Defining the optimal treatment of locally advanced esophageal cancer: a systematic review and decision analysis

CRD summary
This review, which assessed the effectiveness of treatments for locally advanced oesophageal cancer, concluded that chemoradiotherapy followed by surgery maximises quality-adjusted life-years, except in certain patients when surgery alone may be the preferred option. Overall, these conclusions are based on modelling data and survival data from trials directly comparing the different treatment modalities and which have methodological limitations that may limit their reliability.

Authors' objectives
To identify the most effective treatment for locally advanced oesophageal cancer.

Searching
MEDLINE/PubMed (1966 to October 2004), EMBASE (1980 to October 2004), CINAHL (1982 to October 2004), the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched. In addition, study bibliographies were searched and experts in the field contacted. The search strategy is available on request.

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

Specific interventions included in the review
Studies comparing surgery alone with either chemoradiotherapy followed by surgery, chemotherapy followed by surgery, or surgery with adjuvant chemoradiotherapy, were eligible for inclusion. The included studies identified the following surgical procedures: right thoracotomy, laparotomy, surgeon's choice, transhiatal or transthoracic. Radiotherapies included treatment with 20 to 45 grays; chemotherapy was usually with cisplatinum alone, or with cisplatinum or cisplatin in combination with fluorouracil, vinblastine, leucovorin and/or bleomycin. Treatment durations varied between 2 and 3 cycles or 21 days, and doses varied by treatment type; further details were provided in the review.

Participants included in the review
Studies involving patients with locally advanced oesophageal cancer, defined as malignant disease in the mid or lower third of the oesophagus or gastro-oesophageal junction and regional lymph nodes (clinical stages T2N0M0, T3N0M0, T1N1M0, T2N1M0 and T3N1M0) were eligible for inclusion. Studies involving patients receiving palliative treatment were excluded. The majority of included patients had cancers of squamous origin.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported survival and quality of life as the primary outcome. The included studies also reported health-related quality of life (HRQOL), which was measured using the 36-item Short-Form health survey. Follow-up was from 6 to 36 months.

How were decisions on the relevance of primary studies made?
One reviewer screened studies for relevance.

Assessment of study quality
Two reviewers independently assessed validity according to the Jadad checklist.

Data extraction
Two reviewers extracted the data from the included studies, with consensus reached through discussion. Dichotomous
data on mortality were converted into relative risks (RRs) with 95% confidence intervals (CIs), while HRQOL measures were converted into utility scores, with 0 representing death and 1 perfect health.

**Methods of synthesis**

**How were the studies combined?**

RRs of mortality were pooled using a random-effects model where appropriate. An assessment of publication bias was not reported. Survival and utility data were combined and used in a decision analysis.

**How were differences between studies investigated?**

The chi-squared test was used to assess statistical heterogeneity. The effects of treatment type and varying baseline mortality estimates on the quality-adjusted life-years (QALYs) gained and survival were modelled.

**Results of the review**

Twelve RCTs (reported as 14) were included in the review (1,359 received surgery and 1,390 received the comparator). The included studies scored between 1 and 3 on the Jadad scale for quality. The sample size ranged from 22 to 402 participants.

Based on RRs, only one comparison, which compared surgery with the other multimodal therapies, resulted in a statistically significant difference in survival. This favoured surgery over surgery and chemotherapy at 12 to 36 months' follow-up (RR 0.72, 95% CI: 0.59, 0.89). This, however, was based on only one RCT. The remaining comparisons at 0 to 6 months, 6 to 12 months and 12 to 36 months' follow-up failed to find statistically significant differences between surgery and multimodal therapies. All comparisons were subject to significant statistical heterogeneity (p=0.001).

**Cost information**

Utilities were modelled using a Markov process. The QALYs gained were 2.07 (95% CI: 2.01, 2.12) for surgery alone, 2.18 (95% CI: 1.77, 2.59) for chemoradiotherapy followed by surgery, 2.12 (95% CI: 1.55, 2.69) for chemotherapy followed by surgery and 1.99 (95% CI: 1.91, 2.07) for surgery with adjuvant chemoradiotherapy. Further analyses for QALYs were reported in the paper. There was no decrease in utility estimates after 12 months.

**Authors' conclusions**

Chemoradiotherapy followed by surgery is effective in increasing QALYs in patients with locally invasive oesophageal cancer, but patients potentially at risk from multimodal treatments may benefit from surgery alone.

**CRD commentary**

The review question was clear and was supported by appropriate inclusion criteria. Relevant literature searches were undertaken using several electronic databases. In addition, manual searches were carried out using the references from original articles. It is unclear whether publications were restricted by language, which means language bias cannot be ruled out. This, together with the fact that there was no apparent search for unpublished material, means it is possible that relevant papers were missed. Validity was assessed according to published criteria. Although attempts were made to minimise error and bias during the data extraction and validity assessment processes, only one reviewer determined eligibility in the study selection process.

Appropriate methods were used to pool the results, although survival data were reported as RRs and not the preferred hazard ratios. Statistical heterogeneity was investigated and shown to be significant for the pooled survival data and potentially important clinical characteristics were not reported, making it difficult to assess the reliability of the pooled data. The included survival studies had several methodological limitations and few were of high quality, which again makes the reliability of these data unclear. The reliability of data from the decision model was also unclear as it used utility estimates from varying sources, as the authors acknowledged. Overall, the authors’ conclusions are based on modelling data and survival data from trials directly comparing the different treatment modalities, and which have methodological limitations that may limit their reliability.
Implications of the review for practice and research

Practice: The authors stated that clinical uncertainties in the estimates of utility scores may influence the type of treatment chosen.

Research: The authors stated that future studies should research HRQOL to identify more reliable assessment tools. Studies assessing the cost-effectiveness of different treatments would also be beneficial.

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