Comparison of the efficacy and acute toxicity of weekly versus daily chemoradiotherapy for non-small-cell lung cancer: a meta-analysis

CRD summary
This meta-analysis of 10 trials found that chemoradiotherapy had a small beneficial effect on death rate in people with inoperable non-small-cell lung cancer, but increased severe acute toxicity compared with radiotherapy alone. The results were not different for daily or weekly chemoradiotherapy. However, these general findings should be treated with caution because the primary studies differed in terms of tumour stage and treatment regimens.

Authors' objectives
To compare the efficacy and toxicity of (1) concurrent chemotherapy and radiotherapy (chemoradiotherapy) versus radiotherapy alone, and (2) daily versus weekly chemoradiotherapy for people with inoperable non-small-cell lung cancer (NSCLC).

Searching
The authors searched MEDLINE (1966 to May 2001), EMBASE (1980 to May 2001) and the Cochrane Controlled Trials Register (to June 2001); the search terms were reported. There were no language restrictions. The proceedings of the American Society for Clinical Oncology were searched for ongoing trials, but only published trials were included.

Study selection
Study designs of evaluations included in the review
Randomised and quasi-randomised controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies comparing radiotherapy versus chemoradiotherapy were eligible for inclusion. Concurrent chemoradiotherapy was defined as cytotoxic therapy during a course of radical radiotherapy. Radical radiotherapy was defined as delivering, by conventional fractionation or altered fractionation, at least 4000 cGy to the gross tumour volume by conventional fractionation or altered fractionation. Studies assessing the effect of hypoxic sensitisers were excluded.

The studies were divided into daily chemoradiotherapy and weekly chemoradiotherapy regimens. In daily regimens, chemotherapy was delivered on sequential days during radiotherapy. In weekly regimens, chemotherapy was generally delivered over sequential weeks during radiotherapy, although there were some variations in individual studies.

The included studies varied in the type, dose, and frequency of drug therapy. However, in most cases, daily regimens involved the delivery of lower doses of chemotherapy and weekly protocols involved relatively higher doses of chemotherapy delivered less frequently. In some studies chemotherapy was not delivered throughout the duration of radiotherapy.

The authors reported the drugs, timing of chemotherapy, and radiotherapy regimen for each included study. In 9 of the 10 studies a cisplatin or carboplatin-containing chemotherapy regimen was used. The total dose of radiotherapy ranged from 45 to 69.6 Gy. Five studies used conventional fractionation and 5 studies used altered fractionation schemes.

Participants included in the review
Studies of people with inoperable NSCLC were eligible. NSCLC was defined as inoperable when there were medical contraindications to surgery or unresectable disease. People with stage I, II or III histologically confirmed disease and no clinical or radiological evidence of distant metastases were included. The authors reported the disease stage of participants in the individual studies. They did not report demographic or other clinical characteristics.

Outcomes assessed in the review
The authors did not explicitly state any outcomes that the studies had to include in order to be eligible for the review. The main outcome measure of the review was mortality from any cause (relative risk of death) at 1, 2 and 3 years after diagnosis. The secondary outcomes included: significant toxicity, defined as incidence of grade 3 or 4 (using the World Health Organization classification); acute oesophagitis and/or oesophageal fibrosis or fistulas; acute pneumonitis and/or pulmonary fibrosis; and acute neutropenia.

How were decisions on the relevance of primary studies made?
The authors reported that each study identified for inclusion was reviewed, but they did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on treatment regimens, disease stage and outcomes were extracted. Where available, the authors extracted raw numbers of events (death and grade 3 or greater acute toxicity). When this was not possible, the authors estimated the number of events from published survival curves. The relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
The results of the primary studies were combined in a meta-analysis based on published data. The authors used a random-effects model when there was statistically significant heterogeneity between studies, and a fixed-effect model when no heterogeneity was identified. They calculated the pooled RR and 95% CI of death at 1, 2 and 3 years after diagnosis of lung cancer, and the RR of grade 3 or greater acute toxicity between chemoradiotherapy and radiotherapy alone.

How were differences between studies investigated?
The authors calculated chi-squared tests for statistical heterogeneity between studies (p<0.1 taken as being significant).

Results of the review
The review included 10 studies with 1,802 participants. Both randomised and quasi-randomised controlled trials were eligible, but the authors did not report the number of each type of study included in the review.

Mortality.
The pooled data from 10 trials suggested that the addition of chemotherapy to radiotherapy slightly reduced 1-, 2- and 3-year mortality compared with radiotherapy alone, although the effect at 1 year was not statistically significant. The RR of death was 0.89 (95% CI: 0.77, 1.02, P=0.09) at 1 year (heterogeneity P=0.048), 0.92 (95% CI: 0.88, 0.97, P=0.002) at 2 years (heterogeneity P=0.029) and 0.93 (95% CI: 0.88, 0.98, P=0.007) at 3 years (heterogeneity P=0.026). These results were subject to significant statistical heterogeneity.

The results remained similar when the results of trials of weekly chemoradiotherapy (6 trials) and daily chemoradiotherapy (5 trials) were pooled separately.

Toxicity.
Chemoradiotherapy was associated with an increase in the toxicities assessed in this review compared with radiotherapy alone, but there was no statistically significant difference in the risk of acute pneumonitis.

The RR of grade 3 or greater acute oesophagitis (9 studies) was 1.77 (95% CI: 1.27, 2.48, P=0.0008; heterogeneity...
The RR of significant acute neutropenia (5 studies) was 9.15 (95% CI: 4.16, 20.12, P<0.00001; heterogeneity P=0.84).

Both weekly and daily administration of chemotherapy were associated with similarly increased levels of acute toxicity.

**Authors' conclusions**

Chemoradiotherapy may reduce the risk of death compared with radiotherapy alone, but the effect is small and is associated with increased severe acute toxicity for people with inoperable NSCLC. The authors found no evidence to suggest a difference between the efficacy or toxicity of daily versus weekly chemoradiotherapy regimens. They concluded that the paucity and heterogeneity of current trials means that it is not possible to recommend an optimal regimen of concurrent chemotherapy and radiotherapy.

**CRD commentary**

This review had a defined research question and inclusion criteria. The search strategy appears appropriate as there were no language restrictions and several different sources were searched. The authors did not report the methods used to select studies for the review. They did not assess study quality, nor were they explicit about the designs of each individual study included. This made it difficult to assess the validity of the review and the studies on which it was based. Also, although they outlined the disease stage of the participants in included studies, the authors did not report the participants' demographic or other clinical characteristics. The authors noted that it is uncertain whether the comparison groups were balanced with respect to tumour stage. This may make it more difficult to draw implications for practice, as treatment types and prognosis may be influenced by demographic characteristics, tumour type and co-morbidities.

The method of analysis appeared appropriate and statistical tests for heterogeneity were conducted. The authors found significant statistical heterogeneity between studies for many of the efficacy outcomes, and noted that this might be due to differences in the quality and design of studies, the radiotherapy and chemotherapy regimens used, and participant characteristics. It is therefore questionable whether the data should have been pooled quantitatively given the clinical diversity of the studies.

Although the data presented support the authors' conclusions, differences between the included studies suggest that caution is needed when applying the findings in practice; particularly in relation to the findings for efficacy.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that additional studies are needed to directly compare different concurrent chemoradiotherapy regimens in order to identify an optimal regimen with greatest therapeutic benefit for people with inoperable NSCLC.

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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.