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Review Article

Cytoreductive surgery combined with intraperitoneal chemotherapy in the treatment of colorectal peritoneal metastasis: a meta-analysis

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Abstract: To use meta-analysis to investigate the effect and safety of cytoreductive surgery combined with intraperitoneal chemotherapy (CRS+IPC) in the treatment of colorectal peritoneal metastasis (CPM). Large databases such as PubMed, Cochrane Library, OVID, and Wanfang were used for literature retrieval. Literatures that compared the effect of CRS+IPC with that of traditional therapies in the treatment of CPM were selected. In addition, literatures that compared the effect of mytomycin C with that of oxaliplatin in intraperitoneal chemotherapy were chosen. The overall survival and the incidence of related complications were evaluated as the main assessment indices. Eight trials were involved in the first group, involving 684 patients who were divided into CRS+IPC group (n=413) and control group (n=272). Compared with control group, the overall survival of the CRS+IPC group was much higher, with a total HR of 0.46 (95% CI, 0.37-0.56; P<0.00001). The outcome was the same when comparing CRS+IPC group with CRS+SC group (HR, 0.41; 95% CI, 0.28-0.60; P<0.0001). In CRS+SC group, the incidence of related complications such as hemorrhage, intestinal leakage, and intestinal obstruction was higher than that in CRS+IPC group, whereas chemotherapy-related side effects in CRS+SC group were less than CRS+IPC group (OR, 0.9; 95% CI, 0.56-1.45; P=0.67), suggesting that the difference between the two groups was not statistically significant. Four case-control literatures were involved in the second group, involving 780 patients who were divided into oxaliplatin group (n=253) and mytomycin C group (n=527). Compared to mytomycin C group, the overall survival of oxaliplatin group was lower (HR, 1.39; 95% CI, 1.04-1.87; P=0.03). The difference of the incidence of complications between the two groups was not statistically significant (OR, 1.04; 95% CI, 0.50-2.20; P=0.91). The present study demonstrates that CRS+IPC has a better outcome of overall survival compared with traditional therapies for CPM. In addition, mytomycin C has a better outcome of overall survival compared with oxaliplatin.

Keywords: Peritoneal metastasis, colorectal cancer, intraperitoneal chemotherapy, cytoreductive sugery, oxaliplatin, mytomycin C

Introduction

Colorectal peritoneal metastasis (CPM) is found in about 40% colorectal cancer patients at the first time of diagnosis [1]. In addition, most patients who die of colorectal cancer have combined peritoneal metastasis [2-4]. A multicenter study shows that CPM patients who receive systemic chemotherapy (SC) using 5-fluorouracil and calcium folinate have a survival time shorter than 7 months, and FOLFOX or FOLIRI chemotherapy can only achieve a median survival time of 23.4 months [5]. Since 1980s, "sugar-baker" regimen has been used to perform cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy (IPC) (CRS+IPC) in the treatment of CPM [6]. It has been reported that CRS combined with hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) can achieve a maximal overall survival time of 63 months and a five-year survival rate of 51% in the treatment of peritoneal metastatic carcinoma [7]. Researchers have realized that peritoneal metastasis is a form of local dissemination of colorectal cancer, and CPM patients who undergo rigorous screenings can be treated with repeated local intraperitoneal chemotherapy [8]. However, it is unknown whether CRS+IPC can alleviate the prognosis

of CPM patients. In the present study, we perform a meta-analysis to evaluate the effectiveness and safety of CRS+IPC.

Material and methods

Literature search

Studies published in English and Chinese were carefully searched in biological databases (PubMed, OVID, Cochrane Library, and Wanfang, etc.) between January 1990 and February 2015. The search terms (both English and Chinese) included colorectal cancer, peritoneal metastasis, cytoreductive sugery (CRS), intraperitoneal chemotherapy (IPC), oxaliplatin, and mytomycin C. For the same group of people in randomized controlled trial, the latest published literatures were included in the analysis. For repeated publication, the literature with the most complete data was included.

Inclusion and exclusion criteria

Randomized controlled trials (RCT), prospective case-control study (PCS) and retrospective case-control study (RCS) were all included in the analysis, and the included literatures met the following criteria: i) The patients had primary or recurrent CPM (excluding appendiceal cancer), aged less than 70 years, had no serious heart and lung diseases, incurable diseases, or severe abdominal diseases such as intestinal obstruction; ii) COX model, observed and estimated values of events or Kaplan-Meier survival curve should be provided in literatures on overall survival rate, while outcome measures in literatures on complications should include at least one of anastomotic fistula, abdominal infection (or abdominal abscess), hemorrhage and renal toxicity associated with intraperitoneal chemotherapy; iii) indicators such as sugar-baker scores [9], degree of cell inactivation, follow-up time, intraperitoneal chemotherapy drugs, and complication rate should be provided; iv) included literatures had to be published or included into database; and v) the number of cases observed in the literature exceeded 20.

Relative outcome indices

Overall survival rate was the main outcome index for the comparison between CRS+IPC group and SC group, or between CRS+IPC group and CRS+SC group. Overall survival rate, incidence of anastomotic fistula, and incidence of abdominal infection (or abdominal abscess) were the main outcome indices for the comparison between oxaliplatin group and mytomycin C group.

Data extraction and quality assessment

Two investigators independently reviewed the titles and abstracts of the literatures, and selected literatures strictly following the inclusion and exclusion criteria. The quality of the included studies was evaluated and the data were extracted independently. In case of any disagreement between the two investigators regarding inclusion or exclusion, quality assessment, or data extraction, the decision was made by all researchers after thorough discussion. Quality assessment of included randomized clinical trials was performed using improved JADAD evaluation tool [10], and quality assessment of case-control study and cohort study was carried out using Newcastle-Ottawa-Scale (NOS) evaluation tool [11].

Statistical analysis

Meta-analysis was carried out using RevMan 5.3 software (http://www.cochrane.org/). The combined effect of dichotomous variables was expressed as odds ratio (OR) and its 95% confidence interval (CI). The combined effect of inverse variance variables was expressed as HR and its 95% CI. Differences with $P<0.05$ were considered statistically significant. Heterogeneity among studies was tested using Cochrane Q test. When $I^2>50\%$, significant heterogeneity was confirmed to exist. A fixed effect model was used to merge the results of studies with no significant heterogeneity, while the results of studies with significant heterogeneity were combined using a random effect model.

Results

Characteristics of the included studies

A total of 309 literatures were acquired by searching. By reviewing titles and abstracts, 225 literatures (reviews, animal experiments, other cancer types, unmatched data types) were excluded. Among the remaining 84 literatures, 72 were excluded due to small sizes of cases, non-case-control experiments, non-CRS+IPS case-control trials, or multicenter

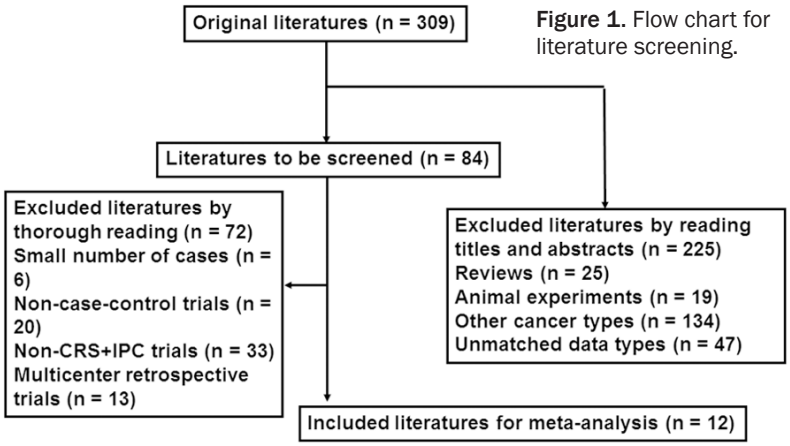

Figure 1. Flow chart for literature screening.

retrospective trials. Finally, 12 literatures [10-16] were included in the meta-analysis (**Figure 1**). The characteristics of the 12 literatures included intervention measures, grouping situations, follow-up time, median survival time, two-year survival rate, five-year survival rate, and drugs and means for intraperitoneal chemotherapy. All studies were completed independently, and the numbers of observed subjects ranged from 35 to 180. All patients had primary or recurrent CPM (excluding appendiceal cancer), aged less than 70 years, had no serious heart and lung diseases, incurable diseases, or severe abdominal diseases such as intestinal obstruction. Among the 12 literatures, 8 were group studies between CRS+IPC and SC (**Table 1**), and 4 were studies comparing intraperitoneal chemotherapies with oxaliplatin and mytomycin C (**Table 2**). The follow-up time ranged from 11.5 months to 110 months.

Quality assessment of the included studies

To assess the quality of randomized clinical trials, improved JADAD evaluation tool was used, and those with 0-4 points were low-quality literatures and those with 4-8 points were high-quality literatures. To evaluate the quality of case-control trials, NOS evaluation tool was employed, and literatures with more than 6 asterisks were considered to be of high quality. JADAD showed that 3 literatures had high quality (**Table 3**), and NOS showed that 2 literatures had high quality (**Table 4**).

Analysis of effectiveness

To determine the effectiveness of the treatments, overall survival rates were examined. According to different regimens, the control group was divided into SC and CRS+SC subgroups. The combined results of the two subgroups had no significant heterogeneity ($P>0.05$, $I^2>50\%$). In addition, the overall survival rate of CRS+IPC group was significantly higher than that in SC subgroup (HR= 0.46; 95% CI, 0.37-0.56; P<0.0001) (**Figure 2**). Similarly, the overall survival rate of CRS+IPC group was also significantly higher than that of CRS+SC subgroup (HR=0.41; 95% CI, 0.28-0.60; P<0.0001) (**Figure 3**). According to different drugs used in IPC, oxaliplatin and mytomycin C subgroups were examined. The combined results of the two subgroups had no significant heterogeneity ($P>0.05$, $I^2>50\%$). Of note, the overall survival rate of oxaliplatin subgroup was significantly lower than that of mytomycin C subgroup (HR=1.39; 95% CI, 1.04-1.87; P=0.03) (**Figure 4**). The results suggest that CRS+IPC and use of mytomycin C are more effective in enhancing overall survival rate.

Analysis of safety

To evaluate the safety of the treatments, incidence of postoperative complications was measured. The data showed that the incidence of postoperative hemorrhage, intestinal fistula or intestinal obstruction in CRS+IPC group was lower than that in CRS+SC subgroup, and the incidence of hypoproteinemia and liver and kidney dysfunction in CRS+IPC group was higher than that in CRS+SC group, but both had no statistical significance (OR= 0.90; 95% CI, 0.56-1.45; P=0.67) (**Figure 5**). Similarly, the incidence of anastomotic fistula, abdominal infection and postoperative hemorrhage was not significantly different between oxaliplatin and mytomycin C subgroups (OR=1.04; 95% CI, 0.50-2.20; P=0.91) (**Figure 6**). The results indicate that safety is not different between groups.

Examination of heterogeneity

To detect heterogeneity, Cochrane Q test was used. For contrast groups with high hetero-

Table 1. Characteristics of included literatures in the first group

Literatures	Study design	Intervention	Groups	Longest follow-up time	Intraperitoneal chemotherapy drugs and dosage	Overall five-year survival rate	Median survival time (months)	Incidence of complications	Data type
Werwaal, 2008	RCT	CRS+HIPEC vs SC ± PS	54 vs 51	115 months	MMC (45 mg/m^2)	19% vs 10%	22.3 vs 12.6	NG	KM survival curve
Eias	CRS*	CRS+HIPEC vs SC ± DS	48 vs 48	95.7 months	CRS: 5-FU (400 mg/m^2) + calcium folinate (20 mg/m^2); HIPEC: OX (460 mg/m^2) 43°C, 30 min	51% vs 13%	62.7 vs 23.9	NG	KM survival curve
Franko, 2010	CRS*	CRS+HIPEC+SC vs SC	67 vs 38	N/A	MMC 40 mg 43°C, 100 min	26% vs 5%	34.7 vs 16.8	NG	HR and 95% CI
Diane	PS*	CRS+HIPEC+SC vs CRS+SC	139 vs 41	74 months	OX ± IRI	NG	NG	NG	HR and 95% CI
Matheme	RCT	DS+EPIC+SC vs SC+DS	18 vs 17	N/A	N/A	28% vs 5%	32 vs 14	NG	KM survival curve
Eias, 2004	PS*	CRS+EPIC+SC vs CRS+SC	16 vs 19	N/A	MMC on the first day after surgery; 5-FU on days 2-5 after surgery	NG	NG	50% vs 37%	KM survival curve
Wei et al, 2014	RCT	CRS+HIPEC+SC vs CRS+SC	38 vs 29	N/A	5-FU (1 g) in abdominal cavity, 6 cycles of chemotherapy using 5-FU (20 mg/m^2) + MMC (10 mg) after surgery	NG	23 vs 11	35.1% vs 13.6%	KM survival curve
Huang et al, 2013	CRS*	CRS+HIPEC+SC vs CRS+SC	33 vs 29	110 months	NG	NG	14.5 vs 8.5	57.4% vs 15.6%	HR and 95% CI

Note: RCT, randomized clinical trials; CRS*, retrospective studies; PS*, prospective studies; HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; PS, palliative surgery; DS, radical surgery; NG, not given in original text; N/A, data not clear.

Table 2. Characteristics of included literatures in the second group

Literatures	Study design	Intervention	Groups	Longest follow-up time	Median survival time (months)	Three-year survival rate	Intestinal fistula	Anastomotic fistula	Abdominal infection	Hemorrhage	Biliary fistula	Death	Data type
D Hompes, 2014	CRS*	OX vs MMC	39 vs 36	66 Months	31.7 vs 26.5	54% vs 41%	5 vs 6	NG	2 vs 5	4 vs 2	1 vs 0	0 vs 0	HR and 95% CI
Arancha	CRS*	OX vs MMC	155 vs 392	N/A	31.4 vs 32.7	NG	NG	NG	NG	NG	NG	NG	HR and 95% CI
A Rouers 2006	CRS*	OX vs MMC	8 vs 13	N/A	N/A	NG	1 vs 0	2 vs 2	1 vs 0	NG	NG	0 vs 1	O-E value
Gabriel	CRS*	OX vs MMC	40 vs 40	NG	NG	NG	1 vs 1	0 vs 3	2 vs 0	1 vs 2	0 vs 1	1 vs 0	O-E value

Note: CRS*, retrospective studies; NG, not given in original text; N/A, data not clear; O-E, event observation and occurrence values.

Table 3. Improved JADAD scoring

Included studies	Correct random sequence generation	Allocation concealment	Blind approach to researchers and participants	Blind approach to outcome evaluator	Reasons for follow-up and withdrawal	Scores
Matheme	?	?	+	+	+	6
Werwaal, 2008	?	?	+	+	+	6
Wei et al, 2014	?	?	+	+	+	6

Note: +, 2 points; -, 0 point; ?, 1 point.

Table 4. Newcastle-Ottawa Scale scoring

Eias, 2009	*	*	*	*	*	*	******
Franko, 2010	*	*	*	*	*	*	******
Diane.Goe're, 2015	*	*		*	*	*	*****
Eias, 2004	*	*	**	*	*	*	*******
Huang et al, 2013	*	*	*	*	*	*	******
D Hompes, 2014	*	*	*	*	*	*	******
Arancha, 2014	*	*		*	*	*	*****
A Rouers, 2006	*	*	*	*	*	*	******
Gabriel, 2013	*	*	**	*	*	*	*******

Note: high quality is indicated by at least 6 asterisks.

geneity (I^2>50%), random effect model was employed to eliminate causes of heterogeneity. In this analysis, the combined results of five contrast groups and related subgroups had no significant heterogeneity. The result suggests that the present meta-analysis is reliable.

Analysis of sensitivity

To test the sensitivity of the meta-analysis, controlled trials with relatively low quality [12, 13] were excluded. Combined analysis of indices in the remaining literatures showed that combined analysis results concurred with previous results. This indicates that the present meta-analysis is reliable and robust.

Discussion

Liver metastasis is considered to be a relative contraindication to CRS+IPC surgery. If the number of liver metastatic nodules is less than three, the patient is sensitive to chemotherapy and the nodules can be completely resected, the survival rate of patients who receive CRS+IPC surgery will not be negatively affected [17]. For patients who are insensitive to chemotherapy or have other abdominal metastasis and retroperitoneal lymph node enlargement, CRS+IPC should be absolutely prohibited [17]. IPC measures include HIPEC and EPIC. Elias et al have performed case-control studies on the effectiveness and safety of HIPEC and EPIC [18, 19]. Compared with HIPEC, EPIC is easier to perform, but has higher risk for anastomotic fistula. The advantages of HIPEC include: i) good controllability enables chemotherapy drugs to completely cover intraperitoneal tissues including small foci; ii) temperature between 42 and 43°C increases permeability of tumor cell surfaces, and antitumor effects of the drugs are enhanced; iii) less possibility for the occurrence of anastomotic fistula. It is reported that the antitumor activity of mitomycin at 43°C is 40 times of that at 37°C [20]. However, we have not analyzed the effectiveness of HIPEC and EPIC in the present study due to limited number of cases.

The range and degree of CRS+IPC surgery are relatively high, and intraperitoneal chemotherapy can sometimes cause losses of body fluid, plasma proteins and trace elements. As a result, the incidence of postoperative complications after CRS+IPC surgery is higher than that of traditional treatment methods [14-16]. Common complications include anastomotic fistula, intraperitoneal infection or abscess formation, hyponatremia, hemorrhage and HIPEC-related renal toxicity. It is reported that the incidence of perioperative complications for CRS+IPC surgery is 14.8-57.0%, and the mortality rate is up to 12.0% [21].

Despite lack of large amount of evidence, CRS+IPC is considered to be the only effective treatment method for CPM. Indeed, the present study demonstrates that CRS+IPC is more effective than traditional treatment methods. The target of CRS is to achieve the complete elimination of tumor cells. Therefore, its incidence of postoperative complications is usually higher than that of traditional treatments. However, it is reported that the mortality and morbidity rates of CRS+IPC are similar to that of conventional gastrointestinal surgeries, within acceptable ranges [22].

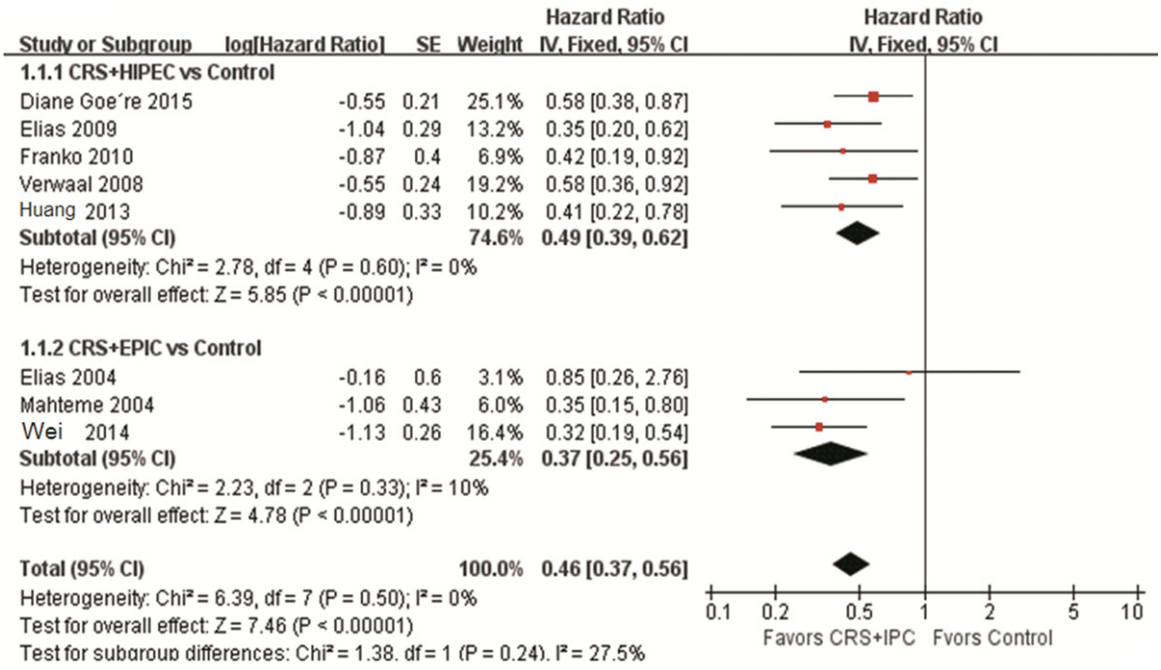

Figure 2. Forest plot for the effect of CRS+IPC or SC on overall survival rate.

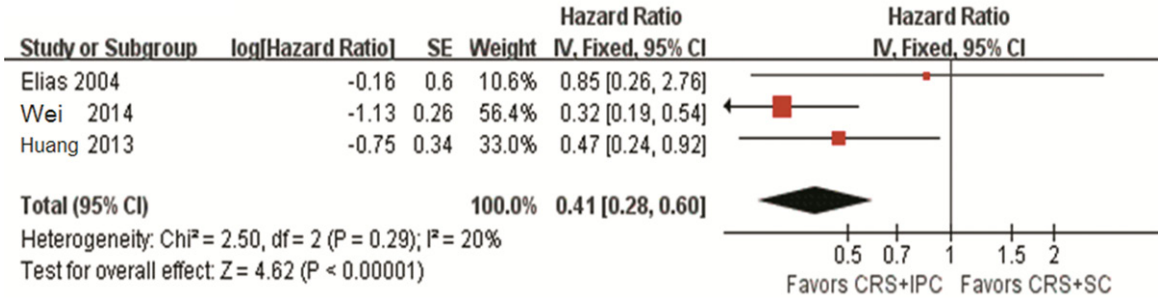

Figure 3. Forest plot for the effect of CRS+IPC or CRS+SC on overall survival rate.

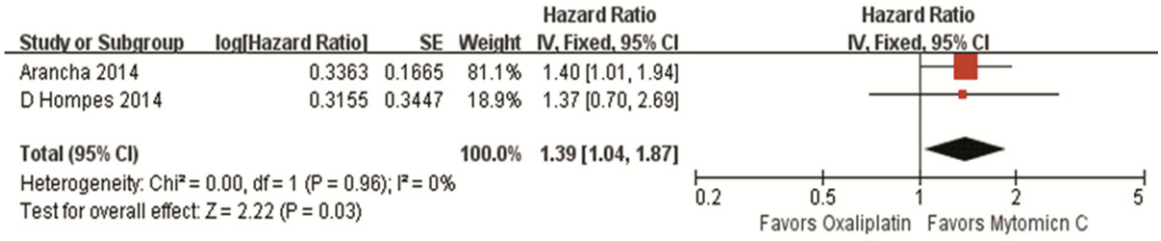

Figure 4. Forest plot for the effect of oxaliplatin or mytomycin C on overall survival rate.

The reason why CRS+IPC can prolong the survival time is that peritoneal incision without HIPEC can significantly enhance the risk for transfer of free tumor cells to other parts in the abdominal cavity, and the incidence of complications [23]. Consistently, the present study also demonstrates that the therapeutic effect of CRS+IPC is much better than that of CRS+SC, benefiting for the survival of CPM patients.

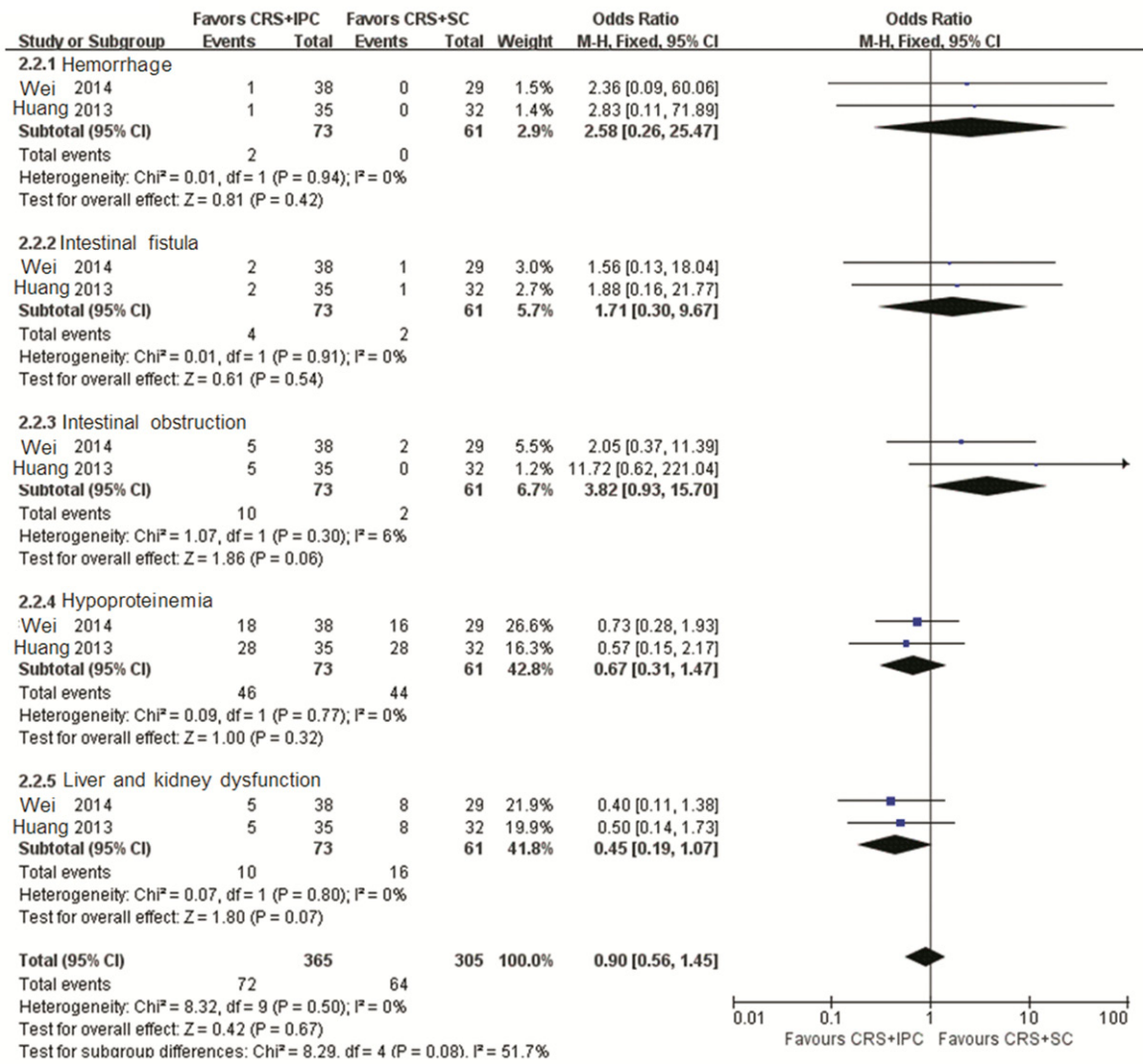

Figure 5. Forest plot for the effect of CRS+IPC or CRS+SC on the incidence of postoperative complications.

Oxaliplatin and mytomycin C are currently considered to be suitable for HIPEC, because their molecules are large enough to accumulate in peritoneum instead of entering the blood circulation. In addition, these drugs have good therapeutic effects for peritoneal metastatic carcinoma and little systemic side effect. Due to insufficient data, there is no unified stipulation in the selection of chemotherapy drugs when using HIPEC to treat CPM. The results of the present study show that the effect of mytomycin C in enhancing overall survival rate is stronger than that of oxaliplatin, but the incidence of postoperative complications between the two drugs is not significantly different. However, it is also reported that for patients with Peritoneal Surface Disease Severity Scoring grades I and II, the therapeutic effect of mytomycin C is higher than that of oxaliplatin, while the effect of oxaliplatin is stronger than that of mytomycin C for patients with Peritoneal Surface Disease Severity Scoring grades III and IV. In conclusion, the present study demonstrates that CRS+IPC has a better outcome of overall survival compared with traditional therapies for CPM. In addition, mytomycin C seems to have a better outcome of overall survival compared with oxaliplatin.

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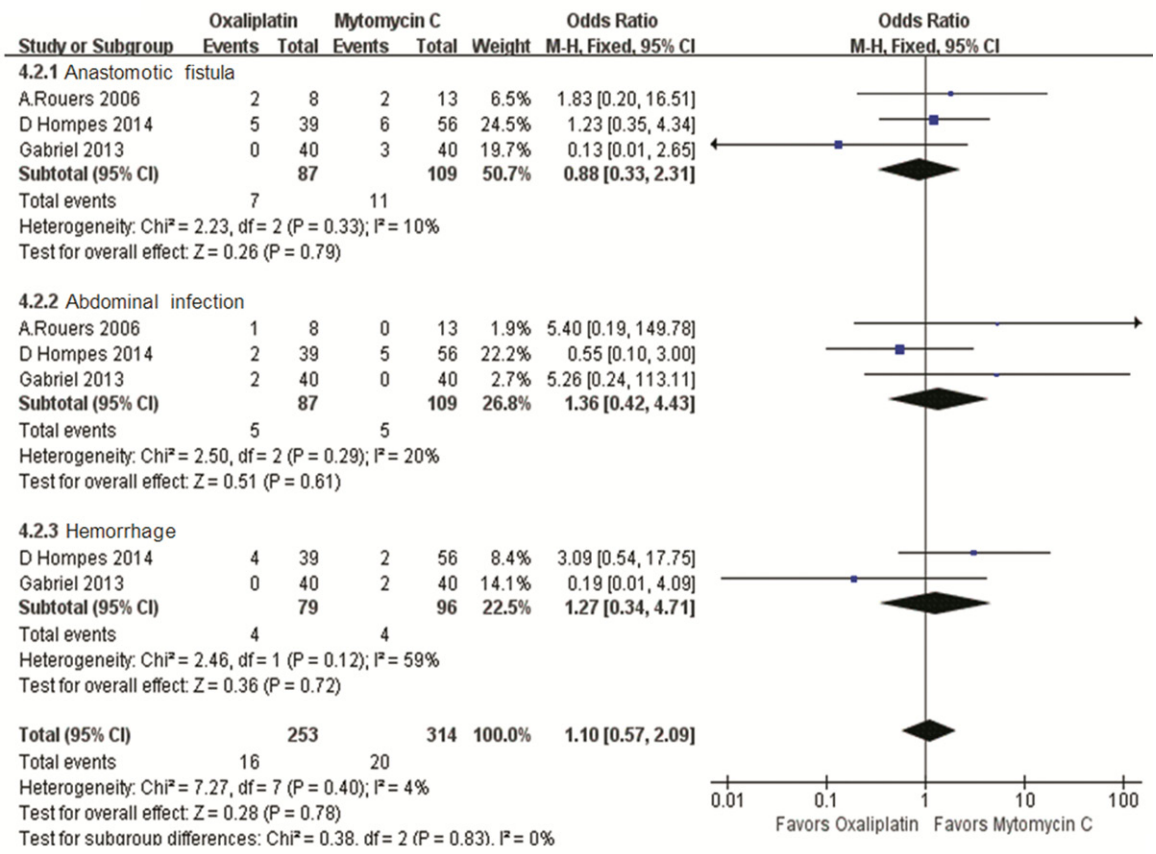

Figure 6. Forest plot for the effect of oxaliplatin or mytomycin C on the incidence of postoperative complications.

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Disclosure of conflict of interest

None.

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