Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

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Authors' objectives
To assess the effect on survival of chemotherapy added to locoregional treatment for non-metastatic head and neck squamous-cell carcinoma.

Searching
MEDLINE and EMBASE were searched (the search strategies were not reported). These were supplemented with handsearches of conference abstracts and reference lists of review articles. The trial registers managed by the National Cancer Institute (PDQ and CLINPROT) were also searched and experts, pharmaceutical companies and those conducting trials in the field were consulted.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) with concealed allocation to treatment group, which were conducted between 1 January 1965 and 31 December 1993.

Specific interventions included in the review
Studies of any of the following interventions were eligible for inclusion:

- locoregional treatment plus chemotherapy compared with locoregional treatment alone;
- neoadjuvant chemotherapy plus radiotherapy compared with concomitant or alternating radiochemotherapy;
- radical surgery plus radiotherapy compared with neoadjuvant chemotherapy plus radiotherapy in responders, or radical surgery and radiotherapy in nonresponders.

The trials included under the first criteria used four different types of chemotherapy: platin and fluorouracil; polychemotherapy with platin; polychemotherapy without platin; and monochemotherapy. The timing of this therapy was adjuvant, neoadjuvant or concomitant.

Participants included in the review
Previously untreated patients with non-metastatic head and neck squamous-cell carcinoma (tumours of the oral cavity, oropharynx, hypopharynx and larynx) were eligible for inclusion. Patients who had been treated for another cancer, or who had nasopharyngeal carcinomas, were excluded.

Outcomes assessed in the review
The inclusion criteria for the outcomes were not specified. The primary outcome of interest was overall survival. For the review question on larynx preservation, a secondary outcome of disease-free survival was also assessed. This took local or distant recurrence, a secondary primary and death into account.

How were decisions on the relevance of primary studies made?
The authors did not explicitly state how decisions on the relevance of the studies were made.

Assessment of study quality
Internal consistency checks were conducted and the data were compared with the trial protocol and published reports. Ranges were checked and any extremes were checked with the trial authors. The data analysis was conducted separately for each individual trial and the trial investigators then reviewed the survival analyses. The authors did not state explicitly how judgements of validity were made, in terms of who made the decisions or the criteria used.
Data extraction
Data on patient age, gender, tumour site, tumour-node-metastasis classification or stage, histology, performance status, allocated treatment, date of randomisation, date and site of the first recurrence and second primary, were obtained from the trial investigators. Updated data were obtained for survival status and date of last follow-up.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis of IPD. The studies were combined in three separate meta-analyses to address the three review questions. Data were analysed on an intent-to-treat basis. The log rank observed minus expected number of deaths (O-E) and its variance were used to calculate hazard ratios (HRs) for each individual trial, which were then pooled in a meta-analysis using a fixed-effect model. The absolute differences at 2 and 5 years were calculated with the baseline event rate in the control arm and the HR. Non-stratified Kaplan-Meier curves were provided for the treatment and control groups.

How were differences between studies investigated?
The trials in the main meta-analysis, which examined the effects of chemotherapy on survival, were stratified according to the timing of chemotherapy: adjuvant, neoadjuvant, and concomitant. They were also stratified according to the type of chemotherapy used.

Chi-squared tests were used to assess heterogeneity. The relationship between treatment and particular covariates (age, gender, performance status, stage, site) was investigated. A sensitivity analysis was also carried out; further information on this is available on The Lancet website, although a subscription may be required for access.

Results of the review
IPD from 63 RCTs (n=10,741) were included in a meta-analysis on the effects of chemotherapy on survival; a second meta-analysis with 6 RCTs (n=861) assessed the effect of the timing of chemotherapy on survival; a third meta-analysis with 3 RCTs (n=602) assessed larynx preservation.

Effect of chemotherapy on survival (63 trials).
At the 2- and 5-year follow-up, there was a survival benefit in favour of chemotherapy with locoregional treatment in comparison with locoregional treatment alone: the HR of death was 0.90 (95% confidence interval, CI: 0.85, 0.94, P<0.0001). The absolute survival benefit at both follow-up points was 4%: from 50 to 54% at 2 years, and from 32 to 36% at 5 years. There was statistically-significant heterogeneity between the trials (P<0.0001) and for chemotherapy timing (P=0.005). The stratified analysis for the timing of chemotherapy indicated no significant benefit of chemotherapy adjuvant (8 trials) or neoadjuvant (31 trials) to locoregional treatment. There was a significant overall benefit of chemotherapy in the concomitant trials (26 trials), but there was statistically-significant heterogeneity. The authors stated that a sensitivity analysis supported the overall findings and confirmed the uncertainty of the findings in the concomitant group.

Effect of timing of chemotherapy on survival (6 trials).
The participants in this group of trials were older and had tumours at a higher stage than in the first meta-analysis. The pooled HR death favoured concomitant or alternating chemotherapy, though this was not statistically significant: HR 0.91 (95% CI: 0.79, 1.06, P=0.23). There was a survival benefit of 3% at both follow-up points. There was no statistically-significant heterogeneity.

Larynx preservation (3 trials).
There was a non significant trend in favour of the control group in comparison with the chemotherapy group: HR 1.19 (95% CI: 0.97, 1.46, P=0.1). Survival was reduced by 6% (from 45 to 39%) in the chemotherapy group at the 5-year follow-up. There was statistically-significant heterogeneity between the trials (P=0.05).

Authors' conclusions
The authors concluded that there was only a small benefit on survival when chemotherapy was added to locoregional
treatment in patients with non-metastatic head and neck squamous cell carcinoma, therefore, the routine use of chemotherapy in this situation is debatable. They pointed out that most of the benefit was due to the concomitant or alternating radiochemotherapy, although it was difficult to draw firm conclusions about this therapy because of the heterogeneity between the trials. The authors also concluded that, given the non significant negative effect of chemotherapy in the larynx preservation trials, this procedure must remain investigational.

CRD commentary
The review addressed a clear question in terms of the intervention, participants and study design. The inclusion criteria for the outcomes were not specified, but the authors clearly identified the primary outcome of interest. Relevant databases were searched and the authors attempted to identify unpublished data. The authors also reported the number of patients for whom data were unavailable. The validity of eligible trials was assessed through checking, reanalysing the raw data and communicating with trial investigators to resolve any problems. The data were analysed using appropriate techniques for the meta-analyses and heterogeneity was assessed. Significant heterogeneity was present and the implications of this for the interpretation of pooled estimates were appropriately discussed. The authors' conclusions are supported by the evidence presented.

Implications of the review for practice and research
Practice: The authors made a number of statements in relation to implications for practice. Namely, the routine use of chemotherapy in patients with non-metastatic head and neck squamous cell carcinoma is debatable; adjuvant and neoadjuvant modalities should not be used outside of clinical trials, as they were not shown to provide significant benefit; and larynx preservation must remain investigational.

Research: The authors stated that future trials on larynx preservation should be adequately powered to enable the treatment effect to be evaluated by site and subsite. In relation to chemotherapy in patients with non-metastatic head and neck squamous cell carcinoma, the authors stated that it was important that future trials evaluate morbidity, quality of life and cost-benefit, and that they focus on concomitant/alternating radiochemotherapy.

Bibliographic details

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Additional Data URL
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)72561-7/fulltext

Other publications of related interest

Additional data relating to this study are available on the following website: http://www.sciencedirect.com/science/article/pii/S0140673600900114 [accessed July 2014].

Indexing Status
Subject indexing assigned by NLM

MeSH
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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.