Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb non-small cell lung cancer: a meta-analysis

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Authors' objectives
To investigate whether combined radiotherapy and chemotherapy improves survival among patients with Stage III non-small cell lung cancer (NSCLC) compared with radiotherapy alone.

Searching
MEDLINE was searched for English and foreign language papers, and references from review articles and abstracts were examined.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), which directly compared radiotherapy plus chemotherapy with radiotherapy alone, were included.

Specific interventions included in the review
Radiotherapy plus chemotherapy, radiotherapy alone. Both cisplatin- and non-cisplatin-based chemotherapies were included, along with various strategies for combining radiotherapy and chemotherapy.

Participants included in the review
People with unresectable NSCLC, classified as stage IIIa or IIIb on Mountain's system, were included.

Outcomes assessed in the review
Survival at 1, 2, 3 and 5 years was assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Methodological quality was assessed using a checklist prepared by Chalmers (see Other Publications of Related Interest), which covered aspects of internal validity (methods and efficacy of randomisation, blinding, compliance and follow-up, use of a priori estimates of sample size, loss to follow-up and subsequent investigation, response evaluation, estimate of beta-error) and external validity (adequacy of information about patient characteristics, therapeutic regimen and side-effects, consideration of non-enrolled eligible patients, consideration of timing of events). Three authors independently (not blinded) scored the publications and resolved possible conflicts by discussion.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
Studies involving cisplatin- and non-cisplatin-based chemotherapy were treated independently.

For survival at 1 and 2 years, the odds ratios (OR) were estimated and pooled using a modified Mantel-Haenszel
method.

For survival at 3 and 5 years, point estimates with confidence intervals (CIs) for the differences in survival between the two trial arms, were used.

How were differences between studies investigated?
No statistical tests for heterogeneity were reported. Cisplatin- and non-cisplatin-based chemotherapies were treated separately. The authors noted that there were differences between studies in terms of courses and doses of chemotherapy, and whether chemotherapy was given sequentially, concurrently or in rapid alteration with radiotherapy. Sensitivity analyses were not reported.

Results of the review
Fourteen RCTs, of which 10 involved cisplatin-based chemotherapy, were included.

OR for radiotherapy plus chemotherapy versus radiotherapy alone.

Survival at 1 year: cisplatin-based, 0.76 (95% CI: 0.6, 0.9); non-cisplatin based, 1.05 (95% CI: 0.7, 1.5).

Survival at 2 years: cisplatin-based, 0.70 (95% CI: 0.5, 0.9); non-cisplatin based, 0.82 (95% CI: 0.5, 1.3).

The differences in survival between the two trial arms were not clinically-significant (15%) in any study at 3 or 5 years.

Authors' conclusions
Combined treatment with chest irradiation and cisplatin-based therapy improves the survival at 1 and 2 years of patients with inoperable Stage IIIa and IIib NSCLC, with a reduction in mortality of 24% and 30%, respectively, compared with radiotherapy alone. No significant differences in survival were found between the two arms at 3 and 5 years. Cisplatin-based therapy appears better than non-cisplatin based therapy.

The authors believe that combined therapy with a cisplatin-based regimen should be given to patients with unresectable NSCLC. However, the benefits (in terms of survival) should be considered in conjunction with quality of life, toxicity and cost concerns.

The quality of the original studies was modest, and this could have influenced the result.

CRD commentary
A more comprehensive search strategy might have identified additional studies. The authors have pointed out some weaknesses among the RCTs included in the review, and alerted readers to variations in the doses and administration patterns of chemotherapy and radiotherapy used. However, no formal tests for heterogeneity were reported. The review focuses on survival but includes no assessment of the quality of life for patients receiving the different treatments.

Implications of the review for practice and research
Radiotherapy plus cisplatin-based chemotherapy increases survival rates (compared with radiotherapy alone) at 1 and 2 years for people with Stage III NSCLC. However, it is difficult to draw conclusions about its effects on longer term survival because few trials have studied this, and the number of patients surviving for 3 or more years is small.

The effects of the treatment regime on quality of life need to be considered.

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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.