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Assessment of the efficacy and safety of intraperitoneal chemotherapy in patients with advanced gastric cancer in Chinese population: a meta-analysis

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Abstract

To investigate the safety and efficacy of intraoperative intraperitoneal chemotherapy in treating advanced gastric cancer. A randomized controlled trial (RCT) of gastric cancer surgery combined with intraoperative intraperitoneal chemotherapy for the efficacy and safety were screened by computer search PubMed, Medline, Springer, Elsevier Science Direct, Weipu, Wanfang and China National Knowledge Infrastructure (CNKI) with the last report up to October 2019. The control group underwent radical gastrectomy, and the experimental group underwent intraoperative intraperitoneal chemotherapy and radical gastrectomy. A total of 997 (Experimental group 453; Control group 544) participants were considered in this meta-analysis. Compared with the control group, the experimental group has higher 1-year survival rate [OR=2.40, 95%CI (1.34, 4.33), P=0.003], 2-year survival rate [OR=3.45, 95%CI (2.08, 5.75), P<0.00001], 3-year survival rate [OR=2.70, 95%CI (2.05, 3.54), P<0.00001] and 5-year survival rate [OR=2.90, 95%CI (1.93, 4.37), P<0.00001]. There is no significant difference in postoperative bleeding (P=0.95), postoperative infection (P=0.26), postoperative anastomotic leakage (P=0.41), and postoperative intestinal obstruction (P=0.11). Intraoperative intraperitoneal chemotherapy with advanced gastric cancer in the Chinese population can improve patients' survival rate after surgery and does not increase the incidence of postoperative complications, so it is clinically significant and safe.

Keywords: advanced gastric cancer; intraperitoneal chemotherapy; meta-analysis.

Practical Application: The efficiency and security of intraperitoneal chemotherapy in patients with advanced gastric cancer in Chinese population.

1 Introduction

According to the 2018 Global Cancer Report (Bray et al., 2018), there are 103,370 new cases and 782,685 deaths in 2018, ranking second and third in global morbidity and mortality, and the burden of disease is heavy. Gastric cancer is currently one of the highest mortality rates and serious cancers in all of the world (Xiao et al., 2018; Yu et al., 2019; Zare et al., 2019). The incidence of gastric cancer usually has no obvious symptoms and signs (Zhang et al., 2019). The detection rate of early gastric cancer is deficient, generally with no apparent symptoms. Most patients have developed advanced gastric cancer when they have symptoms (Wu et al., 2018; Xu et al., 2019). About 30% of patients have signs of local spread at the time of diagnosis, and another 30% have metastases at the time of diagnosis of gastric cancer. Radical resection is the primary means of treatment of gastric cancer. The peritoneum in the human body is one of the most common sites of recurrence of gastric cancer, and the prognosis after surgery is also very poor (Zhu et al., 2019).

With improved surgical instruments and surgical techniques, the 5-year survival rate of the standardized lymph node dissection is significantly improved. However, postoperative peritoneal implantation, liver metastasis, and recurrence of primary position are still the main factors affecting gastric cancer prognosis (Stewart et al., 2019). In recent years, establishing a multidisciplinary comprehensive treatment model based on surgery has extended the patient's survival (Li et al., 2019a; Choi et al., 2019; Uemura et al., 2018). However, patients' 5-year survival rate did not significantly improve, about 14% to 43% of gastric cancer patients with peritoneal metastasis, and the peritoneum is a common site of recurrence metastasis (Zhu et al., 2019; Dahdaleh & Turaga et al., 2018). Intraperitoneal chemotherapy is an effective treatment for advanced gastric cancer with peritoneal metastasis (Yarema et al., 2019; Beeharry et al., 2019; Peixoto et al., 2018). Peritoneal perfusion, warming effect, and the pernicious effect of chemotherapy drugs on tumor cells are used to achieve therapeutic purposes.

At present, peritoneal hyperthermic perfusion chemotherapy has been widely used in clinical practice and has achieved ideal clinical results. Peritoneal hyperthermic perfusion chemotherapy has excellent advantages in pharmacokinetics. It has an essential role in tumor cells' cytotoxic effect, sensitization to radiotherapy and chemotherapy, improvement of immune function, and inhibition of tumor metastasis (Zhu et al., 2019). Still, intraoperative intraperitoneal chemotherapy efficacy and safety in treating advanced gastric cancer in the Chinese population are unclear. This study systematically evaluated intraoperative intraperitoneal

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chemotherapy's effectiveness and safety in treating advanced gastric cancer in the Chinese population through meta-analysis.

2 Material and methods

2.1 Search strategy

Public databases were retrieved mainly including PubMed, Medline, Springer, Elsevier Science Direct, Weipu, Wanfang, and China National Knowledge Infrastructure (CNKI) with the last report up to October 2019. The keywords of "gastric", "stomach", "intraperitoneal", "chemotherapy", "carcinoma", "cancer", "tumors", "study" or "trial" were used for searching. Meanwhile, references from retrieved papers were checked for any additional studies. We only recruited data from the full-published Chinese or English paper, not any meeting or conference abstract.

2.2 Included and excluded standards of studies

Included standards of studies

Studies that met the following criteria were included: the design was a randomized controlled trial, regardless of English or Chinese language. The study subjects were aged ≥ 18 years old. The study was a randomized and semi-randomized clinical controlled study with a follow-up of more than 2 years. The study object was advanced gastric cancer, which was confirmed by pathology before the operation. The observed indicators were the incidence of postoperative complications (postoperative bleeding, postoperative intestinal obstruction, anastomotic leakage, and postoperative infection) and a 1-5-year survival rate after surgery. The control group only underwent radical gastrectomy (including distal gastrectomy, total gastrectomy, total gastrectomy; laparoscopic or laparoscopic assistance; feasible D1 or D2 lymph node dissection). The experimental group underwent intraperitoneal chemotherapy and radical gastrectomy. The chemotherapy drug was dissolved in the diluent (no specific requirements for the chemotherapy drug and the dose) and heated to a particular temperature to soak the abdominal cavity. The postoperative treatment measures (such as postoperative chemotherapy) were the same in both groups. The objects were human beings, and participants' age was not limited; studies reported risk ratio as the outcome and sample size were not limited.

2.3 Excluded criteria of studies

Studies were excluded if one of the following existed: 1) Extensive abdominal metastasis or metastasis of other organs has been confirmed in early gastric cancer or during surgery. 2) The original literature study was not aimed at comparing the role of intraperitoneal chemotherapy in advanced gastric cancer. 3) The postoperative follow-up time was less than 2 years. 4) There was insufficient information for the extraction of data.

2.4 Data extraction and quality evaluation

According to the Cochrane Library Intervention System Evaluation Manual, two reviewers independently screened the literature based on the above inclusion criteria. By the pre-determined inclusion and exclusion criteria, two reviewers read the titles and abstracts of the literature, respectively and independently, excluded articles that failed to meet the criteria, and conducted full-text reading and data extraction on articles that meet the criteria. Discussion was adopted in the case of disagreements, and a third reviewer was introduced when necessary. Data extraction includes ①general data: title, authors, published date, etc.; ②basic features of the included literature: research object, interventions, number of cases, basic information of the patients; ③endpoints: postoperative complications (postoperative bleeding, postoperative infection, postoperative anastomotic leakage, and postoperative intestinal obstruction, etc.) and postoperative survival rate (1-year survival rate, 2-year survival rate, 3-year survival rate, and 5-year survival rate). After the data extraction of the literature is completed, cross-checking is performed to ensure the data's accuracy.

2.5 Quality assessment

Cochrane collaboration's tool for assessing the risk of bias for Systematic Reviews of Interventions 6.0 was used for evaluating randomized controlled trials.

2.6 Meta-analysis methods

Meta-analysis was performed using RevMan version 5.3 statistical software. Chi-square test was applied for heterogeneity analysis (I2 values <25% are considered of low heterogeneity, between 25% to 50% moderate heterogeneity, and more than 50% are considered of high heterogeneity). If $P>0.10$, $I^2<50\%$, the heterogeneity level was low, and fixed-effects model analysis was adopted (Mantel & Haenszel, 1959), whereas $P\leq0.10$, $I^2\geq50\%$ indicated a high level of heterogeneity, and a random-effects model was applied to assess sources of heterogeneity (DerSimonian & Laird, 1986). The difference was statistically significant at $P<0.05$. The outcomes as risk ratios (*OR*s) of the postoperative complications effect (postoperative bleeding, postoperative infection, postoperative anastomotic leakage, and postoperative intestinal obstruction, etc.) and postoperative survival rate (1-year survival rate, 2-year survival rate, 3-year survival rate, and 5-year survival rate) association between experimental group and control group in patients of advanced gastric cancer were calculated. We evaluated publication bias of the postoperative complications effect and postoperative survival rate by using the funnel plot.

3 Results

3.1 Characteristics of eligible studies

There were 742 papers potentially relevant to the search terms (PubMed: 51; Medline: 30; Springer: 21; Elsevier Science Direct: 19; Weipu: 158; Wanfang: 246; CNKI: 217). There were 55 potentially relevant reports after removing duplicates or irrelevant studies. During screening the abstracts, 31 of these articles were excluded (15 were review articles; 16 not reported advanced gastric cancer). Then 24 studies were left for full publication review; of these, 13 were excluded (not reported Chinese population data). The study selection process is shown in Figure 1.

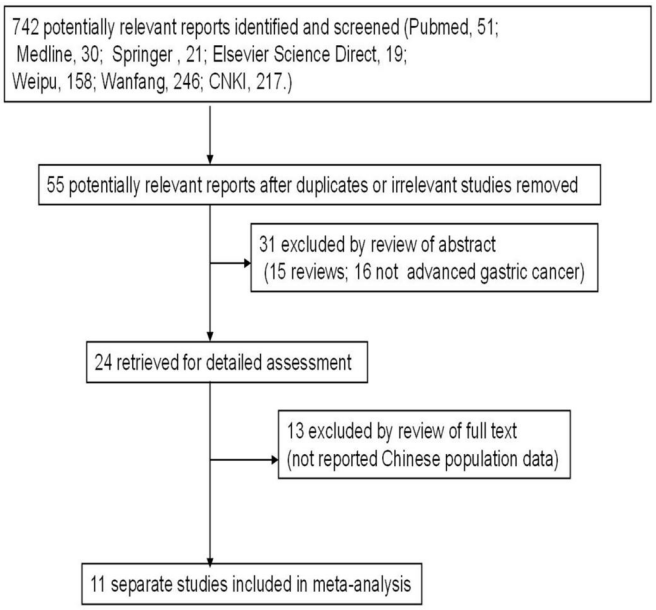

Figure 1. Flow diagram of included studies.

There were 11 studies (Chen et al., 2004, 2005; Wang et al., 2016; Jin, 2007; Shen et al., 2008; Liu, 2015; Guo & Qin, 2016; He, 2017; Dai, 2017; Li et al., 2019b) in the meta-analysis, and the characteristics of the included studies were presented in Table 1. The included studies were published between 2004 and 2019. A total of 997 (Experimental group 453; Control group 544) were conducted in this meta-analysis. The studies' sample sizes were between 39 and 156. Studies had been carried out in China. The risk of bias summary is shown in Figure 2, and the risk of bias graph is shown in Figure 3.

3.2 Meta-analysis of the postoperative complications association between experimental group and control group

Crude ORs with 95% CIs were used to assess the postoperative complications association between the experimental and control groups in patients of advanced gastric cancer. As shown in Figure 4, no significant heterogeneities (*P*-value by χ^2 -based Q testing > 0.1 and I^2 = 0%) were observed, so we used the fixed effect model to determine the postoperative complications association between the experimental group and control group. There is no significant difference in postoperative bleeding (OR=0.94, 95%CI (0.13, 6.69), P=0.95), postoperative infection (OR=0.59, 95%CI (0.23, 1.48), P=0.26), postoperative anastomotic leakage (OR=0.66, 95%CI (0.24, 1.78), P=0.41) and postoperative intestinal obstruction (OR=0.55, 95%CI (0.27, 1.14), P=0.11).

3.3 Meta-analysis of the postoperative survival rate association between experimental group and control group

Crude ORs with 95% CIs were used to assess the postoperative survival rate association between the experimental and control groups in advanced gastric cancer patients. As shown in Figure 5, no significant heterogeneities (*P*-value by χ^2 -based Q testing > 0.1 and I^2 = 0%) were observed, so we used the fixed effect model to

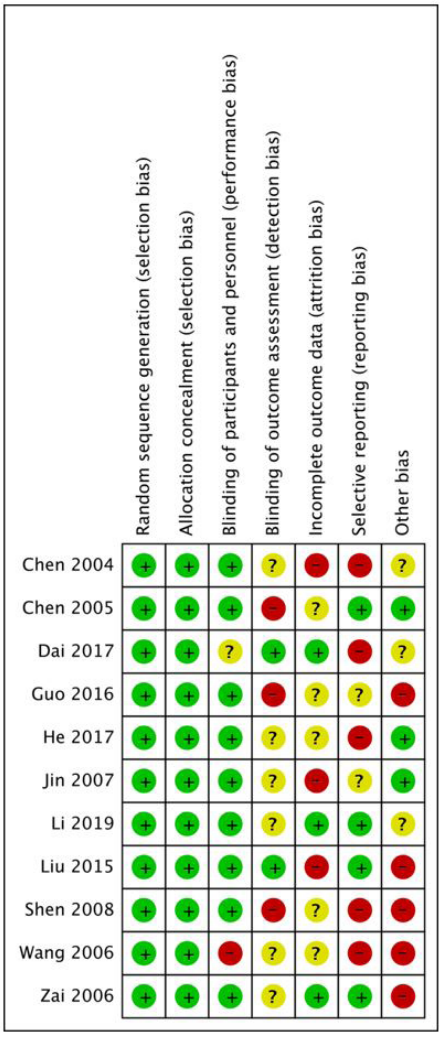

Figure 2. Risk of bias summary.

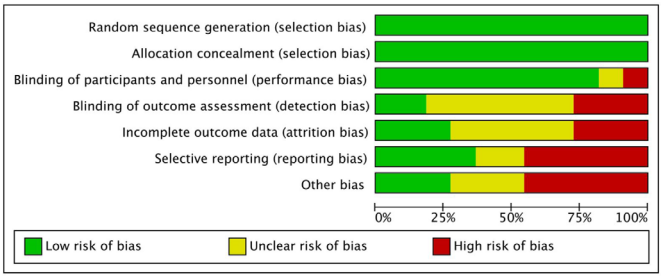

Figure 3. Risk of bias graph.

determine the postoperative survival rate association between the experimental group and control group. Our results showed that compared with the control group, the experimental group has higher 1-year survival rate [OR=2.40, 95%CI (1.34, 4.33), P=0.003], 2-year survival rate [OR=3.45, 95%CI (2.08, 5.75), P<0.00001], 3-year survival rate [OR=2.70, 95%CI (2.05, 3.54), P<0.00001] and 5-year survival rate [OR=2.90, 95%CI (1.93, 4.37), P<0.00001].

Table 1. General demographic characteristics of the subjects.

Study	Intraperitoneal chemotherapy regimen	Postoperative chemotherapy	Experimental group			Control group		
			Sample size	Age, years (mean±SD or min-max)	Male (n)	Sample size	Age, years (mean ± SD or min-max)	Male (n)
Chen et al. (2004)	DDP 100 mg. MMC 30 mg	NA	55	21-77	25	101	20-80	72
Chen et al. (2005)	5-FU 0.5 g/L, MMC 8 mg/L	FAM	30	23-75	25	30	25-72	23
Wang et al. (2006)	DDP 80-100 mg	FM	37	21-72	18	31	26-75	17
Zai et al. (2006)	DDP 80-100 mg	NA	49	42-71	38	47	40-69	38
Jin (2007)	DDP 100 mg. MMC 30 mg	ELF	58	23-70	42	58	25-68	40
Shen et al. (2008)	DDP 120-150 mg	FOLFOX4	50	21-70	22	100	18-72	60
Liu (2015)	OXA 350 mg	NA	19	51.9	12	20	52.8	14
Guo & Qin (2016)	DDP 100 mg, MMC 30 mg	NA	50	53.7 ± 8.8	32	50	53.3 ± 8.5	30
He (2017)	5-FU 1500 mg	mFOLFOX6	47	58.9 ± 7.6	25	49	59.6 ± 8.2	28
Dai (2017)	NaCl 3000-5000 mL	mFOLFOX6	20	56.0 ± 6.1	12	20	57.5 ± 6.5	11
Li et al. (2019b)	OXA 100 mg	NA	38	55.6 ± 6.3	20	38	55.7 ± 6.1	21

NA= not available. DDP: cisplatin; OXA: Oxaliplatin; 5-FU: 5-Fluorouracil; MMC: mitomycin C; FAM: 5-Fluorouracil, doxorubicin, and mitomycin; ELF: Etoposide, l-leucovorin and fluorouracil; FOLFOX4: 5-fluomumcil/leucovorin combined and oxaliplatin; mFOLFOX6: modified 5-fluorouracil, folinic acid, and oxaliplatin.

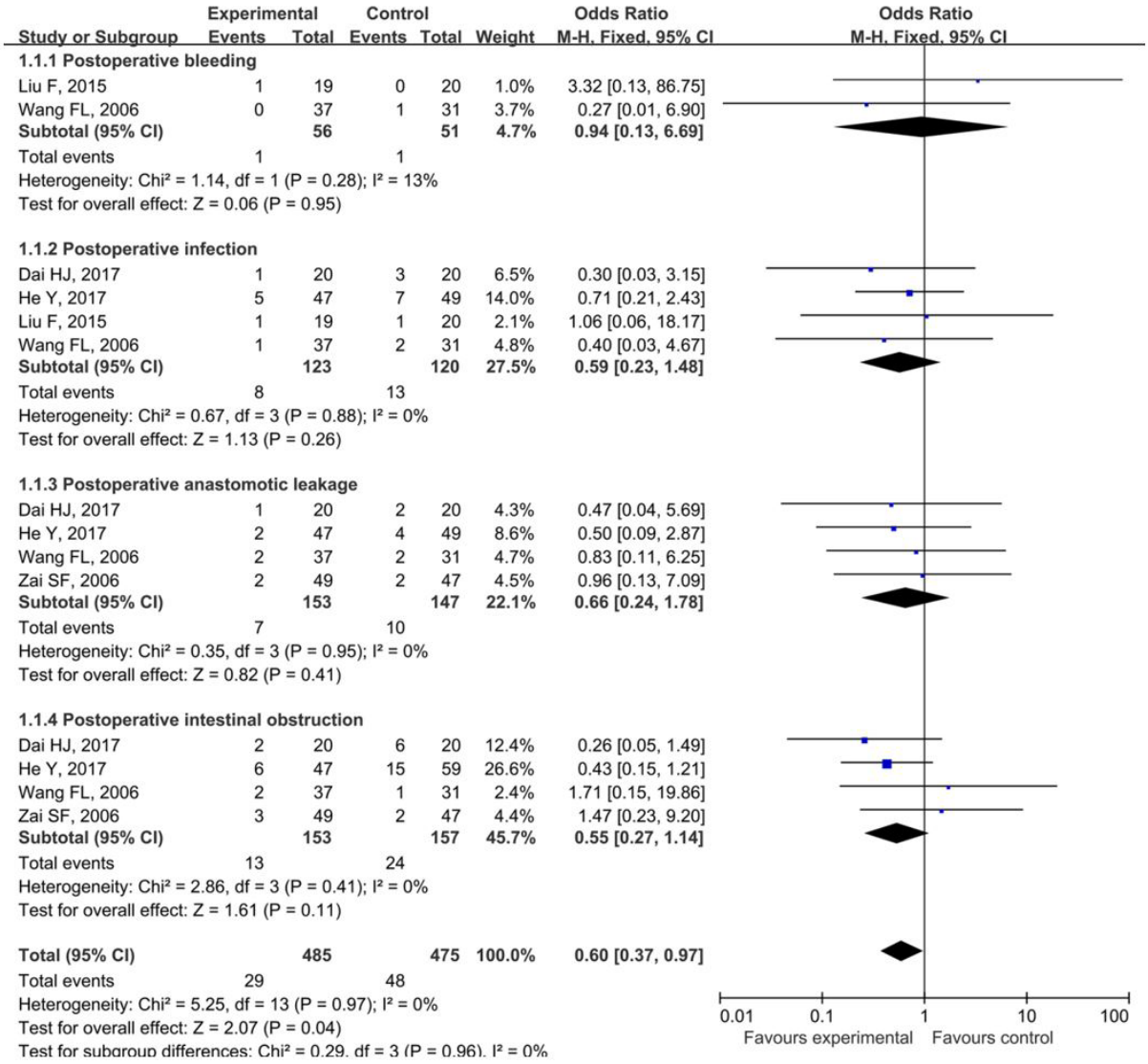

Figure 4. Forest plot of the postoperative complications association between experimental group and control group.

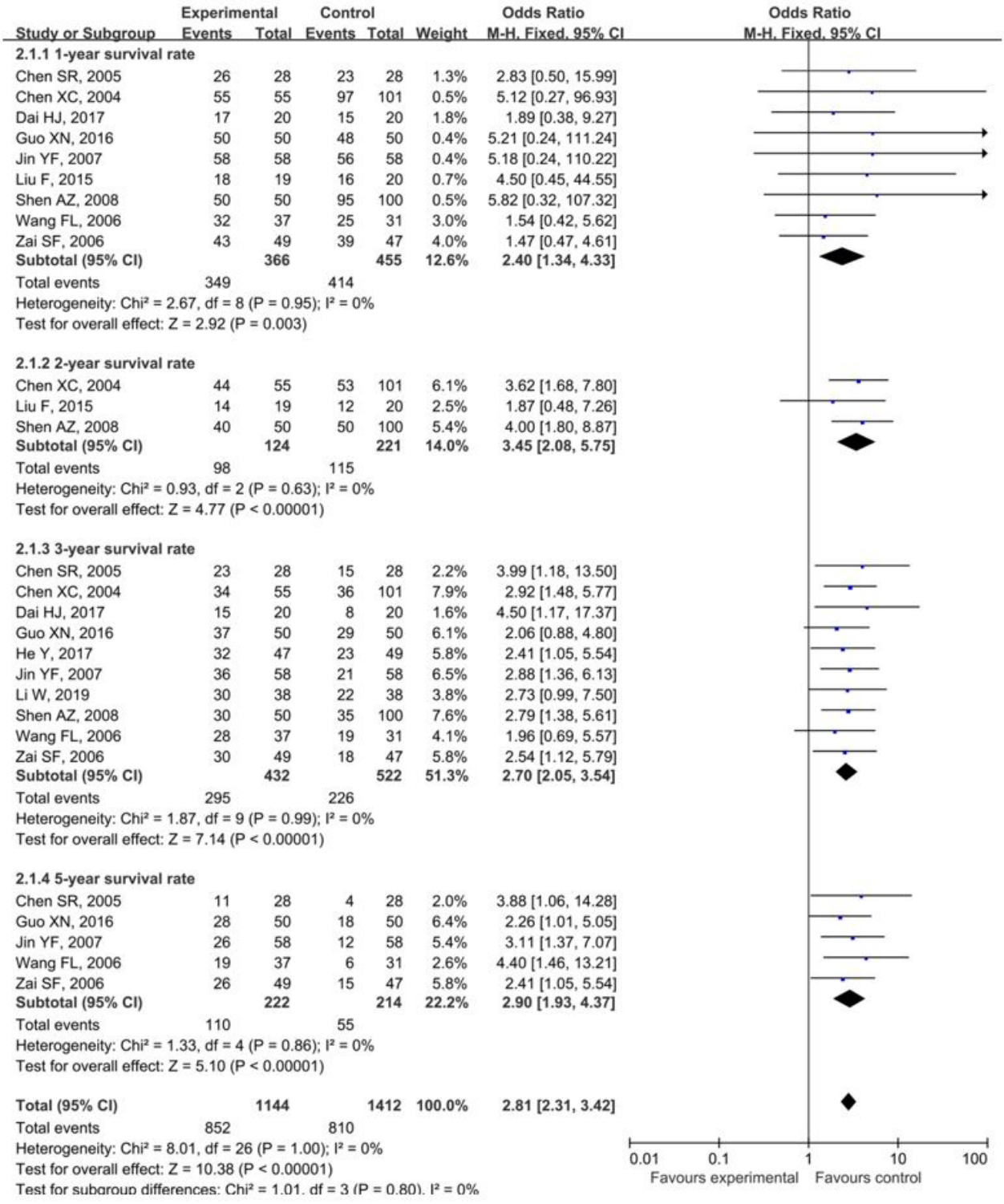

Figure 5. Forest plot of the postoperative survival rate association between experimental group and control group.

3.4 Publication bias

The funnel plot was performed to assess the publication bias of the included studies. No obvious publication bias was found under all models comparison for postoperative complications and postoperative survival rates. The results were shown in Figure 6 and 7.

4 Discussion

Gastric cancer is a common malignant tumor in the clinic (Khorfan et al., 2020; Fanotto et al., 2019). The main metastasis route of gastric cancer is peritoneal dissemination. Complications after gastric cancer surgery are common factors leading to death. Due to the plasma-peritoneal barrier's presence, the clinical

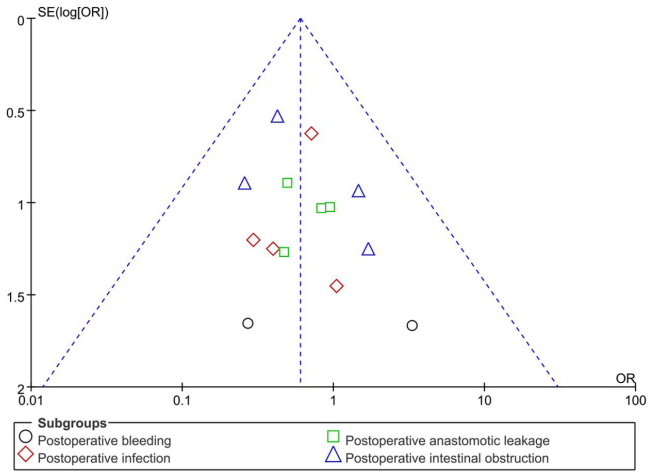

Figure 6. Funnel plot of the postoperative complications association between experimental group and control group.

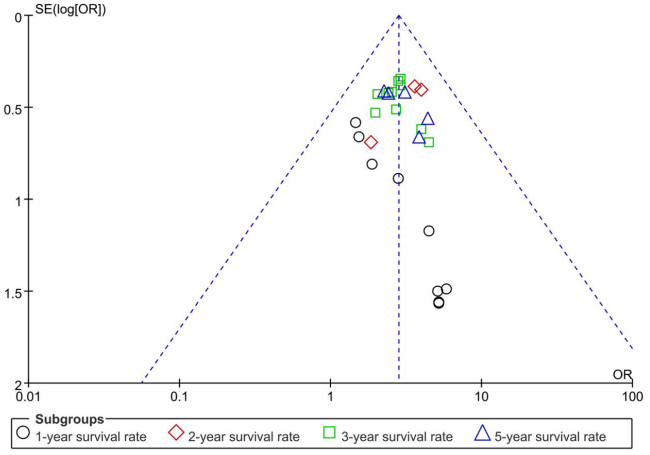

Figure 7. Funnel plot of the postoperative survival rate association between experimental group and control group.

efficacy of intravenous systemic chemotherapy and regional chemotherapy is not very good. The intraperitoneal hyperthermic perfusion chemotherapy developed based on intraperitoneal chemotherapy mainly combines hyperthermia and chemotherapy to provide a new way to treat gastric cancer patients.

The intraperitoneal chemotherapy mainly achieves the therapeutic effect through the high-temperature environment of the abdominal cavity, the liquid's flushing action, and the toxic effect of the chemotherapy drug (Leiting & Grotz, 2019; Kim et al., 2018; Coccolini et al., 2018). The peritoneal thickness is about 90 μm, mainly composed of mesothelial cells and a layer of membranous tissue formed by the support of connective tissue. Tumor cells that break through the serosa layer can stay in the peritoneum. Studies have shown that tumor cells can only survive for 1 h at 43 °C, while normal cells can survive for 1 h at 47 °C high temperatures and accelerate tumor cell death (Garofalo et al., 2006). After the intraperitoneal chemotherapy drugs and liquids are placed, the high temperature can increase the cell membrane and tumor cells' vascular permeability, which is beneficial to the absorption and penetration of chemotherapy drugs. The cancer nodules in the peritoneal cavity are long-term in high-concentration and high-temperature chemotherapy drugs (Ushimaru et al., 2019). The cytotoxic effect of chemotherapy drugs is strengthened. The mobile chemotherapy solution is excreted to achieve therapeutic purposes. This study showed no statistically significant difference in postoperative complications (postoperative bleeding, postoperative infection, postoperative anastomotic leakage, and postoperative intestinal obstruction) between the experimental group and the control group, and the safety was feasible.

Continuous circulation of intraperitoneal hyperthermic perfusion chemotherapy combines hyperthermia and chemotherapy based on traditional chemotherapy, and enhances chemotherapy drugs' efficacy using hyperthermia. Its most significant feature is that it can directly contact the chemotherapeutic drugs and tumor cells, increase the local drug concentration of the lesions, and prolong the drugs' action time. Thereby improving the therapeutic effect and reducing the rate of postoperative tumor metastasis or recurrence. Intraperitoneal hyperthermic perfusion chemotherapy itself has a pernicious impact on tumor cells, mainly in the destruction of tumor cells' membranous structure, inhibition of angiogenesis, improvement of immune function, and induction of apoptosis (Zhu et al., 2019). Intraperitoneal hyperthermic perfusion chemotherapy for advanced gastric cancer is mainly used for cytological examination of peritoneal washing fluid. Free cancer cells are positive, or the naked eye sees tumor invading the serosa without other visible lesions visible to the naked eye. Patients with radical resection can be performed (Mitrousias et al., 2019; Imagami et al., 2019). Seshadri R believes that the basic principle of intraoperative peritoneal hyperthermic chemotherapy for the prevention and treatment of advanced gastric cancer is to dilute gastric cancer cells by diluting free gastric cancer cells and chemotherapy drugs in the peritoneal cavity (Seshadri & Glehen, 2016). The principle of treatment of intraperitoneal chemotherapy in advanced gastric cancer remains to be further studied. In this study, the results demonstrated that intraoperative intraperitoneal chemotherapy combined with radical gastrectomy could improve the postoperative survival rate (1-year, 2-year, 3-year, and 5-year survival rate) to treat advanced gastric cancer. At the same time, intraoperative intraperitoneal chemotherapy is simple, feasible, and can be promoted in clinical practice. Besides, in-depth studies of specific drugs and specific doses of intraperitoneal chemotherapy, chemotherapeutic drug sensitivity, and penetration depth should be explored to provide more evidence for patients' prolonged survival with intraperitoneal chemotherapy.

Limitations of the present study: ① By definition and study design, chemotherapy regimen with the same efficacy but different regimens also have other effects on advanced gastric cancer. Therefore, the quantitative meta-analysis of different kinds of chemotherapy regimens will have certain defects. ② There are few high-quality randomized controlled studies, including the small number of subjects, the lack of description of random methods, allocation concealment, and follow-up implementation. ③ This study did not strictly limit the age, course of the disease, which will also cause a risk of bias in evaluating efficacy. Therefore, the results and conclusion should be used with caution.

5 Conclusion

Intraoperative intraperitoneal chemotherapy with advanced gastric cancer in the Chinese population can improve patients' survival rate after surgery and does not increase the incidence of postoperative complications, so it is clinically significant and safe. However, more multicenter RCTs with a large sample number and high quality should verify the conclusion mentioned above.

Conflict of interest

The authors declare that they have no competing interest.

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