Neoadjuvant chemotherapy versus none for resectable gastric cancer (Review)

Wu AW, Xu GW, Wang HY, Ji JF, Tang JL

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ABSTRACT

Background
Gastric cancer is a major cause of cancer death, and many patients are only diagnosed when the cancer has reached an advanced stage. Neoadjuvant chemotherapy (NAC), that is, chemotherapy administered shortly before surgical treatment, could provide a method of increasing the possibility of complete resection and survival.

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

Search strategy
Electronic databases including Cochrane Library, MEDLINE, EMBASE, CancerLit, Chinese Biomedical Literature Database (CBMDISC) and ongoing clinical trials as well as handsearching of conference proceedings, were searched to retrieve relevant data.

Selection criteria
Randomized controlled clinical trials of neoadjuvant chemotherapy on resectable gastric cancer.

Data collection and analysis
We identified a total of 36 published citations or meeting abstracts. Thirty-two items were excluded. Of the four remaining studies, three stated random allocation but the method of randomization was unclear. Two of these employed allocation concealment by sealed envelope which was controlled by an independent party. None of the trials was double blind. All trials presented a detailed description of the number of withdrawals, dropouts and losses to follow-up.

Main results
Of the four clinical trials enrolled, there were 250 and 332 cases in total, with 106 and 126 deaths at the end of follow-up in the NAC and control group, respectively. The OR (odds ratio) was 1.05 (95%CI: 0.73-1.50), which was not statistically significant. Of the evaluable 129 patients receiving NAC, 28.7% demonstrated either a complete or a partial response. Two studies of NAC in resectable gastric cancer had resection rate data available for analysis The R0 resection rate in the NAC group was comparable to that in the control (OR: 0.96 (95%CI: 0.51-1.83)). The morbidity and mortality of NAC varied with the regimens used preoperatively. Of the 129 patients included in the analyzed studies, some acceptable toxicity was observed.

Authors’ conclusions
There is no definite evidence of the effectiveness of NAC in resectable gastric cancer, in terms of improvements in patient survival, in the trials we reviewed. Neoadjuvant chemotherapy should not be used routinely in clinical setting until further results from randomized clinical are available. Neoadjuvant chemotherapy of gastric cancer should be applied under the framework of clinical trials.
There is no definite evidence to date that neoadjuvant chemotherapy for resectable gastric cancer is effective in terms of improvement of patient survival, or even provides a marginal benefit in terms of the number of patient at the end of follow-up. The negative effect may be the result of lack of activity of regimens. Therefore, neoadjuvant chemotherapy should not be used routinely in clinical setting until further results from randomized clinical are available and should be investigated in the framework of clinical trials.

**BACKGROUND**

Gastric cancer has been among the leading causes of cancer death throughout the twentieth century (Hohenberger 2003). Within much of the world, it represented the leading cause of cancer death 50 years ago (Parker 1996). Gastric cancer incidence rate varies substantially throughout the world, though incidence levels are greatest in eastern Asia, including China and Japan. The incidence and mortality rates 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 reached a plateau (Parker 1997). Thus, gastric cancer remains a threat to peoples’ 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 the newly diagnosed gastric cancer patients can undergo potential curative surgical resection (van de Velde 2003). In Japan, the higher resection rate is related to the routine screening in that country. Yet, in China and even in other developed countries, lower resection rates due to lower rate of early detection could compromise 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 1998; Ichikura 1999). 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 1993). Patients with inoperable, recurrent or metastatic tumours have a poor prognosis with a median survival time of 3 -5 months. Whether or not the cure rate is affected by the type of operation performed is controversial and even patients undergoing a more extensive node dissection are at a substantial risk of failure (Boennkamp 1995; Cushieri 1999; McCulloch 2003).

In order to improve treatment outcome in locally advanced gastric cancers, the role of neoadjuvant chemotherapy is currently being investigated with different protocols. In this way, locally advanced tumours can be rendered resectable by downstaging, which may help the elimination of micrometastases and spillage of tumour cells during surgery; this being important patient’s survival (Leichman 2003). A possible problem with neoadjuvant chemotherapy in resectable cancer is that when the tumour is resistant, it may grow and become unresectable. The rationale for using chemotherapy preoperatively (neoadjuvant chemotherapy) has been suggested (Yamazaki 1989) and many phase II and phase III, including randomized controlled trials, are ongoing or completed. Yet, these trials have produced conflicting results, making the role of neoadjuvant chemotherapy controversial. One randomized clinical trial from the Dutch Gastric Cancer Group detected no significant improvement in either the rate of “curative” resection or downstaging in 59 patients with inoperable gastric cancer (Songun 1999), while two other clinical trials, published as abstracts, from Korea and Japan (Kang 1996; Fuji 1999) failed to show a survival benefit from the neoadjuvant chemotherapy. However, the MAGIC trial demonstrated promising results in favour of neoadjuvant chemotherapy (Cunningham 2005).

This review analyses the results from available randomized controlled trials which investigate neoadjuvant chemotherapy versus none for resectable gastric cancer.

**OBJECTIVES**

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

**CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

**Types of studies**

INCLUSION CRITERIA

All randomized controlled trials were considered for inclusion.

It is not possible to do placebo controlled or blinded in a study comparing neoadjuvant treatment to no neoadjuvant treatment. The control group consisted of gastric cancer patients undergoing surgical resection without preoperative chemotherapy or radiotherapy.

For this review, abstracts or unpublished data were included. If there was sufficient information on study designs, geographic location of the studies, characteristics of participants including TNM stage and interventions and outcomes, the final results were con-
firmed by contacting the study's first author. Trials that related solely to the gastroesophageal junction were excluded.

**EXCLUSION CRITERIA**

Studies enrolling oesophageal carcinoma patients and stage IV with M1 and recurrent cancer patients were excluded except where definite results from gastric cancer subgroups conforming to the inclusion criteria were given.

**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 tumours were not included. An unresectable tumour refers to those invading major vessels or with distant or intraperitoneal metastatic lesions.

Studies that included patients with locally advanced or early stage resectable tumours were included in this review.

**Types of intervention**

Chemotherapy used preoperatively without radiotherapy. All cytotoxic or antineoplastic drug treatments were included.

**Types of outcome measures**

Primary outcome measure: Overall survival on intention to treat analysis.

Secondary outcome measures:

a) Tumour 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 and Pancreatic Diseases Group methods used in reviews.

Searches were conducted, on or around June 29th 2005, with the key words "gastric cancer" or "gastric neoplasm" or "gastric carcinoma" and "neoadjuvant chemotherapy" or "preoperative chemotherapy" and "randomized controlled trials". Studies on preoperative chemotherapy with or without postoperative chemotherapy are also included. The following sources have been searched to identify published and unpublished randomized controlled trials:

1) Electronic searches:

   The Cochrane Controlled Trials Register, Issue 3, 2003 (n=22)

   Medline (1966-) (n=6)

   EMBASE (1974-) (n=6)

   Cancer Lit. (1975-) (n=0)

   CBMDISC(1978-) (n=0)

   Databases of ongoing trials:

   http://www.controlledtrials.com (n=0)

   http://www.clinicaltrials.nci.nih.gov (not accessible)

   http://www.cancertrials.nhi.gov (not accessible)

   http://www.cancertrials.nhi.gov/pdq.htm (transferred to http://clinicaltrials.gov, no trials identified)

   http://www.calgb.uchicago.edu (not accessible)

   http://www.eortc.be (n=1)

   http://www.swog.saci.org (not accessible)

   http://www.ctg-queensu.ca (n=0)

   http://www.CenterWatch.com/ (n=0)

2) Hand searching

Reference lists from trials selected by electronic searching were hand searched to identify further relevant trials. Conference proceedings such as published abstracts from conference proceedings (1985 to 10/2003) from the United European Gastroenterology Week (published in Gut) and 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, as well as the American Society for Clinical Oncology were also hand searched. Using this approach, we identified no data consistent with our inclusion criteria. In addition, members of the Cochrane UGPD Group as well as some experts on this field and some manufacturers of relevant drugs were consulted, but this approach yielded no further trials.

**METHODS OF THE REVIEW**

In order to select studies for further assessment, two independent reviewers scanned the title, abstract section and keywords of every record retrieved. Full articles were taken for further assessment if the information given suggested that the study conformed to our criteria described above. Any doubt regarding these criteria from the information given in the title and abstract was resolved on the basis of full text retrieval and panel discussion. The quality of the eligible studies was assessed blinded by two reviewers independently, with disagreements resolved by a third reviewer until consensus was obtained.

The following criteria were adopted:

1. Was the allocation truly random? score 2: sequence produced by computer or randomized number score 1:”randomized allocation ” was referred to but without definite description score 0: semi- or quasi- randomization

2. Was the treatment allocation concealed? score 2: appropriate allocation concealment sealed envelope controlled by centre or pharmacy
D E S C R I P T I O N O F S T U D I E S

The search strategy identified a total of 36 citations or meeting abstracts. Two reviewers scanned the title, abstract, key words and any studies which did not meet the inclusion criteria were excluded. Further screening of the trials identified by the search strategy excluded 32 items, as they were found to be non-randomized (n=12), uncontrolled (n=2) or focused on basic research (n=4), not latest report (n=3), no detailed data available (n=13) or other (n=1). There was no inconsistency of agreement between the two reviewers on study eligibility. Most of the regimens used preoperatively consisted of 5-Fu and metabolites such as Uracil-Tegafur (UFT), Carmofur (HCFU), and mitomycin C, epiptobin, cisplatin, MTX, leucovorin intravenously or orally. Some clinical trials investigated the effect of intra-arterial chemotherapy, hypertension or stop-flow perfusion. Patients received postoperative chemotherapy with a same regimen in one study (Kobayashi 2000), no postoperative chemotherapy in three studies (Wang 2000; Kobayashi 2000; Nio 2004).

Characteristics of the four trials included in the analysis are shown (Kobayashi 2000; Hartgrink 2004; Nio 2004; Wang 2000). There were 250 patients in the NAC group and 332 patients in the control group. One study enrolled patients with gastric cardia only (Wang 2000). This study enrolled 60 patients with a half in each arm (50 males and 10 females). The regimen of preoperative chemotherapy was FPLC (5-FU, oleic acid, ginseng polysaccharides, bean phospholipid and cholesterol). The postoperative 5-year survival rate was 40% compared with 23% in the control (p=0.17). None of the patients received postoperative chemotherapy or radiotherapy. The four included trials gastric cancer patients of all kinds.

A well designed study from Dutch Gastric Cancer Group (Hartgrink 2004) randomized 59 patients (29 in the NAC group and 30 in the control group). Patients with early gastric cancer and cardia carcinoma were excluded in this trial. However, little more than half of the patients were staged I and II postoperatively. The sample size was small, which undermined its reliability. The patients in the NAC group received FAMTX (5-FU, doxorubicin, and methotrexate). Complete or partial response was registered in 32% of the FAMTX group. With a median follow-up of 83 months, median survival of the FAMTX and the control group was 18 and 30 months, respectively. The conclusion of this trial was opposed to the NAC regimen.

There are two studies from Japan, using oral fluoropyrimidines (5'-DFUR or UFT). One study (Kobayashi 2000) enrolled 171 patients (120 males and 51 females) with balanced characteristics at the baseline. The other was a randomized consent design trial of neoadjuvant chemotherapy with UFT for gastric cancer (Nio 2004). One hundred and ninety-three and 102 patients were assigned in the control and NAC group, respectively. Of note, the NAC group included patients with significantly higher stages of cancer (p=0.0042). The regimen was well tolerated. The survival benefit can be seen, yet in stage 2 and 3 patients. The search strategy identified a total of 35 citations or meeting abstracts. Two reviewers scanned the title, abstract, key words and any studies
which did not meet the inclusion criteria were excluded. Further screening of the trials identified by the search strategy excluded 31 items, as they were found to be non-randomized, uncontrolled or focused on basic research and so on. There was good agreement between the two reviewers on study eligibility.

Characteristics of the four trials included in the analysis are shown (Kobayashi 2000; Hartgrink 2004; Nio 2004; Wang 2000). There were 250 patients in the NAC group and 332 patients in the control group. One study enrolled patients with gastric cardia only (Wang 2000). The other three included gastric cancer patients of all kinds.

**Methodological Quality**

Of the four studies, three stated random allocation but did not definitely describe this, (Nio 2004; Kobayashi 2000; Wang 2000) including one adopting Zelen's method (Nio 2004). Two made appropriate allocation concealment using sealed envelopes controlled by centre (Kobayashi 2000; Hartgrink 2004). None of the trials was double blind. All trials presented with a detailed description of the number of withdrawals, dropouts and losses to follow-up or indicated in the data shown.

Publication bias has long been recognized as a problem in meta-analysis (Sterne 2002; Thompson 2002). A funnel plot was used to investigate the presence of publication bias in the review. By visual examination, the funnel plot was symmetrical. However, our conclusion was that the funnel plot may not have detected publication bias as the number of studies was small.

Since some studies included carcinoma in the low oesophagus, that may be a source of bias.

**Results**

We experienced difficulty in our attempts to retrieve missing data. Some endpoints had to be omitted or analyzed with available data. In order to select studies for further assessment, two independent reviewers and a final decision maker took part in the eligibility screening and quality evaluation. The results are shown in Table 02.

Primary outcome

Death at the last follow-up

Of the four clinical trials enrolled, there were totally 250 and 332 cases, with 106 and 126 deaths at the end of follow-up in the NAC and control group, respectively. For the outcome of death at the last follow-up, the OR (odds ratio) was 1.05 (95%CI: 0.73-1.50) (Hartgrink 2004; Kobayashi 2000; Nio 2004; Wang 2000). The results showed that no statistical significance (Z=1.07, p=0.29) between two groups.

Secondary outcome

a) Tumour response analysis

Tumour response of NAC for gastric cancer could be evaluated histologically and radiologically. Of the 129 patients available for evaluation receiving NAC, 28.7% demonstrated a complete or partial response (Hartgrink 2004; Nio 2004).

b) Time to progression (TTP)

We could not get the data of time to progression (TTP), so we were unable to carry out the analysis on TTP.

c) Secondary resectability in patients with locally advanced gastric cancer and corresponding morbidity and mortality

Two studies of neoadjuvant chemotherapy for gastric cancer had data on surgical resection rates (Kobayashi 2000; Hartgrink 2004). The relatively small number of eligible studies compromised this analysis, and showed no statistical difference between NAC group and the control. The R0 resection rate was 78.0% and 78.0%, respectively. The R0 resection rate in the NAC group was comparable to that in the control. The OR of R0 resection was 0.96 (95%CI: 0.51-1.83).

d) Toxicity, classified according to WHO Common Toxicity Criteria

The morbidity and mortality of NAC varied with the regimens used preoperatively. Of the 129 patients included in the analyzed studies, only 5 cases had grade III or IV toxicity (Nio 2004; Hartgrink 2004). The major toxicities included neutropaenia, thrombocytopenia, nausea, vomiting, liver dysfunction or tumour bleeding.

**Discussion**

Complete surgical resection of gastric cancer with negative margin (that is, R0 resection) is the most effective treatment to date and is related to better outcome. Unfortunately, many gastric cancer patients admitted to hospital are at an advanced stage and unresectable. Strategies to increase the R0 resection rate and overall survival could include both early detection and downstaging of the lesions. Early detection has proved to be useful in Japan, which leads to a large proportion of early stage lesions and better survival outcome. However, in countries with relatively low incidence of gastric cancer, large scale screening may be not cost effective. Despite much effort to treat advanced gastric cancer, such as extended lymphadenectomy, it has proved difficult to achieve much toward the goal of improved treatment leading to better patient outcome.

Although it is generally agreed that patients with inoperable tumours have a poorer prognosis than those who are resectable, some degree of controversy does exist. That is, that surgical resection, whether curative or not, may be associated with a longer survival and removes the risk of potential complications. In the West it is generally considered by that palliative resection is indicated for primarily obstruction, bleeding, and less frequently perforation. They also found that gastrectomy appeared to be linked with a better survival. Sasako stated that even for linitis plastica that do
not cause obstruction, survival of resected patients was superior to that of non-resected (Sasako 1996). Consequently, to downstage the tumor and improve R0 rate should be the primary goals, and to achieve this for gastric cancer, neoadjuvant chemotherapy may be a potential effective therapeutic strategy.

Neoadjuvant chemotherapy has achieved great success in the management of breast cancer, osteosarcoma, rectal cancer, and other malignancies such as cervical cancer. In fact, neoadjuvant chemotherapy of gastric cancer was first attempted some time ago, the first report being published in 1967 (Fujimoto 1969). These data were updated later, in 1976 (Fujimoto 1976). The study was later neglected because of high toxicity and low response rate. Another factor is that gastric adenocarcinoma is only moderately sensitive to cytotoxic agents such as 5-fluoracil, metronomtate, mitomycin, and cisplatin. However, even with continuing efforts made by surgeons, oncologists, and biomedical professionals, the outcome of gastric cancer has not demonstrated a great improvement for decades, especially for those in the advanced stages of the disease. Patients with locally advanced disease who have undergone an R0 resection constitute the best prognostic group, with an estimated 5-year survival of 25% in Western countries and approximately 30% in Japan. However, even in patients who have a curative resection, nearly two thirds suffer from local recurrence and distant metastasis.

It has been widely accepted that neoadjuvant chemotherapy may facilitate the R0 resection, but whether it can improve the overall survival or not is controversial. To date, randomized clinical trials on neoadjuvant chemotherapy for gastric cancer are rare. All that are available are those retrospective or controlled clinical trials, which can be classified as grade III or less. Of the four randomized controlled studies, 250 and 332 patients with gastric cancer were grouped into NAC and the control group, respectively. In terms of the primary outcome of patient death, no statistical significance was found that between the two groups. With careful assessment, we have reached the conclusion that the regimens and protocols published in our included studies, for neoadjuvant chemotherapy, may not improve the overall survival of gastric cancer.

The regimens of NAC have differed between Japan and Western countries. Japanese regimens usually include oral fluoropyrimidines such as 5-Fu, UFT, 5-DFUR while those of Western countries are often administered intravenously. One report from Nio of Japan used UFT preoperatively. The author did not find any difference in the overall survival compared with the control (Nio 2004). Another study from Japan drew a similar conclusion using 5'-DFUR 600mg/day for more than ten days preoperatively for gastric cancer. Wang from China enrolled only gastric cardia cancer patients in the clinical trial with FPLC 220ml/day orally used as NAC therapy (Wang 2000). The FPLC contained 5-Fu, oleic acid, ginseng polysaccharides, bean phospholipid and cholesterol. This study also did not demonstrate a statistical significant survival benefit. The study of Hartgrink, who reported the long-term results of the Dutch randomized FAMTX trial (Hartgrink 2004), which investigated only 59 cases, did not show a beneficial effect of preoperative FAMTX versus surgery alone.

These differences in the practice of chemotherapy regimens in the West and the East are notable. There are also controversies on the nature of gastric cancer in the East and West and whether the diseases are the same or somewhat different. Further studies enrolling both Western and Eastern gastric cancer patients are strongly recommended and appropriate subgroup analyses should be performed on the results of clinical trials of this kind.

It could be concluded that from a general review, NAC does not play an important role in the survival of gastric cancer patients. However, this does not exclude its effect in subgroups of gastric cancer. Comparative survival curves with or without NAC in the stage 2 and 3 patients demonstrated a statistical significance. Another study reported by Takiguchi concluded that neoadjuvant chemotherapy with 5-Fu/CDDP for gastric cancer patients with serosal invasion may reduce positive peritoneal cytology, and improve prognosis (P=0.0042) (Takiguchi 2003). Therefore, NAC might be helpful for selected gastric cancer patients. In addition, the effect of preoperative chemotherapy may be influenced by such factors as chemotherapeutic regimens, different dosage and usage, combination or single chemotherapy, with or without radiation. This meta-analysis solely reviewed studies which adopted chemotherapy methods for gastric cancer and excluded regimens that included radiotherapy. In some areas of the USA neoadjuvant radiation has been recommended as a standard procedure for gastroesophageal junction carcinoma.

The FAMTX regimen produced a response rate of 32% (8/27), while 5 patients (18.5%) experienced early discontinuation for toxicity (Hartgrink 2004). Conversely, NAC-UFT contributed to 2 CR and 27 PR with a response rate of 33.3% (Kobayashi 2000). Generally, the oral regimens had a relatively minor side-effect profile compared with those administered intravenously. The ‘MAGIC’ trial did not report the response rate of the patients, which may partly because of the difficulty of evaluating the response in gastric cancer.

Only two studies presented data about the rate of R0 resection (Kobayashi 2000; Hartgrink 2004). The analysis showed no statistical difference between NAC group and the control. The R0 resection rate was 78.0% in two studies. The OR of R0 resection was 0.96 (95%CI: 0.51-1.83).

The main limitation of this review is that it is limited to studies of neoadjuvant or preoperative chemotherapy, and does not include studies in which post-operative chemotherapy was also administered. For example, the final results of the UK NCRI MAGIC trial (ST02) which were reported at ASCO 2005 (Cunningham 2005) demonstrated a survival benefit for perioperative chemotherapy with the ECF regimen of epirubicin, cisplatin and 5FU. With more than 500 patients recruited, the study found a 25%
reduction of cancer death with perioperative chemotherapy versus surgery alone with ECF. The regimen ECF was related to moderate adverse effects and similar rates of postoperative complications. However, although these results are important, this trial was not designed to show the contributions of the pre and post-operative components of treatment to the survival benefit separately, so that it would not be possible nor appropriate to combine the results of MAGIC in this meta-analysis. The problem however, with the four studies included in the meta-analysis, all of which were negative studies, is that neoadjuvant treatments used might be regarded now as suboptimal chemotherapies. Therefore, in order to give a more balanced view on this issue, we have discussed the MAGIC results here, and suggest that neoadjuvant treatment might have been shown to be beneficial if a regimen such as ECF was used. Furthermore, the efficacy of ECF in an advanced disease setting is supported by a Cochrane systematic review (Wagner 2005). To date, only the MAGIC trial has drawn a convincing outcome with perioperative ECF regimens for gastric cancer, even those located in the GE junction. We recommend that the results of the MAGIC trials should be considered in the design of future clinical trials.

AUTHORS’ CONCLUSIONS

Implications for practice

To date, no definite evidence has proved the effectiveness in improvement of patient survival. However, our data found marginal benefit in terms of the number of patient deaths at the end of follow-up. Therefore, neoadjuvant chemotherapy should not be used routinely in clinical setting until further results from randomized clinical trials are available. Neoadjuvant chemotherapy for gastric cancer should be applied under the framework of clinical trials, which is a recommendation of the NCCN expert panel. Many new antineoplastic regimens have produced promising results in gastric cancer patients. Further high-level clinical trials with new antineoplastic regimens should be carried out.

Implications for research

It is difficult to apply standard randomized controlled methods to NAC for certain reasons: it is hard to do clinical staging preoperatively; there are possible side effects of NAC; the uncertainty of effects for certain regimens and risk of losing the chance of curative surgery. Well-organized randomized controlled studies are therefore rare.

Unfortunately, the available data were incompletely reported and this made the analysis more difficult. In particular, we encountered difficulties in obtaining complete data on preoperative staging. Thus, the difficulty in obtaining accurate preoperative staging affected the evaluation of efficacy of NAC. We recommend that full preoperative staging information is supplied in publications of future trials of NAC for resectable gastric cancer.

POTENTIAL CONFLICT OF INTEREST

The project is funded by “Peking University Evidence-Based Medicine Programme” (Project No:89300-246156097)

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SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Peking University, Evidence-based medicine programme (No. 89300-246156097) CHINA
References to studies included in this review

Hartgrink 2004  [published data only]

Kobayashi 2000  [published data only]

Nio 2004  [published data only]

Wang 2000  [published data only]

References to studies excluded from this review

Becker 2003

Cunningham 2003

Cunningham 2005

Fujimoto 1969

Fujimoto 1976

Huang 2002

Jin 1999

Karcz 1994

Keizer 1997

Kim 1987

Kobayashi 1994

Liu 1997

Liu 1998

Lygidakis 1999

Marcus 2003

Murakami 1996

Nakamura 1992

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Niimoto 1990

Niimoto 1991

Popiela 1998

Sakamoto 2003

Siewert 1998

Songun 1999

Sugamura 1997

Suzuki 1999

Takahayashi 2000

Takiguchi 2003

Tanaka 1995

Tao 2002

Yamaguchi 1996

Yonemura 1993

Yoshinaka 1988

**Additional references**

**Bonenkamp 1995**

**Cushieri 1999**

**Fujii 1999**

**Hohenberger 2003**

**Ichikura 1999**

**Kang 1996**

**Leichman 2003**

**McCulloch 2003**
McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the

Parker 1996

Parker 1997

Roder 1998

Sasako 1996

Sterne 2002

Thompson 2002

van de Velde 2003

Wagner 2005

Wanebo 1993

Yamazaki 1989

### TABLES

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<td>death at the end of follow-up, R0 resection, overall survival, toxicity</td>
<td>Allocation concealment: C – Inadequate</td>
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<tr>
<td>Kobayashi 2000</td>
<td>randomized controlled trial, intention-to-treat basis</td>
<td>resectable gastric cancer, 65 male, 26 female</td>
<td>5’ DFUR</td>
<td>overall survival, death at the end of follow-up, R0 resection</td>
<td>Allocation concealment: A – Adequate</td>
</tr>
<tr>
<td>Nio 2004</td>
<td>randomized controlled trial, intention-to-treat basis</td>
<td>resectable gastric cancer, 70 male, 32 female, median age 65.3 years</td>
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### Characteristics of excluded studies

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<tr>
<td>Karcz 1994</td>
<td>No randomization</td>
</tr>
<tr>
<td>Keizer 1997</td>
<td>Not latest report</td>
</tr>
<tr>
<td>Kim 1987</td>
<td>No indication</td>
</tr>
<tr>
<td>Kobayashi 1994</td>
<td>No randomization</td>
</tr>
<tr>
<td>Liu 1997</td>
<td>No randomization, No detailed data</td>
</tr>
<tr>
<td>Liu 1998</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Lygidakis 1999</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Marcus 2003</td>
<td>No randomization; No detailed data</td>
</tr>
<tr>
<td>Marakami 1996</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Nakamura 1992</td>
<td>No randomization</td>
</tr>
<tr>
<td>Niimoto 1990</td>
<td>No indication</td>
</tr>
<tr>
<td>Niimoto 1991</td>
<td>No indication</td>
</tr>
<tr>
<td>Popiela 1998</td>
<td>No randomization; No indication</td>
</tr>
<tr>
<td>Sakamoto 2003</td>
<td>No control</td>
</tr>
<tr>
<td>Siewert 1998</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Songun 1999</td>
<td>Not latest report</td>
</tr>
<tr>
<td>Sugamura 1997</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Suzuki 1999</td>
<td>No randomization; No detailed data</td>
</tr>
<tr>
<td>Takabayashi 2000</td>
<td>No detailed data</td>
</tr>
<tr>
<td>Takiguchi 2003</td>
<td>No detailed data</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies (Continued)
Tanaka 1995 No randomization
Tao 2002 No randomization; No detailed data
Yamaguchi 1996 No randomization; No detailed data
Yonemura 1993 No indication
Yoshinaka 1988 No indication

ADDITIONAL TABLES

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage IA</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1, N1, M0; T2, N0, M0</td>
</tr>
<tr>
<td>stage II</td>
<td>T1, N2, M0; T2, N1, M0; T3, N0, M0</td>
</tr>
<tr>
<td>stage IIIA</td>
<td>T2, N2, M0; T3, N1, M0; T4, N0, M0</td>
</tr>
<tr>
<td>stage IIIB</td>
<td>T3, N2, M0</td>
</tr>
<tr>
<td>stage IV</td>
<td>T4, N1, M0; T1, N3, M0; T2, N3, M0; T3, N3, M0; T4, N2, M0; T4, N3, M0; Any T, Any N, M1</td>
</tr>
</tbody>
</table>

Table 02. Jadad Score of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Concealed allocation</th>
<th>Double blind</th>
<th>Complete description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nio 2004</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hartgrink 2004</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wang 2000</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kobayashi 2000</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cunningham 2005</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 03. General characteristics of enrolled studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N of study group</th>
<th>N of control group</th>
<th>Regimen</th>
<th>Dosage</th>
<th>Time of chemotherapy</th>
<th>Percentage of GEJ</th>
<th>Time to operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2000</td>
<td>30</td>
<td>30</td>
<td>FPLC</td>
<td>FPLC 20 ml bid po</td>
<td>12.5 days</td>
<td>100</td>
<td>10-14 days after chemotherapy</td>
</tr>
<tr>
<td>Kobayashi 2000</td>
<td>91</td>
<td>80</td>
<td>5'-DFUR</td>
<td>5'-DFUR 610mg/m2</td>
<td>more than 10 days</td>
<td>Not specified</td>
<td>more than 10 days after chemotherapy</td>
</tr>
<tr>
<td>Nio 2004</td>
<td>102</td>
<td>193</td>
<td>UFT</td>
<td>UFT 4-9mg/m2/day</td>
<td>more than 14 days</td>
<td>Not specified</td>
<td>more than 14 days after chemotherapy</td>
</tr>
<tr>
<td>Hartgrink</td>
<td>29</td>
<td>30</td>
<td>FAMTX</td>
<td>MTX 113(56-156)</td>
<td>3</td>
<td>113(56-156)</td>
<td></td>
</tr>
</tbody>
</table>
Table 03. General characteristics of enrolled studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>N of study group</th>
<th>N of control group</th>
<th>Regimen</th>
<th>Dosage</th>
<th>Time of chemotherapy</th>
<th>Percentage of GEJ</th>
<th>Time to operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td>1500mg/m2 d2, 5-Fu</td>
<td>days days after randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1500mg/m2 d2, leucovorin 30mg d3-4, Doxorubicin 30mg/m2 d15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham</td>
<td>250</td>
<td>253</td>
<td>ECF</td>
<td>Epirubicin 50mg/m2 d1, cisplatin 60mg/m2 d1, 5-Fu 200mg/m1 qd1-21</td>
<td>more than 9 weeks</td>
<td>26</td>
<td>3-6 weeks after chemotherapy</td>
</tr>
</tbody>
</table>

ANALYSES

Comparison 01. NAC versus control

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 death at the end of follow-up</td>
<td>4</td>
<td>582</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>1.05 [0.73, 1.50]</td>
</tr>
<tr>
<td>02 R0 resection</td>
<td>2</td>
<td>227</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>0.96 [0.51, 1.83]</td>
</tr>
<tr>
<td>03 objective response (CR+PR)</td>
<td>2</td>
<td>131</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>1.25 [0.12, 12.61]</td>
</tr>
<tr>
<td>04 grade III-IV toxicity</td>
<td>2</td>
<td>131</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>0.73 [0.03, 20.56]</td>
</tr>
<tr>
<td>05 surgical complications</td>
<td>1</td>
<td>295</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>0.94 [0.48, 1.83]</td>
</tr>
</tbody>
</table>

COVER SHEET

Title
Neoadjuvant chemotherapy versus none for resectable gastric cancer

Authors
Wu AW, Xu GW, Wang HY, Ji JF, Tang JL

Contribution of author(s)
Wu AW:
Conceiving the review; Designing the review; Coordinating the review; Data collection for the review; Developing search strategy; Undertaking searches; Data management for the review; Entering data into RevMan; Interpretation of data; Writing the review

Ji JF:
Conceiving the review; Designing the review; Data management for the review; Analysis of data; Interpretation of data

Tang JL:
Conceiving the review; Designing the review; Analysis of data; Interpretation of data; Providing a methodological perspective

Wang HY:
Conceiving the review; Designing the review; Data management for the review; Data collection for the review; Entering data into RevMan; Analysis of data; Interpretation of data

Xu GW:
Designing the review; Interpretation of data; Providing general advice on the review; Securing funding for the review

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**Editorial group code** HM-UPPERGI
### Analysis 01.01. Comparison 01 NAC versus control, Outcome 01 death at the end of follow-up

Review: Neoadjuvant chemotherapy versus none for resectable gastric cancer
Comparison: 01 NAC versus control
Outcome: 01 death at the end of follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC n/N</th>
<th>control n/N</th>
<th>Odds Ratio (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartgrink 2004</td>
<td>24/27</td>
<td>20/29</td>
<td>3.7 [0.86, 15.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobayashi 2000</td>
<td>34/91</td>
<td>29/80</td>
<td>3.60 [0.56, 2.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nio 2004</td>
<td>30/102</td>
<td>55/193</td>
<td>46.7 [0.56, 1.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2000</td>
<td>18/30</td>
<td>23/30</td>
<td>16.0 [0.15, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>250</td>
<td>332</td>
<td>100.0 [0.73, 1.50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 106</td>
<td></td>
<td></td>
<td>127 (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=4.96 df=3 p=0.17 I² =39.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.25 p=0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 01.02. Comparison 01 NAC versus control, Outcome 02 R0 resection

Review: Neoadjuvant chemotherapy versus none for resectable gastric cancer
Comparison: 01 NAC versus control
Outcome: 02 R0 resection

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC n/N</th>
<th>control n/N</th>
<th>Odds Ratio (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartgrink 2004</td>
<td>18/27</td>
<td>19/29</td>
<td>31.8 [0.35, 3.19]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobayashi 2000</td>
<td>74/91</td>
<td>66/80</td>
<td>68.2 [0.42, 2.02]</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>118</td>
<td>109</td>
<td>100.0 [0.51, 1.83]</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Total events: 92</td>
<td></td>
<td></td>
<td>85 (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.04 df=1 p=0.85 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.11 p=0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 01.03. Comparison 01 NAC versus control, Outcome 03 objective response (CR+PR)

Review: Neoadjuvant chemotherapy versus none for resectable gastric cancer
Comparison: 01 NAC versus control
Outcome: 03 objective response (CR+PR)

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC</th>
<th>Outcome</th>
<th>Odds Ratio (Fixed)</th>
<th>Weight</th>
<th>Odds Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hartgrink 2004</td>
<td>8/27</td>
<td>0/1</td>
<td>1.31 [ 0.05, 35.47 ]</td>
<td>48.1</td>
<td></td>
</tr>
<tr>
<td>Nio 2004</td>
<td>29/102</td>
<td>0/1</td>
<td>1.20 [ 0.05, 30.41 ]</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>129</td>
<td>2</td>
<td>1.25 [ 0.12, 12.61 ]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 37 (NAC), 0 ()
Test for heterogeneity chi-square=0.00 df=1 p=0.97 I² =0.0%
Test for overall effect z=0.19 p=0.8

### Analysis 01.04. Comparison 01 NAC versus control, Outcome 04 grade III-IV toxicity

Review: Neoadjuvant chemotherapy versus none for resectable gastric cancer
Comparison: 01 NAC versus control
Outcome: 04 grade III-IV toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC</th>
<th>Outcome</th>
<th>Odds Ratio (Fixed)</th>
<th>Weight</th>
<th>Odds Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hartgrink 2004</td>
<td>5/27</td>
<td>0/1</td>
<td>0.73 [ 0.03, 20.56 ]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>x Nio 2004</td>
<td>0/102</td>
<td>0/1</td>
<td>Not estimable</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>129</td>
<td>2</td>
<td>0.73 [ 0.03, 20.56 ]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (NAC), 0 ()
Test for heterogeneity: not applicable
Test for overall effect z=0.18 p=0.9
### Analysis 01.05. Comparison 01 NAC versus control, Outcome 05 surgical complications

**Review:** Neoadjuvant chemotherapy versus none for resectable gastric cancer

**Comparison:** 01 NAC versus control

**Outcome:** 05 surgical complications

<table>
<thead>
<tr>
<th>Study</th>
<th>NAC</th>
<th>NAC Odds Ratio (Fixed)</th>
<th>Weight (%)</th>
<th>Control Odds Ratio (Fixed)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nio 2004</td>
<td>15/102</td>
<td>0.94 [0.48, 1.83]</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>102</td>
<td>193</td>
<td>100.0</td>
<td>0.94 [0.48, 1.83]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (NAC), 30 ()

Test for heterogeneity: not applicable

Test for overall effect $z=0.19$, $p=0.8$