Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data


CRD summary
This generally well-conducted review concluded that adjuvant chemotherapy after surgery for patients with operable non-small-cell lung cancer improved survival, with or without adjuvant radiotherapy. The results are likely to be reliable, but applicability may be limited given that most participants were male, had stage I to II adenocarcinomas or squamous cell carcinomas, underwent complete resection and received cisplatin regimens.

Authors' objectives
To evaluate the effects of adding adjuvant chemotherapy to surgery, or to surgery plus radiotherapy in patients with operable non-small-cell lung cancer.

Searching
MEDLINE and CANCERLIT were searched, with no language restrictions, to September 2009, using the Cochrane Collaboration optimal strategy with addition topic-specific search terms. Conference proceedings, trial registers and reference lists of trial publications and reviews were also searched. Collaborators on the review were also asked about knowledge of additional studies.

Study selection
Randomised controlled trials (RCTs) conducted since 1965 of patients undergoing potentially curative resection for non-small-cell lung cancer with adjuvant chemotherapy compared with surgery alone, with or without adjuvant radiotherapy in both arms, were eligible for inclusion. Eligible trials were required to include patients who had no history of prior chemotherapy. Trials using long-term alkylating agents for more than one year were excluded. The primary outcome was all-cause mortality.

Most trials used a platinum-based chemotherapy; cisplatin was the most commonly used agent. Where radiotherapy was given, this tended to be after chemotherapy; doses ranged from 15 to 65 Gy. Most of the patients were men. The median age was 61 years (range 18 to 84). Tumours were mostly stage I to II adenocarcinomas or squamous cell carcinomas. Most participants underwent complete resection.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Individual patient data (IPD) were obtained and checked for missing data, validity and consistency. Patterns of treatment allocation and balance at baseline were used to assess the integrity of randomisation. Balance across treatment groups was checked for surviving patients. The final database was verified by the original trialists.

Data extraction
Individual patient data were obtained for all-cause mortality, and recurrence-free and loco-regional and distance recurrence-free survival (definitions and censoring rules provided). Hazard ratios (HR) were calculated using the log-rank expected number of events and variance, along with 95% confidence intervals (CI). Data for 15 trials conducted prior to 1995 were extracted from the authors' previous review (see Other Publications of Related Interest), with only new follow-up data being sought.

Methods of synthesis
Two meta-analyses were conducted using intention to treat data: surgery plus chemotherapy versus surgery alone; and surgery plus chemotherapy plus radiotherapy versus surgery plus radiotherapy. Pooled hazard ratios and 95% confidence intervals were calculated using a fixed-effect model. The X^2 and I^2 statistics and Cox regressions were used to investigate heterogeneity. Non-stratified Kaplan-Meier survival analyses were also conducted. The median follow-up...
for all patients was calculated using the reverse Kaplan-Meier method. Absolute differences in overall survival were calculated; where differences were identified, hazard ratios and control group survival were used to calculate the overall difference between groups; otherwise the overall hazard ratio was used.

**Results of the review**

Thirty-eight RCTs (47 comparisons) were included in the meta-analyses (n=11,107 eligible patients; range 24 to 1,001); median follow-up was 5.5 years (interquartile range 4.4 to 6.6 years).

**Surgery plus chemotherapy versus surgery** (26 RCTs): Of 8,447 patients, 3,323 (39%) died. Survival increased from 60 to 64% at five years, resulting in a statistically significant benefit of chemotherapy as an adjuvant to surgery (HR 0.86, 96% CI 0.81 to 0.92); no significant heterogeneity was observed. When stratified by drug regimen, significant reductions in mortality were observed for platinum plus vinorelbine (HR 0.82, 96% CI 0.70 to 0.97; four RCTs), platinum plus vinca alkaloid plus tegafur and uracil/tegafur (HR 0.79, 96% CI 0.67 to 0.93; eight RCTs) and tegafur and uracil/tegafur (HR 0.76, 96% CI 0.64 to 0.90; seven RCTs), but not platinum plus vinca alkaloid/etoposide (nine RCTs), platinum plus taxane (one RCT), or other platinum regimens (four RCTs). Tegafur and uracil/tegafur showed a non-significant benefit of surgery alone (one RCT).

**Surgery plus chemotherapy plus radiotherapy versus surgery plus radiotherapy** (12 RCTs): Of 2,660 patients, 1,909 (72%) died. Survival increased from 29 to 33% at five years, resulting in a statistically significant benefit of chemotherapy as an adjuvant to surgery (HR 0.88, 96% CI 0.81 to 0.97); no significant heterogeneity was observed. There was no differential effect by chemotherapy category.

Results for recurrence-free survival, and analyses conducted according to accrual decade, geographical region, the use of tegafur with or without uracil, patient age, gender, histology, performance status, and stage of disease and extent of resection, were also reported. Kaplan-Meier curves were also presented.

**Authors’ conclusions**

The addition of adjuvant chemotherapy after surgery for patients with operable non-small-cell lung cancer improved survival, irrespective of whether chemotherapy was adjuvant to surgery alone or with radiotherapy.

**CRD commentary**

The authors addressed a clear research question supported by appropriate inclusion criteria. Several sources were searched with no language restrictions, and both published and unpublished data were sought. Methods used to reduce error and bias during study selection were not reported.

The authors reported that the data were checked for validity and consistency and was verified by the original trialists. Appropriate methods of analyses were utilised, and heterogeneity was investigated.

This was a generally well-conducted review, the results of which are likely to be reliable. However, most of the participants were male with stage I to II adenocarcinomas or squamous cell carcinomas and underwent complete resection receiving cisplatin regimens, so there may be some limitations to the generalisability of the results and conclusions.

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

**Practice:** The authors stated that the results could suggest cautious use of platinum-based chemotherapy in less-fit patients.

**Research:** The authors stated that RCTs assessing whether modern radiotherapy is effective as an adjuvant treatment are required.

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