Adjuvant radiotherapy and chemotherapy for stage II or IIIA non-small-cell lung cancer after complete resection


Authors' objectives
To assess the efficacy of postoperative adjuvant radiotherapy and chemotherapy in the treatment of patients with completely resected stage II or IIIA non-small-cell lung cancer (NSCLC).

Searching
The authors searched the MEDLINE electronic database (1985 to June 1997) for English language publications using the keywords: 'carcinoma', 'non-small cell lung', 'resect', 'stage II', 'stage III', 'radiotherapy', 'chemotherapy', 'adjuvant', 'randomized controlled trial', 'clinical trial', 'guideline', 'research design', 'consensus' and 'recommend'. The bibliographies of review articles were also screened for additional relevant articles. The PDQ database was scanned in June 1997 for ongoing trials with the use of the terms 'non-small-cell lung cancer' and 'adjuvant study'.

Study selection
Study designs of evaluations included in the review
Syntheses of evidence (evidence-based practice guidelines or systematic reviews) and randomised controlled trials (RCTs) with appropriate comparison groups.

Specific interventions included in the review
Surgery, chemotherapy (cisplatin and non-cisplatin based therapy) and radiotherapy alone and in combination. Interventions were compared with each other.

Participants included in the review
Patients with stage II or IIIA non-small-cell lung cancer.

Outcomes assessed in the review
Overall survival and disease-free survival were the primary outcomes in the review. A secondary outcome was local disease control.

How were decisions on the relevance of primary studies made?
Studies were collected and reviewed by 4 members of the Lung Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative.

Assessment of study quality
The authors do not state that they assessed quality.

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

Methods of synthesis
How were the studies combined?
The results of individual trials were grouped according to type of post operative adjuvant therapy and a pooled hazard ratio (HR) with 95% confidence interval (CI) was calculated for non-cisplatin-based chemotherapy; cisplatin-based chemotherapy; and radiotherapy plus chemotherapy according to the type of post-operative adjuvant therapy.
administered. Results of individual trials for radiotherapy were not combined because of heterogeneity and thus were reported in a narrative listing of the individual results.

How were differences between studies investigated?
The authors used the Chi-square statistic to test for homogeneity.

Results of the review
Twenty-two RCTs were included in the review: 6 RCTs (1,042 participants) of surgery and radiotherapy (513 participants) versus surgery alone (529 participants); 6 RCTs (3318 participants) of surgery plus non-cisplatin-based chemotherapy (1808 participants) versus surgery alone (1510 participants); 6 RCTs (1367 participants) of surgery plus cisplatin-based chemotherapy (741 participants) versus surgery alone (626 participants); and 4 RCTs (555 participants) of surgery and radiotherapy and chemotherapy (275 participants) versus surgery and radiotherapy alone (251 participants).

There was no survival benefit with adjuvant radiotherapy alone, although 3 RCTs reported a reduction in the rate of local recurrence among patients treated with adjuvant radiotherapy.

Post-operative adjuvant chemotherapy with alkylating agents was found in the meta-analysis to increase the relative risk of death by 15% (HR 1.15, 95% CI: 1.04, 1.27). The absolute reduction in survival rate was 4% at 2 years, and 5% at 5 years.

Chemotherapy in combination with radiotherapy it resulted in a 6% reduction in the relative risk of death (HR 0.94, 95% CI: 0.79, 1.11; p = 0.46) which was not statistically significant with an absolute benefit of 2% at 2 years and at 5 years. A study involving prolonged adjuvant chemotherapy (busulfan or cytoxan daily for 2 years) reported that 4 of 726 patients had hematologic malignancies. In one study, only 53% of patients received all 4 cycles of chemotherapy with cyclophosphamide- doxorubicin-cisplatin (CAP); in another, 22% of patients refused therapy with CAP because of nausea and vomiting.

The meta-analysis showed that post-operative, cisplatin-based chemotherapy reduced the relative risk of death by 13% (HR 0.87, 95% CI: 0.74, 1.02; p = 0.08) and an absolute benefit of 3% at 2 years and 5% at 5 years which were not statistically significant.

Authors’ conclusions
There is evidence from RCTs that post-operative radiotherapy reduces rates of local recurrence by 11% to 18% (or 1.6 to 19 fold) among patients with completely resected, pathologically confirmed stage II or IIIA NSCLC. If the outcome of interest is a reduction in the frequency of local tumour recurrence, radiotherapy is recommended. However, there is no evidence of a survival benefit from post-operative radiotherapy alone.

CRD commentary
The authors have clearly stated their research question and their inclusion and exclusion criteria. The literature search is limited and may have missed studies published outside the United States by focusing the search on only the MEDLINE database. The authors do not report whether there were any language restrictions on their search or whether they sought unpublished data.

The data extraction is reported in tables and text and the statistical analyses, where calculated, were appropriate. The quality of the included studies was not assessed but the authors have reported on how the articles were selected, and how many of the reviewers were involved in the data selection and extraction.

The authors have tested for homogeneity and their conclusions appear to follow from the results.

Implications of the review for practice and research
Practice: The authors state that post-operative radiotherapy reduces the rate of local occurrence among patients with...
completely resected, pathologically confirmed state II or IIIA NSCLC. However, there is no evidence of a survival benefit from post-operative radiotherapy alone. If the outcome of interest is a reduction in the frequency of local tumour recurrence, radiotherapy is recommended.

Research: The authors state that the resulting guidelines for practice will need to be updated periodically with further literature searches and the results posted on the research group's website.

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**Other publications of related interest**
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