The role of neoadjuvant chemotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck (excluding nasopharynx)

Head and Neck Cancer Disease Site Group

CRD summary
This review was undertaken to update practice guidelines. It found that neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced squamous cell carcinoma of the head and neck (excluding nasopharynx), if the main objective is improved survival. Although information on the methods used was sparse, the findings are likely to be valid.

Authors' objectives
To assess the role of neoadjuvant chemotherapy for patients with locally advanced squamous cell head and neck cancer, other than nasopharyngeal cancer.

Searching
MEDLINE was searched from 1980 to January 2003; the search terms were provided. Cancerlit (to October 2002), the Cochrane Library (Issue 4, 2002), PDQ, and clinical trial and practice guideline Internet sites were also searched, as were abstracts published in the proceedings of the annual meetings of relevant societies (details provided. Article bibliographies and personal files were also searched to November 2002. The search was restricted to English language publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of neoadjuvant chemotherapy prior to local treatment with conventional radiation and/or surgery versus local treatment alone as the control, were eligible for inclusion. Abstracts published in 1994 or later were included if their data could be extracted for analysis.

Specific interventions included in the review
Studies were excluded if chemotherapy was not the first modality used, if the control arm did not use conventional radiotherapy with or without surgery, if chemotherapy was used either with alternating or concurrently with radiation, or if intra-arterial chemotherapy was used.

Participants included in the review
Only studies of patients with squamous cell carcinomas of the head and neck region without distant metastases were considered for inclusion. Studies where a significant fraction of the patients had nasopharynx cancer were excluded. No information on the participants of the included studies was presented. Trials were excluded if they concerned recurrent or metastatic disease, or if the patients had undergone prior treatment.

Outcomes assessed in the review
An inclusion criterion relating to the outcomes was not reported. The outcomes in the included studies were reported in terms of the odds ratio with 95% confidence intervals (CIs).

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 did not state that they assessed validity.
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 primary results were obtained from a published pooled analysis of IPD that included the other studies located by the review.

How were differences between studies investigated?
Differences between the included studies were discussed narratively.

Results of the review
Three systematic reviews and 23 primary studies were located. Data from a number of primary studies were included in the most rigorous systematic review, which used individual patient data (IPD) pooling as opposed to a statistical pooling of the published results; these primary studies were not considered separately. The updated literature search located 3 additional meta-analyses, 12 new or updated primary studies and a quality-of-life study.

Efficacy.
A meta-analysis using IPD from 31 RCTs (5,269 patients) demonstrated no significant survival benefit for neoadjuvant chemotherapy compared with locoregional treatment alone (hazard ratio, HR=0.95, 95% CI: 0.88, 1.01, P=0.10). However, a subgroup analysis of 15 RCTs (2,487 patients) detected significantly improved survival with neoadjuvant chemotherapy using fluorouracil in combination with either cisplatin or carboplatin (HR 0.88, 95% CI: 0.79, 0.97, P<0.05). IPD from 3 RCTs of larynx-preservation versus surgery were pooled in a separate analysis (602 patients). The HR for death, though non significant, favoured surgery over larynx preservation (HR 1.19, 95% CI: 0.97, 1.46, P=0.10).

Two additional RCTs found no significant survival benefit from the addition of neoadjuvant chemotherapy. An RCT, published in abstract form, compared 547 patients allocated to neoadjuvant chemotherapy, radiotherapy alone or concomitant chemotherapy and radiotherapy in a trial of larynx preservation. There were no significant differences between patients randomised to neoadjuvant therapy or to radiotherapy alone in terms of 5-year overall survival (both about 75%; P not reported), locoregional control (61% versus 56%; P not reported), or the number of laryngectomies (43 versus 49; P not reported). Patients allocated to the concomitant treatment arm had similar overall survival, but significantly greater locoregional control and laryngectomy preservation than patients in the other two treatment arms.

Quality of life.
Of the 76 survivors who had participated in the Veterans Affairs Laryngeal Cancer Study, 46 completed health status assessment instruments, including a validated head and neck cancer-specific quality of life questionnaire. Of the 46 respondents, 21 had been randomised to neoadjuvant chemotherapy in combination with radiotherapy and 25 to surgery and radiotherapy. Scores on the mental health and pain domains were significantly better for patients randomised to neoadjuvant chemotherapy and radiation than for those randomised to surgery and radiation (P<0.05).

Authors' conclusions
Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced squamous cell carcinoma of the head and neck if the main objective is improved survival.

CRD commentary
The pre-specified inclusion and exclusion criteria were clearly reported. The literature search was acceptable, but could have included other databases such as EMBASE. The inclusion of non-English language studies would have been
beneficial. Details on the methodology of the review process were not presented. The information on the treatment regimens used and the included participants was limited. While the review only included RCTs and systematic reviews, and the primary results derived from one of the reviews, the validity of these studies was not investigated and few details of them were reported.

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

Practice: Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced squamous cell carcinoma of the head and neck if the main objective is improved survival.

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

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