RESEARCH ARTICLE

Chinese Patients with Gastric Cancer Need Targeted Adjuvant Chemotherapy Schemes

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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 control 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

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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

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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

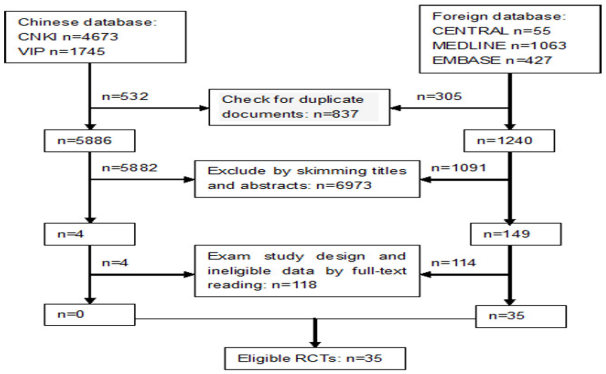

Figure 1. Flowchart of Detail Retrieval Process and Selection

Table 1. Characteristic of Included Studies

Case Source		Regimens	Dosage	Schedule	Patients No. CT	S	Stage	Median (month) follow-up
Douglass 1982	USA	MMC 5-FU 5-FU	150 mg/m² p.o. day 1 325 mg/m² i.v. daily days 1-5 375 mg/m² i.v. daily days 36-40	Every 10 weeks for 2 years	71	71	I-IV	NM
Nakajima 1984	Japan	"5-FU" MMC Ara-C	167 mg/m² i.v. 1.3 mg/m² i.v. 13 mg/m² i.v.	Twice a week for 5 weeks	149	74	I-IV	NM
Engstrom 1985	USA	Methyl CCNU 5-FU 5-FU	150 mg/m² p.o. day 1 350 mg/m² i.v. daily days 1-5 375 mg/m² i.v. daily days 36-40	For 2 years	91	89	I-IV	64
Bonfanti 1988	Italy	Methyl CCNU 5-FU 5-FU	130 mg/m² p.o. day 1 325 mg/m² i.v. daily days 1-5 375 mg/m² i.v. daily days 36-40	Every 10 weeks for 80 weeks	75	69	I-IV	81
Allum 1989	Britain	5-FU MMC	15 mg/kg i.v. 150 ug/kg i.v.	Every 3 weeks for 2 years	141	130	II-IV	100
Allum 1989	Britain	5-FU MMC Adriamycin	600 mg/m² i.v. 4 mg/m² i.v. 30 mg/m² i.v.	Once every 3 weeks interval for 8 courses	138	145	I-IVA	NM
Coombes 1990	Britain	5-FU MMC Adriamycin	600 mg/m² i.v. days 1, 8, 29, and 36 4 mg/m² i.v. day 1 30 mg/ m² i.v. days 1 and 29	Once every 8 weeks for 6 times for 1 year	133	148	II-III	68
Estape 1991	Spain	MMC	20 mg/m² i.v. 1 day	Once every 6 weeks for 24 weeks	33	37	I-III	NM
Krook 1991	USA	5-FU Doxorubicin	350 mg/m² i.v.push. days 1-5 40 mg/m² i.v. day 1	Repeat on days 35 and 70 for 3 cycles	61	64	I-IV	68
Grau 1993	Spain	MMC	20 mg/m² i.v. 1 day	Once every 6 weeks for 24 weeks	68	66	II-III	105
Hamazoe 1994	Japan	MMC Saline	10 ug/ml 48-50°C IPT	Only once	42	40	I-IV	NM
Sautner 1994	Austria	Cisplatin Saline	90 mg/m² 2000ml IPT	Repeated in monthly intervals	33	34	III-IV	72.5
Macdonald 1995	USA	5-FU MMC Doxorubicin	600 mg/m² i.v. days 1, 8, 29, and 36 10 mg/m² i.v. day 1 30 mg/m² i.v. days 1 and 29	Once every 8 weeks for 6 times for 1 year	93	100	I-III	114
Takahashi 1995	Japan	MMC Carbon Saline	50 mg 375 mg 100 ml IPT	Only once	56	57	II-IV	NM
Lise 1995	Italy	5-FU MMC Doxorubicin	400 mg/m² i.v. days 1-3, 22-24 10 mg/m² i.v. day 1 40 mg/m² i.v. days 2 and 23	Repeated every 43 days for 7 cycles	155	159	I-IV	78
Tsavaris 1996	Greece	5-FU MMC Epirubicin	600 mg/m² i.v. days 1, 8, 29, and 36 10 mg/m² i.v. day 1 45 mg/m² i.v. days 1 and 29	Once every 8 weeks for 3 times for 6 months	42	42	II-IV	60
Nakajima 1999	Japan	5-FU MMC UFT	166.7 mg/m² i.v. 1.4 mg/m² i.v. 300 mg/m² p.o. daily	5-FU and MMC, twice a week for 3 weeks; UFT, daily for 18 month	288	285	II-IV	72
Cirera 1999	Spain	MMC Tegafur	20 mg/m² i.v. day 1 400 mg/m² bid p.o.	30 days later, tegafur daily for 3 months	76	72	II-IVA	37
Fujimoto 1999	Japan	MMC Saline	10 ug/ml 48-50°C IPT	Only once	71	70	II-IV	NM
Yu 2001	Korea	MMC 5-FU	10 ug/ml 37°C day 1 IPT 700 mg/m² from day 2 IPT	5-FU was used daily for 4 days	125	123	I-IV	NM
Neri 2001	Italy	5-FU Leucovorin Epirubicin	450 mg/m² i.v. days 1-3 200 mg/m² i.v. days 1-3 75 mg/m² i.v. day 1	Only once	58	40	I-IV	NM
Bajjeta 2002	Italy	Etoposide Adriamycin Cisplatin 5-FU Leucovorin	120 mg/m² i.v. days 4-6 20 mg/m² i.v. days 1 and 7 40 mg/m² i.v. days 2 and 8 375 mg/m² i.v. days 1-5 100 mg/m² i.v. days 1-5	Firstly, two cycles of EAP; secondly, two cycles of FU plus leucovorin. The cycles were restarted after 28 days.	135	136	II-IV	66
Nashimoto 2003	Japan	5-FU MMC Ara-C	166.7 mg/m² i.v. 1.33 mg/m² i.v. 13.3 mg/m² i.v.	Twice weekly for the first 3 weeks	127	123	II-III	69
Hartgrink 2004	Holland	Methotrexate 5-FU Leucovorin Doxorubicin	1500 mg/m² i.v. day 2 1500 mg/m² i.v. day 2 30 mg i.v. day 3, 4 every 6 hours 30 mg/m² i.v. day 15	Every 4 weeks for a maximum of 4 courses.	27	29	II-III	83
Chipponi 2004	France	5-FU Leucovorin CDDP Saline	375 mg/m² i.v. days 1-5 200 mg/m² i.v. daily 15 mg/m² i.v. daily 1L	Repeated every 21 days	93	103	I-IV	101
Bouche 2005	France	5-FU 5-FU Cisplatin	800 mg/m² i.v. days 1-5 1 g/m² i.v. days 1-5 after 4 weeks 100 mg/m² i.v. day 2	The cycles of FUP were repeated every 4 weeks	127	133	II-IV	97.8
Tentes 2006	Greece	5-FU MMC Doxorubicin	1600 mg/m² i.v. days 1 IAR 7 mg/m² i.v. day 3 IAR 15 mg/m² i.v. day 2 IAR	Three cycles with 1-month rest interval	20	20	II-IV	NM
Nitti 2006	Italy	Methotrexate 5-FU Leucovorin Adriamycin Epirubicin	1500 mg/m² i.v. day 1 1500 mg/m² i.v. day 1 15 mg i.v. days 2-4 every 6 hours 30 mg/m² i.v. day 15 or 70 mg/m² i.v. day 15.	Every 4 weeks for a maximum of 6 courses	194	203	IB-IVA	78
Sakuramoto 2007	Japan	S-1	40 mg/m² p.o. daily	For 4 weeks	529	530	IB-III	36
Vita 2007	Italy	5-FU Leucovorin Epirubicin Etoposide	375 mg/m² i.v. days 1-5 100 mg/m² i.v. days 1-5 60 mg/m² i.v. day 1 80 mg/m² i.v. days 1-3	Repeated every 3 weeks for 6 times	112	113	IB-IIIB	60
Nakajima 2007	Japan	Uracil–tegafur	360 mg/m² p.o. daily	Repeated 5 days per weekFor 16 months	93	95	II-III	74.4
Costanzo 2008	Italy	5-FU Leucovorin Epirubicin Cisplatin	300 mg/m² i.v. days 1-4 100 mg/m² i.v. days 1-4 30 mg/m² i.v. days 1 and 5 40 mg/m² i.v. days 1 and 5	Cycles were repeated at 21-day intervals	130	128	IB-IVA	73
Kulig 2010	Poland	Doxorubicin Etoposide Cisplatin	20 mg/m² i.v. days 1 and 7 120 mg/m² i.v. days 4 and 5 40 mg/m² i.v. days 2 and 8	3 courses, administered every 28 days	141	154	IB-IVA	37
Nakajima 1980	Japan	5-FU MMC Ara-C	5 mg/kg i.v 0.04 mg/kg i.v. 0.4 mg/kg i.v.	Twice a week for 5 consecutive weeks	82	38	I-IV	NM
Schlag 1987	Germany	5-FU BCNU	10 mg/kg i.v. days 1-5 40 mg/m² i.v. days 1-5	Repeated every 6 to 8 weeks	49	54	II-III	NM
Li DZ 2009	China	5-FU Leucovorin Oxaliplatin	400-600 mg/m² i.v. days 1-2 200 mg/m² i.v. day 1 85 mg/m² i.v. day 1	Cycles were repeated at 2-week interval for 8 weeks	25	25	II-IIIB	NM
Yang Y 2010	China	Sapylin 5-FU	5KE 500 mg in 5000 ml saline. 43°C IPT	Only once	40	39	I-IV	NM
Zhou JW 2011	China	5-FU Teniposide Oxaliplatin	500 mg/m² i.v. days 1-5 30 mg/m² i.v. days 1-5 85 mg/m² i.v. days 1-5	Cycles were repeated at 3-week interval for 4-6 cycles	45	41	II-III	53
Zhang YQ 2005	China	Cisplatin 5-FU Ondansetron	40-50 mg 750 mg in 5000 ml saline. 43°C IPT 8 mg i.v.	Cycles were repeated at 2-week interval for 3-4 cycles	128	147	I-IV	NM

CT, chemotherapy; S, surgery alone; i.v.: intravenous; p.o.: oral; IPT, intra-peritoneal; IAR, intra-arterial; NM, not mentioned

Table 2. Starting Time of AC in Different Geographic Areas

subgroups	No. of studies	Heterogeneity			Overall effect		Hazard Ratio	95%CI
		Chi^2	P	I^2	Z	P		
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								
within a month	4	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	1	[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	1	—	—	—	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								
within a month	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]

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., 2004; Hartgrink et al., 2004; 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; Nashimoto et al., 2003; Nakajima et al., 2007; Sakuramoto et al., 2007). None of the RCTs conducted in China were included because of a lack of control groups undergoing surgery alone. However, to reflect the recent status of chemotherapy for GC in China, we retained 4 clinical-control trials (CCTs) (Zhang et al., 2005; Li et al., 2009; Yang et al., 2010; Zhou et al., 2011) that provided the final analyses with 238 patients in AC plus surgery groups and 252 in surgery alone groups.

Individual study information from all 39 trials is provided in Table 1. D2 lymphadenectomy was performed in 12 studies (Sautner et al., 1994; Cirera 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; Nashimoto et al., 2003; 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 3. HR of Mortality of D2 Lymphadenectomy-based AC

subgroups	No. of studies	Heterogeneity			Overall effect		Hazard Ratio	95%CI
		Chi^2	P	I^2	Z	P		
D2 lymphadenectomy-based chemotherapy	13	2.66	1	0%	2.1	0.04	0.89	[0.80, 0.99]
Europe	6	0.68	0.98	0%	0.76	0.44	0.94	[0.81, 1.10]
Anti-metabolites + others with anti-tumor antibiotics	4	0.59	0.9	0%	0.47	0.64	0.96	[0.80, 1.15]
Anti-metabolites + others without anti-tumor antibiotics	1	—	—	—	0.53	0.59	0.92	[0.68, 1.25]
Without anti-metabolites	1	—	—	—	0.41	0.68	0.89	[0.52, 1.53]
Asian countries other than China	3	0.44	0.8	0%	1.59	0.11	0.86	[0.71, 1.04]
Anti-metabolites + others with anti-tumor antibiotics	1	—	—	—	0.47	0.64	0.92	[0.65, 1.30]
Without anti-metabolites	2	0.19	0.66	0%	1.59	0.11	0.83	[0.66, 1.04]
China	4	0.5	0.92	0%	1.54	0.12	0.83	[0.66, 1.05]
Anti-metabolites + others with anti-tumor antibiotics	1	—	—	—	0.8	0.43	0.75	[0.38, 1.51]
Anti-metabolites + others without anti-tumor antibiotics	3	0.42	0.81	0%	1.35	0.18	0.84	[0.66, 1.08]

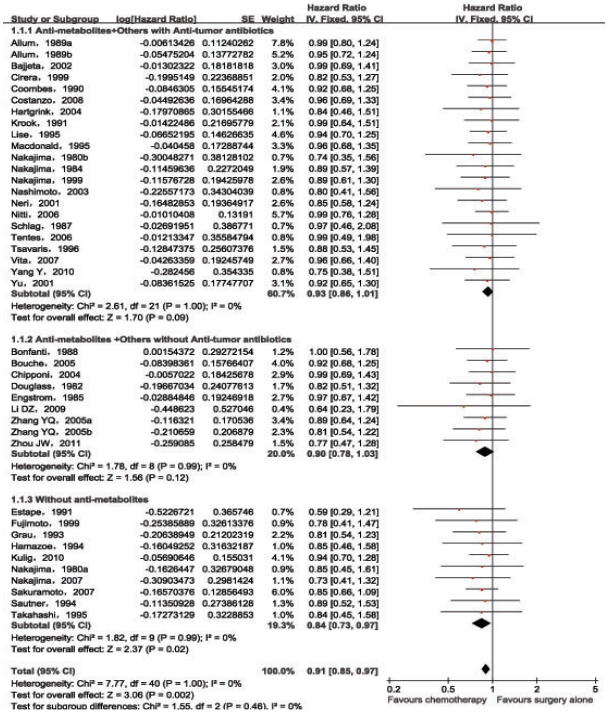

Figure 2. HR of Overall Mortality of Individual Studies Based on Different AC Regimens

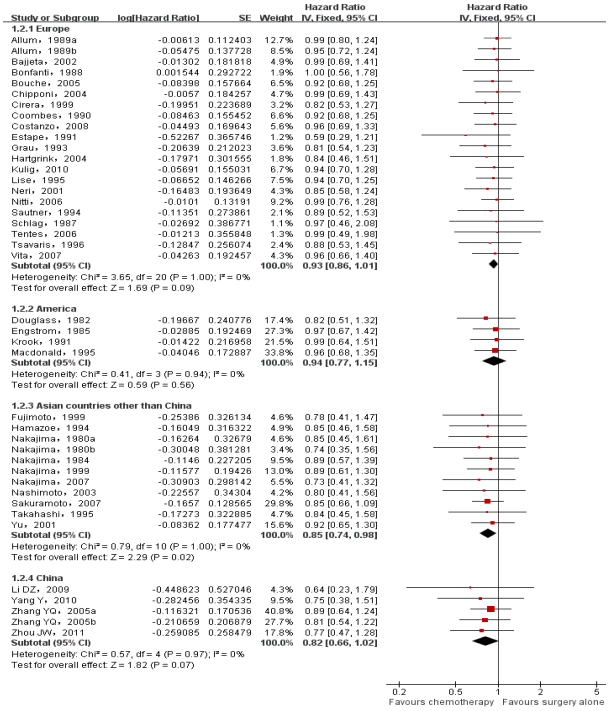

Figure 3. HR of Overall Mortality of Individual Studies Based on Different Geographic Areas

period (Hamazoe et al., 1994; Takahashi et al., 1995; Fujimoto et al., 1999; Yu et al., 2001; Hartgrink et al., 2004; Yang et al., 2010).

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

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 are 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).

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

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

Table 5. GRADE Assessment Based on Different Geographic Areas

No. of studies	Design	Quality assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	No. of patients: Treated (Death/Total)	Control (Death/Total)	Effect: Relative (95% CI)	Absolute	Quality	Importance
Mortality of different areas - Europe											
21	randomised trials	no serious	no serious	no serious	no serious	1298/2158 -60.10%	1297/2048 -63.30%	HR 0.93 (0.86 to 1.01)	27 fewer per 1000 (from 55 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality of different areas - America											
4	randomised trials	no serious	no serious	no serious	no serious	169/345 -49%	188/351 -53.60%	HR 0.94 (0.77 to 1.15)	22 fewer per 1000 (from 90 fewer to 50 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality of different areas - Asian countries other than China											
11	randomised trials	no serious	no serious	no serious	no serious	391/1580 -24.70%	481/1447 -33.20%	HR 0.85 (0.74 to 0.98)	42 fewer per 1000 (from 5 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality of different areas - China											
5	randomised trials	serious1	no serious	no serious	no serious	81/238 -34%	140/252 -55.60%	HR 0.82 (0.66 to 1.02)	70 fewer per 1000 (from 141 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL

[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]

EER, experimental event rate; CER, control event rate; ARR, absolute risk reduction

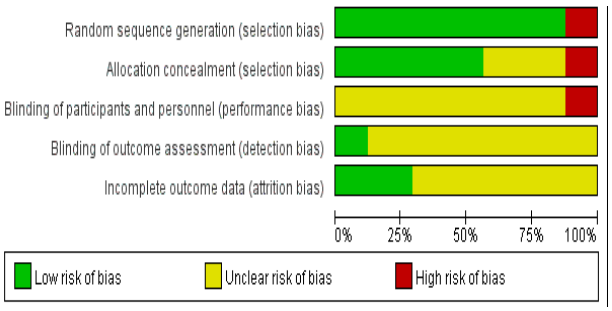

Figure 4. Risk of Bias Graph of Included Studies

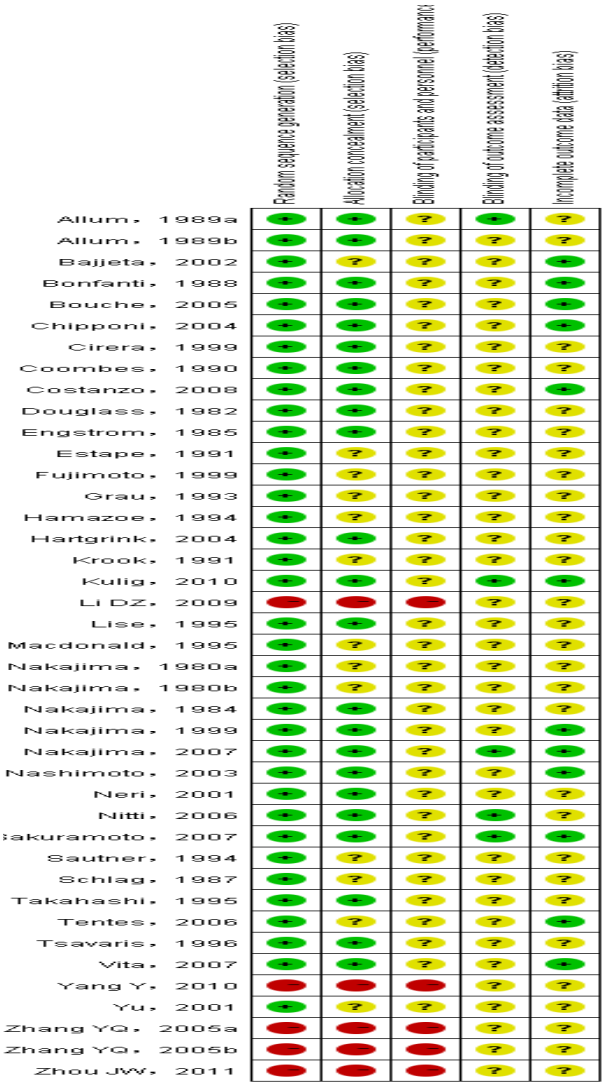

Figure 5. Risk of Bias Summary

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,

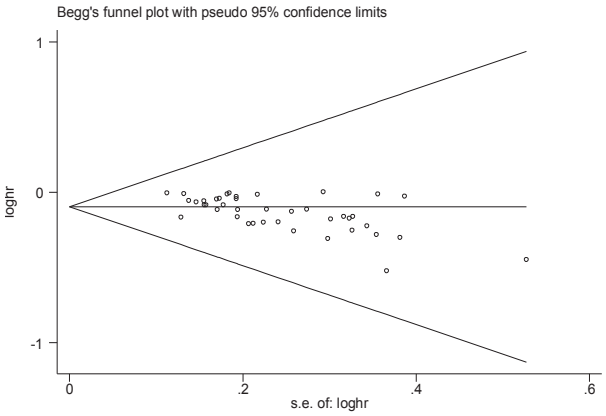

Figure 6. Begg's Funnel Plot of Included Studies

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 gastroesophageal 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.

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References

Ajani JA, Rodriguez W, Bodoky G, et al (2010). Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol,* **28**, 1547-53.

Al-Batran SE, Hartmann JT, Probst S, et al (2008). Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol*, **26**, 1435-42.

Allum WH, Hallissey MT, Kelly KA (1989a). Adjuvant chemotherapy in operable gastric cancer. 5 year follow-up of first British Stomach Cancer Group trial. *Lancet*, **1**, 571-4.

Allum WH, Hallissey MT, Ward LC, Hockey MS (1989b). A controlled, prospective, randomised trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. British Stomach Cancer Group. *Br J Cancer*, **60**, 739-44.

Bajetta E, Buzzoni R, Mariani L, et al (2002). Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. *Ann Oncol*, **13**, 299-307.

Bonenkamp JJ, Hermans J, Sasako M, et al (1999). Extended lymph-node dissection for gastric cancer. *N Engl J Med*, **340**, 908-14.

Bonfani G (1988). Adjuvant treatments following curative resection for gastric cancer. *Br J Surg*, **75**, 1100-4.

Bouche O, Ychou M, Burtin P, et al (2005). Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). *Ann Oncol*, **16**, 1488-97.

Chen Z. Report of the third national mortality retrospective sampling survey. Beijing: Peking Union Medical College Press; 2008.

Chipponi J, Huguier M, Pezet D, et al (2004). Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. *Am J Surg*, **187**, 440-5.

Cirera L, Balil A, Batiste-Alentorn E, et al (1999). Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. *J Clin Oncol,* **17**, 3810-5.

Coombes RC, Schein PS, Chilvers CE, et al (1990). A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. *J Clin Oncol*, **8**, 1362-9.

Cuschieri A, Weeden S, Fielding J, et al (1999). Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer,* **79**, 1522-30.

De Vita F, Giuliani F, Orditura M, et al (2007). Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). *Ann Oncol*, **18**, 1354-8.

Di Costanzo F, Gasperoni S, Manzione L, et al (2008). Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. *J Natl Cancer Inst*, **100**, 388-98.

Douglass HO Jr. (1982). Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. The Gastrointestinal Tumor Study Group. *Cancer*, **49**, 1116-22.

Engstrom PF, Lavin PT, Douglass HO, Jr., Brunner KW (1985). Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Cooperative Oncology Group study (EST 3275). *Cancer*, **55**, 1868-73.

Estape J, Grau JJ, Lcobendas F, et al (1991). Mitomycin C as an adjuvant treatment to resected gastric cancer. A 10-year follow-up. *Ann Surg*, **213**, 219-21.

Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T (1999). Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer*, **85**, 529-34.

Grau JJ, Estape J, Alcobendas F, Pera C, Daniels M, Teres J (1993). Positive results of adjuvant mitomycin-C in resected gastric cancer: a randomised trial on 134 patients. *Eur J Cancer*, **29A**, 340-2.

Guyatt G, Oxman AD, Akl EA, et al (2011a). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol,* **64**, 383-94.

Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A (2011b). GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*, **64**, 380-2.

Hallissey MT, Dunn JA, Ward LC, Allum WH (1994). The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. *Lancet*, **343**, 1309-12.

Hamazoe R, Maeta M, Kaibara N (1994). Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer*, **73**, 2048-52.

Hartgrink HH, van de Velde CJ, Putter H, et al (2004). Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. *Eur J Surg Oncol*, **30** ,643-9.

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) 2011.

Kang YK, Kang WK, Shin DB, et al (2009). Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol,* **20**, 666-73.

Kobayakawa M, Kojima Y (2011). Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: a review comparing it with other fluoropyrimidine-based therapies. *Onco Targets Ther*, **4**, 193-201.

Krook JE, O'Connell MJ, Wieand HS, et al (1991). A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. *Cancer*, **67**, 2454-8.

Kulig J, Kolodziejczyk P, Sierzega M, et al (2010). Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial. *Oncology*, **78**, 54-61.

Li DZ, Zhao YT, Song Z (2009). Effects of FOLFOX4 neoadjuvant chemotherapy protocol on advanced gastric cancer. *J Xinxiang Med College*, **26**, 170-2.

Lise M, Nitti D, Marchet A, et al (1995). Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regimen in resectable gastric cancer. *J Clin Oncol*, **13**, 2757-63.

Macdonald JS, Fleming TR, Peterson RF, et al (1995). Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. *Ann Surg Oncol*, **2**, 488-94.

Nakajima T, Fukami A, Takagi K, Kajitani T (1980). Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5-fluorouracil and cytosine arabinoside after curative resection of gastric cancer. *Jap J Clin Oncol*, **10**, 187.

Nakajima T, Takahashi T, Takagi K, Kuno K, Kajitani T (1984). Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. *J Clin Oncol*, **2**, 1366-71.

Nakajima T, Nashimoto A, Kitamura M, et al (1999). Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. *Lancet*, **354**, 273-7.

Nakajima T, Kinoshita T, Nashimoto A, et al (2007). Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. *Br J Surg*, **94**, 1468-76.

Nashimoto A, Nakajima T, Furukawa H, et al (2003). Randomized trial of adjuvant chemotherapy with mitomycin, Fluorouracil, and Cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. *J Clin Oncol*, **21**, 2282-7.

Neri B, Cini G, Andreoli F, et al (2001). Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer*, **84**, 878-80.

Nitti D, Wils J, Dos Santos JG, et al (2006). Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. *Ann Oncol*, **17**, 262-9.

Panzini I, Gianni L, Fattori PP, et al (2002). Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori*, **88**, 21-7.

Paoletti X, Oba K, Burzykowski T, et al (2010). Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA*, **303**, 1729-37.

Parmar MK, Torri V, Stewart L (1998). Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*, **17**, 2815-34.

Sakuramoto S, Sasako M, Yamaguchi T, et al (2007). Adjuvant chemotherapy for gastric cancer with S-1, an oral

fluoropyrimidine. *N Engl J Med*, **357**, 1810-20.
Sautner T, Hofbauer F, Depisch D, Schiessel R, Jakesz R (1994). Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. *J Clin Oncol*, **12**, 970-4.
Schlag P (1987). Adjuvant chemotherapy in gastric cancer. *World J Surg*, **11**, 473-7.
Scott NW, McPherson GC, Ramsay CR, Campbell MK (2002). The method of minimization for allocation to clinical trials. a review. *Control Clin Trials*, **23**, 662-74.
Takahashi T, Hagiwara A, Shimotsuma M, Sawai K, Yamaguchi T (1995). Prophylaxis and treatment of peritoneal carcinomatosis: intraperitoneal chemotherapy with mitomycin C bound to activated carbon particles. *World J Surg*, **19**, 565-9.
Tentes AA, Markakidis SK, Karanikiotis C, et al (2006). Intraarterial chemotherapy as an adjuvant treatment in locally advanced gastric cancer. *Langenbecks Arch Surg*, **391**, 124-9.
Tsavaris N, Tentas K, Kosmidis P, et al (1996). A randomized trial comparing adjuvant fluorouracil, epirubicin, and mitomycin with no treatment in operable gastric cancer. *Chemotherapy*, **42**, 220-6.
Yang Y, Xu Q, Huang YN, Yang SJ, Du P (2010). Clinical study of intraperitoneal injection of sapylin combined with intraperitoneal hyperchemic hypo-osmolar infusion during radical gastrectomy. *Mod Oncol*, **18**, 1340-2.
Yu W, Whang I, Chung HY, Averbach A, Sugarbaker PH (2001). Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg*, **25**, 985-90.
Zhang YQ, Xu HM (2005). Analysis and evaluation for the effect of postoperative introperitoneal chemotherapy in gastric cancer. *Chin J Clin Oncol*, **32**, 38-41.
Zhou JW, Zhou Y, Luo ZF, et al (2011). Adjuvant chemotherapy of teniposide combined with oxaliplatin and 5-fluorouracil for resected gastric carcinoma. J Chin Pract Diagn Ther, **25**, 641-3.
Zhou XN, Sun XB, Chen WQ, et al (2012). Analysis of incidence and mortality of stomach cancer in China from 2003 to 2007. *Tumor*, **32**, 109-14.