Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials

Earle C C, Maroun J A

Authors' objectives
To assess whether adjuvant chemotherapy after curative resection of gastric cancer increases survival rates.

Searching
MEDLINE (from 1966) and Cancerlit (from 1983) were searched up to January 1999 inclusive using the search strategy described by Haynes et al (see Other Publications of Related Interest no.1). Content terms included "stomach neoplasm" and "adjuvant chemotherapy", and the methodological terms "clinical trials", "phase III", "randomised control trial", "double-blind method" and "random allocation". Bibliographies of all papers, personal reprint files, and reviews were searched. Only the most recent publication was used where results were updated. There were no language restrictions and published abstracts were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that compared adjuvant treatment to observation alone were included if they were conducted in Western (non-Asian) countries and provided either in numerical or graphical form the number of deaths and the total number of patients in each group. Duration of follow-up ranged from 36 to 114 months.

Specific interventions included in the review
The following systemic chemotherapeutic regimes were compared with observation only: 5-fluorouracil (FU), vinblastine, and cyclophosphamide; FU + semustine (mCCNU); FU + carmustine (BCNU); fluorouracil + doxorubicin + mitomycin-C (FAM); FU + doxorubicine; mitomycin-C (MMC); epirubicin + FU + MMC; and epirubicin + FU + folinic acid (FA). Systemic routes included oral and intravenous routes but not intraperitoneal treatment. Combinations of chemotherapy with immunotherapy and/or radiotherapy were excluded.

Participants included in the review
Patients must all have had a potentially curative surgery defined as one that would be considered curative at the time of the initial medical oncology consultation. Patients enrolled in retrospective reviews who were subsequently shown to have residual disease were eligible. Patients with metastatic disease or residual disease after surgery were not included.

Outcomes assessed in the review
Mortality was the primary outcome.

How were decisions on the relevance of primary studies made?
Abstracts were screened and potentially relevant papers examined to determine whether they met the eligibility criteria. Disagreements were resolved by consensus.

Assessment of study quality
Study validity was assessed using the Jadad criteria (see Other Publications of Related Interest no.2). Both reviewers independently assessed study quality.

Data extraction
Both reviewers independently abstracted the outcome data using a pre-designed data extraction form. Data extracted included: assessment of eligibility and trial quality; type of chemotherapy used; number of patients in intervention and control group; and number of deaths in each group.
Methods of synthesis
How were the studies combined?
Results were pooled using a DerSimonian and Laird random-effects model. Crude odds ratio (OR) and 95% CI of mortality in treated and untreated patients was calculated. The relative risk (RR) and 95% CI was also calculated. Publication bias was assessed using the inverted funnel plot. Rosenthal's fail-safe number was also calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed with the Q statistic. Sub-group analyses were conducted to investigate the influence of the following factors: validity (Jadad score > 2 vs score <=2); chemotherapy regime (modern regimes defined as those containing 5-FU and an anthracycline vs others); follow-up time (> 5 years vs <= 5 years); proportion of patients with positive lymph nodes (trials with high vs low proportion of node positive patients). A summary effect was calculated after the inclusion of two trials containing patients with postoperative residual disease.

Results of the review
Thirteen RCTs were included (N = 1990 patients).

All but one of the RCTs had Jadad score of 2 or 3. Mean death rate in the control group was 0.64 (standard deviation 0.15). No significant statistical heterogeneity was found. Neither the funnel plot nor the fail-safe number of 9 suggested any important publication bias.

Overall mortality: just statistically significantly in favour of adjuvant chemotherapy with OR = 0.80 (95% CI: 0.66, 0.97). RR was not statistically significant RR = 0.94 (95% CI: 0.89, 1.00). This represents an estimated 65% of similar patient untreated who would suffer recurrence and die compared with approximately 61% of those treated. Absolute risk reduction = 4%. Number needed to treat to prevent a death = 25.

Subgroup analyses: statistically significant heterogeneity was not detected.

Proportion of patients with disease involving lymph nodes: trend towards larger magnitude of effect with chemotherapy in trials where > 2/3 patients had involved lymph nodes. RR (> 2/3 with positive nodes) = 0.91 (95% CI: 0.85, 0.99) vs RR (<=2/3 with positive nodes) = 1.00 (95% CI: 0.90, 1.11). Chemotherapy regime: non statistically significant trend towards lower relative risk in those receiving modern chemotherapy regimes (5-FU plus an anthracycline). There was insufficient power for a statistically significant result. RR (modern regimes) = 0.92 (95% CI: 0.86, 1.00) vs RR (other regimes) = 0.95 (95% CI: 0.84, 1.08).

Length of follow-up: trials with > 5 years follow-up showed a smaller benefit than those with shorter follow-up. RR (> 5 years) = 0.95 (95% CI: 0.88, 1.02) vs RR (<= 5 years) = 0.91 (95% CI: 0.79, 1.06).

Study validity: higher quality studies showed a smaller magnitude of effect than those of lower quality. RR (Jadad > 2) = 0.97 (95% CI: 0.90, 1.05) vs RR (Jadad <= 2) = 0.91 (95% CI: 0.83, 1.00).

Proportion of patients with positive lymph nodes: Inclusion of patients with post-operative residual disease produced less favourable results than those including only patients with curative resection. RR (14 trials) = 0.98 (95% CI: 0.93, 1.03).

The OR and 95% CI were also given for all the above outcomes.

Authors’ conclusions
The results suggest that adjuvant chemotherapy may produce a small survival benefit of borderline statistical significance in patients with curatively resectable gastric carcinoma. Continued trials to confirm an effective adjuvant strategy are warranted.

CRD commentary
The aims and inclusion criteria were defined. More than one source was used to identify articles. Publication bias was assessed. Methods used to select primary studies, extract data, and assess validity were described. Relevant details of the
primary studies were presented in tabular format. Statistical heterogeneity was assessed and sub-group analysis undertaken to examine the influence of various factors on the results.

The duration of chemotherapy regimes was not reported. An assessment of the quality of life of patients would have added to the evidence base for decision making.

The authors’ conclusion were supported by the evidence.

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

Practice: The authors state that the analysis should not be regarded as definitive in view of the tendency for the meta-analysis to overestimate treatment effects.

Research: The authors state that randomised trials in this area should continue to be undertaken with a supportive care only control arm until a satisfactory strategy can be identified.

**Bibliographic details**


**PubMedID**

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**Other publications of related interest**


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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.