Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer

CRD summary
This individual patient data review concluded that concomitant radiochemotherapy, compared with sequential radiochemotherapy, improved survival in patients with locally advanced non-small cell lung cancer but at the cost of manageable increased acute oesophageal toxicity. These conclusions reflect the evidence available and seem appropriate.

Authors' objectives
To compare the effectiveness and safety of concomitant radiochemotherapy versus sequential radiochemotherapy in patients with locally advanced non-small cell lung cancer.

Searching
MEDLINE, EMBASE, and CANCERLIT were searched; search terms and dates were not reported, but studies were required to have finished recruiting by the end of 2003. There were no publication or language restrictions. Reference lists of reviews, published trials, books and the proceedings of American Society of Clinical Oncology and International Association for the Study of Lung Cancer were searched. Three trial registers and the Cochrane Library were searched to identify unpublished and ongoing studies. All review authors were asked to help identify further trials.

Study selection
Randomised controlled trials (RCTs) that compared thoracic radiotherapy (with curative intent) plus sequential chemotherapy versus thoracic radiotherapy plus concomitant chemotherapy in patients with unresected non-small cell lung cancer (without distant metastases) were eligible for inclusion. The radiotherapy administered had to be similar in both trial arms. Patients should have received no previous radiotherapy or chemotherapy.

The primary outcome was overall survival. Secondary outcomes were progression-free survival, cumulative incidences of locoregional and distant progression, and acute toxicity.

In included trials, all sequential regimens and all but one of the concomitant regimens used cisplatin combined with one or more drugs. Sequential regimens ranged from 40 to 120mg/m$^2$. Concomitant regimens ranged from 5 to 100mg/m$^2$. Most trials used a two-dimensional radiotherapy technique; total doses ranged from 48.5 to 66Gray. The median age of participants was approximately 62 years; around three-quarters were male. Nearly all patients had stage IIIA or IIIB cancer. Most patients had a performance status of zero or one.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Data were checked for missing values and for data validity and consistency across variables, and compared with published results where possible. The integrity of randomisation was assessed by looking for unusual patterns in allocation sequence or imbalances in baseline characteristics. Balance in the degree of follow-up between groups was also assessed. Queries were resolved with the relevant trial investigator or with statisticians.

Data extraction
Individual patient data (IPD) for the intention-to-treat study populations were requested from trialists to calculate hazard ratios (HRs) or relative risks (RRs) with 95% confidence intervals (CIs).

Methods of synthesis
Meta-analyses were performed to calculate pooled hazard ratios or relative risks with 95% confidence intervals, using
a fixed-effect model. Absolute differences in survival rates (at annual intervals) were calculated using survival curves (estimated using annual death rates and hazard ratio). Heterogeneity was assessed using the $\chi^2$ and $I^2$.

A number of subgroup and sensitivity analyses were pre-specified.

**Results of the review**

Seven RCTs were eligible, with six providing IPD (n=1,205 patients). The median follow-up period was six years (range 4.2 to 9.2).

There was a significant survival benefit of concomitant radiochemotherapy compared with sequential radiochemotherapy (HR 0.84, 95% CI 0.74 to 0.95; six trials; $I^2=0\%$), with an absolute survival benefit of 5.7% at three years and 4.5% at five years. Benefit with concomitant radiochemotherapy was also seen for locoregional progression (HR 0.77, 95% CI 0.62 to 0.95; five trials; $I^2=0\%$).

There was no significant difference between groups in progression-free survival (six trials) and distant progression (five trials).

Subgroup and sensitivity analyses found no significant differences between the variables studied, apart from concomitant polychemotherapy (doublet or triplet) which appeared to improve progression-free survival more than concomitant single-agent chemotherapy (HR 0.83, 95% CI 0.72 to 0.95 versus HR 1.15, 95% CI 0.90 to 1.48).

Concomitant radiochemotherapy significantly increased acute oesophageal toxicity (grade 3 to 4) from 4% to 18% (RR 4.9, 95% CI 3.1 to 7.8), but there was no significant difference for acute pulmonary toxicity.

**Authors' conclusions**

Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced non-small cell lung cancer, primarily because of a better locoregional control, but at the cost of manageable increased acute oesophageal toxicity.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken using a variety of methods (although the search terms and dates were not reported). It was unclear whether studies were selected in duplicate, so the possibility of errors or bias affecting the process could not be ruled out.

A full assessment of data integrity, consistency and verification was performed (although results were not reported). Sufficient trial details were provided and appropriate methods were used to pool data and assess statistical heterogeneity.

The authors' conclusions reflect the evidence available and seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that the results clearly supported the use of concomitant radiochemotherapy which should be the reference treatment for locally advanced non-small cell lung cancer.

**Research:** The authors stated that concomitant radiochemotherapy should be considered as the reference treatment for future trials testing new combined treatment approaches integrating the recent developments in three-dimensional conformal radiotherapy. Identification of new cytotoxic or targeted agents that can be combined concomitantly to radiotherapy with more efficacy and less toxicity was warranted.

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