Chinese Patients with Gastric Cancer Need Targeted Adjuvant Chemotherapy Schemes

Wen-Tao Shi1,2*, Lei Wei1,2*, Jin Xiang2,3*, Ke Su1,2, Qiong Ding1,2, Meng-Jie Tang1,2, Ji-Qiang Li2, Yi Guo4, Pu Wang5, Jing-Wei Zhang1*

Abstract

Background: Gastric cancer (GC) is one of the most common cancers in China. Adjuvant chemotherapy (AC) is a routine auxiliary treatment for GC recommended by the guidelines issued in 2011 by the Ministry of Health of the People’s Republic of China, but the relevant credible consequences in China have been insufficient because of China’s late start and ethical concerns. Methods: A series of databases, including Cochrane Library, MEDLINE, EMBASE, the Chinese database of the National Knowledge Infrastructure and the VIP database, were searched by 2 reviewers independently for studies investigating AC for GC through March 2012. The retrieved literature was screened according to the eligibility criteria. Results: A total of 35 randomized controlled trials (RCTs) were subjected to the final analysis, including 4,043 patients in treatment group and 3,884 in the control group, as well as 4 clinical-control trials (CCTs), which accessed the final analysis with 238 and 252 patients, respectively. AC reduced the risk of death as a protective treatment with statistical significance (HR=0.91, 95% CI: [0.85, 0.97], P=0.002), and it seemed more effective for Asian than non-Asian patients. The effects of AC were not influenced by the starting time (P>0.05). D2 lymphadenectomy-based chemotherapy was effective (HR=0.89, 95% CI: [0.80, 0.99], P=0.04). Oral S-1 40 mg/m2 after D2 lymphadenectomy might be a better choice for Asians with advanced GC and might result in a greater reduction of adverse events than in non-Asian patients. GRADE quality assessment determined that the strength of the evidence from foreign studies from Europe, the United States and Asian countries other than China was high, while it was moderate for Chinese studies. Conclusion: AC was effective or even curative in Chinese patients in general, although it is still necessary to optimize a targeted AC scheme for Chinese patients with GC.

Keywords: Adjuvant chemotherapy - gastric cancer - regional scheme - quality assessment

Asian Pacific J Cancer Prev, 13 (10), 5263-5272

Introduction

Gastric cancer (GC) is one of the most common cancers in China. Although nationwide retrospective studies have indicated that mortality from GC is declining, it still ranks in third place, behind bronchial lung cancer and liver cancer, in cancer deaths. According to the GLOBOCAN 2008 statistics, there were almost 989,000 new cases worldwide, while approximately 463,000 new cases arose in China, accounting for 48.6%. Simultaneously, approximately 737,000 deaths caused by GC occurred around the world in 2008, nearly 352,000 deaths in China, accounting for 47.8% (Chen, 2008; Zhou et al., 2012).

In China, adjuvant chemotherapy (AC) is a routine auxiliary treatment for GC. After curative gastrectomy, patients obtained greater survival benefits from AC than from surgery alone through reduced tumor relapse rates and prolonged patient life spans, with a small but significant 3%-5% benefit in the overall survival rate after a 5-year follow-up (Panzini et al., 2002). In 2010, the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) Group’s meta-analysis, based on individual patient data (IPD), indicated that postoperative administration with fluorouracil-based regimes would reduce the risk of death compared with surgery alone (Paoletti et al., 2010). According to these study data, AC has been recommended to cure GC in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for oncology. As a result of consulting those guidelines, AC has been advocated for GC in the guidelines issued in 2011 by the Ministry of Health of the People’s Republic of China. Comparative effectiveness research (CER), recently supported by the U.S. government, emphasizes that curative effects should be based on real-world conditions, while the relevant credible consequence in China has been insufficient

1Dept. of Oncology, Zhongnan Hospital, Hubei Key Laboratory of Tumor Biological Behavior, Hubei Cancer Clinical Study Center, 2Dept. of Pathology and Pathophysiology, Hubei Provincial Key Laboratory of Allergy and Immune-Related Diseases Centre for Medical Research, Research Center of Food and Drug Evaluation, 3Dept. of Pharmacy, 4Dept. of Epidemiology, School of Medicine, 5Dept. of Rehabilitation, Zhongnan Hospital, Wuhan University, Wuhan, China
*Equal contributors *For correspondence: Zhangjingwei.wuhu@gmail.com
because of China’s late start and ethical concerns. Therefore, we attempted to estimate the status of AC as a treatment for GC in China compared with other regions and to explore ways of creating targeted AC schemes for Chinese patients with GC.

Materials and Methods

Study retrieval and eligibility criteria

Two reviewers (Q Ding and K Su) independently searched a series of databases for studies investigating AC for GC; including the Cochrane Library (1992 to Mar. 2012), MEDLINE (1960 to Mar. 2012), EMBASE (1976 to Mar. 2012), as well as Chinese databases such as National Knowledge Infrastructure (1979 to Mar. 2012) and the VIP database (1989 to Mar. 2012). Medical Subject Headings (MeSH) and keywords were used, including “stomach neoplasm,” “adjuvant chemotherapy,” “gastric cancer”, and “adjuvant treatment.” In addition, the reference lists of the retrieved full-text papers were also searched to ensure that there were no omissions.

The following inclusion criteria for the literature were determined by consulting clinicians: 1) patients with adequate organ function and a histologically proven diagnosis of GC; 2) studies comparing surgery plus AC with surgery alone; 3) an endpoint of a hazard ratio (HR) of mortality, with the HR reported or data sufficient for calculating the HR being necessary; and 4) in English or Chinese with a published English abstract. We excluded studies about radiotherapy and/or immuno-chemotherapy combined with chemotherapy, trials of repetition and pseudo-randomized trials.

Study selection and data extraction

The titles and abstracts of the retrieved articles were read by both reviewers (JQ Li and MJ Tang) to identify studies according to the eligible criteria above. Then, we attempted to obtain full-text articles using the databases or the Internet or through correspondence with the authors. Based on the qualified results, important information from the included studies was separately extracted by two reviewers (JQ Li and MJ Tang) using a predefined data extraction form; this information included the authors, years of publication, case sources, regimens, dosages, schedules, numbers of patients, recruitment periods, stages, and median follow-up durations.

Analysis of bias risk

The quality of methodological bias for the included studies was assessed by referring to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.2) (Higgins et al., 2011), including evaluation of randomization, allocation concealment, blinding and intention-to-treat (ITT) analysis. Divergence between the reviewers was reconciled by discussion with a third reviewer (JW Zhang), whenever it arose. When necessary, corresponding authors were contacted to clarify details necessary to optimize the relevant data. In addition, some studies were performed using minimization methods to improve the balance of the baselines (Scott et al., 2002). Though it was a type of non-random method, we considered these trials eligible due to their reliable designs and we rated their randomization as high-level.

Assessment of Grades of Recommendation, Assessment, Development, and Evaluation (GRADE), recommended by the Cochrane Collaboration, provides a quantitative quality evaluation system for systematic reviews and guidelines (Guyatt et al., 2011a). Evidence derived from RCTs was considered to be highly qualified. The assessment was implemented according to explicit criteria concerning study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. In addition, when death details were not provided in the original research, we estimated them according to the survival rate.

Statistical analysis

Review Manager 5.1 was used for the statistical analysis and for the quality assessment of individual studies. Stata 11 was used to detect publication. Gradeprofile 3.6 was employed to rate the quality of the evidence. First, we calculated the log-hazard ratio (log HR) of mortality and its standard error (SE) for each study based on the method described (Parmar et al., 1998), unless the study provided results from a univariate Cox regression analysis with log HR and its SE. Second, heterogeneity was estimated using the Chi-square-based Z statistic for statistical significance. If P<0.05 indicated little heterogeneity, we used a fixed-effect model in generic inverse variance to analyze the data; if not, a random effect model was adopted. The amount of heterogeneity was estimated using the I2 statistic. If I2>50%, it indicated that substantial heterogeneity existed. When I2<75%, the heterogeneity between studies could be accepted. Publication bias and selection bias were tested with Stata 11, using funnel plots with Begg’s test. If P>0.05, it revealed the existence of publication bias and selection bias. Finally, the grading strength of the evidence was assessed, followed by the creation of SoF (summary of findings) tables in detail (Guyatt et al., 2011b). The number needed to treat (NNT) was calculated to reveal the curative effects of AC for GC in patients from different geographic areas.

Results

Characteristics of included studies

The process of retrieval is shown in detail in Figure 1. A total of 35 randomized control trials (RCTs) were

Figure 1. Flowchart of Detail Retrieval Process and Selection
| Source          | Regimens            | Dosage                     | Schedule                                      | Patients No. | Stage       | Follow-up |
|-----------------|---------------------|----------------------------|-----------------------------------------------|--------------|-------------|-----------|
| Doiglass 1982   | USA 5-FU, MMC       | 150 mg/m² i.v. day 1       | Every 10 weeks for 2 years                    | 71           | I-IV       | NM        |
| Nakajima 1984   | Japan 5-FU, MMC     | 325 mg/m² i.v. daily days 1-5 | Twice a week for 5 weeks                      | 149          | I-IV       | NM        |
| Engstrom 1985   | USA 5-FU, MMC       | 350 mg/m² i.v. daily days 1-5 | Every 10 weeks for 80 weeks                   | 75           | I-IV       | 81        |
| Bonfanti 1986   | Italy 5-FU, MMC     | 130 mg/m² i.v. daily days 1-5 | Every 10 weeks for 8 weeks                    | 73           | I-IV       | 81        |
| Allum 1987      | Britain 5-FU, MMC   | 15 mg/kg i.v.              | Every 3 weeks for 2 years                     | 141          | I-IV       | 100       |
| Allum 1988      | Britain 5-FU        | 500 mg/kg i.v.             | Once every 3 weeks for 8 courses              | 138          | I-IV       | NA        |
| Combes 1990     | Britain 5-FU, MMC   | 600 mg/m² i.v. days 1, 8, 29, and 36 | Once every 8 weeks for 6 times for 1 year     | 133          | II-III     | 68        |
| Estape 1991     | Spain 5-FU, MMC     | 50 mg/m² i.v. days 1 and 29 | Once every 8 weeks for 24 weeks               | 33           | I-III      | NM        |
| Krook 1991      | USA 5-FU, MMC       | 20 mg/m² i.v. day 1         | Repeat on days 35 and 70 for 3 cycles         | 61           | I-IV       | 68        |
| Grau 1993       | Spain 5-FU, MMC     | 20 mg/m² i.v. day 1         | Once every 8 weeks for 24 weeks               | 68           | II-III     | 105       |
| Hamazoe 1994    | Japan 5-FU, MMC     | 10 mg/kg 48-50°C IPT       | Only once                                      | 42           | IV         | NA        |
| Sausterm 1996   | Austria 5-FU, MMC   | 90 mg/m²                   | Repeated in monthly intervals                 | 33           | III        | 72.5      |
| MacDonald 1999  | USA 5-FU, MMC       | 600 mg/m² i.v. days 1, 8, 29, and 36 | Once every 8 weeks for 6 times for 1 year     | 103          | I-III      | 114       |
| Takahashi 1995  | Japan 5-FU, MMC     | 50 mg/m²                   | Only once                                      | 56           | II-IV      | NM        |
| Lise 1995       | Italy 5-FU, MMC     | 100 ml i.PT                 | Repeated every 45 days for 7 cycles           | 155          | I-IV       | 78        |
| Tsaris 1996     | Greece 5-FU, MMC    | 10 mg/m² i.v. days 1, 2 and 3 | Once every 8 weeks for 3 times for 6 months   | 42           | II-IV      | 60        |
| Nakajima 1997   | Japan 5-FU, MMC     | 166.7 mg/m² i.v.           | 5-FU and MMC, twice a week for 3 weeks; UFT, daily for 18 month | 288          | II-IV      | 72        |
| Czaja 1999      | Poland 5-FU, MMC    | 20 mg/m² i.v. day 1         | 30 days later, tegafur daily for 3 months     | 76           | II-IV-NA   | 37        |
| Fujimoto 1999   | Japan 5-FU, MMC     | 400 mg/m² bid.p.o.          | Only once                                      | 71           | II-IV      | NM        |
| Yu 1999         | Korea 5-FU, MMC     | 10 mg/kg 57°C day 1 IPT    | 5-FU was used daily for 4 days                | 125          | I-IV       | NM        |
| Neri 1991       | Italy 5-FU, MMC     | 700 mg/m² from day 2 IPT   | Only once                                      | 58           | I-IV       | NM        |
| Bajjeta 1992    | Italy 5-FU, MMC     | 120 mg/m² i.v. days 4-6    | Firstly, two cycles of EAP, secondly, two cycles of FU plus leucovorin | 135          | II-IV       | 66        |
| Nakashima 2000  | Japan 5-FU, MMC     | 166.7 mg/m² i.v.           | The cycles were restarted after 28 days       | 288          | II-IV      | NM        |
| Hartgink 2004   | Holland 5-FU, MMC   | 1500 mg/m² i.v. day 2       | Every 4 weeks for a maximum of 4 courses      | 27           | II-III     | 83        |
| Chiopponi 2004  | France 5-FU, MMC    | 30 mg i.v. day 3, 4 every 6 hours | Repeated every 21 days                         | 93           | I-IV       | 101       |
| Bouche 2005     | France 5-FU, MMC    | 200 mg/m² i.v. daily       | The cycles of FU were repeated every 4 weeks  | 127          | II-IV-NA   | 97.8      |
| Tentes 2006     | Greece 5-FU, MMC    | 1600 mg/m² i.v. day 1 IAR  | Three cycles with 1-month rest interval       | 20           | II-IV      | NM        |
| Niti 2006       | Italy 5-FU, MMC     | 1500 mg/m² i.v. day 1       | Every 4 weeks for a maximum of 6 courses      | 194          | II-IV-NA   | 78        |
| Sakuramoto 2007 | Japan 5-FU, MMC     | 70 mg/m² i.v. day 15        | Once every 8 weeks for 6 times for 1 year     | 59           | I-IV       | 68        |
| Nakaigama 2007  | Italy 5-FU, MMC     | 40 mg/m² p.o. daily         | For 4 weeks                                   | 529          | III        | 36        |
| Costanzo 2008   | Italy 5-FU, MMC     | 100 mg/m² i.v. days 1-5     | Repeated every 3 weeks for 6 times            | 112          | II-IIIB    | 60        |
| Nakajima 2010   | Japan 5-FU, MMC     | 30 mg/m² i.v. days 1-4      | Repeated 5 days per week For 16 months        | 93           | II-III     | 74.4      |
| Kulig 2010      | Poland 5-FU, MMC    | 100 mg/m² i.v. days 1-4     | Cycles were repeated at 21-day intervals      | 130          | II-IV-NA   | 73        |
| Schlag 2011     | Germany 5-FU, MMC   | 10 mg/kg i.v. days 1-5      | Twice a week for 5 consecutive weeks          | 82           | I-IV       | NM        |
| Li 2012         | China 5-FU, MMC     | 20 mg/m² i.v. days 1-5      | Repeated 6 to 8 weeks                         | 49           | II-III     | NM        |
| Yang 2010       | China 5-FU, MMC     | 20 mg/m² i.v. days 1-5      | Cycles were repeated at 2-week interval for 8 weeks | 25           | II-IIIB    | NM        |
| Zhang 2012      | China 5-FU, MMC     | 500 mg/m² i.v. days 1-5     | Only once                                      | 40           | I-IV       | NM        |

CT, chemotherapy; S, surgery alone; i.v: intravenous; p.o.: oral; IPT, intra-peritoneal; IAR, intra-arterial; NM, not mentioned.
subjected to the final analysis, including 4043 patients in the treatment group and 3884 in the control group. Among these trials, 21 studies were performed in European countries (Schlag, 1987; Bonfani, 1988; Allum et al., 1989a; Allum et al., 1989b; Coombes et al., 1990; Estape et al., 1991; Grau et al., 1993; Sautner et al., 1994; Lise et al., 1995; Tsavaris et al., 1996; Cirera et al., 1999; Neri et al., 2001; Bajetta et al., 2002; Chipponi et al., 2003; Bouche et al., 2005; Nitti et al., 2006; Tentes et al., 2006; De Vita et al., 2007; Di Costanzo et al., 2008; Kulig et al., 2010), 4 in the United States (Douglass, 1982; Engstrom et al., 1985; Krook et al., 1991; Macdonald et al., 1995) and the remainder in Asian countries other than China (Nakajima et al., 1980; Nakajima et al., 1984; Hamazoe et al., 1994; Takahashi et al., 1995; Fujimoto et al., 1999; Nakajima et al., 1999; Yu et al., 2001; Bajetta et al., 2002; Bouche et al., 2005; Zhang et al., 2005; Nitti et al., 2006; Tentes et al., 2006; Nakajima et al., 2007; Sakuramoto et al., 2007; Li et al., 2009; Yang et al., 2010). Of these studies, 6 of them were conducted in Europe, 3 were conducted in Asian countries other than China, and 3 were conducted in China. Among these trials, the patients were administered intravenous chemotherapy, except for 7 studies in which intra-peritoneal chemotherapy was administered (Hamazoe et al., 1994; Sautner et al., 1994; Takahashi et al., 1995; Fujimoto et al., 1999; Yu et al., 2001; Zhang et al., 2005; Yang et al., 2010) and 1 study in which intra-arterial chemotherapy was given (Tentes et al., 2006). A total of 34 studies mentioned the start time of chemotherapy. Patients from 14 trials started their chemotherapy within a month after surgery (Nakajima et al., 1984; Allum et al., 1989b; Estape et al., 1991; Sautner et al., 1994; Lise et al., 1995; Tsavaris et al., 1996; Cirera et al., 1999; Nitti et al., 2006; Bouche et al., 2005; Zhang et al., 2005; Nitti et al., 2006; Tentes et al., 2006; Kulig et al., 2010; Zhou et al., 2011), while patients in 14 trials began a month or more after surgery (Douglass, 1982; Engstrom et al., 1985; Bonfani, 1988; Allum et al., 1989a; Coombes et al., 1990; Krook et al., 1991; Grau et al., 1993; Macdonald et al., 1995; Neri et al., 2001; Bajetta et al., 2002; Nakajima et al., 2007; Sakuramoto et al., 2007; Di Costanzo et al., 2008; Li et al., 2009). The chemotherapy schedules in the remainder of the trials were started in the peri-operative

### Table 2. Starting Time of AC in Different Geographic Areas

| Subgroups                                         | No. of studies | Heterogeneity | Overall effect | Hazard Ratio                  |
|---------------------------------------------------|----------------|---------------|----------------|-------------------------------|
|                                                   |                | Chi²           | Z              | P 95%CI                        |
| Anti-metabolites plus Others with Anti-tumor antibiotics |                |               |                |                               |
| Within a month                                    | 8              | 0.87 1 0%     | 1.11 0.27 0.93| [0.82, 1.06]                  |
| Europe                                            | 6              | 0.62 0.99 0%  | 0.89 0.37 0.94| [0.82, 1.08]                  |
| Asian other than China                            | 2              | 0.07 0.79 0%  | 0.78 0.43 0.86| [0.59, 1.25]                  |
| a month or more later                             | 7              | 0.62 1 0%     | 0.73 0.46 0.96| [0.85, 1.08]                  |
| Europe                                            | 5              | 0.6 0.96 0%   | 0.71 0.48 0.95| [0.83, 1.09]                  |
| America                                           | 2              | 0.01 0.92 0%  | 0.22 0.82 0.97| [0.74, 1.26]                  |
| peri-operative administration                     | 3              | 0.28 0.87 0%  | 0.97 0.33 0.87| [0.66, 1.15]                  |
| Europe                                            | 1              | —             | 0.6 0.55 0.84 | [0.46, 1.51]                  |
| Asian other than China                            | 1              | —             | 0.47 0.64 0.92| [0.65, 1.30]                  |
| China                                             | 1              | —             | 0.8 0.43 0.75 | [0.38, 1.51]                  |
| not mentioned                                     | 4              | 0.41 0.94 0%  | 0.79 0.43 0.91| [0.71, 1.15]                  |
| Europe                                            | 2              | 0 0.97 0%     | 0.23 0.82 0.96| [0.69, 1.35]                  |
| Asian other than China                            | 2              | 0.19 0.67 0%  | 0.89 0.37 0.86| [0.61, 1.20]                  |
| Anti-metabolites plus Others without Anti-tumor antibiotics | 7              | 0.47 0.92 0%  | 1.52 0.13 0.87| [0.72, 1.04]                  |
| Europe                                            | 1              | —             | 0.53 0.59 0.92| [0.68, 1.25]                  |
| China                                             | 3              | 0.25 0.88 0%  | 1.5 0.13 0.84 | [0.67, 1.06]                  |
| a month or more later                             | 4              | 0.86 0.84 0%  | 0.75 0.45 0.91| [0.70, 1.17]                  |
| Europe                                            | 1              | —             | 0.01 1 0.57   | [0.56, 1.78]                  |
| America                                           | 2              | 0.3 0.59 0%   | 0.63 0.53 0.91| [0.68, 1.22]                  |
| China                                             | 1              | —             | 0.85 0.39 0.64| [0.23, 1.79]                  |
| not mentioned                                     | 4              | —             | 0.03 0.98 0.99| [0.69, 1.43]                  |
| Europe                                            | 1              | —             | 0.03 0.98 0.99| [0.69, 1.43]                  |
| Without anti-metabolites                          | 3              | 1.38 0.5 0%   | 0.99 0.32 0.88| [0.69, 1.13]                  |
| Europe                                            | 3              | 1.38 0.5 0%   | 0.99 0.32 0.88| [0.69, 1.13]                  |
| a month or more later                             | 3              | 0.2 0.9 0%    | 1.87 0.06 0.82| [0.67, 1.01]                  |
| Europe                                            | 1              | —             | 0.97 0.33 0.81| [0.54, 1.23]                  |
| Asian other than China                            | 2              | 0.19 0.66 0%  | 1.59 0.11 0.83| [0.66, 1.04]                  |
| peri-operative administration                     | 3              | 0.05 0.98 0%  | 1.05 0.29 0.82| [0.57, 1.18]                  |
| Asian other than China                            | 3              | 0.05 0.98 0%  | 1.05 0.29 0.82| [0.57, 1.18]                  |
| not mentioned                                     | 1              | —             | 0.5 0.62 0.85 | [0.45, 1.61]                  |
| Asian other than China                            | 1              | —             | 0.5 0.62 0.85 | [0.45, 1.61]                  |
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Table 3. HR of Mortality of D2 Lymphadenectomy-based AC

| subgroups                                      | No. of studies | Heterogeneity | Overall effect | Hazard Ratio | 95% CI |
|------------------------------------------------|----------------|---------------|----------------|--------------|--------|
| D2 lymphadenectomy-based chemotherapy         | 13             | 2.66          | 0%             | 2.1          | 0.04   | 0.89 [0.80, 0.99] |
| Europe                                         | 6              | 0.68          | 0%             | 0.76         | 0.44   | 0.94 [0.81, 1.10] |
| Anti-metabolites + others with anti-tumor antibiotics | 4             | 0.59          | 0%             | 0.47         | 0.64   | 0.96 [0.80, 1.15] |
| Anti-metabolites + others without anti-tumor antibiotics | 1             | 0.53          | 0%             | 0.59         | 0.92   | 0.68 [0.62, 1.25] |
| Without anti-metabolites                       | 1              | —             | —              | 0.41         | 0.68   | 0.89 [0.52, 1.53] |
| Asian countries other than China               | 3              | 0.44          | 0%             | 1.59         | 0.11   | 0.86 [0.71, 1.04] |
| Without anti-metabolites                       | 2              | 0.19          | 0%             | 0.47         | 0.64   | 0.92 [0.65, 1.30] |
| Anti-metabolites + others with anti-tumor antibiotics | 4              | 0.5           | 0%             | 0.8          | 0.43   | 0.75 [0.38, 1.51] |
| Anti-metabolites + others without anti-tumor antibiotics | 3              | 0.42          | 0%             | 1.35         | 0.18   | 0.84 [0.66, 1.08] |

Synthesis of results

Anti-metabolites, anti-tumor antibiotics, alkylating agents, anti-tumor plant medicines, anti-tumor hormonal medicines, anti-tumor auxiliary drugs and miscellaneous anti-tumor drugs were all commonly used as chemotherapeutic agents for resected GC. Among them, the frequency of applications combining anti-metabolites with anti-tumor antibiotics was highest. To clarify the effects of various combinations, we stratified the 39 trials into 3 subgroups based on the agents: a subgroup containing anti-metabolites plus others with anti-tumor antibiotics; a subgroup containing anti-metabolites plus others without anti-tumor antibiotics; and a subgroup without anti-metabolites. There was one article with 3 study groups (Nakajima et al., 1980) divided into 2 individual studies, as well as 1 Chinese article (Zhang et al., 2005). The relevant forest plot data are shown in Figure 2. Using the Z statistical test for analysis, good heterogeneity was calculated within the 3 subgroups (P=1.00, I2=0%). After synthesis of the 41 trials, a test for the overall HR of mortality yielded 0.91 (95% confident interval [CI]: [0.85, 0.97], Z=3.06, P=0.002). The ordinal HRs of mortality of the 3 subgroups were 0.93, 0.90 and 0.84, respectively, with corresponding 95% CIs of [0.86, 1.01], [0.78, 1.03] and [0.73, 0.97]. A significant difference was only displayed in the without-anti-metabolites subgroup (P=0.02). Although the 2 anti-metabolites-based subgroups exhibited no significant differences, the pooled data supported that AC could reduce the risk of death as a protective treatment for the disease.

The starting time of AC was a confusing problem for the clinicians. Postoperative AC was commonly applied, while some patients were begun a month after surgery or even later. Due to confusion over the starting time, the trials were stratified into 4 groups, including administration within a month, administration a month or more later, peri-operative administration and administration not mentioned. The results are displayed in Table 2. No obvious significant differences in the overall estimates were tested in the subgroups (P>0.05). Our findings suggested that the curative effect of AC was not influenced by the time at which the drugs were started.
administered. Because of the different populations’ varying races and living habits, we divided the patients into subgroups according to geographic area. The results are shown in Figure 3. The results of the Z statistical test showed that intra-group heterogeneity was good (P > 0.1). In the 4 subgroups, the HR of mortality was 0.93 (95% CI: [0.86, 1.01]) in Europe, 0.94 (95% CI: [0.77, 1.15]) in the United States, 0.85 (95% CI: [0.74, 0.98]) in Asian countries other than China, and 0.82 (95% CI: [0.66, 1.02]) in China. Only the HR of mortality in Asian countries other than China was statistically difference between the treatment and control groups (Z = 2.29, P = 0.02), indicating that patients in several Asian countries, such as Japan, Korea, and China, could benefit more from AC than patients in non-Asian countries, including the United States, the United Kingdom, Italy, etc. Diversity appeared not only in morbidity and mortality but also in the effects of chemotherapy drugs across different areas. Thus, based on the stratification above, we divided the trials sequentially according to the drugs administered. Certain potential protective effects of the AC drugs for GC patients in each region were tested (HR < 1) without significant differences (P > 0.05), in addition to the subgroups of Asian countries other than China without anti-metabolites exhibited a marginal benefit in the treated group (Z = 1.97, P = 0.05). Nonetheless, the risk of death was reduced more by AC combinations among Asians than among non-Asian patients.

The effects of D2 lymphadenectomy-based AC on GC constituted another controversial focus between the East and West. The Japanese guidelines and clinical trials reported that patients receiving AC could achieve better survival rates than with surgery alone after D2 lymphadenectomy, while many studies revealed that patients in Europe and the United States failed to benefit more from D2 lymph node dissection. To illustrate the effects of D2 lymphadenectomy-based AC, 13 trials of D2 lymphadenectomy-based AC were extracted and showed in Table 3. Though there was no statistical significance (P > 0.05) in any region, the pooled data indicated that D2 lymphadenectomy-based AC was effective (HR = 0.89, 95% CI: [0.80, 0.99], Z = 2.10, P = 0.04), suggesting that AC drugs should be adjusted to adapt to D2 lymphadenectomy, such as intravenous fluorouracil (5-FU) in a range from 350 to 1500 mg/m2. The data originated from Japan, demonstrating that oral S-1 40 mg/m2 after D2 lymphadenectomy was another good choice for advanced GC and for a reduction of adverse events (Sakuramoto et al., 2007).

Based on the results above, sensitivity analysis was conducted. First, the Chinese studies were eliminated because their imperfect design might have led to obvious bias. We found that the pooled data on D2 lymphadenectomy-based chemotherapy were not stable. After the 4 Chinese trials were removed from analysis, the HR of mortality changed to 0.91 (95% CI: [0.81, 1.02]) without significant difference (Z = 1.58, P = 0.11) between the treatment and control groups. Second, we eliminated 2 Japanese studies due to the high survival rates that they reported. Interestingly, we found the same index also changed. The HR of mortality was 0.91 (95% CI: [0.81, 1.03]) and was not significantly different (Z = 1.54, P = 0.12).

### Analysis of bias risk for eligible RCTs and GRADE assessment

To clarify the credibility of the conclusions of the included individual studies, quality assessment was

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### Table 4. Begg’s Test for Publication bias

| Subgroups             | No. of studies | Begg’s test (Z) | P           |
|-----------------------|----------------|-----------------|-------------|
| Europe                | 21             | -1.93           | 0.053       |
| America               | 4              | 0               | 1           |
| Asian other than China| 11             | -1.95           | 0.052       |
| China                 | 5              | -1.96           | 0.05        |

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### Table 5. GRADE Assessment Based on Different Geographic Areas

| No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Treatment (Death/Total) | Control (Death/Total) | Relative Risk | Absolute Risk Reduction | Quality | Importance |
|---------------|-------|--------------|---------------|--------------|-------------|------------------------|-----------------------|---------------|------------------------|---------|------------|
| Mortality of different areas - Europe | 21 randomised trials | no serious | no serious | no serious | no serious | 1298/2158 | 1297/2048 | HR 0.93 | 27 fewer per 1000 | ★★★★ CRITICAL | HIGH |
|                        | -60.1% | -63.30% | (0.86 to 1.01) | from 55 fewer to 4 more |            |                        |                       |               |                        |         |            |
| Mortality of different areas - America | 4 randomised trials | no serious | no serious | no serious | no serious | 169/345 | 188/351 | HR 0.94 | 22 fewer per 1000 | ★★★★ CRITICAL | HIGH |
|                        | -49% | -53.60% | (0.77 to 1.15) | from 90 fewer to 50 more |            |                        |                       |               |                        |         |            |
| Mortality of different areas - Asian countries other than China | 11 randomised trials | no serious | no serious | no serious | no serious | 391/1580 | 481/1447 | HR 0.85 | 42 fewer per 1000 | ★★★★ CRITICAL | HIGH |
|                        | -24.70% | -33.20% | (0.74 to 0.98) | from 5 fewer to 74 fewer |            |                        |                       |               |                        |         |            |
| Mortality of different areas - China | 5 randomised trials | serious1 | no serious | no serious | no serious | 81/238 | 140/252 | HR 0.82 | 70 fewer per 1000 | ★★★☆ CRITICAL | MODERATE |
|                        | -34% | -55.60% | (0.66 to 1.02) | from 141 fewer to 7 more |            |                        |                       |               |                        |         |            |

1 Randomisation was not performed well

### Table 6. NNT of Each Geographic Area

| Areas                  | EER | CER | ARR | SE | NNT | 95% CI |
|------------------------|-----|-----|-----|----|-----|--------|
| Europe                 | 60.15% | 63.33% | 3.18% | 0.015 | 31.43 | [16.34, 407.73] |
| America                | 48.99% | 53.56% | 4.58% | 0.0379 | 21.85 | [8.34, -35.16] |
| Asian other than China | 24.75% | 33.24% | 8.49% | 0.0165 | 11.77 | [8.53, 18.99] |
| China                  | 34.03% | 55.56% | 21.52% | 0.0439 | 4.65 | [3.32, 7.74] |
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implemented, as shown in Figures 4 and 5. The publication bias based on region is shown in Figure 6 and in Table 4. The GRADE evaluation is displayed in Table 5. The GRADE assessment confirmed that the strength of the evidence from the Chinese studies was moderate because similar domestic research seldom focused on comparisons of the curative effects between surgery and AC and surgery only due to certain late starts and ethical concerns.

The NNTs of the regions were 31.43, 21.85, 11.77, and 4.65 for Europe, the United States, Asian countries other than China, and China, which had 95%CIs of [16.34, 407.73], [NNTB8.33~∞~NNTH35.16], [8.53, 18.99], and [3.32, 7.74], respectively, as shown in Table 6. Our findings indicated that Asians, including Chinese, Japanese, and Korean patients, might benefit more from AC than non-Asians, such as American and European patients.

Discussion

China is a high-risk region for GC. The number of deaths in China from GC account for approximately 23% of all deaths from cancer, with nearly 227,000 deaths every year since AC was applied nationwide in China as a routine auxiliary approach for GC. Raw data from RCTs of AC originated from foreign trials conducted between 1970 and 2004, which might not have been optimized for Chinese GC patients because of differences in race and living habits. Therefore, we conducted this systematic review to identify the effects of AC in Chinese patients with GC compared to other Asian countries, including Japan and South Korea, as well as European countries, such as the United Kingdom and Italy, and the United States, with the aim of exploring ways of creating targeted AC schemes for Chinese patients with GC.

Some RCTs indicated that patients receiving AC obtained no greater survival benefits. The Eastern Cooperative Oncology Group (ECOG) found no treatment benefit from AC with 5-FU plus 1-(2-chloroethyl)-3-(4-methylcyclohexil)-1-itrosourea (Me-CCNU), and they concluded, based on a benefit-risk analysis, that this combination was not recommended for patients after resection because of its toxicity (Engstrom et al., 1985). The British Stomach Cancer Group (BSCG) performed another prospective RCT with 138 patients in the treated group and 145 in the control group. After a mitomycin, doxorubicin, and 5-FU (MAF) regimen was given, the 5-year survival rate was 19% in the treatment group and 20% in the control group without statistical significance (P=0.69) (Hallissey et al., 1994). However, AC has been regarded as efficacious in other trials. A phase Ⅲ RCT (ML17032) assessing capecitabine and cisplatin (XP) compared to 5-FU and cisplatin (FP) for advanced GC revealed that the former treatment led to a higher remission rate of 42% vs. 29%, as well as longer survival of 10.5months vs. 9.3 months (Kang et al., 2009). Neri et al. concluded that treatment was the only significant prognostic factor after administering epidoxorubicin, leucovorin and 5-FU (ELF) to the treatment group with a 5-year follow-up (Neri et al., 2001). Similarly, our data...
were consistent with the viewpoint that AC is an effective intervention for GC patients as a protective factor. Suspecting that an earlier starting time for AC would lead to a better theoretical response, our data indicated that the curative effects of AC were not influenced by the time at which the drugs were administered. Starting time might be not an independent risk factor for mortality.

However, some recent research has indicated that the curative effects with respect to GC are not exactly the same in different geographic areas. The divergence originated from a study of lymph node dissection and application of S-1. Sakuramoto et al. showed that S-1 was an effective adjuvant regimen for East Asian patients after D2 lymph-node dissection for locally advanced GC, with 3-year overall survival rates of 80.1% in the S-1 group (95% CI: [76.1, 84.0]) and 70.1% in the surgery-only group (95% CI: [65.5, 74.6]) (Sakuramoto et al., 2007). Some trials conducted in Europe have proved the classical Japanese D2 resection offered no survival advantage over D1 surgery among European patients (Bonenkamp et al., 1999; Cuschieri et al., 1999), while D2 dissection is the standard surgical technique used in Japan. S-1-based chemotherapy and the combination of S-1 and cisplatin are the most reasonable first-line schemes for unresectable advanced GC used in Japan (Kobayakawa et al., 2011), but their application had been delayed in western countries, not only because they do not provide increased survival but also because of postoperative complications and mortality. Another trial, conducted by the First-Line Advanced GC Study group (FLAGS trial), indicated that S-1 plus cisplatin improved safety significantly but did not prolong survival in advanced GC and gastrointestinal adenocarcinoma when compared with cisplatin plus 5-FU (Ajani et al., 2010). Based on these differences, we found that Asians could obtain a greater reduction in mortality risk from D2 lymphadenectomy-based AC, compared to non-Asians, suggesting that relevant studies could be conducted among Chinese patients with GC for further data.

Some individual studies abroad have determined that patients in particular statuses would benefit more from AC compared to other patients with GC. Kulig et al. indicated that a postoperative etoposide, adriamycin and cisplatin (EAP) regimen offered no survival advantage in GC patients, but their subgroup analysis revealed a survival benefit from chemotherapy in patients with tumors infiltrating the serosa and in patients with 7-15 metastatic lymph nodes(Kulig et al., 2010). A phase III trial performed by Al-Batran et al. found that patients aged 65 years old or older would benefit more from 5-FU, leucovorin and oxaliplatin (FLO) than from 5-FU, leucovorin and cisplatin (FLP) (Al-Batran et al., 2008). These multiple findings supported the idea that qualified trials could be performed in China for further investigation.

Our quality assessment determined that the strength of the evidence from foreign studies, conducted in Europe, the United States and Asian countries other than China, was high, while the strength of the evidence from Chinese studies was moderate. Because of late starts and certain ethical issues, standardized RCTs concerning AC treatment for GC have been insufficient among Chinese studies. Given the positive effects of AC, we should focus on optimizing targeted AC schemes for Chinese GC patients based on therapeutic actuality rather than violating our ethics to perform similar trials.

In Conclusion, AC, as an effective intervention for GC seems beneficial for the Chinese patients, even more than for Asians in general. Its effects were not influenced by the starting time of the administration of AC doses, such as 5-FU administered intravenously in the range from 350 to 1500 mg/m2 after D2 lymphadenectomy. Lymphadenectomy-based D2 and S-1 might be a safer and better choice for Asian patients than for non-Asians. Based on these results, it is necessary to optimize schemes for Chinese patients with GC.

Acknowledgements

The author(s) declare that they have no competing interests.

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