Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

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CRD summary
This updated review found a significant survival benefit for adjuvant chemoradiotherapy or adjuvant chemotherapy followed by surgery over surgery alone for patients with oesophageal cancer. A clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy was not established. Limitations in the review process and the uncertain quality of included trials, mean the authors' main conclusions should be treated with caution.

Authors' objectives
To update a previous review (see Other Publications of Related Interest) that compared survival after neoadjuvant chemoradiotherapy or chemotherapy followed by surgery compared with surgery alone for the initial management of resectable oesophageal carcinoma. Also, to compare neoadjuvant chemoradiotherapy followed by surgery with chemotherapy followed by surgery.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for papers published in English since January 2006 to add to the studies from a previous systematic review. Search terms were reported. Only papers published in English were considered for inclusion. Abstracts of relevant conferences from January 2006 were handsearched. Authors of studies previously only available as abstracts were also contacted for updated publications.

Study selection
Randomised controlled trials (RCTs) of neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy (any regimen) followed by surgery versus surgery alone for the initial management of resectable oesophageal or oesophagogastric junction carcinoma were eligible for inclusion. Adult patients with squamous-cell carcinoma, adenocarcinoma, or mixed tumours were eligible. Included trials had to use an intention-to-treat analysis. All the studies included in the previous meta-analysis were also included. Two comparisons were made: neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy followed by surgery versus surgery alone; and neoadjuvant chemoradiotherapy followed by surgery versus neoadjuvant chemotherapy followed by surgery. The primary outcome was all-cause mortality. The secondary outcome for the comparison with surgery alone was all-cause mortality for each histological subtype (squamous-cell carcinoma or adenocarcinoma).

Half of the included trials compared neoadjuvant chemoradiotherapy followed by surgery with surgery alone; treatments were mostly concurrent, sequential in three trials. Most of the remaining trials compared neoadjuvant chemotherapy followed by surgery with surgery alone. A few trials compared chemoradiotherapy with chemotherapy. Radiotherapy schedules ranged from 20 to 50.4 Grey, with 1.2 to 3.7 Gy per fraction, over 12 days to six weeks. Most trials used two cycles of chemotherapy of cisplatin (20 to 120mg/m²) and fluorouracil at 1,000mg/m² (300 to 2,000mg/m²). The other chemotherapy drugs included bleomycin, paclitaxel, etoposide, carboplatin, vinblastine, vindesine and folinic acid; full details of the regimens were reported. Over half of the trials included patients with squamous-cell carcinoma, two trials included patients with adenocarcinoma, and the rest were of patients with both types of tumour. All patients had stages T0-3, N0-1 disease according to 2002 American Joint Committee on Cancer staging.

Two reviewers performed the literature search, but the authors did not report how many reviewers performed the study selection.

Assessment of study quality
A formal quality assessment was not performed, but two quality criteria were considered since trials were excluded if the randomisation method was not clear or they did not perform an intention-to-treat analysis.
Data extraction
Hazard ratios (HR) and associated variance were extracted from the published data or individual patient data. If this was not available, the hazard ratios were calculated using the methods of Parma et al. Authors were contacted to clarify data where necessary.

Two reviewers performed the extraction.

Methods of synthesis
For the comparisons of neoadjuvant chemoradiotherapy versus surgery alone and neoadjuvant chemotherapy versus surgery alone and the two treatments combined versus surgery alone, pooled hazard ratio estimates were calculated, with 95% confidence intervals (CI), using the weighted variance technique. Between trial heterogeneity was determined using $X^2$ and $I^2$.

To calculate the absolute risk reduction and number needed to treat (NNT), overall two-year survival rates were calculated for control groups using the mean of individual two-year survival rates weighted by sample size, and for intervention groups by applying the hazard ratio to the estimated control rate.

Direct (within individual trials) and indirect (between trials) comparisons were used to analyse neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy. Outcome differences in control groups were measured against the logarithm of the hazard ratio for each trial to give an estimate of the relationship between risk and benefit for neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy. Thirty-day postoperative or in-hospital mortality, with 95% confidence intervals, were also calculated. Histological subgroup analyses were not performed for this comparison.

Subgroup analyses were made for squamous-cell carcinoma, adenocarcinoma and for trials of both histological subtypes combined. Some sensitivity analyses were performed to find the effect of omitting individual trials.

Publication bias was assessed using the method of Gleser and Olkin. Fisher's failsafe N was calculated.

Results of the review
Twenty four trials were identified (4,188 patients, range 39 to 802) including 17 trials from the previous meta-analysis. All trials were RCTs, except for one 2x2 factorial study (159 patients). Median follow-up ranged from 7.5 to 106 months.

There was a significant improvement in all-cause mortality with neoadjuvant chemoradiotherapy compared with surgery alone (HR 0.78, 95% CI 0.70 to 0.88; $I^2$=33%; 13 trials). This treatment showed similar survival benefits in tumour type subgroup analyses for squamous-cell carcinoma (HR 0.80, 95% CI 0.68 to 0.93; $I^2$=0%; nine trials); adenocarcinoma (HR 0.75, 95% CI 0.59 to 0.95; $I^2$=36%; three trials); and combined squamous-cell carcinoma and adenocarcinoma (HR 0.74, 95% CI 0.59 to 0.93; $I^2$=78%; three trials).

The overall absolute survival benefit for neoadjuvant chemoradiotherapy compared with surgery alone was 8.7% at two years, with an number needed to treat of 11.

There was also a significant survival benefit (reduced all-cause mortality) for neoadjuvant chemotherapy compared with surgery alone (HR 0.87, 95% CI 0.79 to 0.96; $I^2$=43%; ten trials). Similar benefits were found for the subgroup analysis of adenocarcinoma alone (HR 0.83, 95% CI 0.71 to 0.95; $I^2$=29%; three trials), but the effect was not significant for the subgroup analysis for squamous-cell carcinoma alone ($I^2$=46%; nine studies). The overall absolute survival benefit for neoadjuvant chemotherapy compared with surgery alone was 5.1% at two years, with an number needed to treat of 19.

There was no significant difference in all-cause mortality between neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy when analysed as a direct comparison ($I^2$=0%; two trials), an indirect comparison (neoadjuvant chemoradiotherapy 12 groups versus neoadjuvant chemotherapy nine groups), or a combination of the two methods.

There was little association between risk of postoperative mortality (both in-hospital and 30-day) and neoadjuvant interventions.
The results of the sensitivity analyses were also reported.

There was no evidence of publication bias using Fisher’s failsafe N.

**Authors’ conclusions**
The updated meta-analysis provided strong evidence of the survival benefits of neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy over surgery alone in patients with oesophageal carcinoma. A clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy was not established.

**CRD commentary**
The review addressed a well-defined question for participants, interventions, study design and relevant outcomes. Relevant databases were searched. Unpublished studies were considered; there appeared to be minimal evidence for publication bias. Only studies published in English were included, so there was a risk of language bias. Review processes to reduce error and bias, such as independent duplicate study selection or data extraction, were not clearly reported.

A formal assessment of trial quality was not made and limited relevant details were provided, which made it difficult to assess trial quality. Statistical heterogeneity was assessed. Although there was evidence for moderate heterogeneity for some outcomes, the authors suggested that no significant heterogeneity was present. The statistical methods used for the meta-analysis of the RCTs seemed appropriate but, since few studies directly compared neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy, the authors suggested that these results should be treated with caution. Relevant subgroup analyses for tumour type were performed.

In view of potential limitations in the review process, language restrictions, and the uncertain quality of included trials, the authors’ main conclusions should be treated with caution.

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

**Practice:** The authors stated that neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy were well known to cause toxicities which potentially increased the risk of surgical morbidity. Treatment decisions for individual patients should take these risks into account and the effects of treatment on quality of life.

**Research:** The authors stated that future trials should include modern staging methods to facilitate appropriate stratification of patients, measures for assessing surgery quality, differentiate between different sites of adenocarcinoma and analyse them separately. RCTs were needed to compare the two strategies of neoadjuvant therapy and identify the optimum regimen; the interventions should aim to minimise treatment toxicities and effect on quality of life. The authors suggested further investigation of taxane-based neoadjuvant chemoradiotherapy.

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