Preoperative chemoradiotherapy in the management of oral cancer: a review

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CRD summary
This review assessed the effects of preoperative chemoradiotherapy and/or preoperative radiotherapy on the management of oral cancer and concluded that evidence to provide sufficient data from prospective randomised studies was missing. The authors' conclusions reflect the evidence presented, but their reliability is uncertain due to lack of validity assessment and inclusion of study designs that lack robustness in their methodology.

Authors' objectives
To compile evidence regarding the effects of preoperative chemoradiotherapy in the management of oral cancer.

Searching
PubMed was searched for studies published in European languages between 1985 and 15 July 2005; EMBASE and the ISI Web of Science were searched with the same date and language restrictions. Search terms used for the PubMed searches were stated. Reference lists of retrieved included studies were searched for further relevant studies.

Study selection
Eligible studies were of any design and had to have the characteristics: tumours in the oral cavity and oropharynx had to constitute less than 45% of the total tumour; the primary tumour was not diagnosed as advanced squamous cell carcinoma; patients had to be treated with preoperative chemoradiotherapy or preoperative radiotherapy; and the study had to report survival rates. Studies were excluded if they overlapped with included studies.

Studies locations included Austria, Denmark, Germany, Hungary, Italy, Japan, Spain, Sweden and USA. On average and where reported, median age of participants was 57.2 years (range 18 to 96 years). Most patients had oral cancer exclusively or were either stage III or stage IV. Enrolment periods ranged from 1969 to 2000. Most studies did not attempt organ preservation. Most studies evaluated chemoradiotherapy; the other studies evaluated radiotherapy or a mixture of chemoradiotherapy and radiotherapy. Further treatment details were reported.

Two reviewers selected papers for inclusion.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
Three reviewers independently extracted data required to calculate (median) survival rates, with 95% confidence intervals (CIs), for the longest available period; disagreements were resolved by consensus.

Methods of synthesis
The review stated that the longest reported median survival rates (with 95% CIs) from studies were pooled using what appeared to be fixed-effect inverse variance meta-analyses. Heterogeneity was assessed using the I² and Q statistics; a threshold of p<0.05 indicated whether studies were heterogeneous.

Ecologic regression analyses were performed to assess the effect on survival rates of study characteristics such as study age (median study enrolment period), whether an organ preservation protocol was used and whether the preoperative protocol was radiotherapy or chemoradiotherapy.

Results of the review
Thirty-two studies (n=2,978, range 20 to 430) were included in the review: three prospective randomised studies (n=676); 15 prospective non-randomised studies (n=948); and 14 retrospective analyses of consecutively treated patients (n=1,354). The median follow-up period was 47 months (range 20.4 to 84.6 months) where reported.
Meta-analyses of median survival rates following preoperative chemoradiotherapy and/or preoperative radiotherapy indicated: a one-year survival rate of 83.00% (95% CI 70.55 to 95.45%; one study, $I^2$ not applicable); a two-year survival rate of 64.51% (95% CI 57.95 to 71.07%; four studies, $I^2$=0%); a three-year survival rate of 70.44% (95% CI 67.38% to 73.50%; 13 studies, $I^2$=84.5%); a four-year survival rate of 48.81% (95% CI 39.03% to 58.58%; two studies, $I^2$=93.0%); and a five-year survival rate of 54.87% (95% CI 51.61% to 58.12%; 12 studies, $I^2$=83.7%)

Results of meta-regression analysis were reported.

**Authors' conclusions**
Hard evidence that provided sufficient data from prospective randomised studies was missing for preoperative chemoradiotherapy.

**CRD commentary**
This review addressed a clear review question using appropriate study selection criteria. Several relevant sources were searched. Some attempts made to reduce language bias. No efforts to reduce publication bias were reported. No study quality assessment was reported, so the risk of bias due to poor quality studies could not be ruled out. The review included a large number of retrospective studies and studies that used uncontrolled and non-randomised designs, which have multiple biases. Appropriate methods were used to reduce reviewer error and bias in study selection and data extraction. Sufficient primary study details were reported. The synthesis generally appeared appropriate. Most pooled results reported high levels of statistical heterogeneity, so a random-effects model may have been more appropriate.

The authors' conclusions reflect the evidence presented, but their reliability is uncertain due to lack of validity assessment and inclusion of study designs that lack robustness in their methodology.

**Implications of the review for practice and research**
*Practice:* The authors stated that the findings of the review did not justify any treatment recommendations.

*Research:* The authors stated that prospective randomised studies that compared five-year survival rates after preoperative chemoradiotherapy or radiotherapy were essential

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