Palliative thoracic radiotherapy for lung cancer: a systematic review

CRD summary
The authors concluded that no significant differences were observed between high-dose and low-dose radiotherapy schedules for specific symptoms in patients with lung cancer, although survival was improved with high-dose radiotherapy. Evidence appeared to support the authors’ conclusions about specific symptoms, but the survival benefit of high-dose regimens was limited to one-year survival and not beyond.

Authors' objectives
To determine the optimal radiotherapy schedule in patients with lung cancer that maximises symptom palliation and survival and minimises the need for re-irradiation and toxicity.

This review is an update of a previous review (see Other Publications of Related Interest).

Searching
PubMed (1966 to 2007), EMBASE (1980 to 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies in any language. Search terms were reported. Reference lists in retrieved articles, reviews and clinical practice guidelines were also screened. Studies had to be published in full.

Study selection
Randomised controlled trials (RCTs) in patients with non small-cell lung cancer were eligible for inclusion if they compared different dose-fractionation schedules of palliative thoracic radiotherapy and assessed a symptom outcome. Trials were excluded if they compared external-beam radiation with another modality, evaluated radiotherapy in combination with another modality, or compared immediate with delayed radiotherapy.

The primary review outcomes were complete symptom response and any degree of symptom improvement (complete plus partial response). Secondary outcomes were survival, toxicity and re-irradiation rate. The review assessed the following symptoms: haemoptysis, cough, chest pain, and overall symptom burden.

Included trials were published between 1985 and 2008. Most patients had locally advanced disease, with or without extrathoracic metastases, and were not suitable for curative-intent treatment. Most included patients had non small-cell lung cancer (95%); in two trials an average of 5% had small-cell lung cancer. Where reported, the mean/median age of patients ranged from 60 to 70 years; most were male (78%). Some trials had performance status entry requirements, but some enrolled patients who did not meet these criteria.

The review assessed physician or self-reported measures. A few trials assessed symptoms using validated questionnaires, with or without modifications; other trials used a variety of assessment methods.

The area of the treatment field varied. Treatment duration ranged from one day to four weeks in low-dose groups, and from one to six weeks in high-dose groups. The biologically equivalent dose ranged from 24.8 to 43.7Gy (most below 35Gy) in low-dose regimens, and from 29.6 to 45.9Gy (almost all above 35Gy) in high-dose regimens.

Two reviewers independently selected studies.

Assessment of study quality
Validity was assessed using the Jadad criteria (randomisation, blinding and withdrawals).

The authors did not state how many reviewers assessed validity.
Data extraction
Two reviewers independently extracted outcomes data for the time point at or closest to four weeks from text, tables and figures. Extracted data were used to calculate or estimate relative risks (RRs) and 95% confidence intervals (CIs). Survival data and patient-assessed toxicity were estimated from figures for some trials. The number of patients presenting with each specific symptom was used to calculate treatment effects for that specific symptom. Intention-to-treat data were used to estimate survival, toxicity and re-irradiation rate.

For trials not reporting the number of patients in each treatment arm, it was assumed that the total number was equally divided between the treatment groups. Results for intermediate dose treatment arms were excluded, only low and high dose treatments data were used.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated, using a random-effects model, for each outcome that was reported in four or more trials with more than 200 patients per treatment arm. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistics.

Sensitivity analysis was performed by combining trials with similar control treatments after conversion to time-adjusted biologically equivalent dose (methods were reported); analyses were performed using five different cut-off points.

Results of the review
Thirteen RCTs were included (n=3,473 patients randomised; range 84 to 509). Five trials reported no information on specific symptom outcomes.

Five trials scored 2 out of 5 points on the Jadad scale; the other trials scored 3 points.

Symptoms
There was no significant difference in complete response between high- and low-dose radiotherapy for haemoptysis (five RCTs), cough (five RCTs), or chest pain (five RCTs).

High-dose radiotherapy was associated with a statistically significant increase in the proportion of patients with some degree of improvement in overall symptom burden compared with low-dose radiotherapy (61% versus 56%; RR 0.86, 95% CI 0.78 to 0.95; four RCTs) but there was no significant difference between treatments in complete response (four RCTs).

Survival (13 studies)
High-dose radiotherapy was associated with a statistically significant increase in survival at one year (discrepancy in year of survival reported in text and figures, but appeared to be one-year survival from forest plot) compared to low-dose radiotherapy (26.5% versus 21.7%, p=0.002), but there was no significant difference between treatments at two year survival. Sensitivity analysis suggested that the probability of improved survival was greater with schedules of 35Gy$_{10}$ biologically effective dose (BED) compared with lower-dose schedules (data presented graphically).

There was no significant heterogeneity for the above analyses, except for the chest pain analysis ($I^2$=63%).

Toxicity
High-dose radiotherapy was associated with a statistically significant increase in physician-assessed dysphagia compared with low-dose radiotherapy (21% versus 15%; p=0.01). Results for patient-assessed dysphagia were not consistent and there was significant heterogeneity ($I^2$=79%; six RCTs).

There was no significant difference between high-dose and low-dose radiotherapy in myelopathy (ten RCTs with three confirmed cases) or pneumonitis (six RCTs; $I^2$=60.8%).
There was no significant difference between high-dose and low-dose radiotherapy in the re-irradiation rate (five RCTs; $I^2=54.3\%$).

**Authors' conclusions**

No significant differences were observed between high-dose and low-dose radiotherapy schedules for specific symptoms in patients with lung cancer, although survival was improved with high-dose radiotherapy.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched. Attempts were made to minimise language bias, but no attempts were apparently made to minimise publication bias. Methods were used to minimise reviewer errors and bias in the selection of studies and extraction of data, but it was not clear whether similar steps were taken during the validity assessment.

Study quality was assessed, but only aggregate scores were reported. The authors acknowledged that there was clinical heterogeneity among trials with respect to assessment methods, definitions and completeness of follow-up. Statistical heterogeneity was assessed and appropriate methods were used for most of meta-analyses where no heterogeneity was found; heterogeneity was found for some analyses. It was not clear why some results in the text were reported as odds ratios and not relative risks.

Evidence appeared to support the authors' conclusions about the lack of difference between regimens in specific symptoms, but the survival benefit of high-dose regimens was limited to one-year survival and not beyond.

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

**Practice:** The authors stated that consideration of palliative thoracic radiotherapy doses of at least 35Gy$_{10}$ biologically equivalent dose may be reasonable, but the risks of increased toxicity and greater time requirements have to be taken into account. Patients should be informed about the potential benefits and risks.

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

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**Other publications of related interest**

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Record Status
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.