Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer

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CRD summary
This review evaluated the effects of the timing of radiation therapy on survival in limited-stage small-cell lung cancer. The authors concluded that there is evidence that early radiation therapy is beneficial for overall survival when hyperfractionated radiation therapy and/or platinum-based chemotherapy are used. Given the uncertain quality of the included studies, the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effects of early versus late timing of thoracic radiation therapy on overall survival and progression-free survival in limited-stage small-cell lung cancer (LS-SCLC).

Searching
MEDLINE and Cancerlit were searched for trials published in peer-reviewed journals. In addition, materials referenced in review articles and trial reports were investigated, and both authors of trials identified from the search and experts in the field were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) published after 1985 were included in the review.

Specific interventions included in the review
Trials that addressed the timing of radiation relative to chemotherapy were eligible for inclusion. Early radiation therapy (ERT) was defined as beginning before 9 weeks after the initiation of chemotherapy and before the third cycle of chemotherapy. Late radiation therapy (LRT) was defined as beginning at least 9 weeks after the initiation of chemotherapy or after the beginning of the third cycle of chemotherapy. The total doses of radiation therapy ranged from 40 to 54 Gy and three of the studies used a hyperfractionated scheme. Whether studies gave radiation therapy concurrently or sequentially with chemotherapy varied across studies. Five of the 7 studies used either cisplatin or carboplatin in the chemotherapeutic regimen. Use of prophylactic cranial radiation varied across the studies.

Participants included in the review
Studies of participants with LS-SCLC were included in the review. Two studies included patients with involvement of contralateral or bilateral supraclavicular lymph nodes; these patients were excluded from the other studies.

Outcomes assessed in the review
No inclusion criteria for the outcomes were stated. The outcomes used in the review were 2- and 3-year overall survival and the number-needed-to-treat (NNT) to prevent one death.

How were decisions on the relevance of primary studies made?
The authors 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.

Where available, overall survival data were extracted from the published articles. If the data were not explicitly reported, percentages were obtained from actuarial curves and multiplied by the number of patients in the corresponding study arm to estimate the number surviving at a given time point. Overall survival at 2, 3 and 5 years was calculated. However, the data reported for overall survival at 5 years were insufficient to be included in the analysis. Relative risk ratios for survival at a given time point were calculated for each study.

**Methods of synthesis**

How were the studies combined?
Relative risk ratios were combined in a meta-analysis using a fixed-effect model (Mantel-Haenszel). In addition, the risk difference and NNT to prevent one death were calculated for all studies combined. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test; subgroup analyses were performed where there was heterogeneity. In addition, meta-regression was used to determine the effects of between-study differences on the results. The effects of 3 trials that used sequential or alternating strategies for chemotherapy were investigated in sensitivity analyses. Subgroup analyses investigated whether the studies used hyperfractionation (once daily versus twice daily chemotherapy), whether the chemotherapeutic regimen was platinum-based or non-platinum-based, and whether radiation was delivered concurrently with chemotherapy.

**Results of the review**

Seven RCTs with a total of 1,524 participants were included in the review.

There was no indication of publication bias (P=0.66).

Two-year overall survival was significantly greater with ERT than with LRT (risk ratio, RR=1.17, 95% confidence interval, CI: 1.02, 1.35, P=0.03). The result for 3-year overall survival still favoured ERT over LRT, but was no longer statistically significant (RR 1.13, 95% CI: 0.92, 1.39, P=0.23). No statistically significant heterogeneity was detected. The NNT for one additional survivor was 19 at 2 years and 42 at 3 years.

In sensitivity analyses, the removal of two of the trials using sequential or alternating strategies for chemotherapy had little effect on 2- or 3-year overall survival. However, after the removal of one large study which used concurrent chemotherapy in the ERT arm, but a sequential strategy for the LRT arm, there was no longer a significant benefit of ERT over LRT at 2 years' follow-up (RR, 1.09, 95% CI: 0.93, 1.28, P=0.28).

Studies using a twice daily regimen showed a statistically significant benefit of ERT over LRT for both 2-year overall survival (RR 1.44, 95% CI: 1.17, 1.83, P=0.001; NNT 6) and 3-year overall survival (RR 1.39, 95% CI: 1.02, 1.90, P=0.04; NNT 11). No significant benefit of ERT over LRT was seen for patients receiving a once daily regimen. Studies using platinum-based chemotherapy demonstrated a statistically significant benefit of ERT over LRT at both 2-year overall survival (RR 1.30, 95% CI: 1.10, 1.53, P=0.002; NNT 10) and 3-year overall survival (RR 1.35 95% CI: 1.07, 1.70, P=0.01; NNT 14). No significant benefit of ERT over LRT was seen for studies using non-platinum-based chemotherapy. Neither the studies using concurrent chemotherapy nor those not using concurrent chemotherapy showed a statistically significant difference between ERT and LRT for 2- or 3-year overall survival.

Results of the meta-regression found an absolute benefit in 2-year overall survival of 5% for ERT versus LRT when once daily radiation and platinum-based chemotherapy were used, compared with the referent category (once daily radiation and non-platinum-based chemotherapy). However, this did not reach statistical significance. When twice daily radiation and platinum-based chemotherapy were used, there was an 18% absolute benefit associated with ERT compared with LRT (P=0.002). There was a 9% absolute benefit in 3-year overall survival for ERT versus LRT when once daily radiation and platinum-based chemotherapy were compared with the referent category (P=0.03). When twice daily radiation and platinum-based chemotherapy were used, there was a 14% absolute benefit associated with ERT.
compared with the referent category (P=0.004).

Authors' conclusions
A small but significant improvement in 2-year overall survival for ERT compared with LRT in LS-SCLC was demonstrated. A greater difference was seen for hyperfractionated radiation therapy and platinum-based chemotherapy.

CRD commentary
The authors set out a clear objective at the beginning of the review and the inclusion criteria were defined clearly in terms of the participants, interventions and study design. Two relevant databases were searched for studies, although it was not stated whether any language restrictions were applied to the search. Publication bias was assessed and not detected. The methods used to select studies and extract the data were not reported and this makes it difficult to assess the potential impact of bias on the results, which can arise if these tasks are carried out by one reviewer alone. The quality of the included studies was not assessed, which made it difficult to assess the validity of either the combined or single study results.

Details of the included studies were presented clearly and, despite some differences between the studies, statistical pooling seemed appropriate. Statistical heterogeneity was assessed and the effects of clinical heterogeneity were investigated. This review has some methodological limitations and, given the uncertainty regarding the quality of the included studies, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that there is sufficient evidence to support the use of ERT as one part of a combined-modality approach which uses platinum-based chemotherapy and hyperfractionated radiation therapy.

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

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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.