Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients

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CRD summary
This well-conducted individual patient data meta-analysis combined data from 87 trials and demonstrated the additional effectiveness of chemotherapy over loco-regional treatment alone for patients with head and neck cancer. Concomitant therapy appeared superior to induction chemotherapy, but was less effective amongst older patients. These conclusions are likely to be reliable, but some uncertainty surrounds the subgroup analyses.

Authors' objectives
To update a previously published individual patient data meta-analysis of the effect of chemotherapy on survival in patients with head and neck cancer.

Searching
Searches of MEDLINE, CLINPROT, PDQ, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (search dates unreported) were supplemented with handsearches of references in reviews and meeting abstracts. Search terms were not reported. Experts and trialists were asked to identify relevant trials.

Study selection
Randomised trials were eligible if they accrued previously untreated patients with head and neck cancer and compared chemotherapy and loco-regional treatment with loco-regional treatment alone. The primary outcome was overall survival. Event-free survival, cancer and non-cancer mortality, cumulative loco-regional and distant failure were secondary endpoints.

Trials that included only nasopharyngeal carcinomas were excluded.

Median follow-up was 5.6 years. Seventy-four per cent of patients were over 50 years old and 84% were male. Nine per cent had stage I or II cancer, 31% had stage III and 60% had stage IV. Poly chemotherapy (mainly 5-FU and/or Platin) and unspecified mono chemotherapies were the main types of chemotherapy in the included trials.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Individual patient data were obtained and checked for internal consistency and compared to trial protocols and publications. Trialists resolved discrepancies and verified the final dataset.

Data extraction
Trialists were asked to provide individual patient data that specified age, sex, tumor site, TNM Classification of Malignant Tumors or stage, performance status, treatment allocated, date of randomisation, date and site of first recurrence, date of second primary cancer, survival status, date of last follow-up and cause of death (where available).

Methods of synthesis
Time to event data were extracted for each endpoint on the basis of intention to treat and used to calculate hazard ratios. Survival curves were were generated using the Kaplan-Meier method. Hazard ratios (HR) were pooled using two stage meta-analysis based on a common effect stratified by trial. Subgroup analyses were undertaken by examining covariates stratified by trial and performing tests for interaction. Subgroups were based on sex, performance status, stage, tumour site and age as well as group level covariates based on the timing (concomitant, induction or adjuvant) and type (single or combination) of chemotherapy. I^2 was used to quantify heterogeneity.

Results of the review
Individual patient data was obtained from 87 trials (16,485 patients).

Chemotherapy increased overall survival (HR 0.88, 95% CI 0.85 to 0.92) with an absolute benefit of 4.5% at five years. Event-free survival was increased by chemotherapy (HR 0.87, 95% CI 0.84 to 0.90). There was significant heterogeneity ($I^2=41\%$) for overall survival, which was explained in part by timing. There was a statistically significant benefit of concomitant chemotherapy on overall survival (HR 0.81, 95% CI 0.78 to 0.86), but not for induction chemotherapy (HR 0.96, 95% CI 0.90 to 1.02).

A subset of six trials allowed direct comparison of timing. There was no benefit of concomitant chemotherapy for overall survival (HR 0.88, 95% CI 0.77 to 1.04), but improved outcomes for event-free survival (HR 0.81, 95% 0.69 to 0.96) and loco-regional failure (HR 0.77, 95% CI 0.64 to 0.92).

Within concomitant chemotherapy there was a decreasing effect of chemotherapy with age (p=0.003). Other individual patient characteristics were not significant.

**Authors’ conclusions**
Chemotherapy resulted in higher overall survival and lower recurrence than loco-regional treatment alone. Concomitant therapy was superior to induction chemotherapy for survival, event-free survival and loco-regional failure. The benefit of concomitant therapy was less in older patients.

**CRD commentary**
This robust individual patient data meta-analysis combined data from 87 trials and demonstrated the additional effectiveness of chemotherapy over loco-regional treatment alone for patients with head and neck cancer.

A search of multiple databases was undertaken. Few details of the search were reported. The number of patients excluded because data were unavailable was not stated. Validity assessment and use of intention-to-treat data minimised potential quality biases. The two-stage methods used to pool results were appropriate for deriving overall effects and subgroup effects were tested for interactions. There was potential for uncertainty regarding the subgroup analyses given the number of potential interactions and analyses in such a large complex dataset. In particular, age was not considered as a continuous variable and may interact with the timing of chemotherapy. The superiority of concomitant chemotherapy relied on indirect comparison with respect to overall survival as the direct comparison did not illustrate a significant difference.

The results and conclusions of this high-quality review are likely to be reliable.

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

**Practice:** Mono chemotherapy with drugs other than cisplatin should not be recommended in routine practice.

**Research:** Ongoing trials to evaluate induction chemotherapy before concomitant chemotherapy were justified and should include a concomitant chemoradiotherapy arm.

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**Bibliographic details**

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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.