Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck

Head and Neck Cancer Disease Site Group

CRD summary
The published data on hyperfractionated radiotherapy were of limited quality, making it difficult to draw conclusions. However, hyperfractionated radiotherapy has higher rates of acute toxicity compared with conventional radiotherapy. Therefore it should not be offered routinely to adults with newly-diagnosed, locally advanced squamous cell carcinoma of the head and neck. The data presented in this review support these conclusions.

Authors' objectives
To assess whether hyperfractionated radiotherapy improves loco-regional control or survival compared with conventionally fractionated radiotherapy; the toxicity associated with hyperfractionation; and whether hyperfractionation enhances the therapeutic toxicity/benefits ratio in people with newly-diagnosed, locally advanced squamous cell carcinoma (SCC) of the head and neck suitable for curative radical radiotherapy.

Searching
MEDLINE (from 1966 to January 2003), Cancerlit (1983 to October 2002), the Cochrane Library (Issue 4, 2002), PDQ (to January 2003), CMA Infobase: Clinical Practice Guidelines (to January 2003), the National Guideline Clearinghouse (to January 2003), proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2002) and the American Society for Therapeutic Radiology and Oncology (1999 to 2002), article reference lists, and personal files were searched; the search terms were reported. Abstracts and full reports, unrestricted by language, were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and meta-analyses of RCTs were eligible for inclusion.

Specific interventions included in the review
Studies were eligible for inclusion in the review if they compared hyperfractionated radiotherapy with a control arm using conventional radiotherapy for 5 days per week. Three-arm trials that assessed the addition of chemotherapy or radiosensitisers were eligible if information could be extracted to compare hyperfractionated versus conventional radiotherapy. The authors tabulated individual treatment regimens in detail. Conventional fractionation of radiotherapy usually involves daily fractions of 180 to 250 cGy, 5 days per week; the total dose is 50 to 70 Gy over 4 to 7 weeks. Hyperfractionated protocols deliver higher total doses using multiple fractions per day and smaller doses per fraction over the same treatment timeframe. Most hyperfractionation regimens use fractions of 1 to 1.2 Gy delivered two or three times daily.

Participants included in the review
Studies were eligible if they included adults with newly-diagnosed, locally advanced SCC of the head and neck (stage III to IV) suitable for radical radiotherapy with curative intent. The authors tabulated disease site and disease stage data for each included trial. No information about the participants' age or gender was provided.

Outcomes assessed in the review
The primary outcomes of interest were overall survival and loco-regional control. Toxicity and changes in therapeutic benefit/toxicity ratios were also considered.

How were decisions on the relevance of primary studies made?
Two members of the Head and Neck Cancer Disease Site group and methodologists selected and reviewed the studies. The authors did not provide further details about how the studies were selected for the review.
Assessment of study quality
The authors did not state that they assessed validity. This review was developed using the Practice Guidelines Development Cycle, which has been reported elsewhere (see Other Publications of Related Interest).

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on publication details, sample size, disease site, disease stage, treatment strategies, duration of follow-up, loco-regional control and response, survival outcomes, and toxicity.

Methods of synthesis
How were the studies combined?
The authors collated the findings narratively. They did not pool the findings because only a small number of trials contained complete information and some had methodological problems. They reported a pooled analysis from a published meta-analysis, but noted methodological limitations with these data.

How were differences between studies investigated?
The authors tabulated the study characteristics and reported any differences narratively.

Results of the review
The review included 10 studies: one meta-analysis of summary data, one meta-analysis of individual patient data, and 8 RCTs. The 8 RCTs had a total of 2,978 participants (range: 53 to 1,113).

Most of the 8 available trials had methodological limitations. Three out of 6 trials reporting data on overall survival found a significant benefit favouring hyperfractionation. A published meta-analysis of data from 3 trials found a significant reduction in mortality favouring hyperfractionation (odds ratio 0.48, 95% confidence interval: 0.40, 0.58, P<0.0001).

The authors reported findings from seven trials about the effects of hyperfractionated radiotherapy on loco-regional control. Four trials found significantly better loco-regional control with hyperfractionated radiotherapy, as did the published meta-analysis.

Data about acute toxicity were reported from 6 trials. Hyperfractionated radiotherapy was associated with increased mucosal and skin toxicity. There were no significant differences in late toxicity in the 4 trials that reported this outcome.

Authors' conclusions
The authors stated that it is difficult to draw conclusions about hyperfractionated radiotherapy because published data is of limited quality. Hyperfractionated radiotherapy has higher rates of acute toxicity compared with conventional radiotherapy. Therefore, the authors suggested that hyperfractionated radiotherapy should not be offered routinely to adults with newly-diagnosed, locally advanced SCC of the head and neck.

CRD commentary
This review comprised several broad research questions. The search strategy appears adequate. Although the authors discussed methodological problems, they did not report how they assessed the studies for relevance or validity. This makes it difficult to consider the overall quality of the review and the studies on which it was based. Details of other aspects of the primary studies were presented in tabular format.

Given the methodological differences between the studies, it seems appropriate that the authors combined the data narratively, rather than pooling it quantitatively. The authors clearly described methodological flaws in previous studies and the impact of these on their conclusions. The authors addressed each of their research questions when
drawing conclusions. The data and study characteristics were clearly presented, allowing readers to assess the findings. The authors' conclusions could be considered conservative, but the data presented in this review tend to support these conclusions.

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

Practice: The authors stated that hyperfractionated radiotherapy cannot be recommended as routine clinical practice for adults with newly-diagnosed, locally advanced SCC of the head and neck (stage III to IV) suitable for curative radiotherapy. These patients should be considered for concomitant chemotherapy and conventional radiotherapy.

Research: The authors stated that longer follow-up data and more complete information on late complications are needed before hyperfractionated and conventional radiotherapy can be compared fully.

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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.