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REVIEW ARTICLE

The short- and long-term survival of hyperthermic intraperitoneal chemotherapy (HIPEC) in the advanced gastric cancer with/without peritoneal carcinomatosis: a systematic review and meta-analysis of randomized controlled trials

Huachu Deng[1] · Baibei Li[2] · Xingan Qin[1]

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Abstract
To evaluate the short- and long-term survival of hyperthermic intraperitoneal chemotherapy (HIPEC) in the patients with advanced gastric cancer (AGC) through randomized controlled trials (RCTs). We analyzed the endpoints of AGC patients including 1-, 2-, 3-, and 5-year overall survival (OS), intestinal anastomotic leakage, myelosuppression, nausea and vomiting from included studies. And we retrieved RCTs from medical literature databases. Risk ratios (RR) was used to calculated the endpoints. Totally, we retrieved 13 articles (14 trial comparisons) which contained 1091 patients. They were randomized to HIPEC group and control group. The results showed that there was no significant differences in survival rates between HIPEC group and control group at 1-, 2- and 3-year follow-up, while a statistical significant overall survival effect was found at the 5-year follow-up [RR: 1.20, 95% CI 1.01 to 1.43, $I^2 = 0.0\%$]. And there is no significant difference in the risk of intestinal anastomotic leakage, myelosuppression and nausea and vomiting. Compared with the control group, HIPEC could improve the long-term OS without increasing the risk of adverse effect in AGC patients with/without peritoneal carcinomatosis, but there was no benefit at short-term OS.

Keywords Hyperthermic intraperitoneal chemotherapy · Advanced gastric cancer · Short- and long-term survival

Background

Gastric cancer is one of the most common malignant tumors of digestive tract [1]. According to the global cancer statistics in 2020, the incidence of gastric cancer ranks fifth among malignant tumors, and the fatality rate ranks fourth [2]. The incidence of gastric cancer is hidden, and there are no obvious symptoms in the early stage of gastric cancer. Therefore, when gastric cancer is found, it is mostly advanced gastric cancer (AGC), which has a poor prognosis and a high mortality rate [3]. AGC refers to cancer tissue that has invaded the muscularis or even serosa layer of the gastric wall, regardless of the size of the lesion or the presence or absence of metastasis. Postoperative local recurrence and peritoneal metastasis are important factors affecting the prognosis of patients with AGC, and peritoneal metastasis is the most common outcome and cause of death in AGC [4]. The diagnosis rate of peritoneal metastasis in patients with gastric cancer is 14–30%. Even if there is no peritoneal metastasis in the initial treatment, the incidence of peritoneal recurrence after radical gastric cancer surgery is 34–60% [5].

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an adjuvant therapy technology that infuses mixed lavage solution of chemotherapy drugs into the abdominal cavity and kills tumor cells by the synergistic mechanism of temperature and chemotherapy drugs [6]. In 1980, Spratt et al. [7] first reported the treatment of pseudomyxoma of peritoneum by HIPEC, which officially began the clinical exploration and practice of HIPEC treatment. HIPEC has been widely used in the treatment of various primary and

Huachu Deng and Baibei Li contributed equally to this work.

✉ Xingan Qin
drqinxingan@126.com

[1] Department of Gastrointestinal and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

[2] Department of Hepatobiliary, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

secondary peritoneal tumors and their complicated malignant ascites [8–10]. At present, the application of HIPEC in advanced gastric cancer is mainly divided into prophylactic and therapeutic [11]. At present, prophylactic HIPEC is mainly used after R0 resection in patients with advanced gastric cancer who have high risk factors but do not have visible peritoneal metastasis [12, 13]. Therapeutic HIPEC is mainly applied to gastric cancer patients with peritoneal metastasis or accompanied by cancerous ascites, with the main purpose of alleviating the symptoms of cancerous ascites and trying to prolong the survival time to the maximum [14].

In the past 5 years, a number of studies on the role of HIPEC in AGC have been published. The effectiveness of HIPEC to AGC remains hot and controversial. Therefore, the purpose of this meta-analysis is to systematically explore and summarize the efficacy and safety of HIPEC in patients with AGC through randomized controlled trials, and to report the relationship between HIPEC and complications for the first time.

Materials and methods

Search strategy

We searched published studies following the preferred report items of systematic review and meta-analysis (PRISMA) guidelines [15]. We conducted a systematic search for RCTs in databases, such as the Cochrane Library, PubMed, Embase, Pubmed, Google Scholar, Baidu Scholar and other databases. We searched for relevant studies published up to January 20th, 2022 with language restriction to English. Combining the main keywords and free words, the complete search strategy was as follows: ("hyperthermic intraperitoneal chemotherapy" OR "intraperitoneal chemotherapy" OR "hyperthermic perfusion chemotherapy" OR "intraperitoneal hyperthermic perfusion chemotherapy" OR "chemotherapy for peritoneal perfusion" OR "HIPEC") AND ("advanced gastric cancer" OR "stomach cancer" OR "gastric cancer" OR "AGC"). Besides, we reviewed the reference list of retrieved articles to look for other potential experiments.

Study selection

The studies included in this meta-analysis were RCTs which evaluate the efficacy of HIPEC in the ACG. The main endpoints were 1-, 2-, 3- and 5-year overall survival (OS) of patients with gastric cancer, while the safety endpoints were intestinal anastomotic leakage, myelosuppression, nausea and vomiting. Summary studies, animal, cellular studies, or low-quality studies were excluded.

Data extraction

Two authors (H.D. and B.L.) independently extracted the following data from each included study: study design, author, publication date, study country, participant characteristics, gender, age, HIPEC regimen, interventions, treatment cycle and endpoint indicators. When differences arise, all the authors negotiate together until the differences are resolved.

Quality assessment of study and evidence

The quality assessment is based on the Cochrane bias risk standard and is independently assessed by two reviewers (H.D. and B.L.) [16]. Five items were used to estimate bias in each study, including bias due to deviations from intended interventions, bias arising from the randomization process, bias in selection of the reported result, bias in measurement of the outcome and bias due to missing outcome data.

Statistical analysis

The aggregate risk ratio (RR) and 95% confidence interval (CI) of hyperthermic intraperitoneal chemotherapy and unexposed intraperitoneal chemotherapy are the criteria for measuring the efficacy of hyperthermic intraperitoneal chemotherapy. Q test ($p < 0.05$) was used to assessed the heterogeneity among included studies. The Higgins I^2 statistic was also examined, I^2 value > 50 and 75%, respectively, means substantial heterogeneity and high heterogeneity existed in the trials. A random-effects model was used when significant heterogeneity was detected; otherwise, a fixed-effects model was preferred. If there were more than ten studies assessed one endpoint, we examined the publication bias and explored sources of heterogeneity by funnel plot. We conducted a subgroup analysis to evaluate the sources of heterogeneity. And sensitivity analysis was used to determine the reliability and stability of the pooled results. All statistical analyses were performed with the STATA 12.0 (Stata Corporation, College Station, Texas, USA). A threshold of $p < 0.05$ was considered significant without anything special.

Results

Literature retrieval process and baseline characteristics of included studies

According to PRISMA guidelines, 678 studies were enrolled. We then eliminated a portion of the articles by

screening the abstracts, and identified the final articles for inclusion after reading the full text. Finally, 13 studies [17–29] (14 trial comparisons) were included which contained 1091 patients as shown in (Fig. 1). 556 patients (51.0%) were randomized to HIPEC group whereas 535 patients (49.0%) were randomized to control group. All of included studies used HIPEC as a preemptive strategy. All included studies were RCTs. The basic characteristics of the included studies are described in Table 1.

Assessment of quality of the studies

Two authors evaluated the quality of the retrieved studies by The Cochrane Risk of Bias criteria [30]. 13 studies [17–29] described random sequence generation and allocation concealment. None of the studies described other biases. The included studies were all RCTs. The literature quality score is shown in Table 2.

Endpoints

Overall survival (OS)

The overall survival analysis in AGC showed no significant differences in survival rates between HIPEC group and control group at 1-year [RR: 1.23, 95% CI 0.89 to 1.70, $I^2 = 82.2\%$, Fig. 2], 2-year [RR: 1.14, 95% CI 0.59 to 2.17, $I^2 = 78.6\%$, Fig. 3] and 3-year [RR: 1.21, 95% CI 0.86 to 1.70, $I^2 = 75.7\%$, Fig. 4] follow-up, while a statistical significant overall effect was found at the 5-year follow-up [RR: 1.20, 95% CI 1.01 to 1.43, $I^2 = 0.0\%$, Fig. 5] favoring the HIPEC procedure.

And we performed a subgroup analysis by country, peritoneal carcinomatosis and year of publication. The results of the subsequent subgroup analysis showed that there was no significant difference between HIPEC group and control group at 1, 2, 3-year OS, regardless of country and peritoneal carcinomatosis as show in (Table 3). And included studies published before 2010 demonstrated that HIPEC could improve 1- and 3-year OS as show in (Table 3). According to the country subgroup analysis, the heterogeneity of China subgroup decreased at 2-year OS ($I^2 = 0.0\%$), 3-year

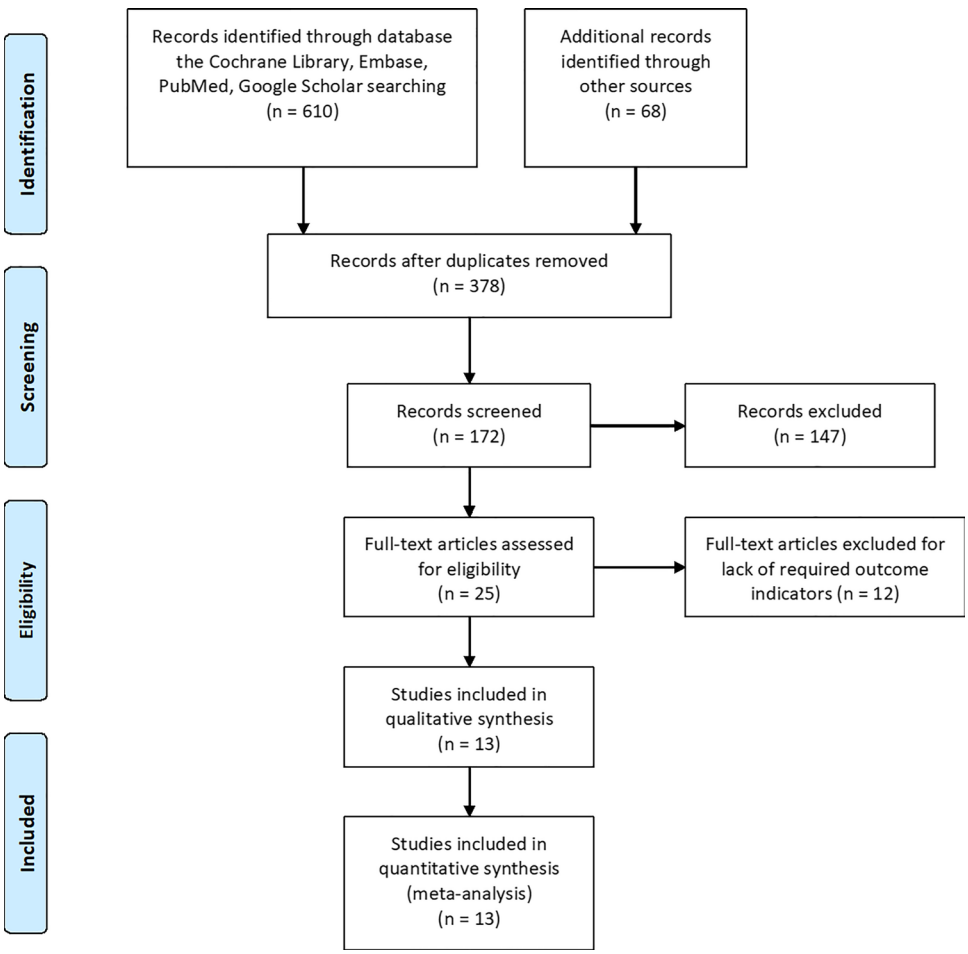

Fig. 1 Flowchart of included studies

Table 1 Characteristics of included studies in meta-analysis

Author	Year	Selection criteria	Country	Sample size		Average age (years) Mean ± SD		HIPEC regimen	Intervention		Endpoints
				HIPEC	Control	HIPEC	Control		HIPEC group	Control group	
Koga et al.	[17]	cT4	Japan	32	28	NA	NA	8 to 10 mg/l of mitomycin C and 2000 ml saline were infused into the peritoneal cavity with inflow and outflow temperatures of 44-45 and 40–42 ℃	Radical surgery + HIPEC	Radical surgery	3-year os, intestinal anastomoticleakage
Kaibara et al.	[18]	cT4	Japan	42	40	NA	NA	Mitomycin C and saline were infused into the peritoneal cavity with inflow and outflow temperatures of 44-45and 40-42 ℃	Radical surgery + HIPEC	Radical surgery	5-year os,
Hamazoe et al.	[19]	cT4	Japan	42	40	56.5 ± 10.4	63.4 ± 9.6	10 μg/ml of mitomycin C and saline were infused into the peritoneal cavity with inflow and outflow temperatures of 44-45 and 40-42 ℃	Radical surgery + HIPEC	Radical surgery	5-year os, intestinal anastomoticleakage
Fujimura et al.	[20]	cT4	Japan	22	18	60.2	62.9	Normal saline were infused into the peritoneal cavity with temperature of 41-42 ℃	Radical surgery + HIPEC	Radical surgery	1-year os, 2-year os, 3-year os, intestinal anastomoticleakage, myelosuppression
Ikeguchi et al.	[21]	cT3	Japan	78	96	NA	NA	8-10 L fluid containing 80-100 mg/m^2 mitomycin C was perfused at a rate of 100-200 ml/min. with inflow and outflow temperatures of 44-45 and 40-42 ℃	Radical surgery + HIPEC	Radical surgery	5-year os,

Table 1 (continued)

Author	Year	Selection criteria	Country	Sample size		Average age (years) Mean ± SD		HIPEC regimen	Intervention		Endpoints
				HIPEC	Control	HIPEC	Control		HIPEC group	Control group	
Fujimoto et al.	[22]	cT4	Japan	71	70	58.5 ± 8.1	59.2 ± 9.1	3–4 L of perfusate containing mitomycin C, 10 mg/mL, was circulated for 120 min with inflow and outflow temperatures of 44.5–45.0 and 43.0–44.0 ℃	Radical surgery + HIPEC	Radical surgery	2-year os, intestinal anastomoticleakage, myelosuppression
Yonemura et al.	[23]	cT2-T4	Japan	48	47	NA	NA	Peritoneal cavity was perfused with 6-8 L of heated saline at 42-43 ℃ with 30 mg of mitomycin C and 300 mg of cisplatin by a extracorporeal circulation machine.	Radical surgery + HIPEC	Radical surgery	5-year os,
Yang et al.	[24]	GCPC	China	34	34	50	51	Cisplatin 120 mg and mitomycin C 30 mg each in 6000 ml of normal saline at 43 ± 0.5 ℃ for 60–90 min	Cytoreductive Surgery + HIPEC	Cytoreductive Surgery	1-year os, 2-year os, 3-year os, intestinal anastomoticleakage
Cui et al. a	[25]	cT4	China	48	48	55	55	On day 1 and 4, the intraperitoneal hyperthermic perfusate consisted of 60 mg/m2 cisplatin and 3,000 ml normal saline, while on day 2 and 3, the perfusate consisted of 0.75 g fluorouracil and 3,000 ml normal saline.	Radical surgery + Neoadjuvant chemotherapy + HIPEC	Radical surgery + Neoadjuvant chemotherapy	1-year os, 3-year os, nausea and vomiting, myelosuppression

Table 1 (continued)

Author	Year	Selection criteria	Country	Sample size		Average age (years) Mean ± SD		HIPEC regimen	Intervention		Endpoints
				HIPEC	Control	HIPEC	Control		HIPEC group	Control group	
Cui et al. b	[25]	cT4	China	48	48	53	56	On day 1 and 4, the intraperitoneal hyperthermic perfusate consisted of 60 mg/m2 cisplatin and 3,000 ml normal saline, while on day 2 and 3, the perfusate consisted of 0.75 g fluorouracil and 3,000 ml NS.	Radical surgery + HIPEC	Radical surgery	1-year os, 3-year os, nausea and vomiting, myelosuppression
Huang et al.	[26]	cT3-T4	China	21	21	57.3	56.8	A pre-warmed cisplatin solution (43–45 ℃ 20 μg/mL, cisplatin dissolved in NaCl 0.9% infusion solution) was perfused into the peritoneal cavity at the rate of 150 mL/min for 60 min	Cytoreductive surgery + Intraperitoneal chemotherapy with 120 mg cisplatin after surgery + HIPEC	Cytoreductive surgery + Intraperitoneal chemotherapy with 120 mg cisplatin after surgery	1-year os, 2-year os, 3-year os, intestinal anastomoticleakage, nausea and vomiting
Rudloff et al.	[27]	GCPC	USA	9	8	45	52	A closed circuit of oxaliplatin solution at 460 mg/m^2 in 5% dextrose in water) at 41 °C for 30 min	Cytoreductive surgery + systemic chemotherapy (FOLFOXIRI regime) + HIPEC	systemic chemotherapy (FOLFOXIRI regime)	1-year os,
Lu et al.	[28]	GCPC	China	28	20	52.4 ± 7.9	54.3 ± 6.6	The circulating injections of 1500-2500 ml of hot saline (44 °C), cisplatin (40 mg/m2), 5-FU (500 mg/m2) the outlet was controlled at 41 °C, and the inlet was controlled at 44 °C. One perfusion every other day for a total of 3 perfusions	Systemic chemotherapy + HIPEC	Systemic chemotherapy	1-year os, 3-year os, nausea and vomiting, myelosuppression

Table 1 (continued)

Author	Year	Selection criteria	Country	Sample size		Average age (years) Mean ± SD		HIPEC regimen	Intervention		Endpoints
				HIPEC	Control	HIPEC	Control		HIPEC group	Control group	
Fan et al.	[29]	cT3-4	China	33	17	61	60	Cisplatin (50 mg/L) was diluted in heated 0.9% sodium chloride and then circulated for 30 min. Perfusion rate was 400–500 ml/min. The circulation temperature was 42.5—43.0 °C	Radical surgery + systemic chemotherapy(SOX regime) + HIPEC	Radical surgery + systemic chemotherapy(SOX regime)	3-year os, intestinal anastomoticleakage, myelosuppression

GCPC gastric cancer peritoneal carcinomatosis, *OS* overall survival

OS ($I^2 = 64.7\%$). And the heterogeneity of Japan subgroup decreased at 3-year OS ($I^2 = 46.9\%$). According to peritoneal carcinomatosis subgroup analysis, the heterogeneity of peritoneal carcinomatosis subgroup decreased at 3-year OS ($I^2 = 0.0\%$). According to year of publication subgroup analysis, the heterogeneity of studies published after 2010 subgroup decreased at 1-year OS ($I^2 = 79.5\%$) 2-year OS ($I^2 = 0.0\%$), 3-year OS ($I^2 = 64.7\%$).

Safety endpoints

The safety endpoints mainly including the risk of intestinal anastomotic leakage, myelosuppression, nausea and vomiting. There was no significant difference between HIPEC group and control group in the risk of intestinal anastomotic leakage (RR: 0.89, 95% CI 0.38 to 2.13, $I^2 = 0.0\%$, Supplementary 1), myelosuppression (RR: 1.09, 95% CI 0.90 to 1.32, $I^2 = 0.0\%$, Supplementary 2), nausea and vomiting (RR: 1.22, 95% CI 0.98 to 1.52, $I^2 = 12.5\%$, Supplementary 3). The random effect model was applied.

Sensitivity analysis and publication bias

The funnel plots show a low probability of publication bias (all the $p > 0.05$) for the included studies, as shown in Supplementary 4–5. The results of the sensitivity analyses show the heterogeneity mainly comes from the studies of Cui et al. [25] and Huang et al. [26] as shown in Supplementary 6-8.

Discussion

HIPEC could selectively kill tumor cells by inhibiting DNA replication, transcription and repair. Under high temperature, the fluidity of cancer cell membrane is enhanced, and the permeability of cell membrane and tumor blood vessels is increased, which is conducive to the penetration and absorption of chemotherapeutic drugs [31]. It refers to the precise constant temperature, circulating perfusion, filling the abdominal cavity and maintaining it for a certain time, to prevent and treat the implantation and metastasis of the peritoneal cavity [32]. HIPEC is an adjuvant therapy for abdominal malignant tumors. It has unique therapeutic effects in the prevention and treatment of peritoneal carcinomas, colorectal cancer, ovarian cancer, gastric cancer, and so on [33, 34]. The advantage of HIPEC is that drug directly acts on cancer cells, affecting the peritoneal microenvironment and inhibiting the implantation of cancer cells. Another advantage is that the adverse reaction is small [35].

Advanced gastric cancer is often accompanied by peritoneal metastasis [36]. Even with D2 radical surgery, peritoneal metastasis and recurrence may occur [37]. How to treat peritoneal metastasis of ACG is the key to prolong

Table 2 Assessment of methodological quality of included studies

Study	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Koga et al.	Low	Low	Low	Low	Low	Low
Kaibara et al.	Some concerns	Low	Low	Low	Low	Some concerns
Hamazoe et al.	Low	Low	Low	Low	Low	Low
Fujimura et al.	Low	Low	Low	Low	Low	Low
Ikeguchi et al.	Low	Low	Low	Low	Low	Low
Fujimoto et al.	Low	Low	Low	Low	Low	Low
Yonemura et al.	Low	Low	Low	Low	Low	Low
Yang et al.	Low	Low	Low	Low	Low	Low
Cui et al.	Low	Low	Low	Low	Low	Low
Huang et al.	Low	Low	Low	Low	Low	Low
Rudloff et al.	Low	Low	Low	Low	Low	Low
Lu et al.	Low	Low	Low	Low	Low	Low
Fan et al.	Low	Low	Low	Low	Low	Low

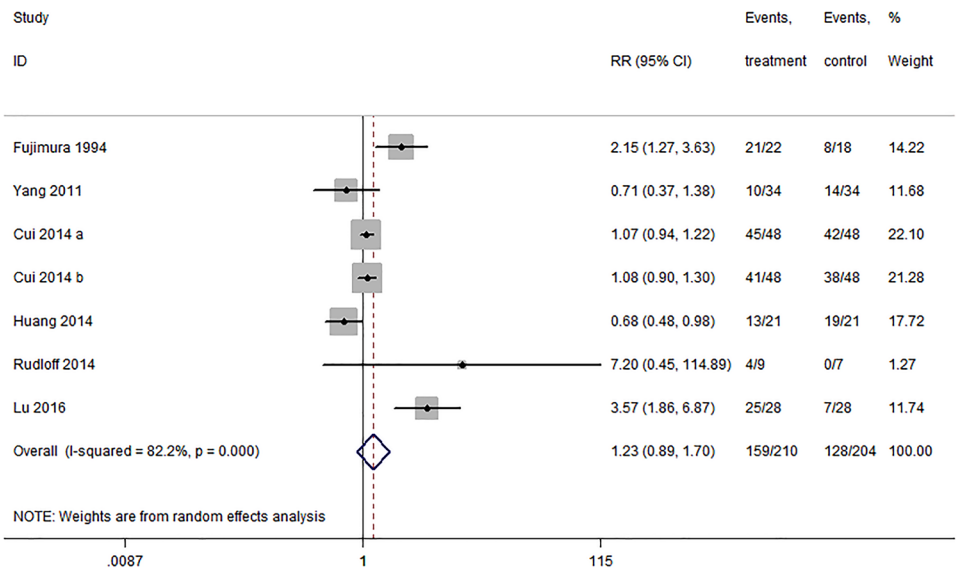

Fig. 2 Forest plot of OS at 1-year follow-up. *RR* risk ratio, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival

the survival of patients and improve the quality of life of patients.

Since Koga et al. [17] first applied HIPEC to gastric cancer patients in 1988, domestic and foreign scholars have conducted in-depth research on this method. HIPEC can effectively remove peritoneal free cancer cells and micro metastases, and prevent and treat peritoneal metastasis of gastric cancer.

Nowadays, there are a few meta-analyses to study the efficacy and safety of HIPEC in the AGC patients with/without peritoneal carcinomas. In 2017, Desiderio et al. [38] conducted a meta-analysis to evaluate the role of HIPEC in gastric cancer and clarify its effectiveness at different stages of peritoneal disease progression. They found that preventive HIPEC could bring survival benefits. In particular, patients whose disease burden is limited to positive cytology and limited nodal involvement may benefit the most from HIPEC. The authors included both RCTs and nRCTs, while we included only RCTs, In addition, a number of other studies on the role of HIPEC in AGC have been published in the last 5 years. Liu et al. [39] comprehensively analyzed the effect of HIPEC for gastric cancer patients by including twenty-one trials. They concluded that HIPEC had a beneficial effect on 3-year survival rate and complete response in patients with AGC and peritoneal metastases. But they did not report the relationship between the HIPEC and complications. Besides,

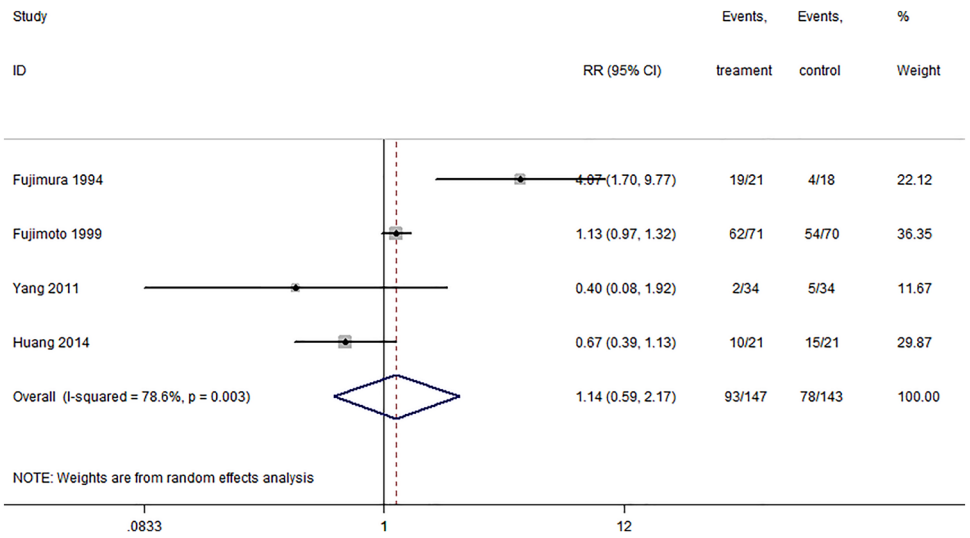

Fig. 3 Forest plot of OS at 2-year follow-up. *RR* risk ratio, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival

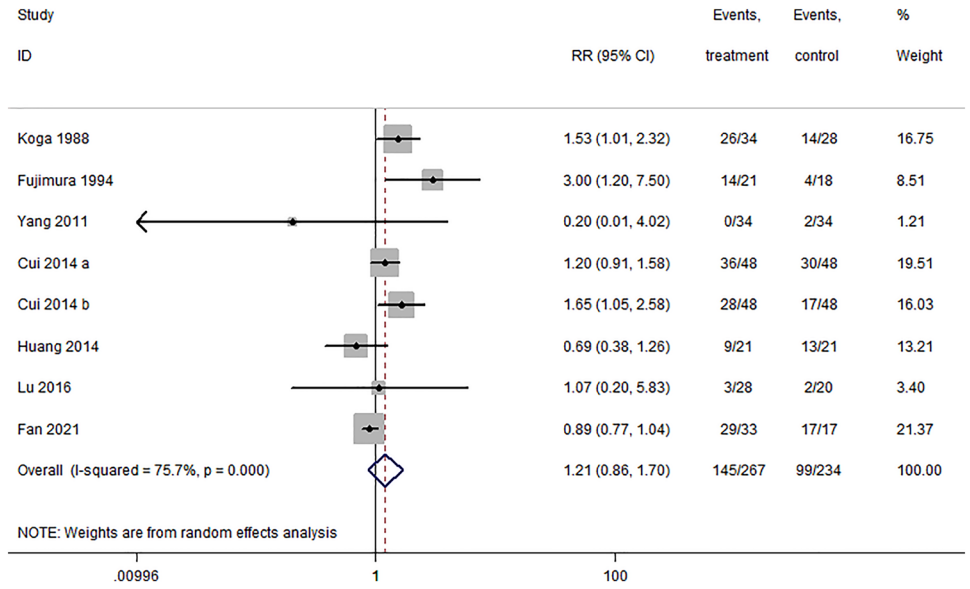

Fig. 4 Forest plot of OS at 3-year follow-up. *RR* risk ratio, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival

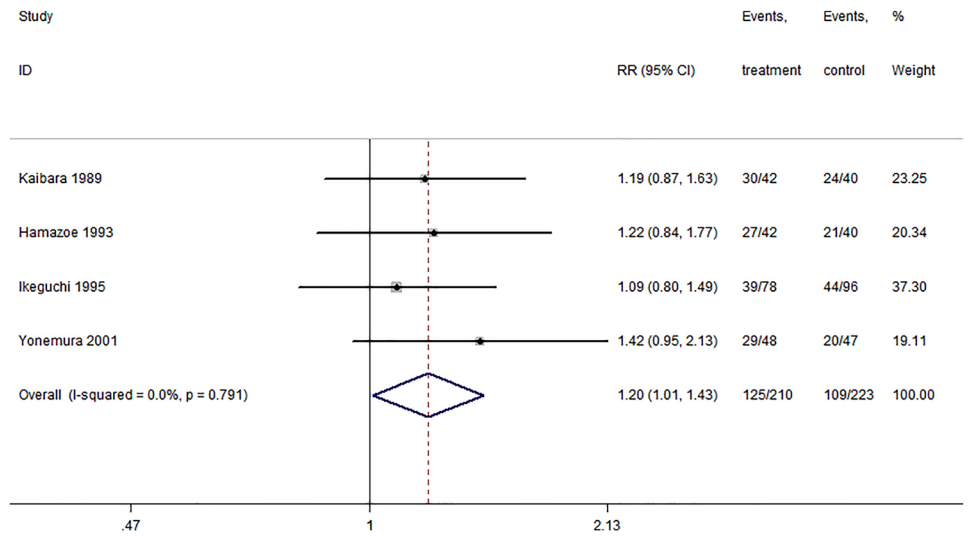

Fig. 5 Forest plot of OS at 5-year follow-up. *RR* risk ratio, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival

Table 3 Subgroup analysis of OS at 1-year, 2-year, and 3-year follow-up

Subgroup	Pooled RR (95% CI)					
	1-Year OS	I^2 (%)	2-Year OS	I^2 (%)	3-Year OS	I^2 (%)
Publishing time						
< 2010	2.15(1.27–3.63)	–	2.03(0.47–8.82)	90.9	1.90(1.00–3.63)	46.9
≥ 2010	1.11(0.81–1.52)	79.5	0.63(0.39–1.04)	0.0	1.04(0.76–1.43)	64.7
Peritoneal carcinomatosis						
Yes	2.05(0.50–8.33)	84.3	0.40(0.08–1.92)	–	0.71(0.16–3.12)	0.0
No	1.08(0.84–1.40)	76.7	1.31(0.64–2.67)	84.7	1.25(0.87–1.80)	83.2
Country						
Japan	2.15(1.27–3.63)	–	2.03(0.47–8.82)	90.9	1.90(1.00–3.63)	46.9
China	1.08(0.80–1.46)	81.3	0.63(0.39–1.04)	0.0	1.04(0.76–1.43)	64.7
USA	7.20(0.45–114.89)	–	–		–	

all of included studies in their meta-analysis were from China, which is unrepresentative and limited.

Our meta-analysis evaluated the efficacy and safety of HIPEC in patients with AGC. The results showed that no significant differences in survival rates between HIPEC group and control group at 1, 2 and 3-year follow-up, while a statistical significant overall effect was found at the 5-year follow-up. And there is no significant difference in the risk of intestinal anastomotic leakage, myelosuppression and nausea and vomiting.

There is a large heterogeneity in the endpoint of 1, 2 and 3-year OS ($I^2 = 82.2$, 78.6 and 75.7%). Through sensitivity analysis, we found that the heterogeneity mainly comes from the study of Cui et al. [25] and Huang et al. [26] We consider that this may be because the sample size of Huang's study is small ($n = 42$), which may affect the reliability of the pooled effect size. And Cui et al. and Huang et al. are from China, while most of the other studies are from Japan, which may have ethnic and geographical differences, leading to correlation bias. Besides, the HIPEC regimens in Cui's and Huang's studies were different from the other included studies which may lead to methodological heterogeneity.

The potential clinical implications of this meta-analysis are as follows: (1) this is an updated meta-analysis to evaluate the efficacy and safety of HIPEC in AGC patients with/without peritoneal carcinomatosis. Compared to previous studies, we included 13 RCTs that contained a large sample size of 1091 participants. (2) Sensitivity analyses and subgroup analyses were conducted to explore heterogeneity. We found the source of heterogeneity (Cui's and Huang's studies). And we successfully decreased the heterogeneity of OS by performing a subgroup analysis according country and peritoneal carcinomatosis. (3) All the included studies were RCTs and the literature was of high quality. (4) Only 2 studies [26, 27] had a sample size of less than 45. (5) There was a low probability of publication bias for the included studies. (6) Compared to control group, HIPEC had no benefit in short-term OS, but in long-term OS, which is different from the conclusion of previous studies. And the pooled effect of long-term OS (5-year OS) was derived from studies conducted prior to 2001, and there was doubt whether the findings were still relevant, which needs to be further confirmed by large sample size and higher quality RCTs.

The limitations of our study are as follows: (1) several baseline characteristics (HIPEC regimes, preoperative nutritional status, and related underlying diseases) were not considered which may lead to mixed bias. (2) Most of included RCTs did not describe the blinding method used, which may lead to selection bias. (3) The data of 5-year OS were prior to 2001, which was too far away from now. (4) Included studies were mainly from Japan and China, lacking studies from other regions, which was not representative. (5) The heterogeneity of this meta-analysis was high at 1-, 2-, and 3-year OS and the conclusions were not reliable enough. (6)The role and timing of adjuvant chemotherapy and its impact on multimodal treatment approaches have not been clearly described.

In summary, our meta-analysis has demonstrated that compared with the control group, HIPEC could improve the long-term OS without increasing the risk of adverse effect in AGC patients with/without peritoneal carcinomatosis, but there was no benefit at short-term OS.

For AGC patients, peritoneal metastasis still occurs frequently, chemotherapy including HIPEC has not been widely adopted, and peritoneal metastasis still exist. In this context, the next steps in developing treatment regiments should consider combining with neoadjuvant chemotherapy, immunotherapy, targeted therapy and surgical treatment. And large sample size, multicenter and long-term follow-up RCTs are necessary to conducted to further evaluate the efficacy of HIPEC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13304-022-01376-5.

Data availability The author could be contacted for data requests.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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