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Authors' objectives
To assess the clinical effectiveness and cost-effectiveness of non-conventional radiotherapy regimens, compared with standard radiotherapy regimens, in inoperable non-small-cell lung cancer (NSCLC).

Searching
MEDLINE (from 1966 to November 2001), EMBASE (from 1980 to November 2001), Cancerlit (from 1966 to November 2001) and the Cochrane Library (Issue 3, 2001) were searched. The authors also contacted experts in the field, searched the Internet, and checked the citations of studies and reviews obtained for additional studies. The search terms used were reported in detail. There were no language restrictions. It appears that unpublished literature was eligible, although the authors did not explicitly state this.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials of clinical effectiveness were eligible for inclusion in the review. Studies of resource use were eligible if based on costs in the UK. The authors did not provide detailed inclusion and exclusion criteria for study designs assessing resource use.

Specific interventions included in the review
Comparisons of non-conventional radiotherapy with standard radiotherapy were eligible for inclusion in the review. Non-conventional radiotherapy was defined as hyperfractionated, accelerated or combined hyperfractionated and accelerated regimens, with or without adjuvant chemotherapy. More specifically, studies were eligible for inclusion if they compared the clinical or cost effectiveness of:

- accelerated radiotherapy, alone or combined with adjuvant chemotherapy, versus standard radiotherapy;
- hyperfractionated radiotherapy, alone or combined with adjuvant chemotherapy, versus standard radiotherapy;
- hyperfractionated split-course radiotherapy, alone or combined with adjuvant chemotherapy, versus standard radiotherapy; and
- combined hyperfractionated and accelerated radiotherapy (CHART), alone or combined with adjuvant chemotherapy, versus standard radiotherapy.

The authors reported full details of the schedules and regimens used in the primary studies in the review. Although these differed somewhat, the general characteristics can be described as follows. Accelerated radiotherapy was defined as two or more fractions of standard fraction size daily, up to the conventional total dose. The number of fractions is increased each week, shortening the overall treatment time. One study included in the review used this method, with 60 Gy in 30 fractions of 2 Gy twice daily for 3 weeks.

Hyperfractionated (non-accelerated) radiotherapy was defined as two or more fractions daily of smaller than conventional fraction size. Three studies included in the review used this method, with total doses varying between 66 and 71.5 Gy over 6 weeks split between 60 and 52 fractions, respectively.

Hyperfractionated accelerated radiotherapy was defined as two or three fractions of smaller than standard fraction size daily, delivered over a shorter period of time than conventional radiotherapy. Variants include CHART and continuous hyperfractionated accelerated radiotherapy weekend-less (CHARTWEL). One study included in the review used this method, with 54 Gy in 36 fractions of 1.5 Gy three times daily for 12 continuous days.
Spilt-course radiotherapy divides the total dose into at least two separate courses with an interruption of 10 to 14 days. Two studies included in the review used hyperfractionated split-course treatment. These divided courses of 60 or 72 Gy by a 2-week rest period, using varying fractionation.

Standard radiotherapy was defined as a regimen considered 'conventional' within the United Kingdom (approximately 2 Gy fractions given once daily to a total of 60 to 70 Gy). Standard radiotherapy varied between the studies included in the review, but was predominantly 60 Gy in 30 fractions of 2 Gy once daily for 6 weeks.

The authors excluded studies of standard radiotherapy combined with chemotherapy.

Participants included in the review
Adults with inoperable, but not widespread (not stage IV) NSCLC were eligible for inclusion in the review. The authors did not report the overall descriptive characteristics (e.g. average age across all primary studies, or proportion of women), but characteristics of the participants in the individual primary studies were provided in an appendix. These were summarised by intervention and included age, histology, disease stage and gender. The characteristics of the participants varied widely. For example, between 63 and 97% of the participants in different primary studies were men.

Outcomes assessed in the review
Studies that assessed clinical effectiveness, cost-effectiveness/resource use, or both were eligible for inclusion in the review. The primary outcome for clinical effectiveness was overall survival, measured using definitions as per the primary studies. The secondary outcomes included adverse events, clinical response and quality of life (although few studies included data on quality of life). Studies that included an assessment of resource implications or costs were also eligible for inclusion. The primary outcome for cost-effectiveness, calculated for the review, was the cost per life-year gained. It was not possible to include the cost per quality-adjusted life-year as an outcome due to insufficient quality of life data.

How were decisions on the relevance of primary studies made?
One author assessed the abstracts of all potential studies using a list of inclusion criteria. The full text of studies was assessed where relevant information was not available in abstract form. Twenty per cent of potential papers were checked by a second author. A Kappa score was calculated to detect inter-rater agreement.

Assessment of study quality
A modified version of the Jadad checklist for randomised controlled trials (see Other Publications of Related Interest no.1) was used to assess study quality. The checklist included an assessment of selection bias (randomisation), confounding (concealment), assessment bias (blinding of outcome) and attrition bias (intention-to-treat analysis). An overall total quality score of between 1 and 5 was calculated for each trial.

Studies including a cost-effectiveness analysis were assessed using headings adapted from the ‘Guidelines for authors and peer reviewers of economic submissions to the BMJ’ (the Drummond checklist: see Other Publications of Related Interest no.2). One author assessed study quality using the modified Jadad checklist and a second author checked the validity assessments. Any differences of opinion were resolved by consensus.

Data extraction
Data on the study characteristics, study quality and outcomes were extracted by one author and checked by another using standardised data extraction forms. Any differences of opinion were resolved by consensus. The authors calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for the clinical effectiveness outcomes. They also calculated the cost per life-year gained from data in studies on resource use.

Methods of synthesis
How were the studies combined?
The authors described each individual study and provided a narrative synthesis of implications. In the clinical effectiveness analysis, where more than one trial was identified on a particular radiotherapy regimen, the authors presented pooled HRs and 95% CIs.
How were differences between studies investigated?
The authors reported chi-squared tests for heterogeneity for each pooled estimate of the clinical effectiveness of different radiotherapy regimens. They also described differences between the studies and listed study characteristics in the appendices.

Results of the review
Seven randomised controlled trials on clinical effectiveness and 2 cost-impact studies were identified. The 7 trials on clinical effectiveness contained a total of 1,569 participants (range: 36 to 563). These trials were conducted in Australia, China, Europe (including the UK), Japan, North America and Turkey. The 2 studies of resource use were cost-impact studies rather than cost-effectiveness studies. One of these studies was based on a clinical trial of CHART versus conventional radiotherapy from a societal and National Health Service (NHS) cost perspective. The number of participants was not reported in the review. The other cost impact analysis was based on an audit of hospitals in one UK region (227 participants). This focused solely on the NHS costs of various management and treatment strategies for NSCLC.

Clinical effectiveness.
Two non-conventional radiotherapy regimens, CHART and split-course hyperfractionated radiotherapy, had a significant overall survival advantage over standard radiotherapy. For CHART versus standard radiotherapy, the HR for death was 0.78 (95% CI: 0.66, 0.94), based on one study with 562 participants. For split-course hyperfractionated radiotherapy versus standard radiotherapy, the HR was 0.48 (95% CI: 0.33, 0.7), based on 2 studies with a total of 126 participants. The authors noted that the two studies were heterogeneous (chi-squared test statistic for heterogeneity 4.96, P=0.026). There did not appear to be an increased incidence of adverse events with either of these non-conventional radiotherapy regimens, although the reporting was poor in one trial. Participants receiving CHART had more pain on swallowing and heartburn in the short-term.

A Kappa score was calculated to detect inter-rater agreement when deciding whether to include or exclude studies from the review. The Kappa score was 0.81 (possible range 0 to 1), indicating good agreement between the two authors making the selection.

The authors reported that, overall, the quality of most studies of clinical effectiveness was relatively poor, and little data were supplied on adverse events or quality of life. A modified Jadad scale was used to assess study quality. The total quality score for studies included in the review ranged from 1 to 4 on a 5-point scale; most scored 2 or 3 out of 5.

Cost information
Based on two cost-impact studies, the authors calculated that all non-conventional radiotherapy regimens included in the review, except accelerated regimens alone, may be associated with a cost increase of up to £3,000 per patient per year in the UK. The cost per life-year gained was £11,227 (95% CI: 6,062, 50,520) for CHART and £2,311 (95% CI: 1,231, 5,778) for split-course hyperfractionated radiotherapy with chemotherapy. The authors concluded that these regimens are likely to be cost-effective, but these estimates do not include quality of life data and the costs of potential adverse events.

Authors' conclusions
CHART and split-course hyperfractionated radiotherapy with chemotherapy may be clinically and cost-effective in comparison with standard radiotherapy in NSCLC.

CRD commentary
This review addressed well-defined research questions. The inclusion and exclusion criteria were reported and the search strategy was relatively comprehensive. It is likely that most studies meeting the inclusion criteria were identified by the search strategy, although the authors were not explicit about whether unpublished studies were eligible for inclusion in the review. It may have been appropriate to search conference proceedings for new or ongoing trials, and 'grey literature' for information on resource use since economic studies may have been undertaken for policy purposes.
and not published. The authors did, however, search the Internet for these types of sources.

The study selection, quality assessment and data extraction processes were all verified by a second author. Sufficient details were provided in the report to assess the quality of the primary studies and the review itself. The methods used appear appropriate. Based on the details reported, this appears to be a high-quality review, using standardised search and appraisal criteria. However, the review may be limited by the paucity of available data and the quality of the existing studies.

The authors synthesised the data appropriately. They provided a description of the findings of each study included, presented HRs for effectiveness outcomes, and pooled the results where appropriate. Although the characteristics of the individual studies were tabulated in an appendix, a general description of the overall sample in all nine included studies might have been useful. This would have allowed readers to gain a better impression of participant characteristics such as gender, age and disease stage, and thus assess the generalisability of findings for particular patient populations. The authors calculated statistics to assess heterogeneity. However, the outcomes for one of the non-conventional radiotherapy regimens found to increase survival over standard radiotherapy were based on two heterogeneous studies, one of which may have involved translation difficulties. The authors did not pool 'overall' results for all non-conventional versus standard radiotherapy regimens. This appears appropriate given the diversity of regimens and clinical characteristics of the samples.

The authors addressed their research questions clearly. The report was clearly structured, providing sufficient details about the selection processes, trial quality and data analysis to allow readers to assess the conclusions. However, the authors may have overgeneralised the findings about cost-effectiveness. No studies of cost-effectiveness were identified. The two cost-impact studies identified did not measure quality of life or the cost of adverse effects from treatment, nor did they compare resource use with treatment efficacy.

The authors drew general conclusions about clinical effectiveness that appear to be supported by the data presented. However, they identified limited literature on some regimens and no detailed information on cost-effectiveness. Care is advised when interpreting the findings, especially those on cost-effectiveness, since the review was based on a limited number of trials, some of which were small or flawed. Comparisons with standard radiotherapy plus chemotherapy were also excluded from this review. This means that the authors cannot comment on whether non-conventional radiotherapy regimens including chemotherapy are more effective because of the radiotherapy regimen or due to the use of chemotherapy. This is important because one of the two non-conventional regimens found to increase survival over standard radiotherapy included adjuvant chemotherapy.

Implications of the review for practice and research
Practice: The authors suggest that the CHART regimen and split-course hyperfractionated radiotherapy with adjuvant chemotherapy may be clinically effective and cost-effective, compared with standard radiotherapy, in NSCLC. However, they note that adopting the CHART regimen may require a change of working practices in the UK, including 'out of hours' use of staff and hospital beds.

Research: The authors note there is a lack of studies assessing quality of life, adverse events and cost-effectiveness. They suggest that further studies are needed that focus on these outcomes, especially for non-conventional radiotherapy regimens where there is some evidence of clinical effectiveness. The authors identify one ongoing trial into the CHARTWEL regimen due for completion in 2006. The results of this trial may alter the conclusions of the review.

Bibliographic details

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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.