Controlled trials of synchronous chemotherapy with radiotherapy in head and neck cancer: overview of radiation morbidity

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Authors' objectives
To review the trials of simultaneous chemotherapy with radiotherapy in a published systematic review (see Other Publications of Related Interest no.1) for data concerning both acute and late radiation morbidity.

Searching
All the trials from the published systematic review (see Other Publications of Related Interest no.1), which investigated synchronous chemotherapy and radiotherapy for head and neck cancer, were included. In the original review, MEDLINE and the PDQ clinical trials database were searched between 1963 and August 1993. Relevant textbooks (see Other Publications of Related Interest nos.2-3) and the proceedings of the American Society of Clinical Oncologists were searched from 1979 to 1993. If the same data had been published more than once, the most recent data were used.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Comparisons of simultaneous chemotherapy and radiotherapy with radiotherapy alone. Three trials were of multi-agent and 16 of single-agent chemotherapy. In 17 trials, the same dose of radiotherapy was given with and without chemotherapy; in the other two, an effectively lower radiation dose was given in the chemotherapy arm. The chemotherapy agents used were: cisplatin, methotrexate, bleomycin, mitomycin C, fluorouracil, hydroxyurea, 'multiple', mitomycin C plus fluorouracil, cisplatin plus fluorouracil, and mercaptopurine.

Participants included in the review
People with head and neck cancer of any type.

Outcomes assessed in the review
Acute and late radiation toxicity, including acute mucositis, bone necrosis, soft tissue necrosis and fibrosis, were assessed.

How were decisions on the relevance of primary studies made?
The author of the original review did not report how the studies were selected for the review, although as there was only one author it is likely that only one person performed the selection.

Assessment of study quality
The author of the original review did not state that they assessed validity.

Data extraction
In the original review, the data were abstracted from photocopies of the original publications and entered onto a spreadsheet. The author did not report how many of the reviewers extracted the data, although as there is only one author it is likely that only one person performed the data extraction.

The data were extracted into the following categories: sample size; chemotherapy drug; radiation dose in chemotherapy and control arms; odds ratio (OR) for survival (from the original review); acute normal tissue effects and OR; and late normal tissue effects and OR. The analysis was performed on published data: there was no attempt to obtain data on individual patients. The data on mucositis permitted the incidences and ORs in each trial to be calculated. In the case of
late effects, the ORs were derived from the absolute numbers of complications.

**Methods of synthesis**

How were the studies combined?
The pooled ORs and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel fixed-effect method. The author states that in a trial in which there is a difference in survival between the two arms, the method of calculating late-effect morbidity will tend to underestimate the relative risk in the arm with the lower survival. However, in most of the trials, the survival differences were small.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the chi-squared test.

**Results of the review**

Nineteen RCTs (n=2,926) were included.

The pooled OR for late effects in trials using the same radiotherapy dose in both arms was 1.82 (95% CI: 1.02, 3.26). There was no significant heterogeneity in this result (chi-squared 4.5). The pooled OR for acute mucosal morbidity in trials using the same radiotherapy dose in both arms was 2.86 (95% CI: 2.15, 3.81). There was significant heterogeneity in this result (chi-squared 24.5, p<0.001); the author states this reflects the different drugs and dosages used in the various trials. The pooled ORs for acute and late morbidity were also reported for each chemotherapy drug. The author states that bleomycin appears to have the greatest enhancing effect on both acute and late radiation toxicity (although for the late toxicity result, the 95% CI includes 1.00)

**Authors’ conclusions**

It was found that chemotherapy significantly enhanced both acute and late radiation morbidity effects, suggesting that the chemotherapy drugs may be merely dose-modifying. Future trials should be designed to determine whether or not chemotherapy improves the therapeutic ratio.

**CRD commentary**

The review question and the study selection criteria were clear as they related to the previous review. The search carried out for the previous review was reasonably comprehensive, but may have benefited from the inclusion of other databases such as EMBASE. The review from which the included studies were taken was published two years previously; it is unclear whether other relevant RCTs had been published in the meantime, although it was not the stated objective of this review to update the previous review. No validity assessment was performed and no attempt was made to obtain unpublished data, which may have led to an approximation of the data in some cases and, therefore, inaccuracies in the results. No details of the review process were given although, with only one author, it is likely that only one reviewer was involved. Pooling of the results seems appropriate with regard to the stated review objective. However, it should be noted that when pooled ORs are calculated for each chemotherapy agent, rather than all together, none show a significant increase in late radiation morbidity, and two (cisplatin and mitomycin C) do not show a significant increase in acute radiation morbidity.

The author’s conclusions should be treated with caution due to these observations and while the results of further research, preferably on an individual patient basis, are awaited.

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

Practice: The author did not state any implications for practice.

Research: The author states that future trials should address the question of therapeutic ratio in trials that use different doses of radiotherapy in the chemotherapy and control arms. The patients in a radiotherapy-only arm should be treated with a dose-fraction regimen in accordance with accepted international standards, or a hyper-fractionation scheme that
has been demonstrated to be superior in the tumour sites and stages eligible for the trial. The radiation dose in a combined chemotherapy-radiotherapy regimen should be chosen in an endeavour to produce the same normal tissue effects as in the control group. Pilot studies may be needed to establish the optimum dose. The careful documentation of late effects during a follow-up period of at least 5 years is essential.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

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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.