Neoadjuvant chemotherapy versus none for resectable gastric cancer (Protocol)

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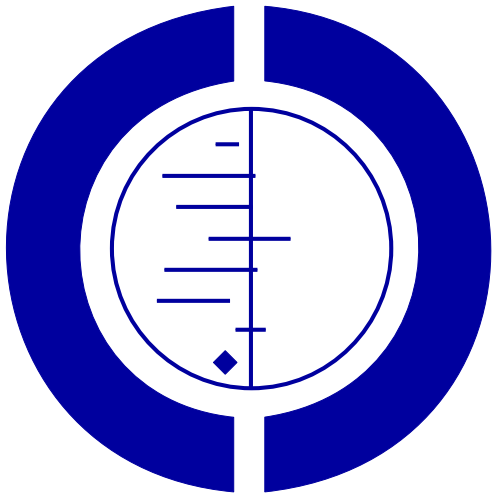

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
To evaluate the effect of neoadjuvant chemotherapy versus none for gastric cancer patients in terms of efficacy and toxicity

BACKGROUND

Gastric cancer has been a main cause of cancer death through most of the twentieth century (Hohenberger P, 2003). Throughout much of the world, it represented the leading cause of cancer death 50 years ago (Parker SL, 1996). Gastric cancer incidence rate varies substantially throughout the world, though it hits eastern Asia (including China and Japan) most. The incidence and mortality of gastric cancer have experienced a drastic decrease in the United States in past 40 years. However, the incidence of gastroesophageal cancer has risen steadily and the fall in incidence of gastric cancer appears to have plateaued in some countries (Parker SL, 1997). Thus, gastric cancer remains a threat to people's health in both Eastern and Western countries.

Moreover, the fall in gastric cancer mortality seems to be explained by decreasing incidence rather than improved treatment outcome. Only 50-60% of newly diagnosed gastric cancer patients can undergo potential curative surgical resection (Van de Velde,2003). In Japan, the higher resection rate benefits from routine screening in that country. Yet, in China and even developed countries, the resection rate might be low, compromising the therapeutic efficacy. Complete resection is the only potentially curative therapy for gastric cancer to date. Stage I-IV M0-tumors (Table 01) are principally resectable (Roder JD, 1998; Ichikura T, 1999). But although surgery carries a high cure rate for stage IA and IB cancers, the results for stage IIIA and IIIB cancers are poor. Many patients with advanced disease, especially stage IIIA/B, are technically inoperable. Unfortunately, even after a "curative" gastrectomy, relapse rates in prospective studies are in the range of 40-60% (Wanebo HJ, 1993). Patients with inoperable, recurrent or metastatic tumors have a poor prognosis with a median survival time of 3 -5 months. Even so, whether or not the cure rate is affected by the type of operation performed is controversial and even patients undergoing more extensive node dissection are at substantial risk of failure (Bonenkamp JJ, 1995; Cuschieri A, 1996; McCulloch P). In order to improve treatment outcome in locally advanced gastric cancers, the role of (neo) adjuvant chemotherapy is currently investigated with different protocols. In this way, locally advanced tumours can be rendered resectable by downstaging, elimination of micrometastases and spillage of tumours cells during surgery (Leichman L, 2003). The rationale for using chemotherapy preoperatively (neoadjuvant chemotherapy) has been prompted (Yamazaki H, 1989). Many phase II and phase III and even randomized controlled trials are ongoing or even finished. Yet these trials have produced conflicting results, making the role of neoadjuvant chemotherapy more controversial (Kang YK, 1996). One randomized clinical trial from the Netherlands detected no significant improvement in either the rate of "curative" resection or downstaging in 59 patients with inoperable gastric cancer (Songun I, 1999), while other two clinical trials from Korea and Japan (Fujii M, 1999; Kelsen D, 1998) failed to show a survival benefit from neoadjuvant chemotherapy. Cumulative evidence from clinical trials including randomized controlled trials on neoadjuvant chemotherapy of gastric cancer is available.

OBJECTIVES

To evaluate the effect of neoadjuvant chemotherapy versus none for gastric cancer patients in terms of efficacy and toxicity

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

INCLUSION CRITERIA
Randomised controlled trials will be sought. Quasi-randomised studies will also be included for sensitivity analysis.
The control group should include gastric cancer patients undergoing surgical resection without preoperative chemotherapy or radiotherapy.
Abstracts or unpublished data will be included, if sufficient information on study design, geographic location of the studies, characteristics of participants including TNM stage, interventions and outcomes are available and if full information as well as final results can be confirmed by contact to the first author. Trials that relate solely to the gastroesophageal junction should be excluded.

EXCLUSION CRITERIA
Studies enrolling esophageal carcinoma patients and stage IV with M1 and recurrent gastric cancer patients should be excluded except where definite results of the gastric cancer subgroups conforming to the inclusion criteria are available.
"Cross-over" studies will be excluded in order to assess the overall treatment effect on survival. Here the "cross-over" studies do not refer to the cross over between surgery and chemotherapy, but the different protocols used preoperatively.

Types of participants

Patients with histologically confirmed primary adenocarcinoma of the stomach or gastroesophageal junction without any prior chemo- or radiotherapy. Recurrent cancer patients or those with unresectable tumors are not included. Unresectable tumors refers to those invading major vessels or with distant or intraperitoneal metastatic lesions.
Studies include patients with locally advanced or early stage resectable tumors can be included.

Types of intervention

Chemotherapy used preoperatively with or without radiotherapy can be enrolled in the study. The regimen might encompass all cytotoxic or antineoplastic drug treatment.

Types of outcome measures

Primary outcome measure:
Overall survival on intention to treat analysis.
Secondary outcome measures:
a) Tumor response
b) Time to progression (TTP)
c) Secondary resectability in patients with locally advanced gastric cancer and corresponding morbidity and mortality
d) Toxicity, classified according to WHO Common-Toxicity-Criteria

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Upper Gastrointestinal & Pancreatic Diseases Group methods used in reviews.

A search will be conducted to identify all published and unpublished randomised controlled trials. The search strategy will identify studies in all languages and when necessary non English language papers will be translated so that they could be fully assessed for potential inclusion in the review

Trials will be identified by searching the following electronic databases - The Cochrane Library, Medline, Embase, and The Chinese Biomedical Disk(CBMdisc).

The search strategy for the review will be constructed by using a combination of subject headings and text words relating to the use preoperative chemotherapy or neoadjuvant chemotherapy for the treatment of gastric cancer.

The following websites will also be searched for reports of ongoing trials:

http://www.controlledtrials.com
http://www.clinicaltrials.nci.nih.gov
http://www.cancertrials.nci.nih.gov
http://www.cancernet.nci.nih.gov/pdq.htm
http://www.calgb.uchicago.edu
http://www.eortc.be
http://www.swog.saci.org
http://www.ctg.queensu.ca
http://www.CenterWatch.com/

Reference lists from trials selected by electronic searching will be handsearched to identify further relevant trials. In addition published abstracts from the following conference proceedings will be handsearched:

The United European Gastroenterology Week (published in Gut)
Digestive Disease Week (published in Gastroenterology)
The European Society for Medical Oncology (published in the Annals of Oncology)
The European Council of Clinical Oncology (published in the European Journal of Cancer)
The American Society for Clinical Oncology.

In addition, members of the Cochrane UGPD Group as well as experts in the field and manufacturers of relevant drugs will be

contacted and asked to provide details of ongoing clinical trials and any relevant unpublished material.

METHODS OF THE REVIEW

TRIAL SELECTION:
In order to select studies for further assessment, two independent reviewers will scan the title, abstract section and keywords of every record retrieved. Full articles will be assessed if the information given suggests that the study conformed to our criteria described above.
If there is any doubt regarding these criteria from the information given in the title and abstract, the full article will be retrieved for clarification. If differences in opinion exist, they will be resolved by discussion. If no clarification is provided, the review group editorial base will be consulted.

QUALITY ASSESSMENT OF TRIALS:
The quality of the eligible studies will be assessed blinded by two reviewers independently, with disagreements resolved by a third reviewer until consensus is obtained. Data will be extracted using an assessment form designed for the topic of this review (Jadad AR, 1996)
The following criteria will be considered:
1. Was the allocation truly random?
score 2: sequence produced by computer or randomized number
score 1:"randomized allocation " was referred without definite description
score 0: semi- or quasi- randomization
2. Was the treatment allocation concealed?
score 2: appropriate allocation concealment sealed envelope controlled by center or pharmacy
score 1: inappropriate allocation concealment: allocation according to published sequence produced through randomized number or no description
score 0: semi- or quasi- randomization
3. Was the study double blinded?
score 2: detailed description of proper methods of double blinding
score 1: only simple reference to "double-blindedness "
4. Were the number of withdrawals, dropouts and losses to follow-up in each group completely described? The drop-out-rate will be recorded
score 1: detailed description
score 0: without reference
Based on these criteria, the studies will be broadly subdivided into certain categories of quality and we will report on each option independently.
This classification will be used as the basis of a sensitivity analysis.

DATA EXTRACTION:
Details of study population, interventions and outcomes will be extracted independently by two reviewers using a standardized data extraction form. This form will include at least the following items:
1.independent criteria and the scoring of the four questions for quality assessment (Jadad criteria)
2.General information of the data: title, authors, source, contact address, country, published/unpublished, language and year of publication, sponsoring of trial
3.Trial characteristics including design, duration/follow-up and quality assessment criteria as specified above
4.Patient characteristics including control: in- and exclusion criteria, sample size, baseline characteristics (including age, gender, tumor location, differentiation if available, stage), similarity of groups at baseline (p value should be noted if available), withdrawals and losses to follow up
5.Interventions: dose, route, timing of interventions and control
6.Outcomes: hazard Ratios and their 95% confidence intervals, log rank chi square, log rank p-values, number of events, number of patients per group, median-, 1-, 2-, and 3-year survival rates, 5-year survival rates in patients with locally advanced, secondary resectable tumors
A template data extraction form will be developed and tested in a pilot study. Data extraction and data entry will be performed independently in duplicate by two evaluators. Differences in data extraction will be resolved by consensus with a third reviewer, referring back to the original article. If data are missing in a published report, the reviewers will contact the first author.
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DATA ANALYSIS:
Hazard ratios (HR) and 95 % confidence intervals (CI) as relevant effect measures will be estimated directly or indirectly from the given data (Altman 2001).
Data analysis will be carried out with the terms of primary outcome parameters such as overall survival, 1-, 2-, and 3-year as well as 5-year survival. Secondary outcomes as tumor response rate assessed according to the WHO criteria, time to progression (TTP), resection rate and toxicity caused by chemotherapy and subsequent surgical resection should be included. In those indirect comparisons the balance in prognostic factors from randomization is no longer valid. They depend on the case-mix of relevant prognostic factors (tumor stage, and number of metastatic sites) and therefore have to be interpreted with caution. For this reason, they will be presented in the discussion section of the review.
Results will be stratified according to whether radiotherapy has been used as an intervention.

STATISTICAL METHODS FOR DATA ANALYSIS:
Results will be stratified according to whether radiotherapy was used as an outcome. The fixed effect model will be used for meta-analysis, with overall survival as primary outcome measure. Programs will be RevMan, and for more sophisticated analysis: STATA (Sterne 2001). All outcomes concerning overall survival will be recalculated (or at least approximated) by the effect measure hazard ratio for which the practical meta-analysis is performed.

INVESTIGATING HETEROGENEITY:
Seeking for statistical heterogeneity between studies Cochrane Q-test will be performed (with a significance threshold of alpha =0.1). Additionally, some quantitative measure of heterogeneity will be calculated (Thompson 2002). Where significant heterogeneity is detected, possible explanations will be investigated informally and the data summarised using a random effects model, The following factors will be evaluated as a check for any heterogeneity in the study outcomes.
1. Differences in prognostic factors
2. Quality of studies
3. Second-line therapy permitted versus no second line therapy
4. Type of agents used
5. Dose
6. Number of chemotherapy cycles
7. Different surgical procedures
8. Other managements used.
9. Publication bias

POTENTIAL CONFLICT OF INTEREST

None known.

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ADDITIONAL TABLES

Table 01. TNM staging system of gastric cancer (UICC,1997)

stage	TNM classification
stage IA	T1, N0, M0
Stage IB	T1, N1, M0; T2, N0, M0
stage II	T1, N2, M0; T2, N1, M0; T3, N0,M0
stage IIIA	T2, N2, M0; T3, N1, M0; T4, N0, M0
stage IIiB	T3, N2,M0
stage IV	T4, N1, M0; T1, N3, M0; T2, N3, M0; T3, N3, M0; T4, N2, M0; T4, N3, M0; Any T, Any N, M1

COVER SHEET

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Authors	Aiwen W, Guangwei X, Hongyuan W, Jiafu J, Jinling T
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