RESEARCH ARTICLE

Comparison Different Methods of Intraoperative and Intraperitoneal Chemotherapy for Patients with Gastric Cancer: A Meta-analysis

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Abstract

Purpose: To investigate the efficacy and safety of intraperitoneal chemotherapy (IPC) for patients with gastric cancer and to compare effects between different regimens of IPC. Method: Randomized controlled trials comparing the effects of surgery plus intraperitoneal chemotherapy with surgery alone or comparing the efficacy between different regimens of intraperitoneal chemotherapy were searched for in Medline, Embase, Pubmed, the Cochrane Library and the Chinese BioMedical Disc and so on by two independent reviewers. After quality assessment and data extraction, data were pooled for meta-analysis using RevMan5.16 software. Tests of interaction were used to test for differences of effects among subgroups grouped according to different IPC regimens. Results: Fifteen RCTs with a total of 1713 patients with gastric cancer were included for quality assessment and data extraction. Ten studies were judged to be of fair quality and entered into meta-analysis. Hyperthermic intraoperative intraperitoneal chemotherapy (HR=0.60, P<0.01), hyperthermic intraoperative intraperitoneal chemotherapy plus postoperative intraperitoneal chemotherapy (HR=0.47, P<0.01) and normothermic intraoperative intraperitoneal chemotherapy (HR=0.70, P=0.01) were associated with a significant improvement in overall survival. Tests of interaction showed that hyperthermia and additional postoperative intraperitoneal chemotherapy did not impact on its effect. Further analysis revealed that intraperitoneal chemotherapy remarkably decrease the rate of postoperative hepatic metastasis by 73% (OR=0.27, 95% CI=0.12 to 0.67, P<0.01). However, intraperitoneal chemotherapy increased risks of marrow depression (OR=5.74, P<0.01), fever (OR=3.67, P=0.02) and intra-abdominal abscess (OR=3.57, P<0.01). Conclusion: The present meta-analysis demonstrates that hyperthermic intraoperative intraperitoneal chemotherapy and normothermic intraoperative intraperitoneal chemotherapy should be recommended to treat patients with gastric cancer because of improvement in overall survival. However, it is noteworthy that intraperitoneal chemotherapy can increase the risks of marrow depression, intra-abdominal abscesses, and fever.

Keywords: Gastric cancer - intraperitoneal chemotherapy - meta-analysis - hepatic metastasis - overall survival - safety

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Introduction

Gastric cancer is the fourth most common cancer in the world and currently is the second leading cause of cancer-related death. Each year almost a million new cases of gastric cancer are reported worldwide (Ferlay et al., 2010). Although radical surgery and intravenous chemotherapy have been widely used for gastric cancer, the long-term survival rate is still limited (five-year survival rate 55.3% (Paoletti et al., 2010)). Therefore, in addition to surgery and intravenous chemotherapy, a search for more effective adjuvant treatment method is crucial.

In recent years, intraperitoneal chemotherapy (IPC) has been increasingly used to treat patients with gastric cancer due to the appealing theoretical rationales. Intraperitoneal chemotherapy could concentrate the chemotherapeutic drugs in the abdominal cavity (Howell et al., 1981) and allow them to directly act on the free tumor cells and peritoneal cancerous nodules. Drugs absorbed through the peritoneum enter the portal vein, and also have a chemotherapeutic effect on the liver(Speyer et al., 1981). With the development of IPC, different regimens have occurred. Based on randomized controlled trials(RCT) reporting efficacy of IPC for gastric cancer patients, intraperitoneal chemotherapy mainly can be summarized as the following five types: hyperthermic intraoperative intraperitoneal chemotherapy (HIIC), hyperthermic intraoperative intraperitoneal chemotherapy combined with postoperative intraperitoneal chemotherapy (HIIC+PIC), normothermic intraoperative intraperitoneal chemotherapy (NIIC), normothermic postoperative intraperitoneal chemotherapy (NPIC) and hyperthermic

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postoperative intraperitoneal chemotherapy (HPIC). It remains unclear whether there are differences of effects between these regimens of intraperitoneal chemotherapy. The most concerns may be the timing of drug delivery and the efficacy of hyperthermia. Moreover, whether it is necessary to perform additional postoperative IPC after intraoperative IPC is disputable. In addition to these, safety of IPC is still controversial.

The purpose of the present study is to conduct a systematic review and meta-analysis of published RCTs investigating the effects and safety of intraperitoneal chemotherapy for patients with gastric cancer and to compare effects between different regimens of intraperitoneal chemotherapy.

Materials and Methods

Search strategy

Computer searches were performed by two independent reviewers. The following databases were searched from inception to May 2012: Medline, Embase, Pubmed, the Cochrane Library and the Chinese BioMedical Disc. Combinations of the following search terms were used: 'intraperitoneal chemotherapy', 'peritoneal perfusion', 'gastric cancer', 'stomach cancer', 'gastric carcinoma', 'stomach carcinoma', 'gastric neoplasm' and 'stomach neoplasm'. The languages were set as English and Chinese. The National Medical Journal of China, the Chinese Journal of Surgery, the Chinese Journal of Gastrointestinal Surgery, and the Chinese Journal of Evidence-Based Medicine were searched manually. References of the included literatures were also tracked. The authors of the papers were contacted to follow-up on the data and the complete text when necessary.

Inclusion and exclusion criteria

All included papers had to satisfy the following three requirements: The study had to be a Randomized Controlled Trial (RCT), comparing the treatment effects of surgery plus intraperitoneal chemotherapy with surgery alone or comparing the efficacy between different regimens of IPC; all patients included in the studies had to have primary gastric cancer confirmed by pathology; to remove the interference of intravenous chemotherapy, patients in the experimental group and in the control group had to either not received intravenous chemotherapy at all or received it with the exact same parameters (including therapeutic schedule, dosage, interval, number of treatments, starting time, and so on).

We used the following exclusion criteria: The studies were not clinically relevant, such as animal studies; distant metastasis had occurred in the patients; the follow-up rate was lower than 80%; the patients had received radiotherapy, immunotherapy or molecular targeted therapy. RCTs before 1995 was also excluded considering that significant changes were introduced in surgery (Ravichandran et al., 1995; Roder et al., 1995; Ohtsu et al., 2006;).

For studies conducted by the same research institute at different times, the newer, more complete paper was used.

Data extraction and quality assessment

Data extraction and quality assessment were carried out independently by two investigators. Discrepancies between the two investigators were resolved by discussion or consensus with a senior investigator.

The following data from eligible articles was extracted: first author, year of publication, country of study, patient numbers, proportion of male, regimens of intraperitoneal chemotherapy, characteristics of two arms of RCT and follow-up.

The quality assessments of studies were performed with criteria which were recommended by the National Health Service Centre for Reviews and Dissemination case series quality assessment criteria (University of York) and that were used by Yan et al. (2007). There were seven aspects related to the quality assessment for RCTs used to determine: 1) whether the RCTs was truly random; 2) whether correct concealment of allocation was used; 3) whether the baseline of groups was similar; 4) whether the inclusion criteria were showed; 5) whether proper blinding was conducted; 6) whether loss to follow-up in each group was stated and 7) whether intention-to-treat (ITT) analysis was performed. A trial with seven or six 'yes' to the questions was regarded as high quality. A study with answers of five or four 'yes' was taken for fair quality. If a study had three or fewer 'yes' answers, it was a low quality literature. To avoid compounding bias, low quality studies would not take part in further meta-analysis.

Statistical methods

The primary outcome measure was overall survival (date of resection to date of death). Secondary outcome measure was rates of peritoneal recurrence, distant metastasis and morbidity and mortality.

Overall survival was expressed as the hazard ratios (HR) with 95% confidence intervals (CI). If an HR and the associated 95% CI were not given, we calculated the HR and its CI from other data provided in the article(i.e. the log rank P-value, or from the Kaplan–Meier survival curves directly) with the method reported by Parmar et al(Parmar et al., 1998) and Tierney et al(Tierney et al., 2007). Engauge Digitizer V4.1 software was used to read survival rates from the Kaplan–Meier survival curves. The software used for HR and CI calculations was designed by Matthew Sydes and Jayne Tierney of the Medical Research Council Clinical Trials Unit, London, UK(Tierney et al, 2007).

Odds ratio was used as a summary statistic for secondary outcome measure, because in all RCTs only the absolute numbers of events were given and the time to event was not available.

The meta-analysis was performed using RevMan5.16 software provided by the Cochrane Collaboration. Subgroup analysis was conducted according to regimens of IPC. A random-effect analysis model was applied in order to reduce interstudy heterogeneity. A HR or OR of lower than 1 indicated an advantage for IPC. Heterogeneity was assessed using a Chi-square test. When a P-value of the Chi-square test was less than 0.10, it reflected the presence of significant heterogeneity. We calculated the I^2 statistic to quantify the degree of heterogeneity and an

Table 1. Trial Characters of 17 Included RCTs

First author	Publication year	Country of study	Patient numbers (treatment: control)	Regimens of IPC	Characteristics of two arms of RCT	Follow-up (years)
Fujimoto	1999	Japan	141(71: 70)	Intraoperative delivery of 10 mg/L MMC in 3-4 L perfusate at 43-45oC for 120 min	HIIC vs no IPC	10
Yang	2011	China	68(34: 34)	Intraoperative delivery of 120 mg CDDP and 30 mg MMC in 6 L perfusate at 42-44 oC for 60-90 min	HIIC vs no IPC	5
Yonemura	2001	Japan	139(92: 47)	Intraoperative delivery of 30 mg MMC and 300mg CDDP in 6-8 L perfusate at 42-43.5 oC (48 patients)or 37 oC(44 patients) for 60 min	HIIC vs NIIC vs no IPC	10
Wei	2005	China	156(101: 55)	Intraoperative delivery of 1000 mg/L 5-FU in 4-5 L perfusate at 42-45 oC for 60 min(52 patients) or intraoperative chemotherapy combined with early postoperative delivery of 1000 mg/m² 5-FU (5 times) and 60 mg/m² CDDP (1 time) in 1 L perfusate(49 patients)	HIIC vs HIIC+PIC vs no IPC	3
Kuramoto	2009	Japan	88(59: 29)	Intraoperative delivery of CDDP 100 mg/body in a perfusate at room temperature for 60 min	NIIC vs no IPC	5
Rosen	1998	Australia	91(46: 45)	Intraoperative delivery of 50 mg MMC and 375 mg Activated carbon in a perfusate at room temprature for 24 h	NIIC vs no IPC	3
Takahashi	1995	Japan	113(56: 57)	Intraoperative delivery of 50 mg MMC and 375 mg Activated carbon in 0.5 L perfusate at room tempreture for 180 min	NIIC vs no IPC	3
Yu	2001	Korea	248(125: 123)	Early postoperative delivery of 10 mg/m² MMC in 1 L perfusate at 37 oC for 23 h (1 time) and 700 mg/m² 5-FU in 1 L perfusate for 23 h (4 times)	NPIC vs no IPC	5
Gao	2002	China	120(60: 60)	Intraoperative delivery of 150 mg CDDP and 20 mg MMC in 1.5-2 L perfusate at 43-45 oC for 30 min combined with early postoperative delivery of CDDP 150 mg and 20 mg MMC in 1.5-2 L perfusate at 43-45 oC for 4-6 h	HIIC+PIC vs no IPC	3
Zhang G	2007	China	212(92: 120)	Intraoperative delivery of 100 mg CDDP and 30 mg MMC in 2 L perfusate at 43-45 oC for 30 min	HIIC vs no IPC	5
Deng	2009	China	85(44: 41)	Intraoperative delivery of 1000-1500 mg 5-FU and 20 mg MMC in 3 L perfusate at 42-43 oC for 60-90 min combined with early postoperative delivery of 1000-1500 mg 5-FU in 3 L perfusate at 42-43 oC for 60 min	HIIC+PIC vs no IPC	3
Shimoyama	1999	Japan	29(13: 16)	Intraoperative delivery of 10 mg MMC in 0.5 L perfusate at room temperature for 60 min	NIIC vs no IPC	5
Zhang W	1998	China	63(37: 26)	Intraoperative delivery of 750 mg 5-Fu in 4-5 L perfusate at 42-44oC for 30-45 min	HIIC vs no IPC	3
Ding	2007	China	78(41: 37)	Early postoperative delivery of 60 mg/m² CDDP in 2.5-3.5 L perfusate at 42-44oC for 30 min(4 times)	HPIC vs no IPC	3
Zuo	2004	China	82(46: 36)	Delayed postoperative delivery of 80-100 mg CDDP and 1000mg 5-Fu in 1.75-2 L perfusate at 41-43oC for 60 min(3 times)	HPIC vs no IPC	3

Table 2. Study Quality of Included RCTs

Study	Truly random	Allocation concealment	Baseline character	Inclusion criteria	Proper blinding	Loss to follow-up	Intention to treat	Study quality
Fujimoto	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Fair
Yang	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Fair
Yonemura	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Fair
Wei	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair
Kuramoto	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Fair
Rosen	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Fair
Takahashi	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Fair
Yu	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair
Gao	Yes	Unclear	Yes	No	Unclear	Yes	Yes	Fair
Zhang G	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Fair
Deng	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Poor
Shimoyama	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Poor
Zhang W	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Poor
Ding	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Poor
Zuo	Unclear	Unclear	Yes	No	Unclear	Yes	Yes	Poor

I^2 statistic greater than 50% was considered substantial heterogeneity. Reasons for significant heterogeneity were explored by using sensitivity analyses that removal of certain studies from the analysis as suggested by the forest plot. Publication bias was assessed with the funnel plot. Tests of interaction reported by Altman et al (Altman and Bland, 2003) were used to test for differences of efficacy among subgroups grouped according to different IPC regimens. All p-values in this study were two-sided.

Results

Quantity and quality of studies

Reading of titles or abstracts from 1254 articles resulted in 33 potentially relevant literatures. After carefully reading the full texts of the 33 researches, three studies were excluded because imbalanced intravenous chemotherapy between the experiment group and the control group was used and 4 literatures were excluded due to receiving immunotherapy of patients. Nine duplicated trials were also excluded. In addition, two studies that were reported before 1995 were excluded. The remaining 15 RCTs (Takahashi et al., 1995; Rosen et al., 1998; Zhang et al., 1998; Fujimoto et al., 1999; Shimoyama et al., 1999; Yonemura et al., 2001; Yu et al., 2001; Gao et al., 2002; Zuo et al., 2004; Wei et al., 2005a; Ding et al., 2007; Zhang et al., 2007; Deng et al., 2009; Kuramoto et al., 2009; Yang et al., 2011) were included for data extraction and quality assessment.

In these 15 studies, 1713 patients were randomly allocated, of whom 917 patients were to receive IPC and 796 patients were in the control group. All eligible RCTs were published between 1995 and 2011. Trial characters of 15 included RCTs are summarized in Table 1. Six studies reported the efficacy of hyperthermic intraoperative intraperitoneal chemotherapy. 5 trials studied the efficacy of normothermic intraoperative intraperitoneal chemotherapy. There was only one RCT investigating the efficacy of normothermic postoperative intraperitoneal chemotherapy. 3 researches evaluated the combined effect of hyperthermic intraoperative intraperitoneal chemotherapy plus postoperative intraperitoneal chemotherapy. Efficacy of hyperthermic postoperative intraperitoneal chemotherapy was reported by two literatures. Two studies compared effects of different IPC regimens directly (Yonemura et al, 2001; Wei et al., 2005b).

In all included RCTs, 11 studies were truly random, six literatures used adequate allocation concealment and 10 studies stated that baseline was similar between treatment group and control group. All expect one research reported the inclusion criteria. There were five RCTs that specified numbers lost to follow-up and 8 studies performing ITT analysis. Blinding is impossible in all studies due to intervention measures (IPC). As a result, 5 studies were graded as poor quality. The remaining 10 RCTs were fair quality and would enter into further meta-analysis. Unfortunately, there were no RCTs of high or fair quality that reported efficacy of HPIC. Assessments of study quality of included RCTs are listed in Table 2.

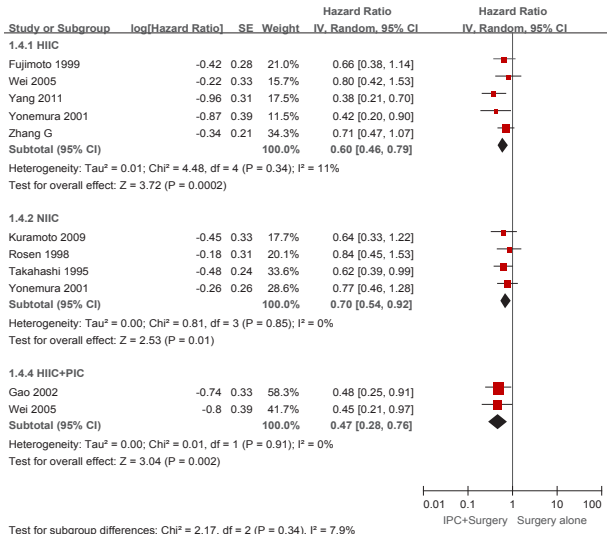

Figure 1. Forest Plot of the Hazard Ratio (HR) of the Overall Survival with Intraperitoneal Chemotherapy Versus Controls for Gastric Cancer

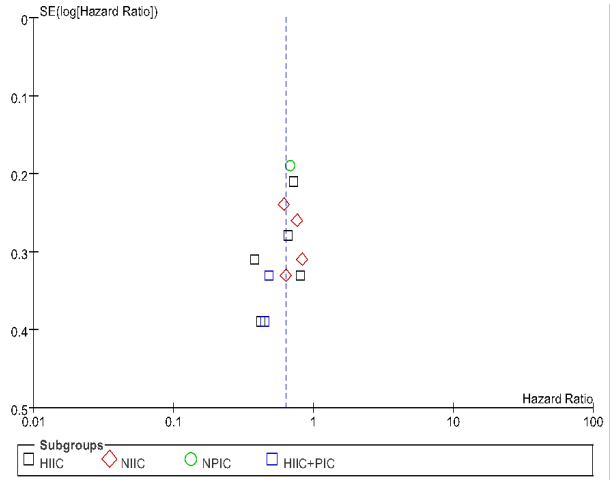

Figure 2. Funnel Plot of the Publication Bias with Intraperitoneal Chemotherapy Versus Controls for Gastric Cancer

Table 3. Tests of Interaction of Overall Survival for Different IPC Chemotherapy

Comparison of subgroups	Ratio of HR	95% CI of ratio of HR	P value
HIIC vs NIIC	0.86	0.59 to 1.25	0.43
HIIC vs HIIC+PIC	1.28	0.72 to 2.25	0.4

Overall Survival

Subgroup analysis was performed according to different intraperitoneal chemotherapy regimens (Figure 1). Hyperthermic intraoperative intraperitoneal chemotherapy and hyperthermic intraoperative intraperitoneal chemotherapy plus postoperative intraperitoneal chemotherapy showed significant survival improvement (HIIC: HR=0.60, CI=0.46 to 0.79, P<0.01; HIIC plus PIC: HR=0.47, CI=0.28 to 0.76, P<0.01). Normothermic intraoperative intraperitoneal chemotherapy was also associated with statistically significant reduction in hazard of death as compared with control (HR=0.70, CI=0.54 to 0.92, P=0.01). However, analysis of normothermic postoperative intraperitoneal chemotherapy was not performed because there was only one RCT. There was no substantial statistical heterogeneity among the trials in each subgroup (Figure 1). Funnel plots showed no evidence of publication bias (Figure 2).

Tests of interaction were performed to compare HIIC with NIIC and to compare HIIC with HIIC plus PIC. No statistic significances were observed (Table 3).

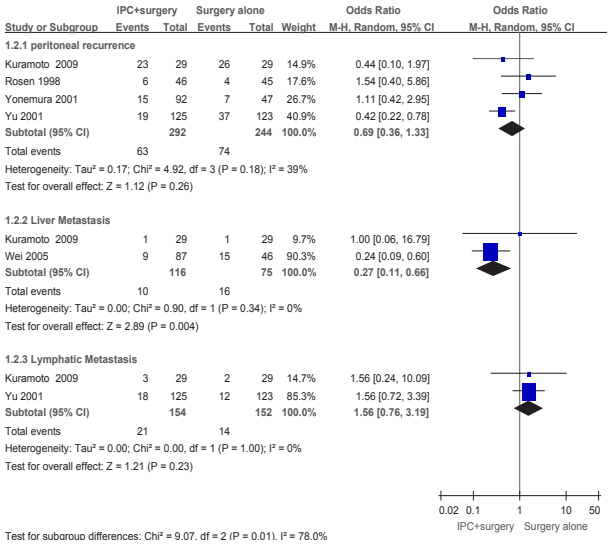

Figure 3. Forest Plot of the Postoperative Relapse and Metastasis Rate with Intraperitoneal Chemotherapy Versus Controls for Gastric Cancer

The effects of IPC on postoperative relapse and metastasis

Postoperative peritoneal relapse rates were reported by 4 RCTs. The number of patients that had occurred postoperative liver metastasis was available in 2 literatures. There were two studies documented the incidence of postoperative lymphatic metastasis. As the number of papers that reported relapse or metastasis rate was small, subgroup analysis based on different intraperitoneal chemotherapy regimens was impossible and instead subgroup analysis based on the anatomical position of relapse or metastasis was performed.

The heterogeneity test showed that there was no heterogeneity within the subgroups. Funnel plots showed there was no publication bias (data not shown). The meta-analysis demonstrated that IPC could significantly decrease the postoperative hepatic metastasis rate: OR=0.27, 95% CI=0.11 to 0.66, P<0.01, suggesting that IPC could decrease the postoperative hepatic metastasis rate by 73%. No effects on decreasing the postoperative peritoneal relapse rate were observed: OR=0.69, 95% CI=0.36 to 1.33, P=0.26. The present meta-analysis revealed that IPC did not significantly change the postoperative rate of lymphatic metastasis (OR=1.56, 95% CI=0.76 to 3.19, P=0.23).

Assessment of Morbidity and Mortality

Data were available for 8 studies (1220 patients) for perioperative mortality, 7 literatures (1012 patients) for anastomotic leakage, 4 RCTs (440 patients) for ileus, 3 researches (393 patients) for bowel perforation, 2 studies (230 patients) for pancreatic fistula, 6 RCTs (888 patients) for marrow depression, 2 literatures (204

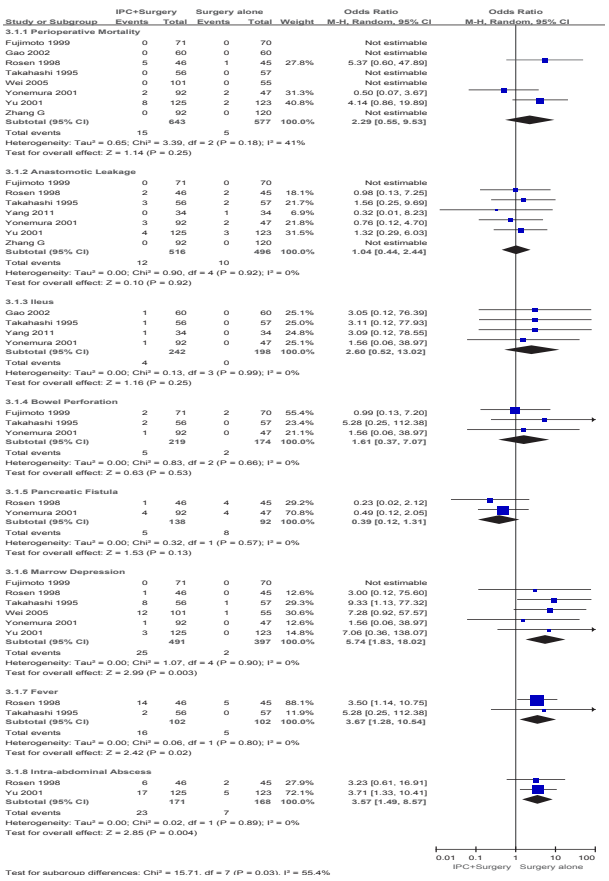

Figure 4. Forest Plot of the Incidence of Postoperative Complications with Intraperitoneal Chemotherapy Versus Controls for Gastric Cancer

patients) for fever, and 2 studies (339 patients) for intra-abdominal abscess. All subgroups showed no significant heterogeneity (Figure 4). Intraperitoneal chemotherapy could significantly increase the incidence of marrow depression after the treatment (OR=5.74, 95% CI=1.83 to 18, P<0.01). IPC was also characterized by a significantly higher incidence of fever and intra-abdominal abscess (Figure 4). There were no significant differences between IPC and control for perioperative mortality, anastomotic leakage, ileus, bowel perforation and pancreatic fistula (Figure 4). No obvious publication bias was obtained in each subgroup (data not shown).

Discussion

The present meta-analysis demonstrates that hyperthermic intraoperative intraperitoneal chemotherapy and hyperthermic intraoperative intraperitoneal chemotherapy plus postoperative intraperitoneal chemotherapy were associated with a significant improvement in overall survival. The efficacy of normothermic intraoperative intraperitoneal chemotherapy was modest but also statistically significant.

Hyperthermia has been considered to have a synergistic or additional anti-tumor activity for IPC (Nakao et al., 2000; Hildebrandt et al., 2002; Coffey et al., 2006; Roti Roti, 2008). To determine this, tests of interaction were conducted to compare hazard ratios between HIIC subgroup and NIIC subgroup. The ratio was 0.86 with 95% CI from 0.59 to 1.25 and P value was 0.43. Thus, no statistically significant variation in the beneficial effect of intraperitoneal chemotherapy on overall survival was seen when hyperthermia was added to. Of all included RCTs in the present meta-analysis, only one RCT reported by Yonemura et al. (2001) directly compare the efficacy of overall survival between hyperthermic intraoperative intraperitoneal chemotherapy and normothermic intraoperative intraperitoneal chemotherapy. Yonemura and co-workers randomized 139 patients with serosal invasion into three groups: hyperthermic intraoperative intraperitoneal chemotherapy plus surgery (48), normothermic intraoperative intraperitoneal chemotherapy plus surgery (44), and surgery alone (47). The overall 5-year survival rate was significantly higher in the HIIC plus surgery group (61 per cent) than in the NIIC plus surgery group (43 per cent) and in those having surgery alone (42 per cent). However, it was noteworthy that this meta-analysis included patients of all stages (from I to IV). For patients with a certain stage or a certain type (such as with serosal invasion), adding hyperthermia to IPC might be effective. These possibly explain some of the discrepancy between our results and those of previous studies.

Because there was only one RCT that reported efficacy of normothermic postoperative intraperitoneal chemotherapy, we could not perform an analysis to evaluate the effect of normothermic postoperative intraperitoneal chemotherapy. We also could not perform tests of interation between normothermic intraoperative intraperitoneal chemotherapy and normothermic postoperative intraperitoneal chemotherapy to decide whether timing of drug delivery could impact effects of IPC. But it should be noted that postoperative intraperitoneal chemotherapy should be carried out as early as possible. This is due to the fact that the tumor burden is still small immediately after the surgery, and abdominal adhesions have not been formed yet; therefore drugs perfused into the abdominal cavity can function fully. If IPC is performed on postoperative 1 month or later, there is barely any therapeutic effect. Because there were no RCTs of high or fair quality that reported efficacy of HPIC, effects of timing of drug delivery on hyperthermic intraperitoneal chemotherapy could not be also concluded.

In recent years, postoperative intraperitoneal chemotherapy (PIC) has been added to HIIC to treat gastric cancer in some studies (Gao et al, 2002; Wei et al, 2005a; Deng et al, 2009). But whether it is necessary to add additional PIC to hyperthermic intraoperative intraperitoneal chemotherapy is controversial. Tests of interaction showed that there were no statistically significant differences of overall survival between HIIC and HIIC plus PIC (ratio of HR=1.28, 95%CI=0.72 to 2.25, P=0.4). This result suggests that adding PIC to HIIC has no additional effect on overall survival. However, additional postoperative intraperitoneal chemotherapy leads more costs of patients and has greater toxicity (Newman et al., 2005; Brenner et al., 2006; Matharu et al., 2011). Thus, there is no need to add additional intraperitoneal chemotherapy to hyperthermic intraoperative intraperitoneal chemotherapy after surgery.

The peritoneum, liver and lymph nodes are the most common anatomic sites for treatment failure of gastric cancer after surgical surgery and intravenous chemotherapy. Our meta-analysis showed intraperitoneal chemotherapy did not demonstrate any significant reduction of peritoneal relapse, as compared to the control arm. Also, IPC has no effect on prevention of lymph metastasis. In contrast, IPC could decrease the postoperative rate of hepatic metastasis in gastric cancer patients by 73%. However, effects of IPC in preventing relapse and metastasis could not be answered directly from this meta-analysis. It is acknowledged that this may be mostly due to not taking the time to event into account and difficulty in precisely detecting relapse and metastasis by radiological methods.

The safety of intraperitoneal chemotherapy has always attracted a wide spread attention. Our results showed that intraperitoneal chemotherapy did not increase perioperative mortality or the incidence rates of postoperative anastomotic leak, ileus or bowel perforation. However, we have to point out that the temperature of the abdominal cavity should not exceed 43oC during hyperthermic intraperitoneal chemotherapy to prevent potential damage to the intestinal wall that could result in bowell perforation (Yonemura et al., 2001). Compared to intravenous chemotherapy, intraperitoneal chemotherapy has a relatively lower toxicity and fewer side effects, but the present meta-analysis showed that IPC was associated with an increased risk of marrow depression, intra-abdominal abscess and fever.

Even though the latest advance in intravenous chemotherapy and surgery, the treatment of gastric cancer has still been a challenge for oncologists due to the relative lower survival. Therefore, in addition to surgery and intravenous chemotherapy, other adjuvant therapy such as intraperitoneal chemotherapy is needed. However, IPC has not entered into standard front-line therapy so far in part due to lack of the recognized method. Our meta-analysis resolved this problem and suggested that intraoperative and intraperitoneal chemotherapy should be recommended as conventional treatment for patients with gastric cancer.

Some limitations of this study must be discussed. First, most RCTs included in the present meta-analysis were conducted on Asian patients; therefore, it is unclear whether the results can be applied to European and American patients. Second, all data were obtained from published literatures, even though no obvious publication bias was observed. Third, since no sufficient randomized controlled trials were available, we were not able to further perform subgroup analysis based on different drug schemes.

In conclusion, hyperthermic intraoperative intraperitoneal chemotherapy and normothermic intraoperative intraperitoneal chemotherapy should be recommended to treat patients with gastric cancer because of improvement in overall survival. Hyperthermic intraoperative intraperitoneal chemotherapy plus postoperative intraperitoneal chemotherapy is not recommended because additional postoperative intraperitoneal chemotherapy has no affection on overall survival. However, it is necessary to note that intraperitoneal chemotherapy can increase the risks of marrow depression, intra-abdominal abscesses and fever.

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