The role of postoperative adjuvant chemotherapy following curative resection for gastric cancer: a meta-analysis

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CRD summary
This review assessed the effects of postoperative adjuvant chemotherapy on survival rates in gastric cancer and concluded that some slightly significant benefits were observed compared to surgery alone. However, as the authors acknowledged, potential problems with selection bias, poor study quality and small sample sizes may compromise the reliability of their conclusions.

Authors' objectives
To assess the effects of postoperative adjuvant chemotherapy on survival rates following curative resection of gastric cancer in different population groups with different regimens.

Searching
MEDLINE and EMBASE were searched up to September 2006 without language restrictions. Search terms were reported. Bibliographies of retrieved studies and reviews and the authors personal files were also searched.

Study selection
Randomised controlled trials (RCTs) of postoperative adjuvant treatment, comparing intravenous chemotherapy to postoperative observation alone, in patients with histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, where distance metastases or residual post surgical disease were absent, were eligible for inclusion. All except one study evaluated 5-fluorouracil in combination with a range of concomitant treatments. Most interventions were compared to no observation or control but some had active comparators. Follow-up ranged from 36 to 114 months. The primary outcomes were overall survival and five-year disease-free survival. Two reviewers selected studies for inclusion and any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers assessed the included RCTs using the Jadad 5-point scale. RCTs with score of two or more were included in the review. There were no disagreements between reviewers.

Data extraction
The incidence of five-year overall and disease free survival were extracted, from which relative risks (RR) and 95% confidence intervals (CIs) were calculated. Three independent reviewers extracted data into a structured pre-designed form; it was stated that there were no disagreements between reviewers.

Methods of synthesis
Pooled RR and 95% CI were calculated using a fixed effect meta-analysis. Heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Subgroup analyses were conducted to investigate the impact of differences in the study populations and intervention regimens. Publication bias was investigated using a funnel plot.

Results of the review
Seventeen RCTs met the inclusion criteria (n=3,529; range 84 to 573). Data were not available for two RCTs, therefore 15 RCTs were included in the analysis (n=3,292; range 84 to 573). All scored two or three on the Jadad scale. Only seven RCTs reported adequate randomisation methods.

Adjuvant chemotherapy improved the five-year overall survival rate (RR 0.90, 95% CI: 0.84, 0.96, p=0.001; 15 RCTs) and disease-free survival rate (RR 0.87, 95% CI: 0.78, 0.96, p=0.005; 7 RCTs). No statistically significant heterogeneity between studies was observed for either analysis.

Results remained significant when Western and Asian subgroups were analysed separately. When subgrouped by treatment regimen, the meta-analysis suggested slightly better five-year overall survival rates only with mitomycin-
containing regimens, with or without anthracycline. The numbers of studies within these subgroups were small.

The funnel plot showed no evidence of publication bias.

**Authors’ conclusions**
Postoperative adjuvant chemotherapy for gastric cancer confers slightly significant benefits compared to surgery alone.

**CRD commentary**
The review question was clearly defined in terms of participants, intervention and study design. Relevant sources were searched, without language restrictions. There was no specific search for unpublished studies. The authors made some attempts to investigate publication bias. All stages of the review were conducted in duplicate, reducing the potential for error and bias. Validity was assessed using established criteria, and the results for some of the Jadad criteria were reported for each study. Risk ratios were used to assess survival rather than hazard ratios. Investigations into the impact of clinical heterogeneity made despite the lack of statistical heterogeneity in the main analyses, however, many of the subgroup analyses consisted of only two studies, limiting the reliability of the pooled results. Ten authors acknowledge a number of limitations, including the possibility of selection bias, the lack of data on Asian populations and small sample sizes. These factors might impact the reliability of the authors’ conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that with the currently available evidence, they cannot conclude adjuvant chemotherapy for localised resected gastric cancer as a standard option.

Research: The authors recommended a meta-analysis of individual patient data before conducting further RCTs. They also stated that a large, well conducted RCT is needed to define the most effective strategies for gastric cancer.

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