The role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer

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CRD summary
This review investigated the role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer. The authors concluded that cisplatin-based concurrent radiochemotherapy should be routinely offered. The conclusion follows from the results as they are presented.

Authors' objectives
To assess whether the addition of chemotherapy to radiotherapy improves the survival of adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer and, if so, to ascertain the best timing and chemotherapy regimen.

Searching
MEDLINE (from 1966 to October 2003), EMBASE (from 1980 to October 2003), the Cochrane Library (Issue 3, 2003), PDQ, the Canadian Medical Association's Clinical Practice Guidelines Infobase and the National Guideline Clearinghouse were searched. The authors also searched abstracts published in the proceedings of meetings of relevant societies (details given). Personal files and the bibliographies of articles were also checked to October 2003 for evidence relevant to this practice guideline report. The literature search combined nasopharyngeal disease-specific terms with treatment-specific terms and search-specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, RCTs and clinical trials.

Study selection
Study designs of evaluations included in the review
Practice guidelines, systematic reviews, meta-analyses and randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies were eligible if they compared patients who were receiving any combination of chemotherapy and radiation in the neoadjuvant, concurrent or adjuvant setting with a control group receiving radiotherapy alone. Chemotherapy with cisplatin was the most common, but three trials used non-cisplatin-based chemotherapy. Normally fractionated radiotherapy predominated, but two trials used larger than standard fractionation. Chemotherapy was delivered with radiotherapy in the neoadjuvant (8 RCTs), concurrent (4 RCTs) and adjuvant settings (3 RCTs), or was delivered in the neoadjuvant and adjuvant setting (2 RCTs) or as concurrent adjuvant therapy (2 RCTs). One trial reported as an abstract did not report the timing of the chemotherapy, while another failed to report the chemotherapy used; this latter trial and two others did not describe the fractionation schedule used.

Participants included in the review
Only studies of newly diagnosed adult patients with locally advanced (stage III or IV) squamous cell or undifferentiated nasopharyngeal cancer were included. Studies that did not report separate results for patients with nasopharyngeal cancer were excluded.

Outcomes assessed in the review
The primary outcomes were disease-free survival and/or overall survival. The secondary outcomes of interest were local control, response, toxicity and quality of life.

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

The authors appear to have graded the quality of the included studies by comparing their description of the methods used on the basis of the following: method of randomisation, stratification, blinding, source of funding, sample size calculation, intention-to-treat analysis, and the reported completeness of follow-up. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis

How were the studies combined?
The studies were pooled using a random-effects model. The survival curves crossed in 7 RCTs, indicating that the assumption of a constant hazard ratio had been violated. Therefore, the proportion of patients who relapsed and those who died at a specified time point were pooled across studies. To avoid error associated with loss to follow-up or patient censoring, a common time point of 2 years was selected, as most of the RCTs reported sufficient follow-up (greater than 50%) at 2 years and 2-year survival is a clinically reliable point for relapse and/or recurrence. Where 2-year survival data were not reported, the data were estimated from published survival curves. Authors were also contacted for missing data. The outcomes were reported in terms of the odds ratio (OR) and the number-need-to-treat (NNT), along with 95% confidence intervals (CIs), calculated using the inverse of the risk difference. RevMan software was used.

How were differences between studies investigated?
Heterogeneity was assessed statistically using the chi-squared test.

Results of the review

Seventeen RCTs (13 published and 4 in abstract form) with 20 comparisons were included in the review. Two meta-analyses were also included, one of which only included primary studies included in this review.

Disease-free survival.
The data from 12 studies (14 comparisons) were pooled at 2 years. The pooled data suggested that patients treated with radiochemotherapy had higher rates of disease-free survival than those treated with radiotherapy alone (OR 0.69, 95% CI: 0.54, 0.87, P=0.002); however, significant heterogeneity was detected (chi-squared 26.98, d.f.=13, P=0.013). The NNT was 13 (95% CI: 7, 33). The differences were not significant for adjuvant chemotherapy alone or in combination with neoadjuvant therapy. A sensitivity analysis was conducted in which a study with an outlying treatment effect was removed. The heterogeneity was no longer apparent (P=0.66). The OR and NNT remained significant (OR 0.75, 95% CI: 0.64, 0.88, P=0.003; NNT 14, 95% CI: 10, 33).

Radiochemotherapy was significantly superior to radiotherapy alone; more specifically, for neoadjuvant chemotherapy (OR 0.77, 95% CI: 0.59, 0.99, P=0.04; NNT 17), concurrent chemotherapy (OR 0.62, 95% CI: 0.45, 0.86, P=0.004; NNT 10) and concurrent adjuvant chemotherapy (OR 0.32, 95% CI: 0.11, 0.95, P=0.04; NNT 4).

Overall survival.
The data from 13 studies (15 comparisons) were pooled at 2 years. The pooled data suggested that patients treated with radiochemotherapy showed a trend towards higher rates of overall survival than those treated with radiotherapy alone (OR 0.77, 95% CI: 0.59, 1.01, P=0.06); however, significant heterogeneity was detected (chi-squared 24.07, d.f.=14, P=0.045). A sensitivity analysis was conducted in which a study with an outlying treatment effect was removed. The heterogeneity was no longer apparent (P=0.38). The OR was still not significant (OR 0.85, 95% CI: 0.69, 1.06, P=0.14).

Radiochemotherapy was significantly superior to radiotherapy alone; more specifically, for concurrent chemotherapy (OR 0.42, 95% CI: 0.23, 0.76, P=0.004; NNT 10) and concurrent adjuvant chemotherapy (OR 0.31, 95% CI: 0.17, 0.85).
Other arrangements of radiotherapy and chemotherapy were not found to have significant differences with standard timing arrangements.

In terms of treatment-related death, 8 of the 17 RCTs reported rates of death owing to treatment. The death rates ranged from 0 to 8% for patients in the radiochemotherapy arms compared with 0 to 2.5% for patients in the radiotherapy arms. The differences in death rates were significant in only one trial; this trial used an aggressive chemotherapy regimen. With the exception of significantly greater mucositis in the radiochemotherapy arm of one trial, acute radiation toxicity (where reported) did not differ significantly between any of the treatment groups.

The authors also tabulated a summary of the findings of two meta-analyses (see Other Publications of Related Interest).

**Authors’ conclusions**

Cisplatin-based concurrent radiochemotherapy should be routinely offered to patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV).

**CRD commentary**

The pre-specified inclusion and exclusion criteria were reported clearly and the literature search was fairly comprehensive. Details of the methodology of the review process, such as how many reviewers were involved in selecting the studies and extracting the data, were not presented. The information on the included studies was limited. While the review only included RCTs and the validity of these studies was investigated by assessing items which have been validated, the authors did not state how these items were used to assess quality, nor what the results of this quality assessment exercise were. Thus, it is unclear whether the assessment was appropriate. This limits any assessment of the reliability of the results. However, the authors’ conclusions follow from the results as they are presented.

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

Practice: The authors recommended that cisplatin-based concurrent radiochemotherapy be routinely offered to patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV). Of the two trials with cisplatin-based concurrent chemotherapy that showed a significant improvement, one included adjuvant chemotherapy while the other did not. It was therefore recommended that either regime may be offered to this patient population.

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

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**Other publications of related interest**

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