

Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials

Jian-Kun Hu, Zhi-Xin Chen, Zong-Guang Zhou, Bo Zhang, Jing Tian, Jia-Ping Chen, Li Wang, Chao-Hua Wang, Hong-Yan Chen, You-Ping Li

Jian-Kun Hu, Zhi-Xin Chen, Zong-Guang Zhou, Bo Zhang, Jing Tian, Jia-Ping Chen, Chao-Hua Wang, Hong-Yan Chen, General Surgery Department, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China

Li Wang, You-Ping Li, Chinese Evidence-Based Medicine/Cochrane Center, Chengdu 610041, Sichuan Province, China

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Correspondence to: Drs. Jian-Kun Hu and Zong-Guang Zhou, General Surgery Department, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China. fjkcm1111@hotmail.com

Telephone: +86-28-85422479

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Abstract

AIM: To assess the safety and efficacy of different intravenous chemotherapeutic regimens in patients with gastric carcinomas who had undergone gastrectomy.

METHODS: A meta-analysis of all the relevant randomized controlled trials (RCTs) was performed. Language was restricted to Chinese and English. RCTs were identified from Medline and Embase (1980-2001/4), and Chinese Biomedicine Database (1990-2001/1). Literature references were checked at the same time. We included randomized and quasi-randomized trials comparing the efficacy of intravenous chemotherapy after gastrectomy with that of surgery alone in patients with confirmed gastric carcinomas who had undergone gastrectomy. Selection criteria were: randomized or quasi-randomized trials with following-up results; Trials could be double-blind, single-blind or not blind; Chemotherapy groups were given intravenous chemotherapy after gastrectomy without neo-adjuvant chemotherapy, intraperitoneal hyperthermic perfusion, radiotherapy or chemoimmunotherapy; Controlled group included those receiving gastrectomy alone. The following data were extracted: the number of survival and death by the end of the follow-up; the different agents and doses of the intravenous chemotherapy; the baseline of the chemotherapy group and the controlled arm; the serious adverse events; the statistical consideration; cost-effectiveness analysis. The statistical analysis was performed by RevMan4.1 software which was provided by the Cochrane Collaboration. A *P* value of <0.05 was considered statistically significant. Meta-analysis was done with random effects model. Heterogeneity was checked by chi-square test. Sensitivity analysis was performed by excluding the trials in which Jadad-scale was only 1 score. The result was expressed with odds ratio (OR) for the categorical variable.

RESULTS: Fourteen trials involving 4543 patients were included. Meta-analysis was done with random effects model.

Heterogeneity and sensitivity analysis were performed also. The effect of intravenous chemotherapy after gastrectomy was better than surgery alone (odds ratio 0.56, 95 %CI 0.40-0.79). There was a significant difference between the two groups by *u*-test (*P*=0.0008). Sensitivity analysis revealed the same difference (odds ratio 0.81, 95 % CI 0.70-0.94). Of fourteen trials, only three studies were of high quality according to the Jadad-scale (with three score). There was one meta-analysis trial and the others, about ten trials, were of low quality. There was no trial which mentioned sample-size calculation, allocation concealment, intention-to-treat analysis. Most of the trials didn't describe the blind-procedure. There were five trials which detailed the side-effects according to the toxicity grade by WHO standard. The side-effects halting treatment were haematologic and biochemical toxicity, debilitating nausea and vomiting. There were two patients died of chemotherapy toxicity.

CONCLUSION: Based on the review, intravenous chemotherapy after gastrectomy may have positive treatment effect on gastric cancer. However, the evidence is not strong because of the general low methodologic quality of the RCTs. Therefore, we can't make the conclusion that intravenous chemotherapy after gastrectomy may have better treatment effect on gastric cancer than that of surgery alone. Rigorously designed, randomised, double-blind, placebo-controlled trials are required.

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. The outcome of patients with gastric carcinoma has recently been significantly improved with advances in experimental researches, early diagnosis and surgical techniques^[1-44]. Although chemotherapy and radiation therapy have been tried as either an adjuvant or palliative treatment, their values are limited by toxicity or the lack of efficacy^[45]. While surgery remains the mainstay of potentially curative treatment, survival rates for patients able to undergo complete resection are poor^[46]. The five year survival rate for resected gastric cancer is about 30-60 % which has been disappointing. A number of studies have investigated whether intravenous chemotherapy after a resection improves the survival rate or not, but the results are different and disputed. Hermans *et al*^[47] reviewed the randomized controlled trials by meta-analysis, the results indicated that postoperative chemotherapy in general offered no additional survival benefit for patients with curatively resected gastric cancer. Janunger *et al*^[48] performed a systematic overview of chemotherapy effects in gastric cancer by the Swedish Council

of Technology Assessment in Health Care(SBU). A meta-analysis of 21 randomised adjuvant studies revealed a statistically significant survival benefit (OR=0.84, 95 % CI 0.74-0.96).

The aim of meta-analysis is to summarize the results of randomized trials performed to evaluate the effect of intravenous chemotherapy for gastric cancer^[47]. The analysis is restricted to trials published since 1980. Surgical resection without any adjuvant therapy is considered standard treatment. Only intravenous chemotherapy trials with gastrectomy control arm were taken into consideration in this meta-analysis.

MATERIALS AND METHODS

Materials

Randomized or quasi-randomized trials comparing the efficacy of intravenous chemotherapy after gastrectomy with that of surgery alone in patients with confirmed gastric carcinomas who had received gastrectomy were included in this meta-analysis. Language was restricted to Chinese and English.

Selection criteria were: randomized or quasi-randomized trials with following-up results; Trials could be double-blind, single-blind or not blind; Chemotherapy groups were given intravenous chemotherapy after gastrectomy without neo-adjuvant chemotherapy, intraperitoneal hyperthermic perfusion, radiotherapy or chemoimmunotherapy; Controlled group included those receiving gastrectomy alone.

Exclusion criteria were prior malignancy; neo-adjuvant chemotherapy, intraperitoneal hyperthermic perfusion, radiotherapy or chemoimmunotherapy; patients who didn't receive gastrectomy; the controlled studies also included those without gastrectomy.

Methods

Search strategy Search was applied to the following electronic databases: the Cochrane Library, MEDLINE (1980-2001.4), EMBASE (1980-2001.4) and Chinese Bio-medicine Database (1990-2001/1). Literature reference proceedings were handsearched at the same time. The searching words were chemotherapy, stomach neoplasms and surgery.

Data collection and analysis Data were extracted independently by two reviewers. The methodological quality of trials was evaluated using the Jadad-scale plus allocation concealment. Intention-to-treat analyses were performed.

The following data were extracted: the number of survival and death by the end of the follow-up; the different agents and doses of the intravenous chemotherapy; the baseline of the chemotherapy group and the controlled arm; the serious adverse events; the statistical consideration; cost-effectiveness analysis.

The statistical analysis was performed by RevMan4.1 software which was provided by the Cochrane Collaboration. A *P* value of <0.05 was considered statistically significant. Meta-analysis was done with random effects model. Heterogeneity was checked by chi-square test. If the results of the trials had heterogeneity, random effects model was used for meta-analysis. Sensitivity analyses was performed by excluding the trials which Jadad-scale was only 1 score. The result was expressed with odds ratio(OR) for the categorical variable.

RESULTS

There were 1076 papers relevant to the searching words. Through the steps of screening the title, reading the abstract and the entire article, twenty-seven randomized trials were identified. Only fourteen randomized trials comparing the efficacy of intravenous chemotherapy after gastrectomy with that of surgery alone in patients with confirmed gastric carcinomas, including 4543

patients, met the inclusion criteria^[47,49-56,1A-5A]. There were six trials which were excluded for repetitive studies^[57-60,6A,7A], five for having been included in the result of the Hermans' meta-analysis^[61-65], two for no available data^[66,67]. Of fourteen included trials, four trials were conducted in China (see appendix)^[2A-5A], three in England^[50,55,1A], two in Italy^[49,54], two in Spain^[51,56], one in Korea^[52], Germany^[53] and Netherlands^[47] respectively. The average sample size was 324 patients (from 25 to 1967 patients). The follow-up time was from forty-eight months to one hundred and twenty months. The chemotherapy regimens used were FAM,MMC,MFV,MFC,FEM and 5-FU+BCNU(Table 1). All the baselines of the trials were parallel. None of them performed the cost- effectiveness analysis.

Table 1 Data from 14 trials on intravenous chemotherapy versus surgery alone after resection for gastric cancer

Author	Published time	Chemotherapy regimens	Chemotherapy group (number of death/total)	Surgery group (number of death/total)	Follow-up time (months)
Lise	1995	FAM	88/163	99/163	78
Hallisey	1994	FAM	101/138	110/145	60
Estape	1991	MMC	16/33	31/37	120
Kim	1992	FM	54/77	71/94	60
Li LJ	1994	MFV/MFC/FAM	167/308	282/341	60
Wang BD	1994	FM+Ara-C	49/78	36/42	36
Li HX	1994	FM	182/208	192/213	60
Coombes	1998	FEM	36/42	38/42	60
Schlag	1987	5Fu+BCNU	21/42	28/53	72
Neri	1996	Epidoxorubicin	36/48	48/55	36
Zhou GX	1998	FM	35/41	38/40	60
Lawton	1981	5Fu+BCNU	11/13	10/12	60
Cirera	1999	MMC+Tegafur	33/76	44/72	37
Hermans	1993	Meta-analysis	720/1098	588/869	NA

Abbreviations: F/5-Fu, fluorouracil; A,doxorubicin; M/MMC, mitomycin; C/Ara-C,cytarabine; E,etoposide; V,vinblastine; BCNU,1,3-bis-(2-chloroethyl)-1-(nitrosourea); NA,no available.

The effectiveness of intravenous chemotherapy after gastrectomy was better than surgery alone (odds ratio 0.56, 95 % CI 0.40-0.79). The results of the trials showed inconsistency, as checked by the chi-square test ($\chi^2=52.54$, $P<0.00001$). There was a significant difference between the two groups by u-test ($P=0.0008$) (Figure 1). By excluding the low quality trials^[2A-5A], the sensitivity analysis was performed and revealed the same difference between chemotherapy and surgery alone (odds ratio 0.81, 95 % CI 0.70-0.94, $P=0.005$) (Figure 2).

Of fourteen trials, only three studies^[49,50,56] were of high quality according to the Jadad-scale (with three score). There was one meta-analysis trial^[47] and the others, about ten trials were of low quality. There was no trial which mentioned sample-size calculation, allocation concealment, intention-to-treat analysis. Most of the trials didn't describe the blind-procedure. Therefore, the methodologic quality of the RCTs is not strong enough to testify the conclusion.

There were five trials^[49,53-56] which detailed the side-effects of medicine according to World Health Organization grade. The side-effects halting treatment were haematologic and biochemical toxicity, debilitating nausea and vomiting. There were two patients died of chemotherapeutic toxicity (one died of cardiac toxicity and the other of massive alimentary tract

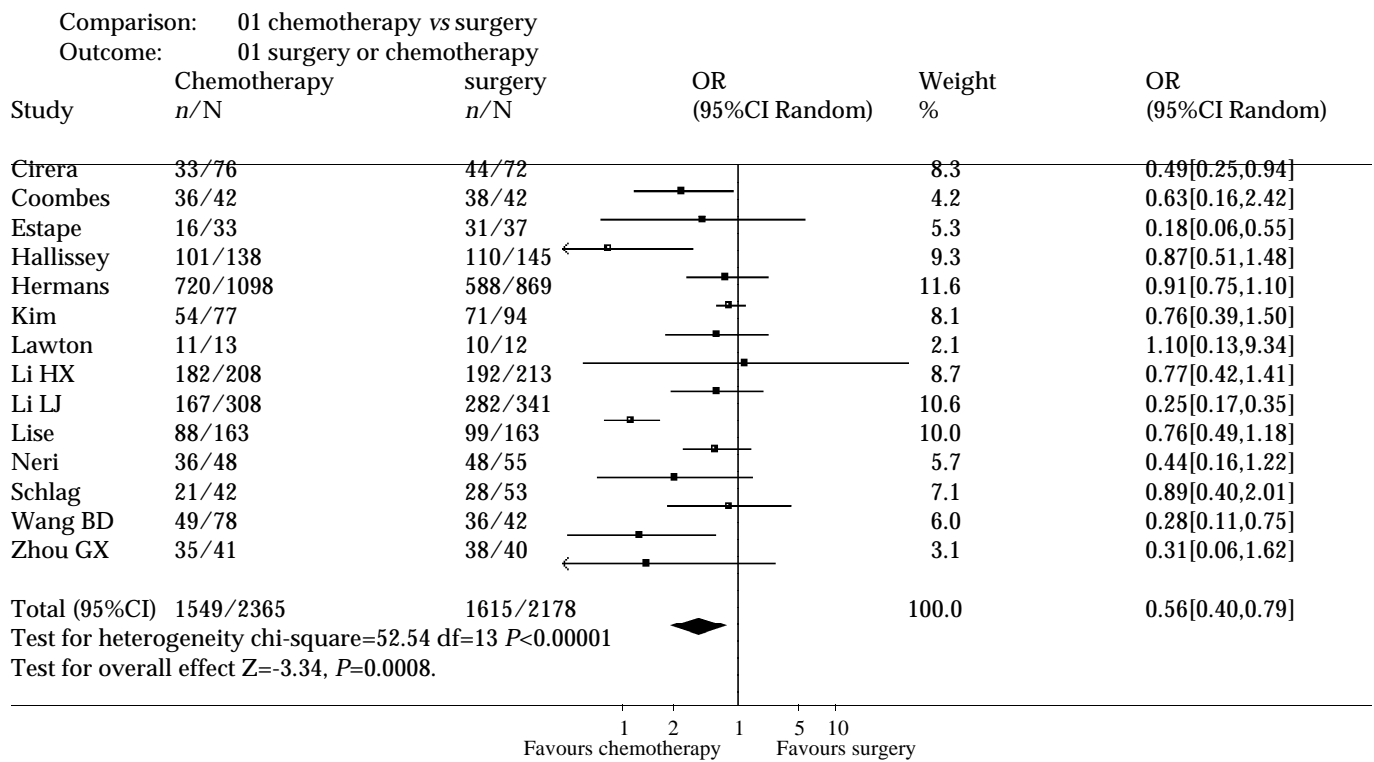


Figure 1 The effectiveness of intravenous chemotherapy versus surgery alone

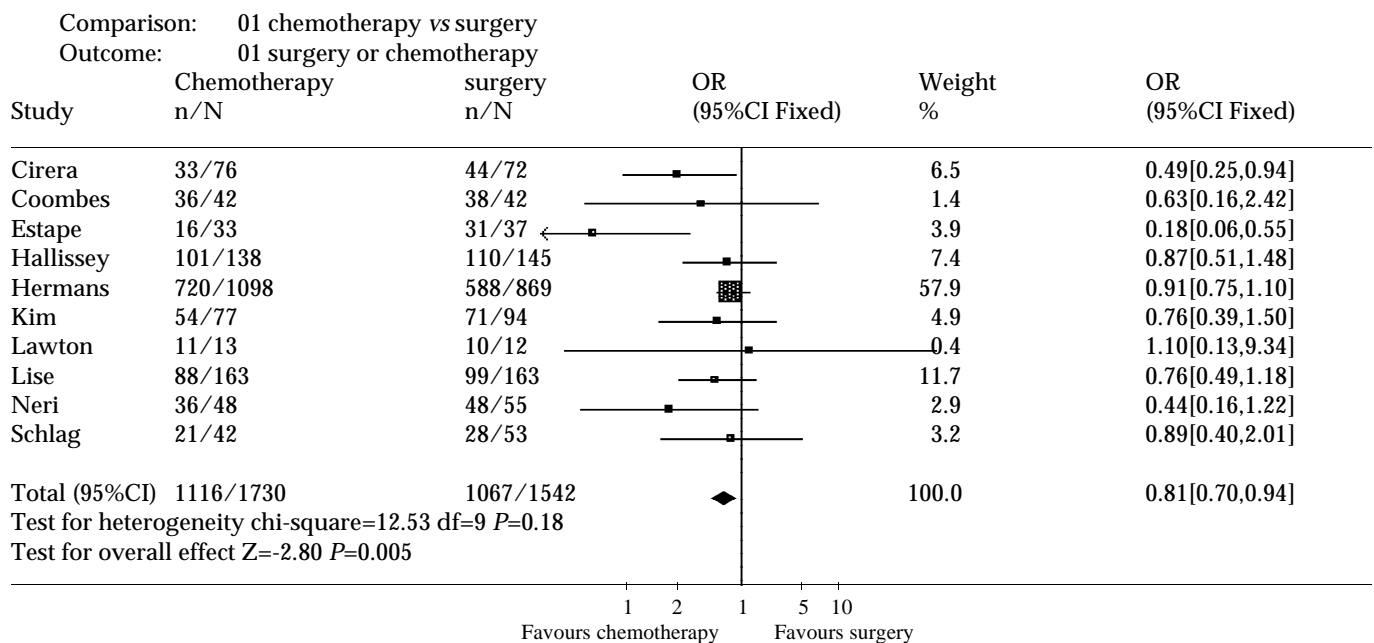


Figure 2 Sensitivity analysis

hemorrhage because of thrombopenia). Severe toxicity (grade 3 or 4 according to the WHO scale) occurred in 5.33 %, with alopecia in 39 patients, leucopenia (WBC values less than 2 000/ μ L) in 18, nausea in 21, thrombopenia (platelet count less than 50 000/ μ L) in 13, anemia in 9, vomiting in 5, diarrhea in 5, gastritis in 5, stomatitis in 4, cardiac toxicity in 4, septicemia in 2 and neural toxicity in 1.

DISCUSSION

It is well recognized that most patients who undergo curative resection of gastric carcinoma remain at high risk of local and systematic relapse. Thus, a worldwide effort has been done to develop effective adjuvant therapy to reduce this risk^[68].

The aim of meta-analysis is to summarize the results of randomized trials performed to evaluate the effect of intravenous chemotherapy for gastric cancer. Surgical resection without any adjuvant therapy is considered standard treatment. Only intravenous chemotherapy trials with gastrectomy control arm were taken into consideration in this meta-analysis. There are two meta-analyses to assess the effect of intravenous chemotherapy for gastric cancer with gastrectomy. Hermans *et al*^[47] researched the randomized controlled trials by meta-analysis; the results indicated that postoperative chemotherapy in general offered no additional survival benefit for patients with curatively resected gastric cancer. Janunger *et al*^[48] performed a systematic overview of chemotherapy effects in gastric cancer by the Swedish Council of Technology

Assessment in Health Care (SBU). A meta-analysis of 21 randomised adjuvant studies revealed a statistically significant survival benefit (OR=0.84, 95%CI 0.74-0.96). But we couldn't get the original article of Janunger, therefore we didn't include the trials in this meta-analysis.

Measuring an effect on survival by calculating the odds ratios was proved to be effective in an analysis^[47]. Only four trials which were performed by Cirera^[56], Estape^[51], Li *et al*^[2A] and Wang *et al*^[4A] respectively, demonstrated a positive effect of intravenous chemotherapy versus the controlled group by calculating the odds ratios.

Of included fourteen trials, only three studies were of high quality according to the Jadad-scale. There was one meta-analysis trial and the others, about ten trials were of low quality. There was no trial which mentioned sample-size calculation, allocation concealment, intention-to-treat analysis. Therefore, the methodologic quality of the RCTs is not strong enough to testify the conclusion. Based on the review, intravenous chemotherapy after gastrectomy may have positive treatment effect on gastric cancer. However, the evidence is not strong because of the general low methodologic quality of the RCTs. Rigorously designed, randomised, double-blind, placebo-controlled trials are required.

The toxicity of medicine is an important factor to influence the outcome of the chemotherapy. But unfortunately, there were only five trials which detailed the side effects of medicine according to World Health Organization grade in this meta-analysis. Hence, in the future research, we should put in mind to observe the side effects carefully and describe them by the WHO grade standard.

Recently, such therapies as intraperitoneal hyperthermic perfusion^[69-74], neo-adjuvant chemotherapy^[75-84], radiotherapy^[85-89] and chemoimmunotherapy^[52] are demonstrated with a positive effect to reduce the relapse risk. Tao *et al*^[90] revealed that preoperative regional artery chemotherapy had the effect to induce growth inhibition and apoptosis of gastric carcinoma cells. Cao *et al*^[91] found that human primary gastric cancer cell *in vitro* were methionine-dependent; methionine-free environment might strengthen the killing effect of chemotherapy on human primary gastric cancer cells. But, the scientific conclusion should be supported by the high quality randomized, double-blind, controlled trials.

Appendix A. RCT reports retrieved in Chinese of chemotherapy for resected gastric cancer

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- 5A **Zhou GX**, Peng YM. Clinical study on the effect of chemical therapy to stomach cancer after operation. *Zhongliu Fangzhi Zazhi* 1998; **25**: 294-295
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