Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis

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CRD summary
This review concluded that survival rates for particle therapy were higher than those for conventional radiotherapy and similar to stereotactic body radiotherapy in stage 1 inoperable non small cell lung cancer. These conclusions were not fully supported by the results and methodological limitations mean the review findings may not be reliable.

Authors' objectives
To compare radiotherapy with photons, protons and carbon-ions in the treatment of non small cell lung cancer (NSCLC).

Searching
PubMed and The Cochrane Library were searched from 1994 to August 2008. Search terms were reported. Reference lists of retrieved articles and specialist journals were screened. The review was restricted to studies reported in English and Dutch.

Study selection
Studies that assessed conventional radiotherapy alone (which included hyper-fractionated radiation schedules, stereotactic radiotherapy, concurrent chemoradiation, proton therapy and carbon-ion therapy) and reported data on two- or five-year survival for one or more disease stages separately were eligible for inclusion. Studies had to include at least 20 patients. Outcomes considered in the review were two- and five-year overall survival and disease-specific survival rates, occurrence of grade 3/4 pneumonitis, oesophagitis and irreversible dyspnoea and grade 5 adverse events (treatment-related death).

Included studies assessed conventional radiotherapy, stereotactic radiotherapy, proton therapy and carbon-ion therapy at various dosages. Median/mean age (where reported) ranged from 63 to 77 years. The proportion of patients with tumours less than 3cm ranged from 19% to 100%. The proportion of medically inoperable patients ranged from 42% to 100%. Median follow-up ranged from 12 to 91 months.

The authors did not state how studies were selected for inclusion.

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

Data extraction
Two reviewers independently extracted data on the proportion of patients with the outcomes of interest. Missing data on study characteristics were imputed using Rubin's multiple imputation procedure.

Methods of synthesis
Meta-analysis was used to estimate summary proportions for each outcome, together with 95% confidence intervals (CIs), separately for each form of radiotherapy. Random-effects models were used in the presence of heterogeneity. Regression analysis was used to investigate the association of study characteristics (age, proportion of tumours smaller than 3cm, proportion of medically inoperable patients and follow-up period) with treatment effectiveness. Characteristics that showed statistically significant associations in the regression models were considered as effect modifiers. Meta-analyses were corrected for these characteristics by estimating the models for the overall mean value of that characteristic. For adverse events, the total number of adverse events for each treatment modality was calculated. Meta-analysis was not used due to the large number of studies with zero events.

Results of the review
Thirty studies (n=2,611) were included in the review: 11 studies on conventional radiotherapy (n=1,326); 11 studies (n=895) on stereotactic radiotherapy; five studies (n=180) on proton therapy; and three studies (n=210) on carbon-ions. All studies except one studies were single-arm studies.

The proportion of medically inoperable patients was the only coefficient to show a significant association in the regression analysis. This variable was corrected for in all meta-analyses. Summary estimates apply to study populations with 82% medically inoperable patients.

**Two-year survival for stage 1 NSCLC**: (29 studies)

Corrected two-year overall survival estimates were 53% (95% CI 46% to 60%) for conventional radiotherapy, 70% (95% CI 63% to 77%) for stereotactic radiotherapy, 61% (95% CI 47% to 75%) for proton therapy and 74% (95% CI 61 to 86%) for carbon-ion therapy. Corrected values for conventional radiotherapy were significantly lower than stereotactic radiotherapy (p<0.001) and carbon-ion therapy (p=0.006). There was no statistically significant difference between the other therapies. Similar results were reported for disease-specific survival rates.

**Five-year survival for stage 1 NSCLC**: (20 studies)

Corrected five-year overall survival estimates were 19% (95% CI 15% to 24%) for conventional radiotherapy, 42% (95% CI 34% to 50%) for stereotactic radiotherapy, 40% (95% CI 24% to 55%) for proton therapy and 42% (95% CI 32% to 52%) for carbon-ion therapy. Corrected values for conventional radiotherapy were significantly lower than stereotactic radiotherapy (p<0.001), proton therapy (p=0.014) and carbon-ion therapy (p<0.001). There was no statistically significant difference between the other therapies. Disease-specific survival rates showed a similar pattern but estimates were higher.

**Adverse events**: Most studies reported zero adverse events. Overall, stereotactic radiotherapy was associated with more adverse events than conventional radiotherapy, proton therapy and carbon-ions. Treatment-related deaths were reported in a single study of stereotactic radiotherapy with a high biological equivalent dose and including peripherally located tumours.

**Authors' conclusions**

Survival rates for particle therapy were higher than those for conventional radiotherapy and similar to stereotactic body radiotherapy in stage 1 inoperable NSCLC. Particle therapy may be more beneficial in stage III NSCLC, especially in reducing adverse events.

**CRD commentary**

The review addressed a clear question supported by defined inclusion criteria. The literature search was adequate for published studies. It appeared that no specific attempts were made to locate unpublished studies. The review was restricted to studies in two languages, so language and publication biases were possible. Appropriate steps were taken to minimise bias and errors when extracting data; it was unclear whether such steps were taken when selecting studies. Study quality was not formally assessed, so the reliability of the included studies was unclear. Relevant study details were summarised in tables. The methods used to pool studies were appropriate and involved assessment and controlling for potential effect modifiers. Comparisons between treatment modalities should be interpreted with caution, as estimates were derived from single-arm studies; comparisons were all indirect and so subject to greater potential bias.

The authors’ conclusions did not fully reflect the data as reported in the paper. Limitations in the review in terms of potential for missing studies, lack of details on methodological quality and the fact that all comparisons were indirect make the conclusions unlikely to be reliable.

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

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

**Research**: The authors stated that further evidence was needed on whether particle therapy was beneficial in advanced stage NSCLC.
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