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## A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer

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### CRD summary

In this review, combined treatment with radiotherapy, chemotherapy and surgery appeared to improve cancer recurrence and survival at three years when compared with surgery alone, but may possibly increase serious side-effects. The authors' conclusions seem appropriate given the results presented, but the lack of detail on the included studies makes it difficult to assess whether the results themselves are reliable.

### Authors' objectives

To conduct a meta-analysis of randomised controlled trials (RCTs) that compared the use of neoadjuvant chemoradiation and surgery for oesophageal cancer with the use of surgery alone.

### Searching

The authors searched PubMed and the reference lists of included studies. The search terms were reported in the paper.

### Study selection

#### Study designs of evaluations included in the review

RCTs were included in the review.

#### Specific interventions included in the review

Selected studies compared neoadjuvant chemoradiation and surgery with the use of surgery alone. Details on the radiation dose and scheduling for individual studies were not provided.

#### Participants included in the review

The authors selected studies including patients with resectable oesophageal cancer.

#### Outcomes assessed in the review

The authors did not state any inclusion criteria relating to the outcomes. The outcomes assessed by the meta-analysis were: 1-, 2- and 3-year survival, rate of resection, rate of complete resection, operative mortality, anastomotic leaks, post-operative pulmonary complications, all treatment mortality, local-regional cancer recurrence, distant cancer recurrence and all cancer recurrence.

#### How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for inclusion in the review.

### Assessment of study quality

The validity of the included studies was assessed using the criteria of Jadad et al. (see Other Publications of Related Interest). Two reviewers independently assessed the validity of the included studies, with any disagreements resolved by consensus.

### Data extraction

Two reviewers independently extracted the data, with any disagreements resolved by consensus. It was not clear precisely what data were extracted from the included studies.

## Methods of synthesis

### How were the studies combined?

Odds ratios (ORs) were calculated for each relevant study outcome and combined using a random-effects meta-analysis.

Publication bias was assessed using funnel plots.

### How were differences between studies investigated?

Clinical heterogeneity between the studies was observed prior to conducting the meta-analysis, but it was not clear whether statistical heterogeneity was assessed. Sensitivity analyses were performed on 3-year survival data to determine the effects of cancer histology and chemoradiation scheduling on survival.

## Results of the review

Nine RCTs (n=1,116) were included.

The quality scores of the RCTs ranged from 1 to 3 (on a 5-point scale), with a mean of 2.1.

Survival of the two patient groups was similar at 1 year (OR 0.79, 95% confidence interval, CI: 0.59, 1.06) and 2 years (OR 0.77, 95% CI: 0.56, 1.05), but 3-year survival was statistically significantly superior in the chemoradiation plus surgery group compared with the surgery alone group (OR 0.66, 95% CI: 0.47, 0.92).

Patients treated with surgery alone were more likely to undergo oesophageal resection than patients treated with chemoradiation plus surgery (OR 2.5, 95% CI: 1.05, 5.96), but were less likely to have complete resection (OR 0.53, 95% CI: 0.33, 0.84).

When the analysis was limited to studies of squamous cancer, the 3-year survival advantage of neoadjuvant chemotherapy and surgery was less apparent (OR 0.75, 95% CI: 0.52, 1.09). The analysis could not be limited to adenocarcinoma as there was only one trial of this type.

In a subgroup analysis of RCTs using concurrent chemoradiation, 3-year survival strongly favoured chemoradiation plus surgery (OR 0.45, 95% CI: 0.26, 0.79). No significant difference between treatments was seen on this outcome for RCTs of sequential radiation (OR 0.82, 95% CI: 0.54, 1.25).

Patients receiving neoadjuvant chemotherapy and surgery had fewer local-regional cancer recurrences (OR 0.38, 95% CI: 0.23, 0.63). Distant recurrence (OR 0.88, 95% CI: 0.55, 1.41) and all cancer recurrence (OR 0.47, 95% CI: 0.16, 1.45) were similar for both patient groups.

There was a non significant trend in favour of surgery alone for both operative mortality (OR 1.72, 95% CI: 0.96, 3.07) and all treatment mortality (OR 1.63, 95% CI: 0.99, 2.68).

## Authors' conclusions

Compared with surgery alone, neoadjuvant chemoradiation and surgery improved 3-year survival and reduced local-regional cancer recurrence. It was associated with a lower rate of oesophageal resection, but a higher rate of complete resection. There was a non significant trend towards increased treatment mortality with neoadjuvant chemoradiation. Concurrent administration of neoadjuvant chemotherapy and radiotherapy was superior to sequential chemoradiation treatment scheduling.

## CRD commentary

This review was based on an adequately defined review question, although this question was not supported by an explicit statement of the study selection criteria. The authors conducted manual and PubMed searches, but only published material was searched and it was unclear whether studies published in languages other than English were identified. While the funnel plots did not suggest that the review was influenced by publication bias, some relevant studies might have been missed. The validity of the included studies was assessed using an established scale, though the

results of this validity assessment were not presented for individual studies, nor did they appear to be utilised in the synthesis. As with the validity assessment, the data extraction was carried out in duplicate to prevent errors, but the actual data extracted from the individual studies were not presented in the review. Consequently, though the authors' conclusions seem appropriate given the results presented, the lack of detailed information on the included studies makes it difficult to assess whether the results themselves were reached in an entirely appropriate way.

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

The authors did not state any implications for practice or further research.

### **Bibliographic details**

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### **PubMedID**

12781882

### **Other publications of related interest**

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.

### **Indexing Status**

Subject indexing assigned by NLM

### **MeSH**

Antineoplastic Agents /therapeutic use; Combined Modality Therapy; Esophageal Neoplasms /mortality /therapy; Esophagectomy /methods; Humans; Neoadjuvant Therapy; Neoplasm Recurrence, Local /prevention & control; Odds Ratio; Radiotherapy, Adjuvant /methods; Randomized Controlled Trials as Topic; Survival Analysis; Survival Rate; Treatment Outcome

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