Meta-analysis of late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy for esophageal carcinoma

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CRD summary
Late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy could improve the rates of survival and local control for patients with oesophageal cancer compared with hyperfractionated radiotherapy alone, but increased acute radiation toxicity. The review had various methodological and reporting weaknesses but overall the authors' conclusions reflect the evidence presented and appear reliable.

Authors' objectives
To assess the efficacy and toxicity of late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy for oesophageal cancer.

Searching
PubMed, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM), and the Wanfang database were searched from 1999 to January 2009. Search terms were reported.

Study selection
Eligible randomised controlled trials (RCTs) evaluated late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy for patients with oesophageal cancer. Control group was accelerated hyperfractionated radiotherapy alone. Studies with a methodological quality score of 3 or above on the Jadad scale were included. The following outcome measures were included: survival rate; local control rate; radiation oesophagitis; bronchitis; haematological and gastrointestinal toxicity. Studies that used non-FP chemotherapy, which combined the intervention with other treatments, duplicate reports and studies with missing data were excluded.

Almost all patients had squamous cell carcinoma. Most tumours were located in the middle and upper sections of the oesophagus. Radiotherapy doses ranged from 49 to 70Gy. Chemotherapy was administered in between two and five cycles. Cisplatin (10 to 50mg, generally during courses of one to five days) was used in all studies, generally in combination with 5-fluorouracil (250 to 750mg in courses lasting one and 10 days).

The authors did not state how many reviewers screened the studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad scale, covering randomisation, double blinding and management of dropouts.

The authors did not report the results of the quality assessment or how many reviewers performed it.

Data extraction
Outcomes (survival rates, local control rates, acute radiation toxicity and chronic radiation toxicity) were extracted from each study to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted the data.

Methods of synthesis
The studies were pooled using fixed-effect and random-effects models. Heterogeneity was assessed using $\chi^2$. When heterogeneity was statistically significant, a random-effects model was used. Otherwise, studies were pooled using a fixed-effect model. Publication bias was assessed using funnel plots.

Results of the review
Twenty-one RCTs were included (2,030 patients). Follow-up ranged from one to five years for survival rates and one to three years for local control rates.
Survival rates at one year were significantly higher for patients receiving combination treatment (79.7%) compared with those on radiotherapy alone (67.4%) (OR 1.92; 95% CI 1.56 to 2.37; 1,874 patients; 20 studies). These differences remained significant at two years (65.0% versus 48.4%; OR 2.01; 95% CI 1.61 to 2.49; 1,396 patients; 14 studies), at three years (50.3% versus 34.9%; OR 1.90; 95% CI 1.57 to 2.29; 1,840 patients; 19 studies) and at five years (40.5% versus 27.0%; OR 1.85; 95% CI 1.06 to 3.24; 226 patients; two studies). Heterogeneity was very low. No significant publication bias was found.

Local control rates were significantly higher for patients in the combined treatment group compared with control at one year (79.9% versus 70.4%; OR 1.69; 95% CI 1.27 to 2.26; 1,045 patients; 11 studies); at two years (69.8% versus 58.4%; OR 1.84; 95% CI 1.39 to 2.42; 915 patients; nine studies) and three years (64.0% versus 48.7%; OR 1.87; 95% CI 1.44 to 2.44; 915 patients; nine studies). Heterogeneity was very low.

Levels of acute radiation toxicity were significantly higher for patients receiving combined treatment compared with those receiving radiotherapy alone. There were no significant differences in chronic radiation toxicity between intervention and control (three studies). Details for individual outcomes were reported in the paper.

**Authors’ conclusions**
Late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy could improve the rates of survival and local control for patients with oesophageal cancer. Acute radiation toxicity levels were increased with combined therapy. Long-term toxicities did not appear to be increased.

**CRD commentary**
The review question and inclusion criteria were clear. Three of the four bibliographic databases were Chinese, and almost all included studies were published in Chinese, which suggests a risk of language bias. It was unclear whether study selection, data extraction and quality assessment were carried out with sufficient attempts to minimise error and bias. No attempts were made at contacting authors in case of missing data. Publication bias was assessed and no evidence of bias was found.

Intervention details were well reported, although patients characteristics (eg. disease severity) were not, making the comparability between studies uncertain. The results of the quality assessment were not reported, which limits the interpretation of the quality of the evidence and reliability of the findings. However, given the relatively large number of trials and patients included in this review and the very low levels of heterogeneity for the main outcomes, it was unlikely that these potential weaknesses significantly affected the reliability of the main conclusions of the review.

There were discrepancies between the graphs and text, in which case the results reported in the text were taken into account. The fact that most studies were published in Chinese and there was limited reporting of patients characteristics (such as disease severity) should be considered when interpreting the applicability of the review findings across populations and settings.

The review had various methodological and reporting weaknesses but overall the authors’ conclusions reflect the evidence presented and appear reliable.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors reported that more research was needed to assess long-term toxicities of late course accelerated hyperfractionated radiotherapy combined with chemotherapy compared with radiotherapy alone. The appropriate concurrent chemotherapy regimen and following treatment also need to be defined so that clinical treatment could be standardised.

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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.