Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer

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CRD summary
This review concluded that post-operative adjuvant chemotherapy was effective in improving overall survival after radical surgery in patients with advanced gastric cancer. While there was a benefit for all examined subgroups, the greatest benefit was seen with Japanese-style D2 radical surgery with oral fluorouracil. The authors’ conclusions are supported by the data presented.

Authors' objectives
To assess the effect of postoperative adjuvant chemotherapy on overall survival after curative surgery in patients with advanced gastric cancer. Additionally, to compare regimens of chemotherapy to identify the most effective combination of anticancer drugs.

Searching
PubMed, EMBASE, the Cochrane library, the American College of Physicians Journal Club, DARE, the Health Technology Assessment Database, the NHS Economic Evaluation Database (NHS EED), ISI Web of Knowledge and the Chinese Biomedical Literature Database (CBM) were searched for articles published between January 1998 and December 2007. Search terms were provided in an appendix. The search included Chinese and English literature. Reference lists of identified articles were also scanned.

Study selection
Randomised controlled trials (RCTs) of patients undergoing subtotal or total gastrectomy for pathologically proven gastric cancer with radical lymph node dissection (D1 or more), with a negative margin, were eligible for inclusion. Patients with intraperitoneal dissemination, other organ metastases or remnant gastric cancer were excluded. Trials containing only patients with T1 gastric cancers were also excluded. Trials had to compare adjuvant chemotherapy after surgery with surgery only. Chemotherapy had to be started within eight weeks of surgery. Trials of intraperitoneal chemotherapy, immunochemotherapy, radiochemotherapy, intra-arterial chemotherapy, or neoadjuvant chemotherapy were excluded. The outcome was overall survival.

Of the included trials, four were from Japan and the rest were from Europe. Mean age of participants was between 54 and 69 years. Seven trials included patients with T1 to T4 tumours, with at least 70% lymph node positive rate. Two trials included patients with T2 to T4 tumours, with at least 80% lymph node positive rate. One trial recruited patients with T2 tumours with 100% lymph node positive rate. Two trials included patients with T1 to T3 tumours, with around 45% lymph node positive rate. Eight trials performed D2 lymphadenectomy. Three trials performed D1 or D0 lymphadenectomy. One trial performed either D1 or D2 lymphadectomy. All trials used 5-fluorouracil as a chemotherapy agent. Other agents commonly used were anthracyclic agents (adriamycin and epirubicin), cisplatin and mitomycin. Patients were followed up for a mean of at least three years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two authors assessed trial quality using a validated scale (Jadad scale) which includes randomisation, blinding and withdrawal/drop-out criteria. To be considered high quality, trials had to score at least 3 points out of a maximum of 5 points.

Disagreements were resolved by discussion and consensus.

Data extraction
Two authors extracted data using specially designed data extraction forms. Disagreements were resolved by discussion and consensus. Items to be extracted were listed. Hazard ratios and 95% confidence intervals were used to assess overall survival. The survival ratio of patients receiving chemotherapy to patients not receiving chemotherapy was calculated. Natural log transformation of hazard ratios was used and the standard error calculated from the 95% confidence
interval. Where trials provided no hazard ratio, natural log hazard ratios and standard errors were estimated from the Kaplan-Meier survival curves or by the indirect method of Parmar and colleagues.

**Methods of synthesis**
In the meta-analysis, the inverse variance method for time-to-event outcomes was used, together with a fixed-effects model if there was no heterogeneity between the trials (as measured by the $\chi^2$ test). A funnel plot was used to assess publication bias. Subgroup analyses were carried out for: percentage of T1 tumours in the trials (0, <10%, about 30%); percent lymph node positive rate (less than 50% or 70% or more); type of surgery (mostly D1 or mostly D2); Japanese trials versus non-Japanese trials; and oral versus intravenous drug administration.

**Results of the review**
Twelve randomised controlled trials (RCTs), with a total of 3,809 participants, were included. All trials had a Jadad quality score of 3 points. The funnel plot suggested there may have been some publication bias.

**Overall survival**: The pooled hazard ratio showed significantly higher survival rates for chemotherapy plus surgery compared to surgery only (hazard ratio 0.78, 95% confidence interval (CI): 0.71, 0.85; 12 RCTs). Of the individual trials, most showed trends for a survival benefit, but only four trials showed a significant result in favour of chemotherapy. No significant heterogeneity was detected in the main meta-analysis ($p=0.15$).

**Subgroup analyses**: Significant hazard ratios in favour of chemotherapy were found in all subgroup analyses.

Overall survival was between 13 and 56% for trials from Western countries and 70 to 84% for the Japanese trials (based on ten RCTs with five-year survival rates, one RCT with three-year survival rates, and one RCT with 10-year survival rates).

No significant difference in hazard ratios appeared to exist for subgroups according to percentage of T1 tumours, percent lymph node positive rate, and type of surgery.

Three trials that used oral fluorouracil agents, showed statistically significant results for survival (hazard ratio 0.63, 95% CI: 0.52 to 0.78). The remaining eight intravenous regimens showed no significant result for survival (hazard ratio was 0.80, 95% CI: 0.71 to 0.89).

**Authors' conclusions**
The meta-analysis suggested that adjuvant chemotherapy was beneficial after radical therapy for advanced gastric cancer, with both oral and intravenous chemotherapy regimens plus surgery providing better survival than surgery alone. Japanese-style D2 radical surgery with oral fluorouracil appeared to be one of the best choices.

**CRD commentary**
This moderate quality review addressed a clearly stated research question. Appropriate inclusion criteria were defined. Measures were taken to avoid the introduction of error and bias during the review process. The literature search included a variety of relevant databases, and the search strategy was listed in an appendix. However, the authors did not describe how trials were selected. A language restriction (English and Chinese) was also applied. The methodological quality of the included trials was assessed using the Jadad scale. Trial quality was deemed to be adequate, but using quality scores is not a very sensitive method of quality assessment. Appropriate subgroup analyses were carried out, but it was not clear whether these were post-hoc analyses. Detailed information on patients, interventions, quality and subgroup analyses was provided in a separate appendix. The authors' conclusions are supported by the data presented.

**Implications of the review for practice and research**
**Practice**: The authors stated that Japanese-style D2 radical surgery with oral fluorouracil appeared to be one of the best choices.

**Research**: The authors did not make any recommendations for further research.

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