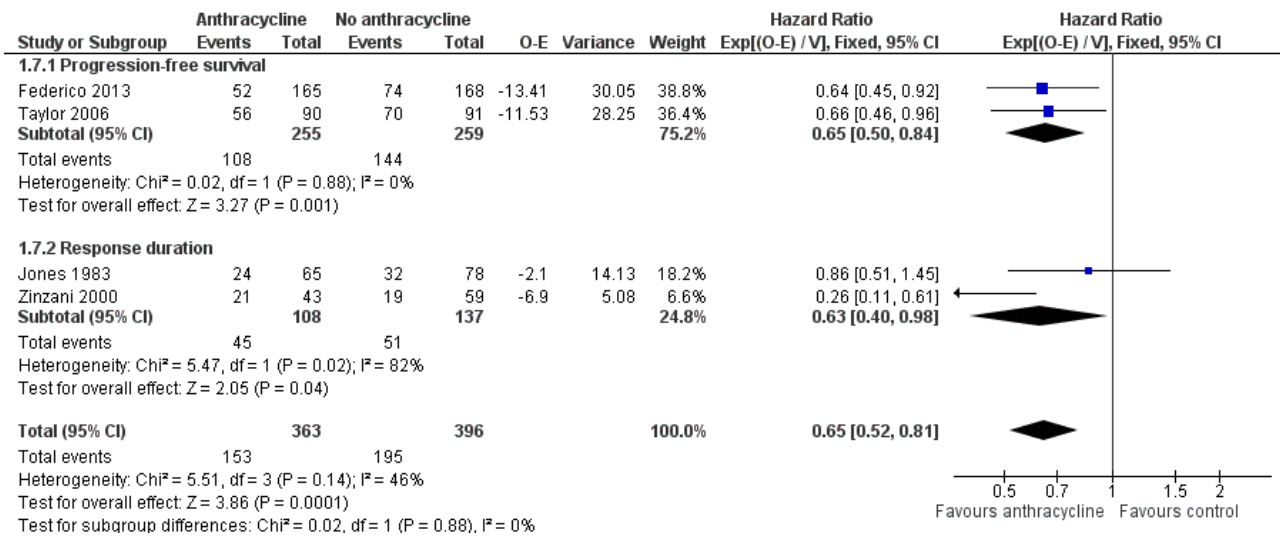
Disease control

Disease control measures were reported in four trials using same chemotherapy (Jones 1983; Zinzani 2000; Taylor 2006; Federico 2013). End points, as specified in studies, were: PFS, RFS, TTTT,

and PFS, respectively (for outcomes definitions see Characteristics of included studies table). However, these measures were often ill-defined, or were not necessarily compatible with common guidelines. Zinzani 2000, for example, used PFS to describe remission duration (RD) in responding patients.

With respect to disease control, ACRs were superior to non-ACRs, with a pooled HR of 0.65 (95% CI 0.52 to 0.81; Figure 6), with some heterogeneity (I² = 46%; P = 0.14) resulting only from differential benefit for ACR.

Figure 6. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.7 Disease control.

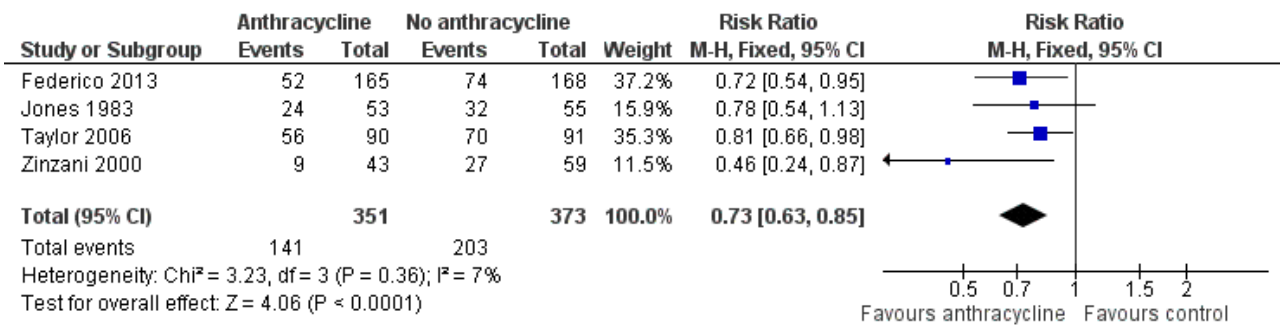


Disease control outcomes could be divided into two groups, according to time from which outcomes were counted: PFS, where outcomes were counted from randomization, and RD, which include only patients responding to treatment from end of therapy. ACRs retained their benefit for PFS (two studies; HR 0.65; 95% CI 0.50 to 0.84) and RD (two studies, HR 0.63; 95% CI 0.40 to 0.98), separately (Figure 6).

Progression or relapse

Progression or relapse was chosen as a complementary dichotomous measure of disease control, relevant in patients with FL. This outcome was assessed in four trials (Jones 1983; Zinzani 2000; Taylor 2006; Federico 2013), and could be extracted at three years in all trials. The pooled RR for previously untreated FL was 0.73 (95% CI 0.63 to 0.85; little heterogeneity I² = 7%; Figure 7), indicating that therapy-naive FL patients treated with ACR had a lower progression rate at three years.

Figure 7. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.8 Progression or relapse at 3 years.



Toxicity

Neutropenia

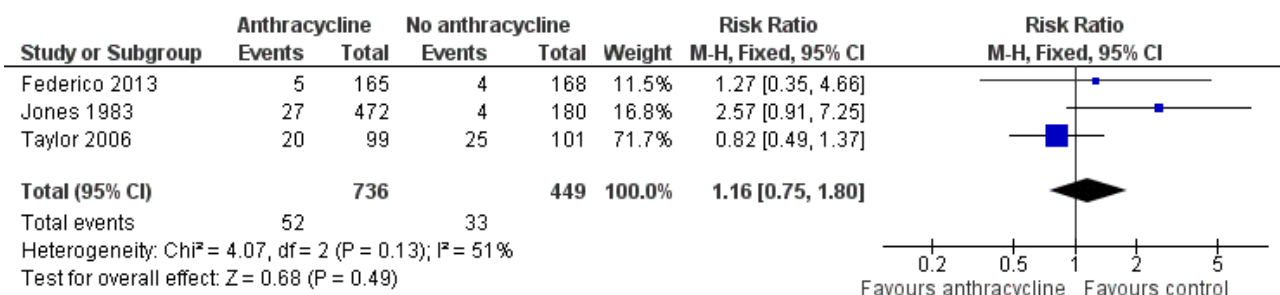
Four trials reported neutropenia as a serious event, but only two (Taylor 2006; Federico 2013) were amenable for meta-analysis, demonstrating a higher rate of grade 3-4 neutropenia with ACR (RR 1.94; 95% CI 1.46 to 2.56; Analysis 1.9). Zinzani 2000 (fludarabine-idarubicin- versus fludarabine) reported equal distribution of neutropenia (toxicity over treatment cycles rather than absolute episodes). However, a higher dose of fludarabine was administered

in the control arm. Jones 1983 gave a qualitative description of more neutropenia in ACR-treated patients.

Infection

The types of infection reported varied considerably between any infection, serious infection, and neutropenic fever. Three trials were included in a meta-analysis considering the infection reported in the study (Jones 1983; Taylor 2006; Federico 2013). The pooled RR of anthracyclines was 1.16 (95% CI 0.75 to 1.80; Figure 8) with considerable heterogeneity (I² = 51%; P = 0.13).

Figure 8. Forest plot of comparison: 1 Anthracycline versus no anthracycline same chemotherapy, outcome: 1.10 Infection.



Cardiotoxicity

Cardiotoxicity was reported in three trials that employed similar regimens. In Jones 1979, 11 cardiac events were recorded in 472 patients receiving ACR (including patients from a third arm of CHOP-BCG). Zinzani 2000 had no cardiac events in both arms. Federico 2013 reported one grade 3-4 event in each study arm.

95% CI 0.41 to 0.81, respectively; P = 0.38 for subgroup difference; Analysis 2.2).

Quality of life

QoL was not assessed in the included trials. However, nausea and vomiting, diarrhea, and mucositis were reported more often with ACR.

All studies were published as peer-reviewed journal articles.

Sensitivity analysis

There was no evidence for OS benefit of anthracyclines in trials reporting adequate allocation concealment or in those with unclear allocation concealment (Analysis 2.1). ACR were superior to non-ACR in terms of disease control, regardless of allocation concealment quality (HR 0.70; 95% CI 0.52 to 0.95 and HR 0.58;

As mentioned above, three studies proceeded to a second randomization (Jones 1983; Lepage 1990; Taylor 2006), and only these trials reported OS. Second randomization did not influence disease control (P value for subgroup difference was 0.26, Analysis 3.1).

Subgroup analysis

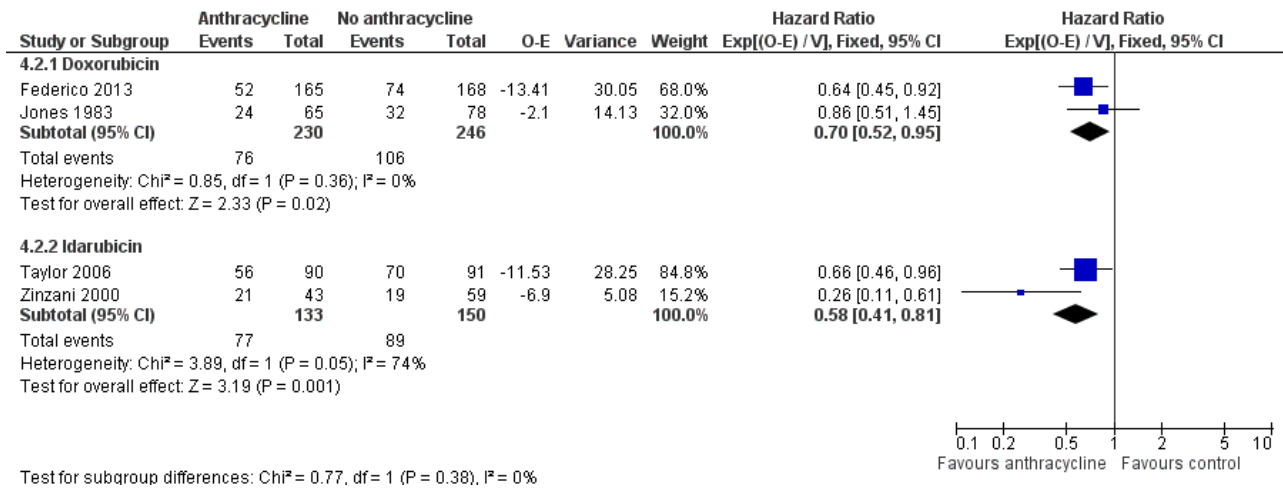
There were not sufficient outcome data for subgroup analysis according to grade of FL or age of patients. Also, all patients included had first-line therapy. Only Federico 2013 had included monoclonal antibodies (rituximab) in study arms. Its results were consistent with those of the other studies.

We undertook subgroup analysis of the different anthracyclines used. Regarding OS, trials employing the same chemotherapies

used either doxorubicin (Jones 1983; Lepage 1990) or idarubicin (Taylor 2006). There was no evidence of survival benefit to either type of anthracycline, as shown in Analysis 4.1. Disease control measures were reported in two trials employing doxorubicin (Jones

1983; Federico 2013) and two trials using idarubicin (Zinzani 2000; Taylor 2006). The advantage of anthracyclines in disease control was preserved regardless of type of anthracycline used, as shown in Figure 9.

Figure 9. Forest plot of comparison: 4 Comparison of different anthracyclines, outcome: 4.2 Disease control.



Studies comparing different chemotherapies

Three trials used different regimens between study arms, and among trials themselves, and therefore could not be summed together.

Peterson 2003 compared CHOP-B with continuous cyclophosphamide PO; Unterhalt 1996 compared prednimustine-mitoxantrone with CVP regimen; and Kimby 1994 evaluated CHOP with chlorambucil-dexamethasone, both given PO (Characteristics of included studies).

The effects of interventions are summarized in Additional Table 4, and graphically in Analysis 5.1; Analysis 5.2; Analysis 5.3; and Analysis 5.4. Consistent with pooled results presented for trials comparing the same chemotherapy, there was no evidence of effect on survival, three-, and five-year mortality for the ACR arms. All trials showed a trend in favour of anthracyclines for disease control. Results for CR and OR were heterogeneous.

Toxicity

Owing to the different regimens used in the ACR and non-ACR arm we did not proceed with a comparative analysis of adverse events from these trials, although a higher rate of myelosuppression was noted with ACR. Peterson 2003 (cyclophosphamide versus CHOP) have reported two cases of cardiotoxicity only in the ACR arm.

Additional analysis - cardiotoxicity (all studies)

Since cardiotoxicity is mainly attributed to anthracyclines we pooled results from all trials reporting cardiotoxicity, regardless of regimen similarity (Jones 1983; Zinzani 2000; Peterson 2003; Federico 2013). The pooled RR of ACRs was 4.55 without heterogeneity, but with a very wide 95% CI (0.92 to 22.49) as shown in Analysis 6.1.

DISCUSSION

Summary of main results

This systematic review was undertaken to evaluate the role of anthracyclines in the treatment of patients with FL. Eight RCTs involving a total of 2636 patients were compatible with the inclusion criteria. Over a half of randomized patients had centrally confirmed FL and were evaluable for analysis. Outcomes were reported separately for FL patients in most trials. All patients were therapy-naive, and most had low-grade, advanced-stage FL. We separated the analysis of trials comparing the same chemotherapy with or without an anthracycline and trials comparing different chemotherapies.

The following findings emerged.

1. There was no evidence that anthracyclines improved OS or mortality at three and five years.
2. FL patients treated with ACR had statistically significantly better disease control (e.g. PFS, RD).
3. Subgroup analysis showed that these effects do not necessarily depend on the type of anthracycline.
4. ACR-treated patients had more side effects than non-ACR-treated patients, including myelotoxicity and cardiotoxicity.

Overall completeness and applicability of evidence

The first-line treatment of patients with FL is still undetermined. In the US, most patients are treated with R-CHOP, an ACR. However, there is no proof that ACRs are superior to non-ACRs. To our knowledge, this is the first systematic review and meta-analysis trying to answer this important question.

The contribution of anthracyclines is best elucidated in trials administering the same regimens in both study arms, as they were designed specifically for this question. We also included trials that involved different regimens in study arms, since anthracyclines

are dominant antitumor agents. However, these trials were designed to compare different chemotherapy combinations, where anthracycline is only one of the components. It is impossible, then, to differentiate the effect of anthracyclines from other chemotherapeutic agents, or their combination. Hence, we have separated the analysis of trials according to similarity of chemotherapies in study arms, and outcome measures were summed only from studies that used the same chemotherapy.

Even among trials with 'same chemotherapy', regimens were not identical between study arms in three out of five studies. Nonetheless, similarity outweighed the difference (e.g. R-CVP eight cycles versus R-CHOP, six cycles in [Federico 2013](#)), and we have chosen to sum outcome data. Moreover, since control arms were more intense in all three trials discussed, any benefit of anthracyclines would only underscore their importance.

All trials, except for two ([Peterson 2003](#); [Federico 2013](#)), randomized patients with NHL, and not specifically FL. However, most patients in these studies had FL, or alternatively, specific data regarding FL patients were reported. Moreover, although diagnosis of FL was usually based on initial pathology, it was confirmed centrally. Thus, even though different classification systems were applied in different trials, it is reasonable to assume that the diagnosis was correct. All FL patients in these trials were previously untreated, and most had advanced-stage, low-grade FL. There were not sufficient data to analyze the role of anthracyclines in untreated early-stage disease, or in persistent or relapsing disease. Subgroup analysis regarding effect of anthracyclines in different grades of FL was not possible.

Follow-up varied between three and 18 years, but most trials reported outcomes at five years, which is reasonable given that until recently the median survival of FL patients was considered to be eight to 10 years. With the introduction of immunotherapy, namely rituximab, longer follow-up periods are desired.

A major limitation to our review is that the trials included were conducted mostly in the pre-rituximab era. Encouraging data came from [Federico 2013](#), which showed a statistically significant improvement in time to treatment failure with R-CHOP compared to R-CVP, at three years' follow-up. An ongoing trial comparing R-CHOP to R-CVP with the addition of R-maintenance ([NCT00801281](#)) is expected to further elucidate the role of anthracyclines in the rituximab era. Other trials are conducted to assess the utility of various R-pixantrone-based regimens in FL patients.

Other important questions that remained unanswered are: the benefit of anthracyclines in high-risk FL patients, according to FLIPI score; their role in molecular remission and its relevance to prolonged PFS; their effect on FL transformation rate; QoL in patients treated with anthracyclines; and the association between anthracyclines and secondary malignancies.

Quality of the evidence

All trials were RCTs, which is the optimal design for assessment of interventions, yet they were not blinded. All of them were multicenter trials. Hence, we believe that the randomization process was adequate in most trials.

In randomized trials, an estimated intervention effect may be biased if some randomized participants are excluded from the analysis. ITT analysis is often recommended as the least biased

way to assess an intervention. In our review, most trials claimed to have used ITT analysis, but in fact reported results for fewer patients than were initially randomized (e.g. only for patients with confirmed FL histology). However, the low drop-out rate in seven trials supports the authors' claim. Protocol violation ([Taylor 2006](#)) and early stopping of trials ([Jones 1983](#), and specifically [Unterhalt 1996](#) who did not complete analysis of recruited patients), also weakens the strength of evidence contributed by them.

By using HR for analysis of time-to-event data, such as OS and disease control measures, we minimized the risk of bias related to measuring death or progression at specific time points. We complemented these results by extracting and calculating RRs for mortality at three and five years, and progression or relapse at three years.

We observed a lack of uniformity related to the reporting of treatment-associated side effects. The most often reported grade 3 and 4 adverse events were myelosuppression, fever, infection, nausea and vomiting, and alopecia.

Potential biases in the review process

Only a few trials were suitable for meta-analysis of the various outcome measures. Hence, publication of new large trials could substantially change the results of this meta-analysis.

Many trials were conducted and published over a decade ago, which might have introduced bias for several reasons. Over the years different classification systems have been used for hematological malignancies, and there is no certainty that analyzed patients would be regarded as FL patients using present guidelines; methods for staging and the definition of response measures have changed as radiology and laboratory methods improved; standard of care including supportive care have changed over the years, allowing patients to withstand more aggressive therapies. Finally, we could not complete missing data in the older trials.

Various protocols, some of which are scarcely administered currently, and different types of anthracyclines have been used making it difficult to assess the role of a specific anthracycline within a given regimen (e.g. doxorubicin in CHOP versus CVP).

There was substantial variability in outcome definition for disease control measures. The definition was often partial and did not necessarily comply with the currently published criteria ([Cheson 1999](#); [Cheson 2007](#)). Death was inconsistently included in trial definitions, and when reported, we had to assume it was death by any cause, and not related to lymphoma specifically.

Adverse events were reported in all trials, but inconsistently, and using different measures (i.e. episodes of fever per cycle or per patient; any infection versus severe infection). Therefore, reporting bias is likely. Qualitatively, adverse events were more often reported with ACR.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first systematic review and meta-analysis regarding use of anthracyclines in FL patients. Conflicting results arose from retrospective studies regarding OS and FFS ([Dana 1993](#); [Rigacci 2003](#)). Most other data came from indirect

comparisons, comparing treatment arms to historical cohorts and published literature, indicating an improved response rate with anthracyclines, with inconsistency in relation to other end points (Brandt 2001; Bendandi 2008; Tilly 2008; Vitolo 2008; Siddhartha 2009).

A previous systematic review of chemotherapy effects in indolent NHL (Brandt 2001) neither focused on FL patients, nor on ACR. Three trials were identified (Kimby 1994 and Unterhalt 1996 were included in our review; Al-Ismaïl 1987 was excluded), all of which compared different regimens in study arms. The authors concluded that there was no evidence that initial combination therapy prolonged survival, with no remark concerning PFS.

Siddhartha (Siddhartha 2009) tried to evaluate the difference between R-CHOP and R-CVP indirectly, based on trials comparing R-CHOP versus CHOP and R-CVP versus CVP. Results suggested better a CR rate with R-CVP, but higher ORR with R-CHOP. However, OS and disease control measures were not addressed.

Notably, our meta-analysis is in agreement with almost all aforementioned studies, in that an improvement of disease control measures (i.e. PFS) did not translate into prolonged survival. This contradiction emphasizes the incurable nature of FL, on the one hand, while underscoring the plentitude of effective salvage therapies and improved supportive care, on the other hand. Another factor to consider that the somewhat more intense regimens in the control-arms of three trials (Jones 1983; Zinzani 2000; Federico 2013), may have underestimated the benefit of anthracyclines in the treatment of FL. Relatively short follow-up periods in included trials and the older population of FL patients, may have a role as well. Yet, the place of PFS in directing therapy choices is still debatable.

Olin et al (Olin 2010) have used decision analysis methodology to show that PFS is the most important factor in maximizing quality-adjusted life years, in advanced-stage, low-grade FL patients. Based on their estimates of PFS and QoL from available literature, R-CHOP is the optimal regimen, followed by R-Flu, while R-CVP consistently generated fewer quality-adjusted life years. QoL assessment could not be assessed in our systematic review.

Since there is no consensus on initial treatment of FL, the NLCS published a report of treatment trends of FL in the US (Friedberg 2009). Over 50% of patients were treated with R-CHOP. Moreover, this has become the recommended treatment for patients with grade 3 FL (Buske 2008). Nonetheless, other authors have expressed doubt regarding the role of anthracyclines (Chau 2003; Nabhan 2007).

The debate concerning best chemotherapy regimen in the rituximab era may seem obsolete, as combination of rituximab with nearly any induction chemotherapy is superior in terms of OS to the same regimen alone (Schulz 2007). This is reinforced by the fact that maintenance rituximab prolongs OS in patients with relapsed, recurrent, or resistant FL (Vidal 2009). However, a clue regarding the importance of anthracyclines in induction therapy for FL came from the international Primary Rituximab and Maintenance (PRIMA) study. This study has shown significant reduction in lymphoma progression with rituximab maintenance as compared with observation. However, in a preplanned Cox regression multivariate analysis, longer PFS was associated with R-CHOP induction therapy (75% of patients), but could not reach

statistical significance for R-CVP therapy (22% of patients) (Salles 2011).

As the role of anthracyclines with immunotherapy remains to be elucidated, an old drug that has recently re-emerged puts the necessity of ACR in FL into question. In one large randomized trial comparing bendamustine-rituximab with R-CHOP, Rummel et al found the non-ACR to be superior with respect to PFS and CR and less toxic, with a median follow-up of 45 months (Rummel 2009; Rummel 2013).

Adverse events were reported more often with ACR, including cardiotoxicity. Various methods have been developed and variably studied in order to reduce them: use of anthracycline-analogues; continuous infusion of adriamycin (as was also shown in one meta-analysis, van Dalen 2009); use of liposomal preparations; or administration of various substances including calcium channel blockers and angiotensin receptor blockers (Outomuro 2007). In our meta-analysis, cardiotoxicity was mostly reported in trials involving doxorubicin. No cardiotoxicity was reported with idarubicin in Zinzani 2000. Al-Ismaïl et al had demonstrated a significantly lower rate of cardiotoxicity from epirubicin, in comparison with adriamycin, in high-grade lymphoma patients (Al-Ismaïl 1987). Zinzani et al (Zinzani 2004) compared CHOP with fludarabine-mitoxantrone (FM), and showed higher CR and molecular remission rate with FM, with fewer adverse events, such as grade 3-4 neutropenia. However, at 19 months of follow-up, there was neither survival nor PFS benefit to either regimen. Moreover, no cardiotoxicity was registered.

AUTHORS' CONCLUSIONS

Implications for practice

ACR, regardless of the chemotherapeutic regimen, increased PFS and RD, in first-line treatment of advanced, low-grade FL patients. There was no notable effect on OS, although disparities in regimens might weaken this result, in favour for ACR. Evidence is of moderate quality.

In an indolent disease with a remitting and relapsing long-term course, importance of PFS prolongation needs to be considered, especially in light of increased toxicity with ACR.

Implications for research

The role of anthracyclines in conjunction with immunotherapy needs to be elucidated in a large-scale RCT. There are a few ongoing trials comparing R-CHOP with R-CVP or with other regimens, and they are most likely to answer this important question. RCTs assessing the role of anthracyclines for early-disease, high-grade FL or as second-line treatment are needed. Prospective trials with long follow-up periods (of 10 years or more) are needed in order to assess OS benefit in FL patients adequately. In addition, the effect of ACR on molecular remission, and its importance as a response measure requires investigation.

The efficacy and adverse events rate of various non-doxorubicin ACR should be investigated, especially in more frail populations. However, the availability of novel and efficacious biologic agents makes it unlikely that new resources will be invested.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Federico 2013

Methods	RCT Location: Italy, multicenter Years: recruited 2006 to 2010 Follow-up: median 34 months Pharmaceutical sponsorship: no Classification system: WHO Central pathology: only for grade 3 FL
Participants	Number of patients randomized: 534 Number of patients analyzed: 504 Numbers of patients with FL: 504 Number of patients included in our analysis: 333 Lymphoma: previously untreated stage II to IV FL, grade 1 to 3a, age 18 to 75 years, ECOG 0 to 2 Line of treatment: first Patients: median age (range) 56 years (30 to 75 years)
Interventions	Same: R-CHOP x 6 + R x 2 versus R-CVP x 8 Note number of courses in each arm
Outcomes	Time to treatment failure Response rate Progression-free survival Overall survival Toxicity

Federico 2013 (Continued)

Notes Unpublished data from authors

This was a triple arm study: R-CVP versus R-CHOP versus R-FM. We extracted data for the first comparison, according to protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization arm was assigned automatically by the EDC system upon verification of eligibility criteria. Arm was communicated on screen and confirmed by email to the investigator. Randomization was based on prepopulated tables that were prepared and uploaded by the IT staff on the EDC system at study start
Allocation concealment (selection bias)	Low risk	Randomization tables could not be accessed or modified, or both, by any investigator or study co-ordinator
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No change from protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors did not believe this will introduce bias

Jones 1983

Methods RCT

Location: US, multicenter, SWOG study

Years: 1974 to 1977

Follow-up: maximum 6 years

Pharmaceutical sponsorship: no

Classification system: Rappaport

Central pathology: yes

Participants Number of patients randomized: 652

Number of patients analyzed: 497 (after central pathology)

Jones 1983 (Continued)

Numbers of patients with FL: 226 (nodular lymphoma)

Lymphoma: advanced-stage NHL

Line of treatment: first or recurrence after RTx

Patients: of 226 patients with nodular lymphoma, grade classification was as follows: NLPD (nodular lymphocytic poorly differentiated or follicular small cleaved cell lymphoma), 160 patients; NM (nodular mixed or follicular small cleaved and large cell lymphoma), 42 patients; NH (nodular 'histiocytic' or follicular large cell lymphoma), 24 patients

Interventions

Same: CHOP-Bleo x 8 versus CVP-Bleo x 8

Control arm: d 1-14 cyclophosphamide 125 mg/m² PO, d 1, 8 vincristine 1.4 mg/m² IV (max 2 mg/dose), d 1-5 prednisone 100 mg/d PO, d 1,8 bleomycin 4 mg/m² IV. 8 cycles, every 21 d

Experimental arm: d 1 cyclophosphamide 750 mg/m² IV, d 1 doxorubicin 50 mg/m² IV, d 1 vincristine 1.4 mg/m² (max 2 mg) IV, d 1-5 prednisone 100 mg/d PO, d 1 bleomycin 4 mg/m² IV. 8 cycles, every 28 d

Outcomes

Overall survival

Response rate

Relapse-free survival

Toxicity

Notes

Published: journal article

Double publication of preliminary data: [Jones 1979](#)

Triple-arm design: CHOP-BCG versus CHOP-Bleo versus CVP-Bleo. Second randomization in patients achieving partial response was: no treatment versus BCG maintenance

CVP-Bleo arm terminated early

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were assigned at random by the SWOG Statistical Office" Comment: assumed proper sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "patients were assigned at random by the SWOG Statistical Office" Comment: assumed concealment of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 652 patients were randomized; 636 were evaluable (Quote: "16 were not evaluable - insufficient data submitted or major protocol violation"); only 497 had central pathology, according to which analysis was made. Data were reported only for 468 patients with chosen diagnoses Data were reported for 226 FL patients. The number of patients with FL at randomization could not be inferred

Jones 1983 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

Kimby 1994

Methods	RCT Location: Sweden, multicenter, LGCS study Years: 1982 to 1988 Follow-up: minimum 57 months Pharmaceutical sponsorship: NR Classification system: Kiel Central pathology: yes
Participants	Number of patients randomized: 259 Number of patients analyzed: 259 Numbers of patients with FL: 76 Lymphoma: advanced-stage, symptomatic, low-grade NHL (CLL, immunocytoma, centrocytic lymphoma, centroblastic/centrocytic lymphoma) Line of treatment: first Patients: mean age 64 years
Interventions	Different: CHOP x 4-8 cycles versus CD x 4-8 cycles
Outcomes	Overall survival Response rate Freedom from progression defined as survival without progression, measured from randomization Response duration - time from CR or PR to relapse or progression Toxicity
Notes	Published: journal article
Risk of bias	
Bias	Authors' judgement Support for judgement

Kimby 1994 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "randomization was centralized" Comment: assumed proper sequence generation, since done by the LGCS
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centralized" Comment: assumed proper allocation concealment, since done by the LGCS
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

Lepage 1990

Methods	RCT Location: France, single center Years: 1981 to 1984 Follow-up: median 59 months Pharmaceutical sponsorship: NR Classification system: working-formulation Central pathology: yes
Participants	Number of patients randomized: 113 Number of patients analyzed: 113 Numbers of patients with FL: 101 Lymphoma: stage II/IV and stage II bulky, low-grade NHL Line of treatment: first Patients: median age (range) 51 years (26 to 70 years), over 90% were advanced stage, 40% with bulky disease, and 65% with bone-marrow involvement
Interventions	Same: PCOP x 6 cycles versus PACOP x 6 cycles

Lepage 1990 (Continued)

Outcomes	Overall survival Response rate Freedom from progression defined as survival without progression Freedom from relapse defined as time from CR to relapse Toxicity
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Notes	Published: journal article Double publication: Gisselbrecht 1987 Second randomization in responding patients to maintenance with chlorambucil versus CVP for 12 months
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	None reported
Allocation concealment (selection bias)	Low risk	Comment: assumed proper since done as central randomization in a multicenter trial
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

Peterson 2003

Methods	RCT Location: USA, multicenter, CALGB study Years: 1980 to 1985 Follow-up: maximum 18 years Pharmaceutical sponsorship: NR
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Peterson 2003 (Continued)

Classification system: REAL

Central pathology: yes

Participants

Number of patients randomized: 228

Number of patients analyzed: 228

Numbers of patients with FL: 189 after reclassification

Lymphoma: advanced FL grade 1 (follicular small cell lymphoma) and grade 2 (follicular mixed-cell lymphoma)

Line of treatment: first

Patients: median age 55 years, 36% of patients were over 60 years, 60% had bone marrow involvement, 50% were asymptomatic at initiation of treatment

Interventions

Different: CHOP-Bleo for a median of 26 months (Bleo only 6 cycles) versus daily cyclophosphamide PO for a median of 28 months

Outcomes

Overall survival

Response rate

TTTP - time to first progression, relapse or recurrence, death from any cause, or discontinuation of treatment for non-responders

CR duration - from first CR to relapse or death by any cause

Toxicity

Notes

Published: journal article

Subgroup analysis of FSCL and FML patients, after reclassification, indicated better outcomes in FML patients treated with CHOP regimen, including overall survival, TTTF and complete remission duration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported. No statement regarding where randomization actually took place
Allocation concealment (selection bias)	Unclear risk	Not reported. No statement regarding where randomization actually took place
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 of 234 randomized patients were cancelled, 3 in each arm (reasons not stated). Data were reported for 228 patients. Another analysis was made to compare between grades of FL (FSCL versus FML), and included 189 patients with after central pathology review
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias)	High risk	Open study

Peterson 2003 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias
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Taylor 2006

Methods	<p>RCT</p> <p>Location: UK, multicenter, SNLG study</p> <p>Years: 1993 to 2000</p> <p>Follow-up: median 58 months</p> <p>Pharmaceutical sponsorship: no</p> <p>Classification system: Kiel/REAL</p> <p>Central pathology: yes</p>	
Participants	<p>Number of patients randomized: 200</p> <p>Number of patients analyzed: 183</p> <p>Numbers of patients with FL: 155</p> <p>Lymphoma: low-grade NHL</p> <p>Line of treatment: first, but previous radiotherapy for localized low-grade NHL was allowed</p> <p>Patients: age was matched across study arms, 34% of patients were over age 60 years; 83% and 94% of patients were stage III/IV, in CID and CD arms, respectively; 15% and 32% had a high FLIPI score</p>	
Interventions	<p>Same: CD (Chlorambucil + dexamethasone) x 6 cycles versus CID (same + idarubicin) x 6. Radiotherapy to bulky disease allowed</p>	
Outcomes	<p>Overall survival</p> <p>Response rate</p> <p>Time to treatment failure - time from entry to the start of subsequent treatment or relapse</p> <p>Toxicity</p>	
Notes	<p>Published: journal article</p> <p>Second randomization in responding patients: no treatment versus IFNα</p> <p>Protocol violation in CID arm with access radiotherapy might have introduced bias</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Taylor 2006 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	17 patients were not analyzed: 2 withdrew consent (1 in each arm); 15 were ineligible on pathology review (9 in CID arm, 6 in CD arm)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

Unterhalt 1996

Methods	<p>RCT</p> <p>Location: Europe, multicenter, GLGLSG study</p> <p>Years: 1989 to 1995</p> <p>Follow-up: NR</p> <p>Pharmaceutical sponsorship: NR</p> <p>Classification system: Kiel/REAL</p> <p>Central pathology: yes</p>
Participants	<p>Number of patients randomized: 442</p> <p>Number of patients analyzed: 246</p> <p>Numbers of patients with FL: 200</p> <p>Lymphoma: advanced-stage FL grade 1-2 and MCL</p> <p>Line of treatment: first</p> <p>Patients: median (range) age 54 years (28 to 77 years), 67% had bone marrow involvement</p>
Interventions	Different: PmM x 4-6 cycles versus CVP x 4-6 cycles
Outcomes	<p>Response rate</p> <p>Event-free interval measured from response to the recurrence of lymphoma or death</p> <p>Toxicity</p>

Unterhalt 1996 (Continued)

Notes Published: journal article
 Triple publication: [Hiddemann 1994](#); [Hiddemann 1998](#)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients underwent a central randomization procedure" Comment: assumed proper sequence generation, since done by the GLGLSG
Allocation concealment (selection bias)	Low risk	Quote: "eligible patients underwent a central randomization procedure" Comment: assumed proper allocation concealment, since done by the GLGLSG
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 344 randomized FL patients, only 200 were fully evaluable for central pathology, 33 of whom withdrew early from study (reasons stated in study), leaving only 167 FL patients for analysis
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

Zinzani 2000

Methods	RCT Location: Italy, multicenter Years: 1995 to 1998 Follow-up: median 19 months (range 6 to 38 months) after end of chemotherapy Pharmaceutical sponsorship: NR Classification system: REAL Central pathology: yes
Participants	Number of patients randomized: 208 Number of patients analyzed: 199 Numbers of patients with FL: 102

Zinzani 2000 (Continued)

Lymphoma: stage II-IV, indolent lymphoma (including FL, immunocytoma, and small lymphocytic lymphoma) or MCL

Line of treatment: first

Patients: median (range) age 54 years (25 to 65 years), 86% were stage III/IV, 12% had bulky disease, all had an IPI of 3 or less, 62% had IPI 0 or 1

Interventions	Same: Fl x 6 cycles versus fludarabine x 6 cycles Fludarabine was given for 5 days in the control arm versus 3 days in the experimental arm
Outcomes	Overall survival Response rate Progression-free survival measured from date of any response until relapse or progression Relapse-free survival measured from CR to relapse or death Toxicity
Notes	Published: journal article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the nine patients who were excluded were so because of incorrect diagnosis (three patients), loss to follow-up (three patients), and protocol violations (three patients)" Comment: data were reported for all other 199 patients
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open study; review authors do not believe this will introduce bias

BCG: Bacillus Calmette Guerin; CALGB: Cancer and Leukemia Group B; CD: chlorambucil, dexamethasone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-Bleo: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; CHOP-BCG: cyclophosphamide, doxorubicin, vincristine, prednisone, Bacillus Calmette Guerin; CID: chlorambucil, idarubicin, dexamethasone; CLL: chronic lymphocytic leukemia; CVP: cyclophosphamide, vincristine, prednisone; CVP-Bleo: cyclophosphamide, vincristine, prednisone,

bleomycin; CR: complete response; d: day; ECOG: Eastern Cooperative Oncology Group; EDC: electronic data capture; FI: fludarabine, idarubicin; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; FML: follicular mixed lymphoma; FSCL: follicular small cleaved lymphoma; GLGLSG: German Low Grade Lymphoma Study Group; IPI: International Prognostic Index; IT: information technology; IV: intravenous; LGCS: Lymphoma Group of Central Sweden; MCL: mantle-cell lymphoma; NHL: non-Hodgkin lymphoma; NR: not reported; PACOP: cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin; PCOP: cyclophosphamide, vincristine, procarbazine, prednisone; PmM: prednimustine, mitoxantrone; PO: oral; R: rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone; R-FM: rituximab, fludarabine, mitoxantrone; RCT: randomized controlled trial; REAL: Revised European-American Classification of Lymphoid Neoplasms; SNLG: Scotland and Newcastle Lymphoma Group; SWOG: South-West Oncology Group; TTTF: time to treatment failure; WHO: World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Acker 1983	No anthracyclines in study arms
Al-Ismael 1987	Did not state the number of FL patients out of low-grade lymphomas
Andersen 1990	Not FL
Ben-Shahar 1998	Did not report relevant outcomes (see Methods)
Bonadonna 1975	Cross-over trial
Cabanillas 1978	Anthracyclines in both study arms
Coiffier 1999	Immunotherapy only in 1 study arm
Engelhard 1986	Not FL
Flinn 2012	No randomization between ACR and non-ACR arms
Gad 1976	No anthracyclines in study arms
Gams 1985	Not low-grade lymphoma
Gisselbrecht 1987	Double publication
Ha 2005	No chemotherapy on control arm (irradiation only)
Hainsworth 2005	Non-randomized trial
Hiddemann 1994	Double publication
Hiddemann 1998	Comparison between FL and MCL, not between therapeutic study arms
Inoue 1993	Non-randomized trial, few patients with low-grade lymphoma
Jones 1979	Double publication
Junmin 2005	Non-randomized trial
Meerwaldt 1991	No chemotherapy on control arm (irradiation only)
Meusers 1989	Not FL
Mukherji 2009	Review article

Study	Reason for exclusion
Niitsu 1997	Non-randomized trial
Parlier 1981	Non-randomized trial
Parlier 1982	Non-randomized trial
Peterson 1985	Double publication
Pettengell 2009	Not FL
Pott 1994	Data could not be retrieved
Prentice 1996	Did not state the number of FL patients out of low-grade lymphomas
Robak 2000	Non-randomized trial
Rummel 2008	Review article
Rummel 2009	Different chemotherapeutic regimens in conjunction with immunotherapy (rituximab)
Rummel 2013	Different chemotherapeutic regimens in conjunction with immunotherapy (rituximab)
Santini 2001	Non-randomized trial
Santoro 2006	Did not state the number of FL patients out of low-grade lymphomas
Somers 1987	Report of a number of studies. No anthracyclines in study arms or anthracyclines in both study arms
Unterhalt 1994	Double publication
Yahalom 1993	No chemotherapy on control arm (irradiation only)
Young 1977	No anthracyclines in study arms

ACR: anthracycline-containing regimens; FL: follicular lymphoma; MCL: mantle-cell lymphoma;

Characteristics of ongoing studies [ordered by study ID]

NCT00551239

Trial name or title	Fludarabine and rituximab with or without pixantrone in treating patients with relapsed or refractory indolent non-Hodgkin lymphoma
Methods	RCT, single blind (outcomes assessor)
Participants	Patients with relapsed or refractory indolent non-Hodgkin lymphoma
Interventions	Combination BBR 2778, fludarabine, and rituximab with the combination fludarabine and rituximab
Outcomes	Primary: progression-free survival
Starting date	August 2007

NCT00551239 (Continued)

Contact information	Cell Therapeutics, Inc (Igor Gorbachevsky, Medical Director)
Notes	Ongoing but not recruiting

NCT00801281

Trial name or title	First-line R-CVP vs R-CHOP induction immunochemotherapy for indolent lymphoma and R maintenance (PLRG4)
Methods	Multicenter, Phase III randomized study
Participants	First-line indolent NHL
Interventions	R-CVP versus R-CHOP and R maintenance
Outcomes	Primary: event-free survival
Starting date	February 2007
Contact information	Polish Lymphoma Research Group
Notes	Recruiting

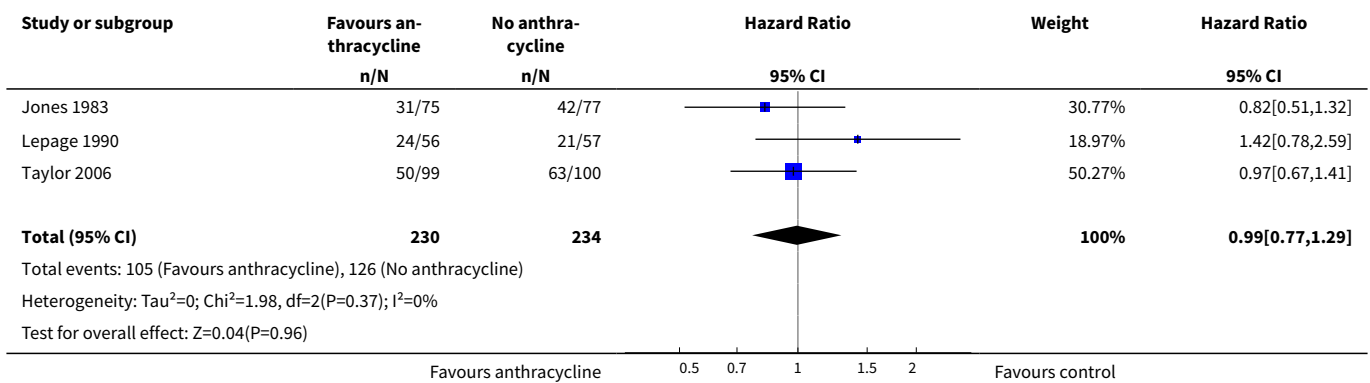
FL: follicular lymphoma; NHL: non-Hodgkin lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone; R-FM: rituximab, fludarabine, mitoxantrone

DATA AND ANALYSES
Comparison 1. Anthracycline versus no anthracycline same chemotherapy

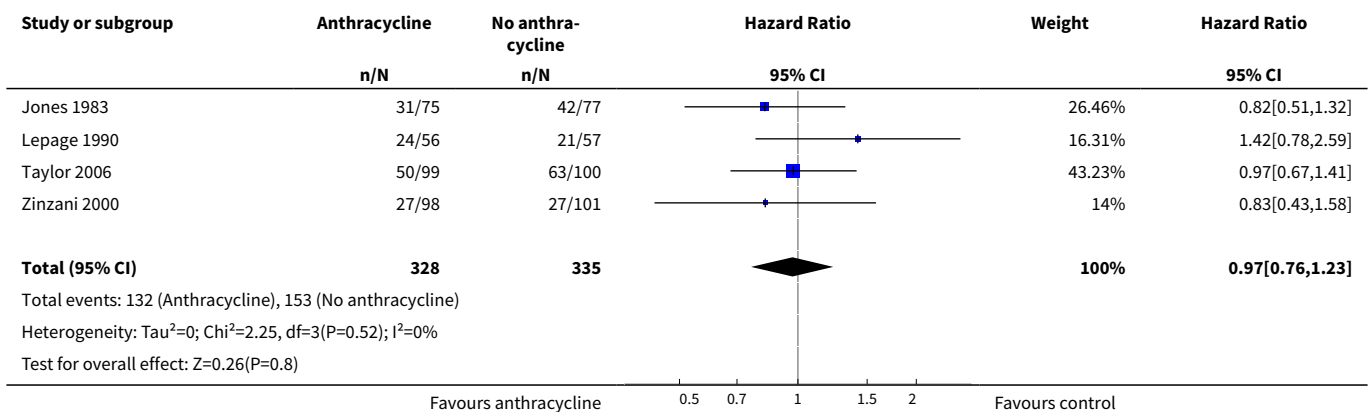
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	464	Hazard Ratio (95% CI)	0.99 [0.77, 1.29]
2 Overall survival with Zinzani	4	663	Hazard Ratio (95% CI)	0.97 [0.76, 1.23]
3 Mortality at 3 years	3	465	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.26]
4 Mortality at 5 years	3	465	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.18]
5 Complete response	5	881	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
6 Overall response	3	616	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.00, 1.12]
7 Disease control	4	759	Hazard Ratio (95% CI)	0.65 [0.52, 0.81]
7.1 Progression-free survival	2	514	Hazard Ratio (95% CI)	0.65 [0.50, 0.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Response duration	2	245	Hazard Ratio (95% CI)	0.63 [0.40, 0.98]
8 Progression/relapse at 3 years	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
9 Neutropenia grade 3-4	2	533	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.46, 2.56]
10 Infection	3	1185	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.75, 1.80]

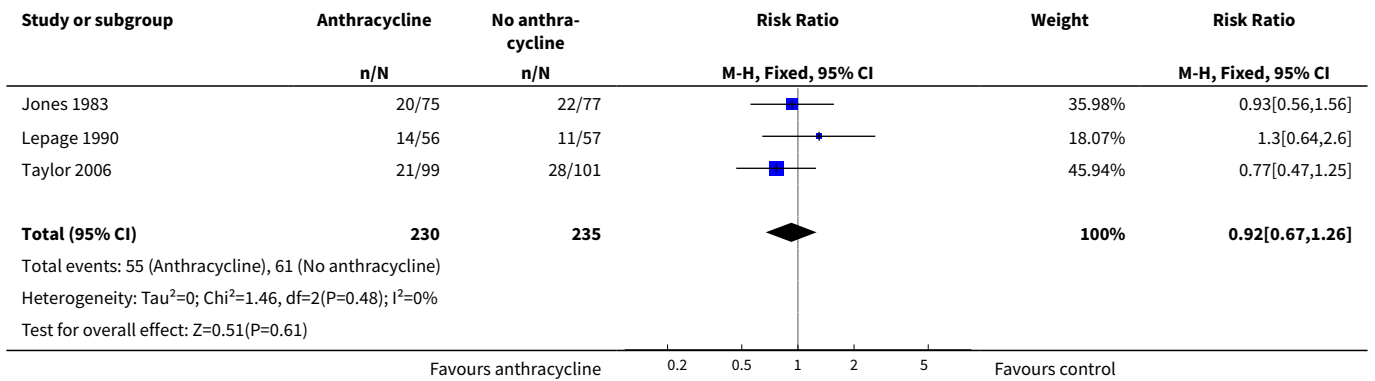
Analysis 1.1. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 1 Overall survival.



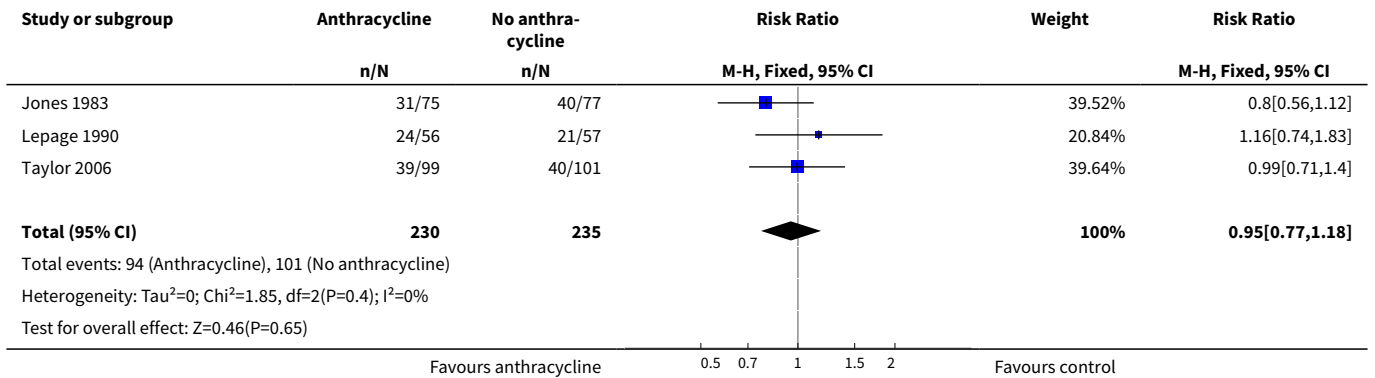
Analysis 1.2. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 2 Overall survival with Zinzani.



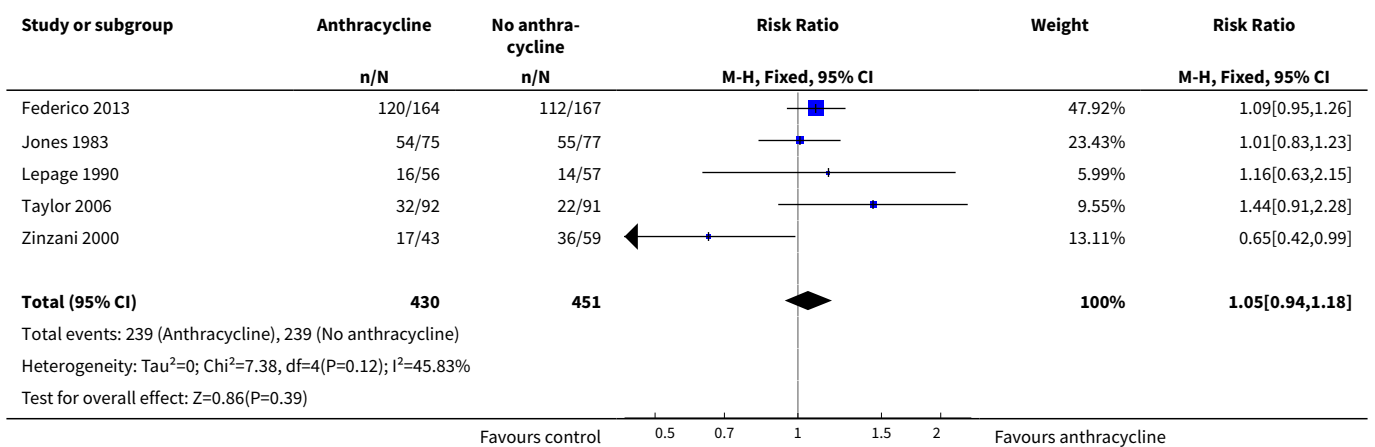
Analysis 1.3. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 3 Mortality at 3 years.



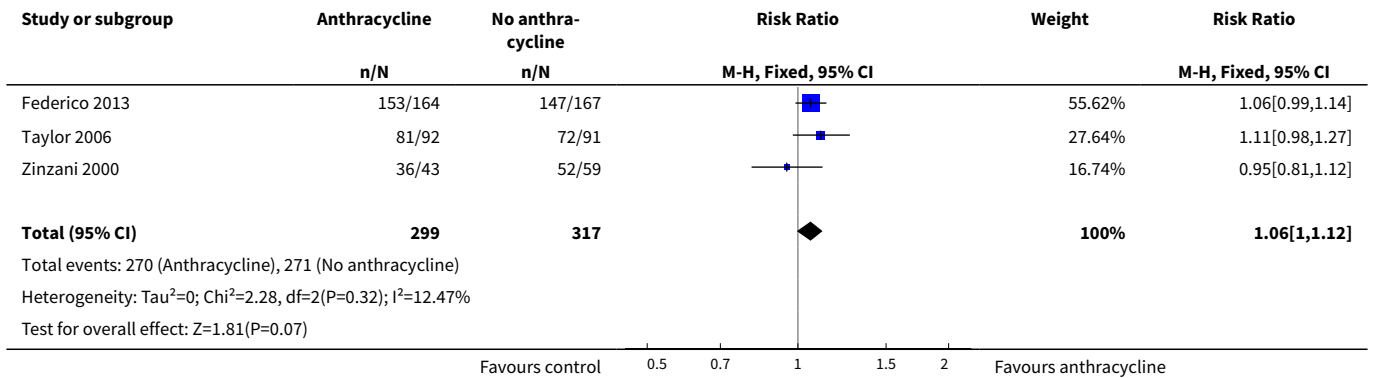
Analysis 1.4. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 4 Mortality at 5 years.



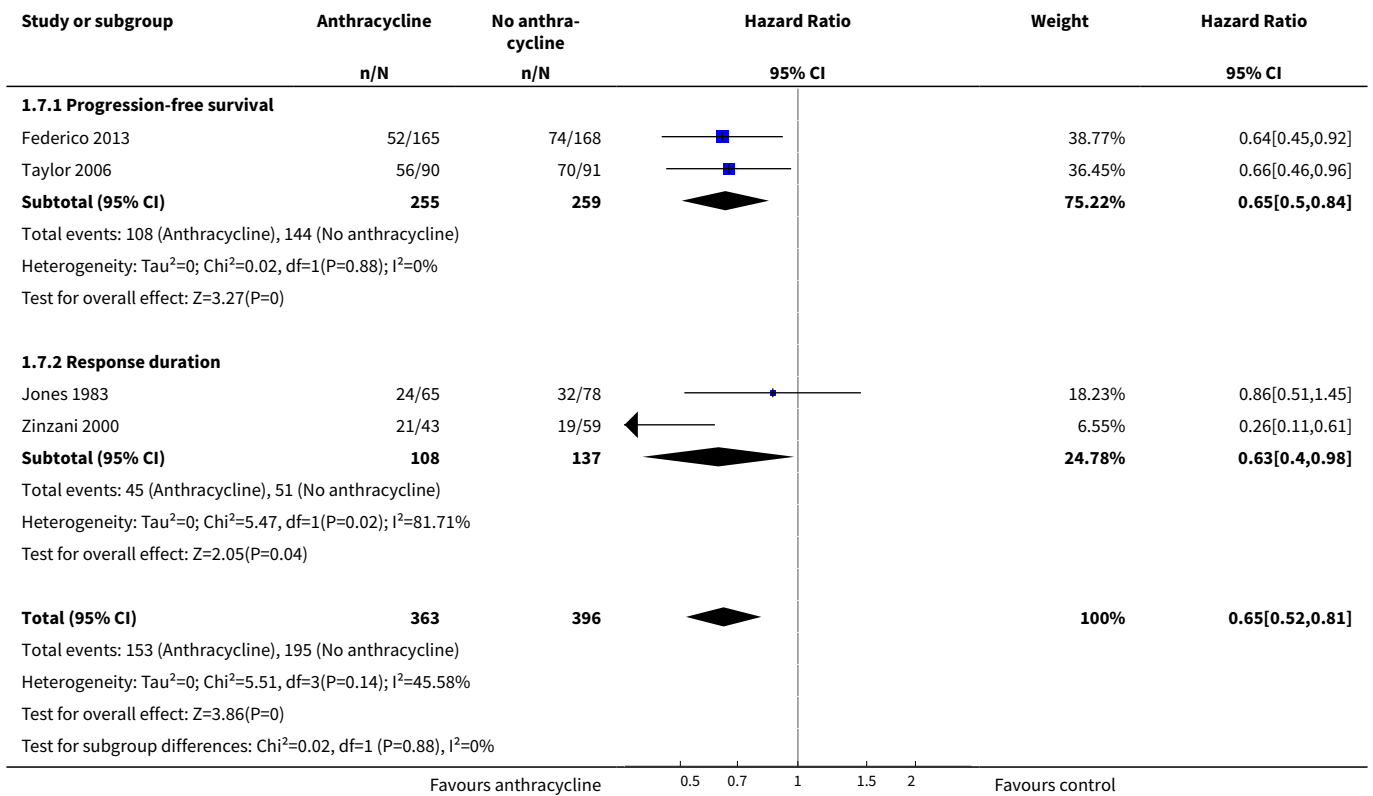
Analysis 1.5. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 5 Complete response.



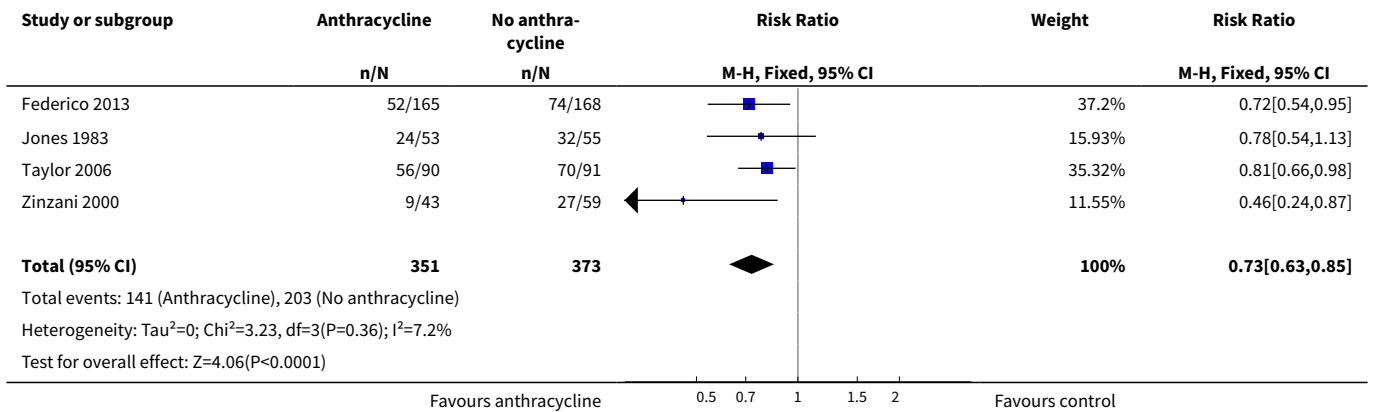
Analysis 1.6. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 6 Overall response.



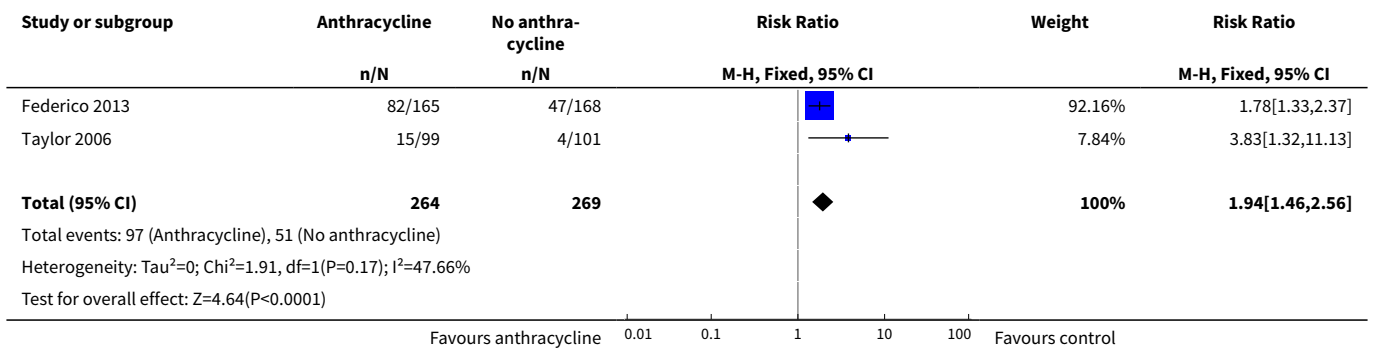
Analysis 1.7. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 7 Disease control.



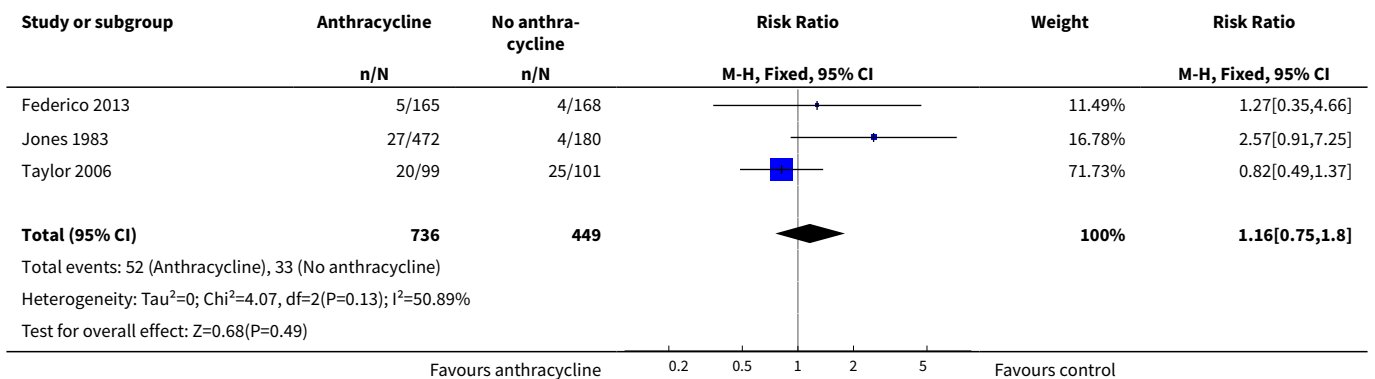
Analysis 1.8. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 8 Progression/relapse at 3 years.



Analysis 1.9. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 9 Neutropenia grade 3-4.



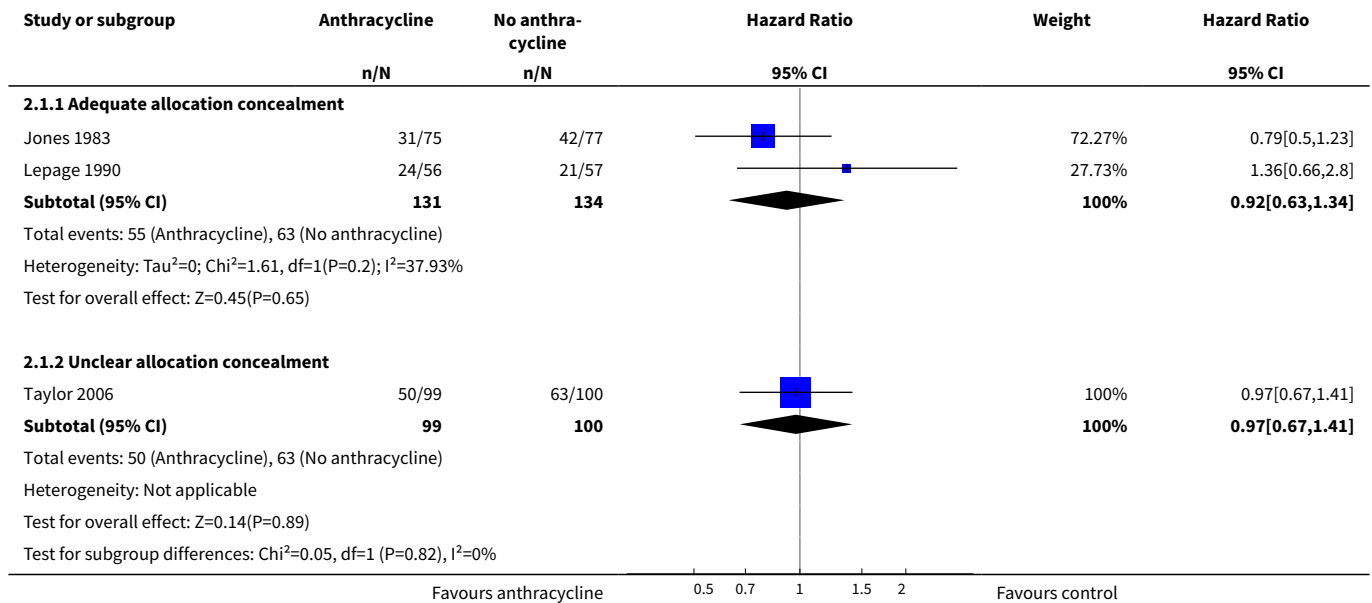
Analysis 1.10. Comparison 1 Anthracycline versus no anthracycline same chemotherapy, Outcome 10 Infection.



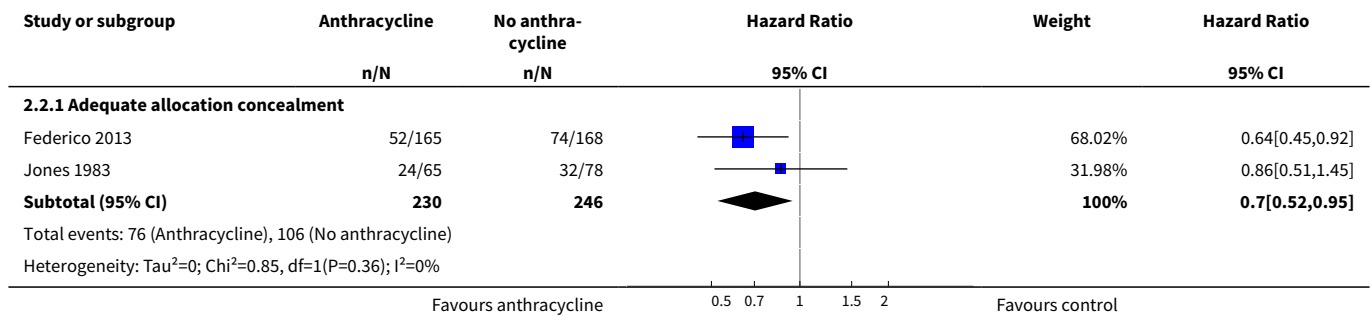
Comparison 2. Sensitivity analysis for allocation concealment

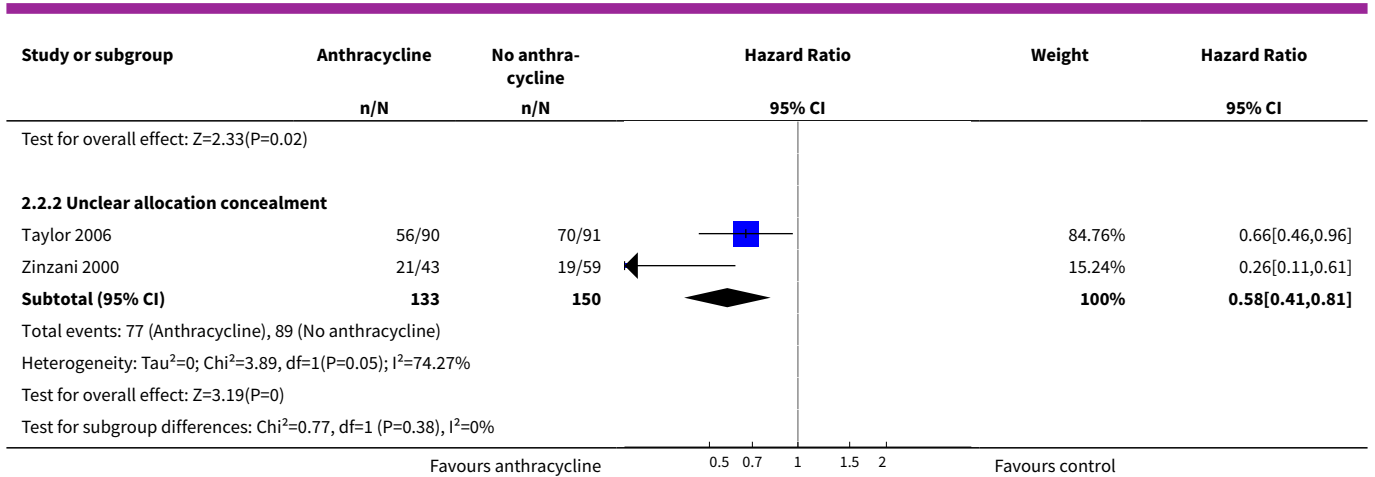
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3		Hazard Ratio (95% CI)	Subtotals only
1.1 Adequate allocation concealment	2	265	Hazard Ratio (95% CI)	0.92 [0.63, 1.34]
1.2 Unclear allocation concealment	1	199	Hazard Ratio (95% CI)	0.97 [0.67, 1.41]
2 Disease control	4		Hazard Ratio (95% CI)	Subtotals only
2.1 Adequate allocation concealment	2	476	Hazard Ratio (95% CI)	0.70 [0.52, 0.95]
2.2 Unclear allocation concealment	2	283	Hazard Ratio (95% CI)	0.58 [0.41, 0.81]

Analysis 2.1. Comparison 2 Sensitivity analysis for allocation concealment, Outcome 1 Overall survival.



Analysis 2.2. Comparison 2 Sensitivity analysis for allocation concealment, Outcome 2 Disease control.

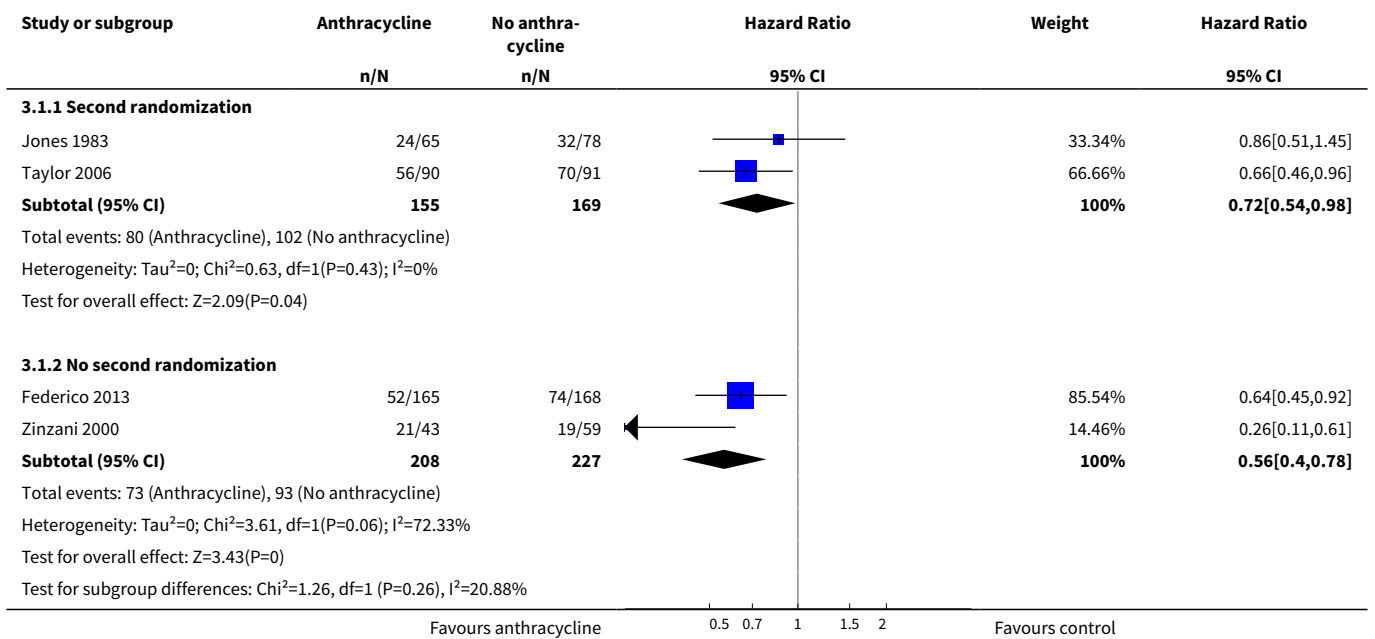




Comparison 3. Sensitivity analysis for second randomization

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control	4		Hazard Ratio (95% CI)	Subtotals only
1.1 Second randomization	2	324	Hazard Ratio (95% CI)	0.72 [0.54, 0.98]
1.2 No second randomization	2	435	Hazard Ratio (95% CI)	0.56 [0.40, 0.78]

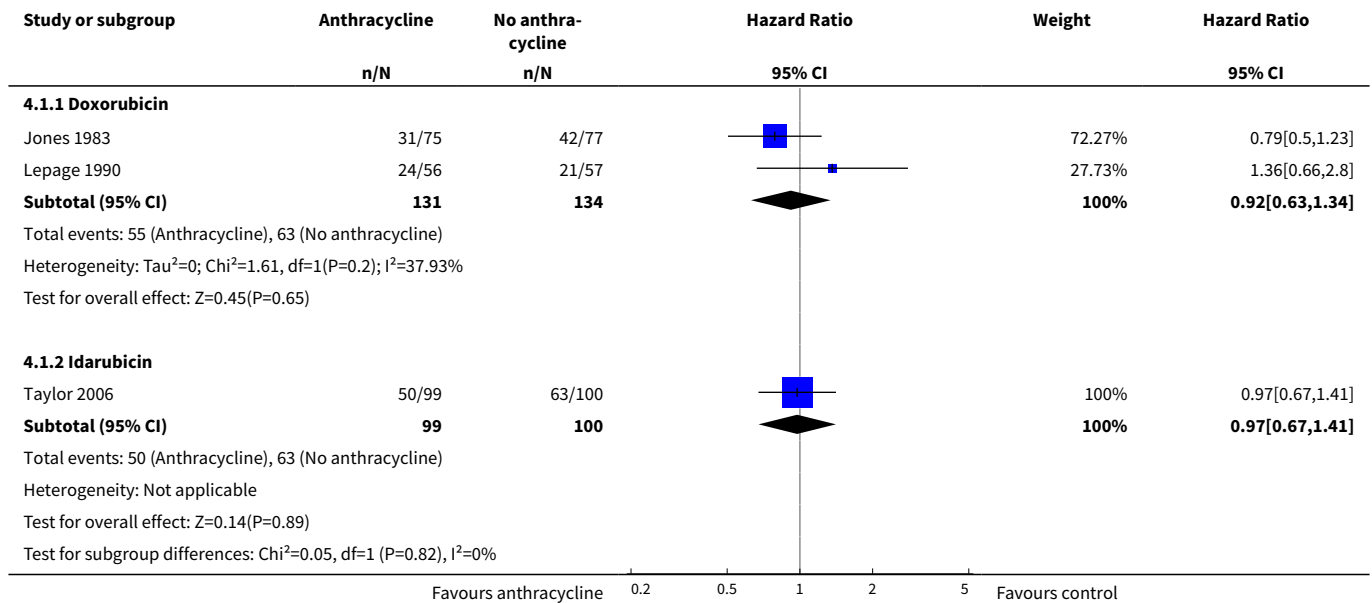
Analysis 3.1. Comparison 3 Sensitivity analysis for second randomization, Outcome 1 Disease control.



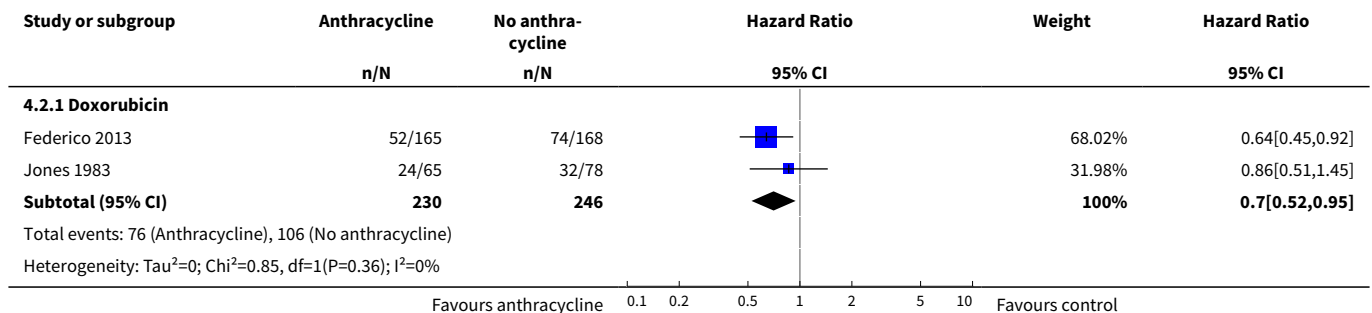
Comparison 4. Comparison of different anthracyclines

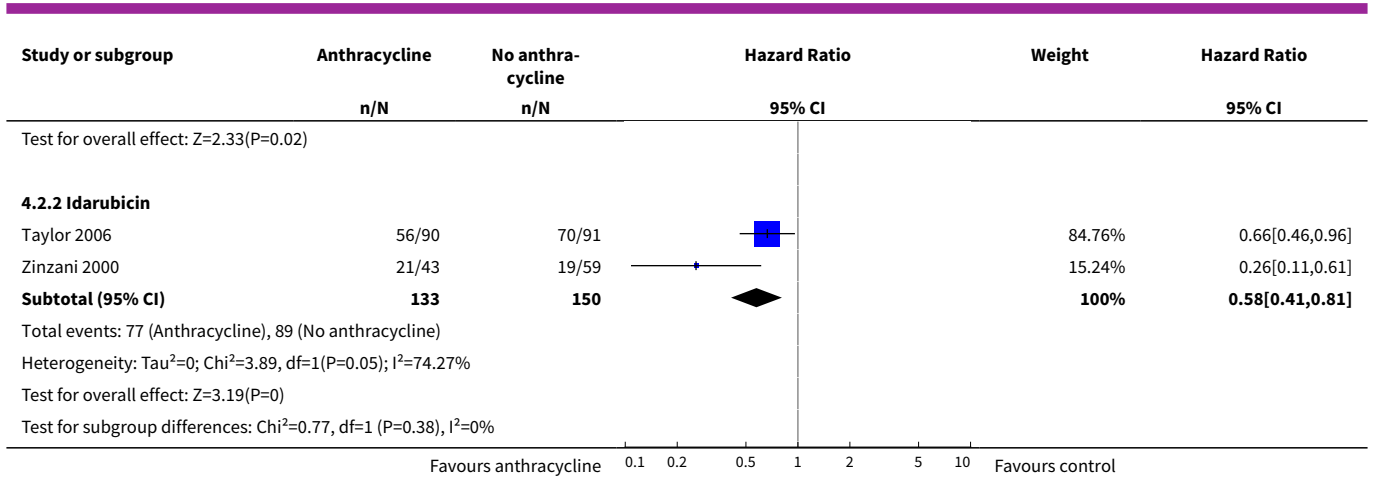
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3		Hazard Ratio (95% CI)	Subtotals only
1.1 Doxorubicin	2	265	Hazard Ratio (95% CI)	0.92 [0.63, 1.34]
1.2 Idarubicin	1	199	Hazard Ratio (95% CI)	0.97 [0.67, 1.41]
2 Disease control	4		Hazard Ratio (95% CI)	Subtotals only
2.1 Doxorubicin	2	476	Hazard Ratio (95% CI)	0.70 [0.52, 0.95]
2.2 Idarubicin	2	283	Hazard Ratio (95% CI)	0.58 [0.41, 0.81]

Analysis 4.1. Comparison 4 Comparison of different anthracyclines, Outcome 1 Overall survival.



Analysis 4.2. Comparison 4 Comparison of different anthracyclines, Outcome 2 Disease control.

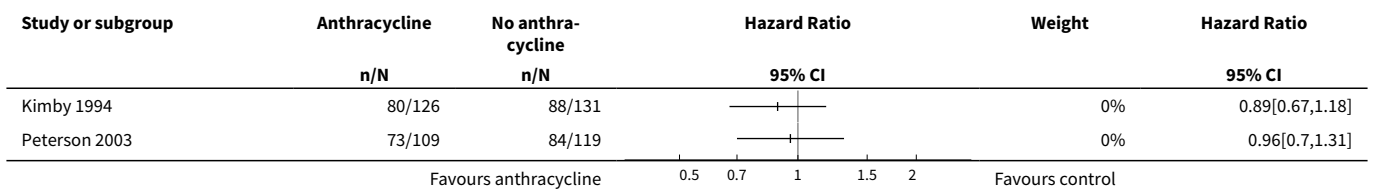




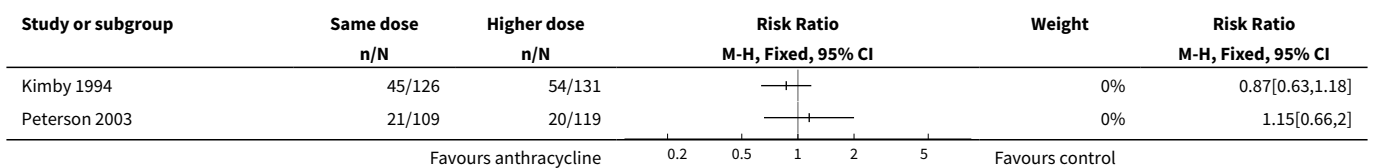
Comparison 5. Anthracycline versus no anthracycline different chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2		Hazard Ratio (95% CI)	Subtotals only
2 Mortality at 3 years	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Complete response	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Disease control	3		Hazard Ratio (95% CI)	Subtotals only

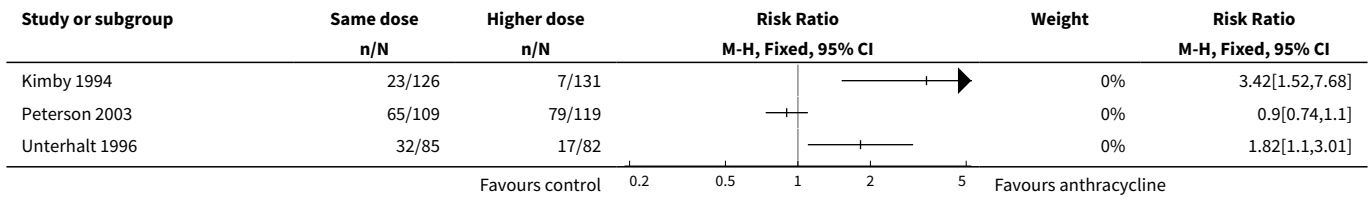
Analysis 5.1. Comparison 5 Anthracycline versus no anthracycline different chemotherapy, Outcome 1 Overall survival.



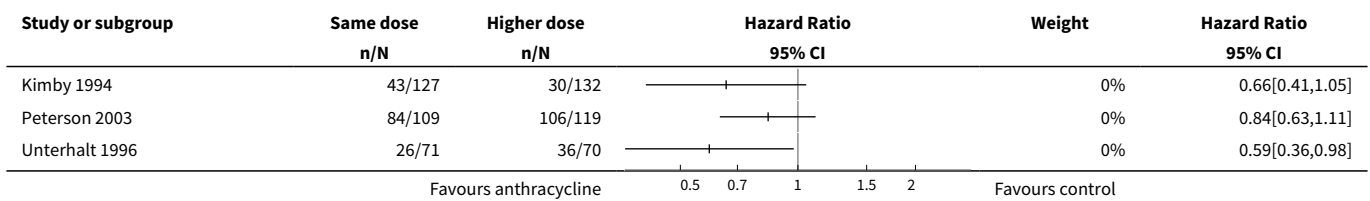
Analysis 5.2. Comparison 5 Anthracycline versus no anthracycline different chemotherapy, Outcome 2 Mortality at 3 years.



Analysis 5.3. Comparison 5 Anthracycline versus no anthracycline different chemotherapy, Outcome 3 Complete response.



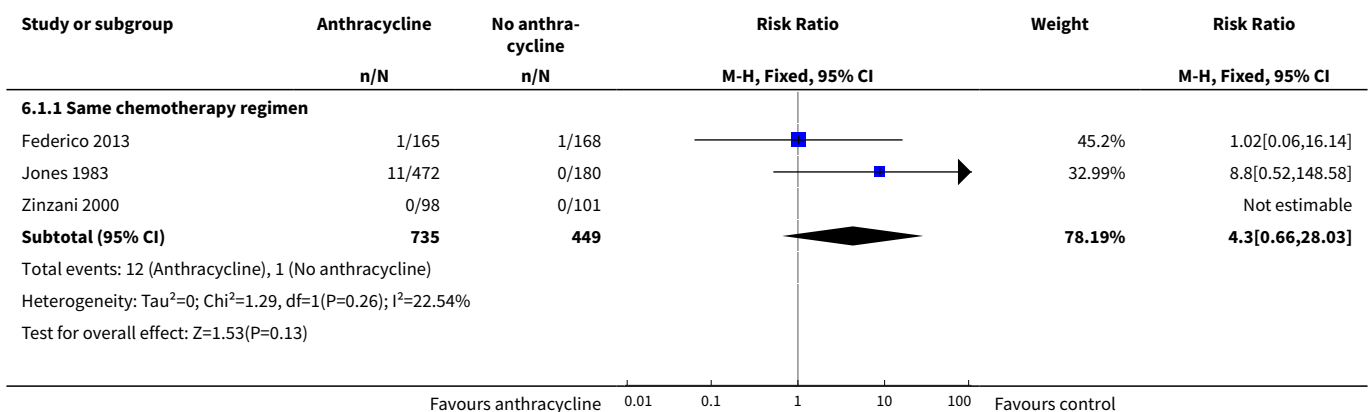
Analysis 5.4. Comparison 5 Anthracycline versus no anthracycline different chemotherapy, Outcome 4 Disease control.

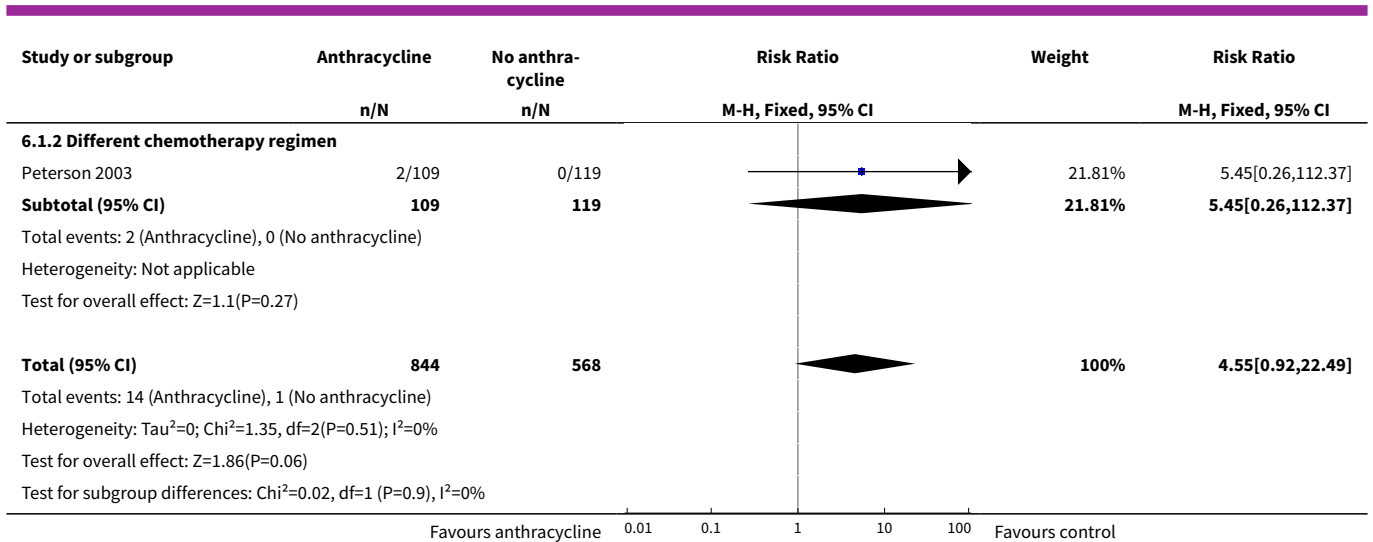


Comparison 6. Cardiotoxicity for all studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiotoxicity	4	1412	Risk Ratio (M-H, Fixed, 95% CI)	4.55 [0.92, 22.49]
1.1 Same chemotherapy regimen	3	1184	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.66, 28.03]
1.2 Different chemotherapy regimen	1	228	Risk Ratio (M-H, Fixed, 95% CI)	5.45 [0.26, 112.37]

Analysis 6.1. Comparison 6 Cardiotoxicity for all studies, Outcome 1 Cardiotoxicity.





ADDITIONAL TABLES

Table 1. Studies included in meta-analysis

Author	Randomized	Analyzed	FL analyzed	FL grade	Data specific for FL
Federico 2013	534	504	504 (333)*	1, 2, 3a	For all outcomes
Jones 1983	652	497	226 (146)*	1, 2, 3	For all outcomes
Lepage 1990	113	113	101	1, 2	For some outcomes
Taylor 2006	200	183	155	Low grade	No
Zinzani 2000	208	199	102	Indolent	For some outcomes
Kimby 1994	259	259	76	1, 2	For some outcomes
Peterson 2003	228	228	189	1, 2	For all outcomes
Unterhalt 1996	442	206	167	1, 2	For some outcomes
Total	2636	2189	1520		

* number of FL patients analyzed in 2 (of 3) arms compared
FL: follicular lymphoma

Table 2. Baseline characteristics of interventions

Author	Publication status	Same/different intervention	Anthracycline	Control arm	Experimental arm
Federico 2013	Full text	Same	Doxorubicin	R-CVP	R-CHOP
Jones 1983	Full text	Same*	Doxorubicin	CVP-B	CHOP-B

Table 2. Baseline characteristics of interventions (Continued)

Lepage 1990	Full text	Same	Doxorubicin	PCOP	PACOP
Taylor 2006	Full text	Same	Idarubicin	ChD	ChID
Zinzani 2000	Full text	Same*	Idarubicin	F	FI
Kimby 1994	Full text	Different	Doxorubicin	Ch-D	CHOP
Peterson 2003	Full text	Different	Doxorubicin	C	CHOP
Unterhalt 1996	Full text	Different	Mitoxantrone	CVP	PmM

* trials with higher non-anthracycline dose in control-arm

Table 3. Detailed therapeutic regimens in included studies

Author	Control arm	Experimental arm
Federico 2013	d 1 rituximab 375 mg/m ² , d 1 cyclophosphamide 750 mg/m ² IV, d 1 vincristine 1.4 mg/m ² (max 2 mg) IV, d 1-5 prednisone 40 mg/m ² PO, 8 cycles, every 21 d <i>[Note: more treatment cycles]</i>	d 1 rituximab 375 mg/m ² , d 1 cyclophosphamide 750 mg/m ² IV, d 1 doxorubicin 50 mg/m ² IV, d 1 vincristine 1.4 mg/m ² (max 2 mg) IV, d 1-5 prednisone 100 mg/d PO 6 cycles, every 21 d. Added 2 cycles of rituximab every 21 d
Jones 1983	d 1-14 cyclophosphamide 125 mg/m ² PO, d 1, 8 vincristine 1.4 mg/m ² IV (max 2 mg/dose), d 1-5 prednisone 100 mg/d PO, d 1, 8 bleomycin 4 mg/m ² IV. 8 cycles, every 21 d <i>[Note: different route of administration for cyclophosphamide; total doses differ for all drugs; cycles are more frequent]</i>	d 1 cyclophosphamide 750 mg/m ² IV, d 1 doxorubicin 50 mg/m ² IV, d 1 vincristine 1.4 mg/m ² (max 2 mg) IV, d 1-5 prednisone 100 mg/d PO, d 1 bleomycin 4 mg/m ² IV. 8 cycles, every 28 d
Lepage 1990	d 1, 8 cyclophosphamide 400 mg/m ² IV, d 1, 8 vincristine 1.4 mg/m ² , d 1, 14 procarbazine 80 mg/m ² PO, d 1-5 prednisone 60 mg/m ² PO. 6 cycles, every 28 d	same + d 1, 8 doxorubicin 20 mg/m ² IV
Taylor 2006	d 1-3 chlorambucil 20 mg/m ² /d, d 1-5 dexamethasone 4 mg bd. 6 cycles, every 21 d	same + d 1-3 idarubicin 10 mg/m ² /d
Zinzani 2000	d 1-5 fludarabine 25 mg/m ² /d IV. 6 cycles, every 28 d <i>[Note: total fludarabine dose is higher by 66%]</i>	d 1-3 fludarabine 25 mg/m ² /d IV, d 1-3, d 1 idarubicin 12 mg/m ² 6 cycles, every 28 d
Kimby 1994	d 1 chlorambucil 0.4 mg/kg PO, d 1-3 prednisone 75 mg PO every 14 d, for 4-8 months	d 1 cyclophosphamide 750 mg/m ² IV, d 1 doxorubicin 50 mg/m ² IV, d 1 vincristine 2 mg/m ² IV, d 1-5 prednisone 50 mg/m ² PO 4-8 cycles every 28 d
Peterson 2003	d 1 cyclophosphamide 750 mg/m ² IV, d 1 doxorubicin 50 mg/m ² IV, d 1 vincristine 1.4 mg/m ² (max 2 mg) IV, d 1-5 prednisone 60 mg/m ² PO, d 1 bleomycin 10 u/m ² IM every 21 d until complete response and then every 28 d up to 2 years, bleomycin up to 6 cycles	100 mg/m ² /d PO until 2 years from maximal response

Table 3. Detailed therapeutic regimens in included studies *(Continued)*

Unterhalt 1996	d 1-5 cyclophosphamide 400 mg/m ² /d IV, d 1 vincristine 1.4 mg/m ² (max 2 mg) IV, d 1-5 prednisone 100 mg/m ² /d PO 4-6 induction cycles every 21 d	d 1-5 prednimustine 100 mg/m ² /d PO, d 1-2 mitoxantrone 8 mg/m ² /d IV. 4-6 induction cycles every 28 d
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d: day; IM: intramuscular; IV: intravenous; PO: oral

Table 4. Outcome measures in trials with different chemotherapeutic regimens

	OS	Mortality at 3 years	Mortality at 10 years	CR	ORR	Disease control	Progression or relapse
Kimby 1994	0.89 (0.67 to 1.18)	0.87 (0.63 to 1.18)	NR	3.42 (1.52 to 7.68)	1.70 (1.30 to 2.23)	0.66 (0.41 to 1.05)	0.90 (0.67 to 1.20)
Peterson 2003	0.96 (0.70 to 1.31)	1.15 (0.66 to 2.00)	0.95 (0.74 to 1.23)	0.90 (0.74 to 1.10)	1.04 (0.96 to 1.13)	0.84 (0.63 to 1.11)	1.03 (0.82 to 1.28)
Unterhalt 1996	NR	NR	NR	1.82 (1.10 to 3.01)	1.02 (0.89 to 1.17)	0.59 (0.36 to 0.98)	NR

CR: complete response; NR: not reported; ORR: overall response rate; OS: overall survival

APPENDICES

Appendix 1. PubMed search strategy

Part I AND part II AND part III

Part I:

((indolent OR follicular OR nodular OR follicle-cell OR centroblastic OR centrocytic OR ((zentroblast* or zentrocytic*) and lymphom*) OR follicle-center OR low-grade OR Brill- symmer) AND lymphoma*) OR Lymphoma, Follicular [Mesh]

Part II:

Doxorubicin [Mesh] OR AD mycin OR adriacin OR adriamycin OR adriablastina OR adriablastine OR adriablastin OR adrimedac OR adrim OR adrosal OR axibin OR biorrub OR biorubina OR candria OR dobixin OR daxotel OR dicladox OR dox-sl OR doxsl OR doxobin OR doxo-cell OR doxolem OR doxomed OR doxotec OR doxotil OR farmiblastina OR fauldoxo OR ifadox OR myocet OR neoxane OR onkodox OR oxocina OR pallengicin OR rastocin OR ribodoxo OR rubex OR rubidox OR doxil OR caelyx OR Doxocris OR Doxokebir OR Doxonolver OR Doxopeg OR Doxorbin OR Doxtie OR Flavicina OR Lipo-dox nagon OR Oncodox OR Oncodria OR Onkostatil OR Ranxas OR Rubinat OR Ribodoxo OR Roxorin OR Serodox OR Roxodox OR Tevadox OR Varidoxo OR daunorubicin [MeSH] OR Daunoblastine OR Daunobin OR Daunomycin OR Rubomycin OR Rubidomycin OR daunoxome OR cerubidine OR cerubidin OR daunoblastina OR daunoblastin OR daunocin OR oncodaunotec OR rubilem OR idarubicin [MeSH] OR Desmethoxydaunorubicin OR Demethoxydaunorubicin OR DMDR IDA OR imi-30 OR imi30 OR nsc-256439 OR nsc256439 OR idamycin OR idaralem OR zavedos OR epirubicin [MeSH] OR anthracin OR bioepicyna OR ciazil OR ellence OR epi-cell OR epilem OR epi-NC OR epirub OR E.P.Mycin OR farmorrubicina OR farmorubicina OR farmorubicine OR farmorubicin megarubicin OR nuovodox OR pharmorubicin OR riboepe OR rubina OR tecnomax OR Epi-DXR OR Epi-cell OR Epicell OR Epi-ADR OR Epiadriamycin OR Axirubine OR Bendaepi OR imi-28 OR imi28 OR nsc-256942 OR nsc256942 OR mitoxantrone [MeSH] OR domitrone OR ebexantron OR elsep OR formyxan OR genefadrone OR haemato-tron OR misostol OR mitaxis OR mitoxal OR mitoxan OR mitoxgen OR mitroxene OR mitroxone OR neotalem OR neoxantron OR norexan OR novantrone OR Mitozantrone OR Novatron OR Onkotrone OR Parlifan OR Ralenova OR anthracyclin* OR anthracenedione

Part III:

#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	drug therapy [sh]
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	animals [mh] NOT humans [mh]
#11	#9 NOT #10

Appendix 2. CENTRAL search strategy

Part I AND part II

Part I:

Anthracycline-containing regimens for treatment of follicular lymphoma in adults (Review)

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((indolent OR follicular OR nodular OR follicle-cell OR centroblastic OR centrocytic OR ((zentroblast* or zentrocytic*) and lymphom*) OR follicle-center OR low-grade OR Brill- symmer) AND lymphoma*) OR Lymphoma, Follicular [Mesh]

Part II:

Doxorubicin [Mesh] OR AD mycin OR adriacin OR adriamycin OR adriablastina OR adriablastine OR adriablastin OR adrimedac OR adrim OR adrosal OR axibin OR biorrub OR biorubina OR candria OR dobixin OR daxotel OR dicladox OR dox-sl OR doxsl OR doxobin OR doxo-cell OR doxolem OR doxomed OR doxotec OR doxotil OR farmiblastina OR fauldoxo OR ifadox OR myocet OR neoxane OR onkodox OR oxocina OR pallagicin OR rastocin OR ribodexo OR rubex OR rubidox OR doxil OR caelyx OR Doxocris OR Doxokebir OR Doxonolver OR Doxopeg OR Doxorbin OR Doxtie OR Flavicina OR Lipo-dox nagan OR Oncodox OR Oncodria OR Onkostatil OR Ranxas OR Rubinat OR Ribodexo OR Roxorin OR Serodox OR Roxodox OR Tevadox OR Varidoxo OR daunorubicin [MeSH] OR Daunoblastine OR Daunobin OR Daunomycin OR Rubomycin OR Rubidomycin OR daunoxome OR cerubidine OR cerubidin OR daunoblastina OR daunoblastin OR daunocin OR oncodaunotec OR rubilem OR idarubicin [MeSH] OR Desmethoxydaunorubicin OR Demethoxydaunorubicin OR DMDR IDA OR imi-30 OR imi30 OR nsc-256439 OR nsc256439 OR idamycin OR idaralem OR zavedos OR epirubicin [MeSH] OR anthracin OR bioepicyna OR ciazil OR ellence OR epi-cell OR epilem OR epi-NC OR epirub OR E.P.Mycin OR farmorrubicina OR farmorubicina OR farmorubicine OR farmorubicin megarubicin OR nuovodox OR pharmorubicin OR riboepe OR rubina OR tecnomax OR Epi-DXR OR Epi-cell OR Epicell OR Epi-ADR OR Epiadriamycin OR Axirubine OR Bendaepi OR imi-28 OR imi28 OR nsc-256942 OR nsc256942 OR mitoxantrone [MeSH] OR domitrone OR ebexantron OR elsep OR formyxan OR genefadrone OR haemato-tron OR misostol OR mitaxis OR mitoxal OR mitoxan OR mitoxgen OR mitroxene OR mitroxone OR neotalem OR neoxantron OR norexan OR novantrone OR Mitozantrone OR Novatron OR Onkotrone OR Parlifan OR Ralenova OR anthracyclin* OR anthracenedione

CONTRIBUTIONS OF AUTHORS

Gilad Itchaki: conception and design, protocol development, searching and selection of trials, data extraction, analysis and interpretation, eligibility and quality assessment, writing the review, and final approval.

Anat Gafter-Gvili: content expert in hematology.

Meir Lahav: conception and design, clinical and scientific advice, and content input.

Liat Vidal: content expert in hematology.

Pia Raanani: content expert in hematology.

Ofer Shpilberg: conception and design, content expert in hematology, clinical advice, and final approval.

Mical Paul: design and protocol development, methodologic advice, data extraction, provision of statistical analysis, writing the review, and final approval.

DECLARATIONS OF INTEREST

No conflicts of interests known.

SOURCES OF SUPPORT

Internal sources

- Rabin Medical Center, Beilinson Hospital, Not specified.

External sources

- No funding, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Exclusion of studies that did not specify the number of FL patients enrolled.
- Data analysis only from trials with over 75% FL patients or in case data were provided specifically for FL patients.
- Explaining use of the outcome: disease control.
- Calculation of analysis with both fixed-effect and random-effects models, to demonstrate differences in results in heterogeneous analysis.
- Documenting previous histologic classifications for FL.

INDEX TERMS**Medical Subject Headings (MeSH)**

Anthracyclines [*therapeutic use]; Antibiotics, Antineoplastic [*therapeutic use]; Antibodies, Monoclonal, Murine-Derived [therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; Induction Chemotherapy [methods]; Lymphoma, Follicular [*drug therapy] [mortality] [pathology]; Maintenance Chemotherapy [methods]; Randomized Controlled Trials as Topic; Rituximab

MeSH check words

Adult; Humans