An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer

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CRD summary
This meta-analysis of chemotherapy in gastric cancer patients following curative resection concluded that chemotherapy improved survival rates and reduced relapse rates, although it was associated with significant adverse effects. The reliability of this generally well-conducted review may be limited by the possibility of publication or reviewer bias.

Authors' objectives
To investigate the effectiveness of chemotherapy for gastric cancer patients following curative resection.

Searching
MEDLINE, EMBASE and CBM disc (Chinese Biomedical Literature Database) were searched up to November 2007 for studies published in journals in English. Search terms were reported.

Study selection
To be eligible for inclusion, studies had to be randomized controlled trials (RCTs) that compared adjuvant chemotherapy with observation alone following curative resection of gastric cancer.

Patients in the intervention group had to receive systemic chemotherapy orally or intravenously. Trials that included patients with metastasis or residual disease, or used immunotherapy and/or radiotherapy in combination with chemotherapy, were excluded.

Included outcomes were mortality, disease-free survival, relapse rates, and adverse reactions.

Included trials used the following chemotherapies: adriamycin, carmustine, cisplatin, cyclophosphamide, cytarabine, epidoxorubicin, fluorouracil (the majority of trials), ftorafur, mitomycin, semustine, S-1 (an oral fluorouracil), tegafur and vinblastine. Chemotherapy was given over three to 10 cycles, one to eight years or to progress.

The authors did not state how studies were selected or differences were resolved.

Assessment of study quality
Two reviewers assessed the quality of trials independently according to the criteria listed in the Cochrane Reviewers' Handbook 4.2.3. These were: method of randomisation; allocation concealment; patient and observer blinding; losses to follow-up; and intention-to-treat analysis. Based on these criteria, the trials were rated as high, moderate or low quality. The authors did not state how disagreements were resolved.

Data extraction
Data used to calculate the relative risk (RR) and 95% confidence interval (CI) for dichotomous outcomes, and the weighted mean difference (WMD) with 95% confidence intervals for continuous data, were extracted.

Two reviewers extracted data independently. The authors did not state how any disagreements were resolved.

Methods of synthesis
The relative risk and 95% confidence interval were calculated for dichotomous data, and the weighted mean difference and 95% confidence interval for continuous data. The number-needed-to-treat (NNT) or number-needed-to-harm (NNH) were also reported for most dichotomous outcomes.

Statistical heterogeneity was considered significant if p was greater than 0.10 for the $\chi^2$ statistic or if $I^2$ was greater than 50%. Relative risks and weighted mean differences were pooled using a fixed-effect model, or, if there was
significant heterogeneity, a random-effects model based on the DerSimonian and Laird estimator.

Sub-group analysis of lymph node invasion, depth of lesion, races, regimens, length of cycles and follow-up period were conducted. A sensitivity analysis of trial quality was also conducted by excluding moderate and low quality trials. Publication bias was tested using a funnel plot.

**Results of the review**

There were 23 RCTs included in the review, reporting data from 24 comparisons of 4,919 patients (2,441 in the adjuvant chemotherapy arm, 2,478 in the observation arm) with between 28 and 1,059 participants followed-up from two to 10 years. It should be noted that there was a discrepancy between the number of patients reported in text and that reported in Table 1; the numbers used in this abstract are taken from the text.

Ten trials were rated as high quality, 12 as moderate quality and one as low quality. Intention-to-treat analyses were performed in nine trials, and allocation concealment was described in eight trials. All except two single-blind trials, were not blinded. There were possible confounders identified in six trials.

**Effects:** The mortality rate (RR 0.85, 95% CI 0.80 to 0.90; NNT=14; 19 trials with 20 comparisons) and relapse rate (RR 0.78, 95% CI 0.71 to 0.86; NNT=11; nine trials) were both significantly lower in the treatment groups. Disease-free survival (RR 0.88, 95% CI 0.77 to 0.99; NNT=13; eight trials) was higher in treatment group.

**Safety analysis:** The treatment group had a significantly higher rate of leukocytopenia (RR 12.89, 95% CI 4.95 to 33.54), thrombocytopenia (RR 3.24, 95% CI 1.31 to 7.97), nausea and vomiting (RR 3.29, 95% CI 1.31 to 8.32; NNH=10) and diarrhoea (RR: 4.23, 95% CI 2.40 to 7.46; NNH=17). Chemotherapy-related death was reported in 10 trials with a total of 15 deaths among 948 patients (1.58%).

Survival rates were still higher in the adjuvant therapy group when sensitivity and subgroup analyses were performed.

The authors stated that there was no obvious publication bias in the funnel plot of survival rates.

**Authors’ conclusions**

Statistically, adjuvant chemotherapy improved the survival rate and disease-free survival rate and reduced the relapse rate in gastric cancer patients following curative resection. However, the clinical benefits of adjuvant chemotherapy still need to be improved.

**CRD commentary**

The review question and inclusion criteria were clear. The restriction to studies that were published in journals and in English may have introduced language or publication bias into the review. The assessment of study validity used appropriate criteria. The authors reported methods designed to reduce reviewer bias and error in the assessment of validity and extraction of data, but these were not described for the selection of studies. In addition, the authors did not describe how disagreements were resolved at any stage. Recommended methods were used to assess statistical heterogeneity and the use of random-effects meta-analysis where heterogeneity was significant was appropriate.

The conclusions of this generally well-conducted review reflect the overall results. However, as there was some potential for publication bias and a lack of detail on the methods used to select studies, extract data and resolve disagreement, the reliability of conclusions may be limited.

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

**Implications for practice:** The authors stated that adjuvant chemotherapy could improve the survival rate and disease free survival rate and decrease the relapse rate in gastric cancer patients following curative resection. However, the clinical benefits of adjuvant chemotherapy still need to be improved.

**Implications for research:** The authors did not state any implications for research.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.