Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis

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CRD summary
This review concluded that the overall survival rate, local-regional recurrence and postoperative mortality of patients with resectable oesophageal adenocarcinoma may be improved by neoadjuvant chemoradiotherapy, with no apparent increase in the complication rate. Overall, these findings appear to be supported by the data presented, although there is some risk that relevant data may have been missed.

Authors' objectives
To compare neoadjuvant chemoradiotherapy and surgery with surgery alone for the treatment of resectable oesophageal carcinoma.

Searching
MEDLINE and EMBASE were searched for fully reported studies published between 1980 and 2008. Search terms were reported. In addition, reference lists of retrieved articles and meta-analyses were screened for additional studies. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared neoadjuvant chemoradiotherapy plus surgery with surgery alone, for the initial management of resectable oesophageal cancer (of any histological type, e.g. squamous cell carcinoma or adenocarcinoma) were eligible for inclusion in the review. Eligible trials had to report survival data using intention-to-treat data and have comparable baseline characteristics across study groups (e.g. sex, age, type of pathology, tumour stage).

In just over half of the included trials, neoadjuvant chemoradiotherapy was given concurrently with surgery; in the remaining trials, treatment was sequential. Surgery was generally undertaken between three weeks and two months after chemoradiotherapy. Radiotherapy schedules varied, but generally used between 1.2 and 3.7 Grays (Gy) per day over a period of 19 days to 5.5 weeks, giving a total dosage of between 20 and 50.4Gy. The majority of chemotherapy schedules involved cisplatin (7 to 100mg) alone or in combination with fluorouracil (10 to 1000mg/m²). Other drugs administered in combination with cisplatin were bleomycin and vinblastine.

Included trials were published between 1982 and 2008, and carried out in the following countries: Australia, USA, China, France, Ireland, Japan, Korea, Norway and Thailand. The majority of included trials only assessed patients with oesophageal squamous cell carcinoma; the remaining trials assessed patients with oesophageal adenocarcinoma alone or in combination with oesophageal squamous cell carcinoma. Where reported, the patients' tumour stage ranged from I to III (1987 criteria of the International Union Against Cancer or UICC) in most cases, although two of the trials included patients with more advanced stage IVa disease.

The authors did not state how papers were selected for review.

Assessment of study quality
Three reviewers independently evaluated the methodological quality of the trials according the following Jadad criteria: blinding, randomisation, and handling of withdrawals and drop-outs. Each trial was awarded a quality score between 0 and 5 points. Any discrepancies were resolved through consensus.

Data extraction
Three reviewers independently extracted the trial data and discrepancies were resolved through consensus. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported for survival and the incidence of recurrence. Intention-to-treat (ITT) data were used, except for postoperative events which were analysed according to the number of patients actually undergoing surgery. If necessary one-year, three-year and five-year survival rates were calculated from Kaplan-Meier estimates. One trial author provided additional survival data.
**Methods of synthesis**
Trials were grouped by outcome and pooled odds ratios, with 95% confidence intervals, calculated using a fixed-effect model. Statistical heterogeneity was assessed using the $\chi^2$ statistic.

Further analyses were performed to assess the effect of histological subtype (squamous cell carcinoma or adenocarcinoma) and scheduling of neoadjuvant chemoradiotherapy (concurrent or sequential) on survival.

Publication bias was assessed using funnel plots.

**Results of the review**
Eleven RCTs were included in the review (n=1,308 patients). The average quality score of the trials was 2.3 (range from 1 to 3) out of 5; double blinding was not possible due to the nature of the interventions, and none of the trials identified a method of randomisation. Nearly all patients in the surgery-only intervention group underwent surgery, but not all patients in the neoadjuvant chemoradiotherapy group underwent the planned treatment regimen due to adverse events or disease progression.

Compared with surgery alone, neoadjuvant chemoradiotherapy plus surgery significantly improved: overall survival at one year (OR 1.28, 95% CI 1.01 to 1.64; nine RCTs); overall survival at three years (OR 1.78, 95% CI 1.20 to 2.66; 10 RCTs); overall survival at five years (OR 1.46, 95% CI 1.07 to 1.99; seven RCTs); and local-regional cancer recurrence (OR 0.64, 95% CI 0.41 to 0.99; seven RCTs). Postoperative mortality was also significantly in favour of patients treated with neoadjuvant chemoradiotherapy (OR 1.68, 95% CI 1.03 to 2.73; 10 RCTs), in comparison with surgery alone.

A significant increase in the resection rate (OR 0.36, 95% CI 0.24 to 0.54) was reported in the surgery alone group, but complete resection was more likely in the preoperative chemoradiotherapy group (OR 2.16, 95% CI 1.58 to 2.97; five RCTs). There were no significant differences in the incidence of postoperative complications (10 RCTs) between the two treatment groups or in the incidence of distant cancer recurrence (seven RCTs). There was no or little evidence of statistical heterogeneity.

Further analyses (data reported in the review) suggested that: patients with oesophageal squamous cell carcinoma did not benefit from neoadjuvant chemoradiotherapy in comparison with surgery alone; patients in the USA and Europe had higher survival rates for chemoradiotherapy in comparison with those in Asia; there appeared to be a survival benefit in patients undergoing concurrent therapy, but not sequential therapy.

Funnel plots did not suggest any evidence of publication bias.

**Authors' conclusions**
The overall survival rate, local-regional recurrence and postoperative mortality of patients with resectable oesophageal adenocarcinoma may be improved by neoadjuvant chemoradiotherapy, with no apparent increase in the complication rate.

**CRD commentary**
This review answered a clearly defined review question. A number of databases were searched for relevant trials and no language restrictions were applied. However, relevant data may have been missed as unpublished trials and abstracts were excluded from the review, which suggested a risk of publication bias. The authors reported that their tests suggested no risk of publication bias, but these tests may not be reliable give the relatively small number of included trials. Some attempts were made to reduce the risk of reviewer error and bias when extracting the study data and assessing the validity of the trials, but it was unclear whether similar precautions were taken when assessing the trials for inclusion.

Trial quality was assessed using appropriate criteria, but given the nature of the interventions, none of the trials employed blinding and all of the trials failed to report randomisation methods. In addition, the authors reported that more participants in the neoadjuvant treatment groups failed to complete the treatment regimen in comparison with those who underwent surgery only. Trial characteristics were summarised in a table and appeared to be relatively
similar; where potential differences were noted, attempts were made to further investigate the potential effects of these differences. Statistical tests also suggested that there was little or no statistical heterogeneity.

Overall, the findings of the review appear to be supported by the data presented, although there is some risk that relevant data may have been missed.

Implications of the review for practice and research

Practice: The authors stated that for patients in Europe and the USA neoadjuvant chemoradiotherapy is an effective and beneficial addition to surgery for patients with oesophageal adenocarcinoma.

Research: The authors stated that further studies are required to investigate the observation that patients with oesophageal adenocarcinoma in Europe and the USA, who are treated with neoadjuvant chemoradiotherapy in addition to surgery, are more likely to experience a benefit than patients in Asia.

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