The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature


CRD summary
This reasonably well-conducted review assessed the addition of chemotherapy to radiation for the treatment of nasopharyngeal carcinoma. The authors found that concomitant chemotherapy was the most effective way to improve survival and to reduce the incidence of locoregional recurrences and distant metastases. However, the authors' conclusion regarding concomitant chemotherapy is based on the results of only 2 trials.

Authors' objectives
To assess the additional value of neoadjuvant, concomitant and adjuvant chemotherapy to radiotherapy in patients with nasopharyngeal cancer (NPC), with regard to improvement in overall survival and the incidence of locoregional recurrences (LRR) and distant metastases (DM).

Searching
MEDLINE, Cancerlit, Excerpta Medica and BIOSIS Previews were searched, as were reference lists of published reports, review articles and relevant books. Only published trials were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
To be eligible, the studies needed to assign patients to receive conventional radiotherapy alone (at least 66 Gy with conventional fractionation to the primary lesion) or to receive radiotherapy combined with chemotherapy. The included trials examined neoadjuvant, concomitant and adjuvant chemotherapy regimens, mostly cisplatin in combination with fluorouracil or other agents. The total doses of radiotherapy ranged from 66 to 70 Gy over 7 to 10 weeks.

Participants included in the review
To be eligible, the studies had to include patients with biopsy-proven NPC (WHO type 1 to 3) without distant metastases at presentation and who had been treated with definitive radiation.

Outcomes assessed in the review
The main outcome was overall survival, defined as the time from random assignment to death. The secondary outcomes were the incidence of local and/or regional recurrence and DM.

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 quality of the studies was assessed, based on the following criteria: description of selection criteria, withdrawals after randomisation, randomisation procedure, power analysis before the study, distribution of pre-treatment variables, and intention-to-treat analysis.

Two reviewers evaluated the quality of the studies independently.

Data extraction
The authors did not state how many authors extracted the data. For survival data, hazard ratios (HRs) and their variance were obtained directly from trial reports or were taken indirectly from survival curves and/or P-values. For the incidence of LRR and DM, the relative risk (RR) was calculated.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined in a meta-analysis. The pooled HR was calculated using a fixed-effect model, weighted according to study variance. The absolute difference in overall survival after 3 years was calculated using the pooled HR and the survival rate in the radiotherapy group, assuming proportional hazards.

**How were differences between studies investigated?**

Subgroup analyses were conducted by type of chemotherapy regimen: neoadjuvant; at least concomitant and adjuvant chemotherapy. A chi-squared test of statistical heterogeneity was conducted.

**Results of the review**

Ten randomised trials (2,458 patients) were included.

A variety of quality issues were identified in the included studies. In particular, only 3 studies clearly described the randomisation procedure, five had no sample size calculation, and six did not report if the analysis was intention-to-treat.

Nine of the 10 studies reported data on overall survival. A survival benefit for chemotherapy was observed (pooled HR of death 0.82, 95% confidence interval, CI: 0.71, 0.95, P=0.01). The estimated absolute survival difference after 3 years was 4%. For concomitant chemotherapy (2 studies), the pooled HR was 0.48 (95% CI: 0.32, 0.72) with a survival benefit of 20% after 3 years. No statistically significant effect on survival was observed with neoadjuvant or adjuvant chemotherapy.

A statistically significant benefit of additional chemotherapy was observed in relation to LRR (RR 0.68, 95% CI: 0.58, 0.79, P<0.0001). Both neoadjuvant and concomitant chemotherapy were associated with statistically significant reductions in LRR, but no such beneficial effect was observed with adjuvant therapy. A statistically significant benefit of additional chemotherapy was also observed for DM (RR 0.72, 95% CI: 0.62, 0.84, P=0.0003). Both neoadjuvant and concomitant chemotherapy were associated with statistically significant reductions in DM but, again, no beneficial effect was observed with adjuvant therapy.

**Authors’ conclusions**

Concomitant chemotherapy in addition to radiation is the most effective way to improve overall survival in NPC.

**CRD commentary**

The authors had a clear review question with defined inclusion criteria for the participants, intervention, study design and outcomes. The searches encompassed a range of databases although only published material was eligible, opening up the possibility of publication bias. It was reported that two authors conducted the quality assessment, but similar details of the study screening and data extraction processes were not reported. Study quality was assessed using appropriate criteria. The methods of analysis seemed reliable although there were limited study details. This was a reasonably well-conducted review and the results appear reliable. However the authors’ conclusion regarding concomitant chemotherapy is based on the results of only 2 trials.

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

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

Research: The authors stated that the addition of induction chemotherapy to concomitant chemoradiotherapy merits...
further investigation.

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