Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review

CRD summary
The review found that addition of radiotherapy to chemotherapy improved tumour control and overall survival when compared with chemotherapy alone in patients with early stage Hodgkin's lymphoma. The authors' conclusions reflected the evidence base and are likely to be reliable due to the low likelihood of bias and appropriate methodology used in the review process.

Authors' objectives
To compare chemotherapy alone with identical chemotherapy plus radiotherapy in patients with early stage Hodgkin's lymphoma with respect to overall survival, tumour control and complete response rates.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from January 1980 to February 2009. There were no language restrictions. No search terms were reported. Proceedings of the American Society of Hematology and abstracts of the American Society of Clinical Oncology (1980 to 2008) and Proceedings of the International Symposium on Hodgkin Lymphoma (2004 onwards) were handsearched.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared chemotherapy alone with identical chemotherapy regimens combined with radiotherapy in newly diagnosed Hodgkin's lymphoma of all ages in clinical stage I and II. Trials with less than 80% of patients in clinical stage I or II were excluded, but included in sensitivity analyses. Trials where the number of cycles varied between treatment arms were included only in sensitivity analyses. Eligible outcomes included overall survival, tumour control and complete response rates.

In the included studies, stage of disease in participants varied. Most studies included patients with early favourable and unfavourable disease. One study included only patients with early favourable disease. One study included only patients with bulky disease. Chemotherapy regimens included adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), epirubicin, bleomycin, vinblastine and prednisone (EBVP) or cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP). Recruitment ranged from the 1970s to 2004. Most studies randomised patients at diagnosis. One study randomised patients after achieving complete response after chemotherapy. Definitions for tumour control varied between studies.

Two reviewers selected studies for inclusion in the review. Discrepancies were resolved through a third reviewer.

Assessment of study quality
Included studies were assessed for randomisation, concealment of allocation, masking of patients, caregivers and outcome assessors, similarity of baseline patient characteristics, documentation of dropouts, withdrawals and intention-to-treat analysis.

Two reviewers undertook quality assessment. Discrepancies were resolved through a third reviewer.

Data extraction
Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for complete response rates. Time to event data for overall survival and tumour control were estimated as hazard ratios (HRs) with 95% CIs. The authors contacted authors of respective studies to obtain missing information.

Two reviewers independently extracted data. Discrepancies were resolved through a third reviewer.
Methods of synthesis
Studies were pooled in meta-analyses and summary effect estimates were calculated. Heterogeneity was assessed with the $I^2$ value. A random-effects model was used where there was significant heterogeneity ($I^2>50\%$); otherwise a fixed-effect model was used. A linear regression test for small trial bias was planned, but not performed as the number of included studies was fewer than 10.

Subgroup analyses were performed for different chemotherapy regimens (CVPP, EBVP, ABVD), radiation fields (extended or involved), different sequences of chemotherapy and radiotherapy, bulky disease and early favourable or early unfavourable disease. Sensitivity analyses were undertaken on quality aspects that differed between trials (intention-to-treat analysis, drop-outs, allocation concealment, length of follow-up and date of recruitment) and the effect of single trials on the overall result. Six trials that did not fulfil the inclusion criteria (where the number of chemotherapy cycles varied between treatment arms or where there were too many patients in advanced stages) were included in sensitivity analyses. Tests for interaction between subgroups were performed. The number needed to treat was calculated for time to event outcomes.

Results of the review
Five RCTs from 10 publications ($n=1,245$ participants) were included in the review. None of the studies reported blinding of the assessor. One study reported an adequate randomisation procedure. Two studies reported intention-to-treat analyses. One trial had more than 10% drop-outs or non-evaluable patients. Median follow-up ranged from two to 11.4 years. Two trials reported interim results.

Complete response rate: There was no evidence of a significant difference in complete response rate between chemotherapy alone and combined treatment (RR 1.07, 95% CI 0.98 to 1.17; four studies). Subgroup and sensitivity analyses were not performed.

Tumour control: Combined treatment with chemotherapy and radiotherapy was associated with better tumour control than chemotherapy alone treatment (HR 0.41, 95% CI 0.25 to 0.66; four studies, NNT=6, 95% CI 5 to 11). Substantial heterogeneity was found in the analysis ($I^2=68\%$). Subgroup analysis by type of tumour control definition reported a significant association ($p=0.01$), which indicated that variation in tumour control definitions may have been responsible for the observed heterogeneity. Other subgroup and sensitivity analyses did not find evidence of significant differences and did not result in a reduction in the observed heterogeneity. The pooled estimate was similar when trials that did not meet the strict inclusion criteria for the review were included in the analysis and when the analysis was restricted to trials that kept the number of cycles the same between treatment groups.

Overall survival: Combined treatment with chemotherapy and radiotherapy was associated with better overall survival than chemotherapy alone treatment (HR 0.40, 95% CI 0.27 to 0.59; five studies, NNT=11, 95% CI 9 to 18) with no evidence of heterogeneity. There was no evidence of significant differences according to subgroups analysed for type of chemotherapy, early favourable or unfavourable disease, bulky or no bulky disease, type and timing of radiation therapy or quality measures. Inclusion of trials that did not meet the inclusion criteria for the review did not find evidence of a significant difference between groups. Exclusion of trials where the number of cycles varied between treatments found a similar statistical difference to the overall survival analysis.

Authors' conclusions
Addition of radiotherapy to chemotherapy improved tumour control and overall survival when compared with chemotherapy alone in patients with early stage Hodgkin’s lymphoma.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate. A number of electronic databases were searched without language restrictions and attempts were made to find unpublished trials by searching conference abstracts; these methods minimised risks of language and publication biases. Appropriate methods were used for study selection, quality assessment of the included trials and data extraction. Trial quality was not high (none were blinded and two reported interim results). Sensitivity analyses were undertaken to assess the differential effects of variation in quality; these had minimal influence on the overall results. Participants included those with both favourable
and unfavourable features and bulky and non bulky disease; subgroup analyses were undertaken to assess the effects of these on results. Different chemotherapy regimens, radiation fields and sequences of chemotherapy and radiotherapy were examined by subgroup analyses. Tests of interaction were performed. These analyses did not find evidence of differential effects. The authors acknowledged that the small number of trials meant that reliable information from subgroup and sensitivity analyses was unlikely. Heterogeneity in the tumour control analysis was likely to reflect differing definitions used for tumour control.

The authors’ conclusions reflected the evidence base and are likely to be reliable due to the low likelihood of bias and appropriate methodology used in the review process.

Implications of the review for practice and research

**Practice:** The authors stated that combined treatment of chemotherapy and consolidation radiotherapy was standard of care in patients with early stage Hodgkin's lymphoma.

**Research:** The authors did not state any implications for research.

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