Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis
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CRD summary
This review used meta-analysis to assess the effect of pre-operative chemoradiotherapy and chemotherapy on the survival of patients with cancer of the oesophagus. Both pre-operative treatments significantly improved survival compared with surgery alone. The review comes from a reputable source, but it was not reported sufficiently well to be certain that the conclusions are reliable.

Authors' objectives
To use meta-analysis to clarify the survival benefits of neoadjuvant chemoradiotherapy or chemotherapy for oesophageal carcinoma.

Searching
MEDLINE, Cancerlit and EMBASE were searched for studies not already identified from previous systematic reviews and meta-analyses, or abstracts from meetings between 1980 and 2006; the search terms were reported. The search was restricted to the English language but not by publication status.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCT) that used intention-to-treat (ITT) analysis were eligible for inclusion. However, one of the studies included in the review did not use ITT analysis.

Specific interventions included in the review
Studies of neoadjuvant chemoradiotherapy or chemotherapy (any regimen) followed by surgery compared with surgery alone as the initial management intervention were eligible for inclusion. Studies of concurrent and sequential chemoradiotherapy were included. Chemotherapy regimens varied; the most common involved two cycles of cisplatin and 5-fluorouracil.

Participants included in the review
Studies in patients with local operable oesophageal carcinoma (squamous cell carcinoma (SCC), adenocarcinoma or mixed tumours) were eligible for inclusion. Most of the included studies only enrolled patients with SCC, one was restricted to adenocarcinoma patients, and a few enrolled patients with either subtype. The median age of the patients (weighted by trial size) was 61 years (range: 32 to 69) for the chemoradiotherapy group and 63 years (range: 36 to 84) for the chemotherapy group; the corresponding ages in the surgery control groups were 62 years (range: 28 to 83) and 62 years (range: 30 to 80), respectively. All the participants had stages T0-3 N0-1 disease.

Outcomes assessed in the review
The primary outcome was all-cause mortality. The secondary outcomes were all-cause mortality for SCC and adenocarcinoma, and all-cause mortality by timing of chemotherapy with radiotherapy (concurrent or sequential). The median follow-up (weighted by trial size) was 55 months (range not reported) in studies of chemoradiotherapy and 37 months (range: 4 to 72) in studies of chemotherapy.

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 stated that a quality assessment was not formally incorporated because of variability in reporting.

**Data extraction**
Where possible, hazard ratios (HRs) and variances were extracted from publications or individual patient data (available for some of the trials), otherwise, other survival data (such as numbers of events and p-values) were extracted or taken from survival curves to calculate the HR and variance. The authors did not state how the data extraction was performed.

**Methods of synthesis**

**How were the studies combined?**

Meta-analysis was used to combine individual study HRs and 95% confidence intervals (CIs). Studies of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy were analysed separately. The studies were weighted by the inverse variance. The absolute benefit (risk reduction) was estimated from a weighted average of the actuarial 2-year survival rate in the control group combined with the pooled HR. Statistical tests were 2-sided and a p-value of 0.05 or less was statistically significant.

Publication bias was assessed using a funnel plot and by using the p-values reported in the published studies to estimate the number of unpublished studies there might be.

**How were differences between studies investigated?**

Details of the treatment regimens in each study were tabulated. A chi-squared test was used to assess statistical heterogeneity in the meta-analysis. Sensitivity analyses investigated the exclusion of unpublished studies, studies for which effect estimates were imputed, and a study that did not use ITT analysis. Subgroup analysis was used to investigate differences by tumour type, concurrent and sequential radiochemotherapy, and between studies started before 1994 and after 1993. Heterogeneity between subgroups was tested statistically.

**Results of the review**

Eighteen RCTs involving a total of 2,933 participants were included.

Most of the studies did not report details of the randomisation method; it was assumed nevertheless that allocation concealment was not compromised.

A meta-analysis of 10 RCTs (n=1,209) showed a statistically significant reduction in all-cause mortality with neoadjuvant chemoradiotherapy compared with surgery alone (HR 0.81, 95% CI: 0.70, 0.93, p=0.002). There was no statistically significant heterogeneity between the trials. The exclusion of two unpublished studies, and other sensitivity analyses, did not change the findings. The absolute difference in survival at 2 years was 13%, based on data from 8 RCTs. The number-needed-to-treat (NNT) to prevent one death was 8. The pooled effect estimates for SCC and adenocarcinoma were similar to the overall results.

A meta-analysis of 8 RCTs (n=1,724) showed a reduction in all-cause mortality with neoadjuvant chemotherapy compared with surgery alone that just reached statistical significance (HR 0.90, 95% CI: 0.81, 1.00, p=0.05). There was no statistically significant heterogeneity between the trials. The absolute difference in survival at 2 years was 7%. The NNT was 15. The pooled effect estimate for SCC showed no significant difference between neoadjuvant chemotherapy and surgery alone, but the one RCT restricted to adenocarcinoma showed a statistically significant benefit (HR 0.78, 95% CI: 0.64, 0.95, p=0.014).

Additional analyses were presented in the report.

Funnel plot evidence for publication bias was inconclusive. The number of unpublished studies was estimated to be nine for neoadjuvant chemoradiotherapy and none for neoadjuvant chemotherapy.

**Authors' conclusions**

There was a significant survival benefit with neoadjuvant chemoradiotherapy and, to a lesser extent, with neoadjuvant
chemotherapy in patients with adenocarcinoma of the oesophagus.

CRD commentary
The review addressed a clear question and stated the inclusion criteria. A reasonable number of sources were searched, but the pragmatic approach taken to identify relevant studies could have introduced citation bias and compounded the potential for English language bias. This could have made studies with non-significant findings less likely to be found. The report did not describe any procedures to minimise reviewer bias and errors in the study selection or data extraction processes. The included studies were summarised clearly. The extraction of data for the analysis appeared meticulous and the analysis thorough. The report did not, however, make explicit to what extent the analysis was defined a priori or if all the analyses conducted were reported. The absence of information on the quality of the included trials precludes an independent assessment of the potential for bias in the individual studies. The assumption that allocation concealment was not compromised is unsupported. This review came from a reputable source and, although it gave the impression of being well conducted, it was not well enough reported to be certain that the conclusions are reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that, in future, trials need rigorous staging of disease before entry and stratification and there should be strict surgical quality control.

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