Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis

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Authors' objectives
To develop clinical recommendations for concomitant chemotherapy (CT) and radiotherapy (RT) in patients with locally advanced squamous cell head and neck cancer (SCHNC).

Searching
MEDLINE (from 1970 to March 2000), Cancerlit (from 1983 to February 2000), HealthSTAR (from 1975 to February 2000), the Cochrane Library (Issue 1, 2000), and relevant conference proceeding were searched. The search strategy included a combination of the MeSH terms 'Head and neck neoplasms' and 'combined modality therapy'; the textwords 'concomitant or combined', 'radiotherapy', 'chemotherapy', 'surgery', 'malignant neoplasms'; and search terms relating to the study design, i.e. randomised trials, systematic review, meta-analysis, double blind method, practice guideline and review. Additional trials were identified from the citation lists of relevant studies and from the personal files of oncologists.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs), systematic reviews and meta-analyses of RCTs were considered. Only studies that analysed the data using an 'intention-to-treat' approach were included.

Specific interventions included in the review
All forms of concomitant schedules of CT and RT were considered for inclusion in the review. An adequate dose of RT had to be used in both arms (equivalent to at least 65 Gy total dose to the primary lesion). Studies that included CT in both the randomised and control arms were excluded, as were studies involving the use of radiation sensitising agents that were not antineoplastic.

The types of CT used by the included studies were: 5-fluorouracil (FU); infusional FU; bleomycin; bleomycin in combination with methotrexate; cisplatin (CP); CP in combination with bleomycin; CP in combination with infusional FU; CP in combination with infusional FU plus leucovorin; mitomycin C (MMC) in combination with infusional FU; MMC in combination with bleomycin; carboplatin; and carboplatin in combination with infusional FU. The type of RT schedules used were conventional, accelerated, hyperfractionated or split-course.

Participants included in the review
Only studies of patients with stage III or IV SCHNC without distant metastases were considered for inclusion. Studies that included more than 20% of patients with nasopharynx cancer were excluded. No information was presented on the participants of the included studies.

Outcomes assessed in the review
Only studies that reported survival as an outcome measure were included. Information relating to the toxicity profiles of the included platinum-based CT studies was also presented in the results.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Summary tables for the RCTs included brief data on the CT regimen and type of RT used, i.e. conventional versus non conventional (accelerated, hyperfractionated or split-course).

Methods of synthesis
How were the studies combined?
The studies were pooled using a random-effects model. The pooled results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The absolute risk difference between the groups and the relative risk (RR) of death were also calculated where appropriate. The studies were also pooled according to the following stratifications: (1) the RT fraction schedule used in the control arm, i.e. conventional continuous versus non-conventional; (2) whether the RT schedules in the control and experimental arms were the same; and (3) whether the CT regime used was single agent versus multiple agent and platinum-containing CP versus others.

How were differences between studies investigated?
Differences between the studies were discussed in the text and investigated statistically (statistical test used not stated), along with a graphical presentation (forest plot) of the results of the individual studies. A sensitivity analysis was performed with and without the inclusion of a study (n=319 evaluable patients) that had not yet published detailed mortality data. The only available publication indicated no difference between the treatment arms, both of which included conventional RT. The reviewers therefore interpreted the results as equivalence of the treatment arms for the purpose of their analysis.

Results of the review
Four systematic reviews (involving meta-analyses) and 18 RCTs (3,192 patients) that included 20 different comparisons were included.

Three of the four included systematic reviews detected an overall survival benefit for concomitant RT plus CT treatment. One systematic review showed that concomitant therapy produced more adverse effects than RT alone.

A formal statistical test for heterogeneity across all trials was not significant for the calculation of the OR (p>0.10), but it was significant for calculation of the overall risk difference (p<0.05). A statistical test for heterogeneity across the platinum-based CT trials was not significant, despite some differences in the baseline risk across the studies.

The pooled analysis of all trials (18 RCTs, 20 comparisons, n=3,192) showed a reduction in mortality for concomitant RT plus CT therapy, compared with RT alone: the OR was 0.62 (95% CI: 0.52, 0.74, p<0.00001), the RR was 0.83, and the risk difference was 11%. The benefit remained roughly consistent across most of the subgroups. Concomitant RT plus CT therapy produced more acute adverse effects than RT alone.

Subgroup analysis of RT schedules.
Same RT schedule in both treatment groups (16 RCTs with 17 comparisons, n=2,700): the OR was 0.62 (95% CI: 0.52, 0.75, p<0.00001) and the risk difference was 10.7%.

Conventional fractionation RT in both treatment groups (12 RCTs with 13 comparisons, n=2,133): the OR was 0.66 (95% CI: 0.52, 0.83, p=0.00041) and the risk difference was 9.2%.

Same nonconventional RT in both treatment groups (4 RCTs, n=567): the OR was 0.51 (95% CI: 0.36, 0.71, p=0.00008) and the risk difference was 16.6%.

Conventional RT in control group only (3 comparisons, n=492): the OR was 0.58 (95% CI: 0.31, 1.09, p=0.093) and the risk difference was 12.5%.
Subgroup analysis of CT.

Platinum-based CT (10 comparisons, n=1,514): the OR was 0.57 (95% CI: 0.46, 0.71, p less than or equal to 0.00001) and the risk difference was 12.1%.

MMC-based CT (4 comparisons, n=522): the OR was 0.54 (95% CI: 0.30, 0.95, p=0.032) and the risk difference was 14%.

FU-based CT (3 comparisons, n=535): the OR was 0.66 (95% CI: 0.39, 1.10, p=0.11) and the risk difference was 10.2%.

Bleomycin-based CT (5 comparisons, n=641): the OR was 0.80 (95% CI: 0.50, 1.29, p=0.36) and the risk difference was 5%.

Authors' conclusions
Platinum-based CT and RT is superior to conventional RT alone on improving survival in locally advanced SCHNC. Subgroup analyses can be used to help choose the most appropriate concomitant regimen.

CRD commentary
Pre-specified inclusion and exclusion criteria were clearly reported and the literature search was fairly comprehensive. Information about the methodology of the review process was not presented, such as how many of the reviewers were involved in making decisions on the relevancy of primary studies and in extracting the data. The information presented on the included studies, e.g. the specific CT and RT regimens used and details of the included participants, was limited. While the review only included RCTs, the validity of these studies was not investigated, thereby limiting any assessment of how reliable the results were. The authors used a random-effects model to compensate to some degree for the questionable comparability across the trials. Bearing in mind the clinical diversity between the studies, it might have been preferable to only pool the results of studies looking at similar interventions.

The authors' conclusions appear to follow from the results presented.

Implications of the review for practice and research
Practice: The authors state that eligible patients with SCHNC who are not part of a clinical trial should be informed about the results of trials on concomitant therapy. For patients in whom RT is being considered as part of the definitive treatment modality, platinum-containing regimens that were associated with positive trials and for which toxicity was relatively mild are recommended.

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

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Other publications of related interest
This paper is based on a Practice Guideline produced by Cancer Care Ontario Practice Guidelines Initiative. The series
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