

Efficacy of hyperthermic intraperitoneal chemotherapy plus cytoreductive surgery for advanced or recurrent ovarian cancer: a systematic evaluation and meta-analysis

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Abstract. – OBJECTIVE: This meta-analysis was performed to investigate the safety and efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) combined with cytoreductive surgery (CRS) in the treatment of advanced or recurrent ovarian cancer.

MATERIALS AND METHODS: An electronic search of databases, including PubMed, Embase, Cochrane, Medline, and Web of Science, was performed to collect controlled studies on HIPEC combined with CRS administered for advanced ovarian cancer. Meta-analysis was conducted based on the outcome indicators extracted from the included studies, including disease-free survival (DFS), overall survival (OS), and adverse events (AEs).

RESULTS: Twelve pieces of literature were included, involving 1,622 participants, with 694 participants in the control group and 928 in the study group. In terms of DFS, the pooled hazard ratio (HR) was 0.70 (95% CI: 0.58, 0.84), with an HR of 0.77 (95% CI: 0.64, 0.93) in the treatment-naïve subgroup and an HR of 0.54 (95% CI: 0.40, 0.74) in the secondary cytoreduction subgroup. In terms of OS, the pooled HR was 0.63 (95% CI: 0.52, 0.77), with an HR of 0.67 (95% CI: 0.54, 0.83) in the treatment-naïve subgroup and an HR of 0.47 (95% CI: 0.29, 0.77) in the secondary cytoreduction subgroup. With regard to AEs, the pooled odds ratio (OR) was 0.79 (95% CI: 0.68, 0.92).

CONCLUSIONS: The benefits of CRS plus HIPEC for the management of advanced ovarian cancer are significant but also associated with an increased risk of adverse events. Thus, clinical use of this co-administration requires caution.

Key Words:

Ovarian cancer, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Disease-free survival, Overall survival.

Introduction

Ovarian cancer is a common gynecologic malignancy, with about 200,000 new cases and 125,000 deaths per year worldwide, ranking first among tumors in terms of mortality. Ovarian cancer is usually diagnosed at an advanced stage due to non-specific early symptoms and the absence of reliable early screening methods¹. For patients with stage III and IV ovarian cancer, cytoreductive surgery (CRS) followed by postoperative chemotherapy is the standard of care. Specifically, the surgery minimizes the tumor burden followed by six cycles of intravenous chemotherapy with carboplatin and paclitaxel^{2,3}. Despite a certain delay in disease progression after standard treatment, patient survival remains poor, with a 3-year survival rate of approximately 50% and a 5-year survival rate of only 40%⁴. Thus, an urgent need exists to explore more treatment alternatives to potentiate the current treatment effects.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a novel treatment modality combining thermotherapy and chemotherapy, and its application in clinical settings is gradually gaining popularity in recent years. Studies^{5,6} have shown that HIPEC provides an improved killing effect on ovarian cancer tumor cells or residual tumor tissue and micro-metastases. Moreover, HIPEC has been reported to significantly prolong the overall survival of stage III ovarian cancer patients after primary cytoreductive surgery^{7,8}. In current clinical practice, preoperative neoadjuvant chemotherapy combined with CRS is commonly adopted for the management of patients with advanced ovarian cancer, as it significantly shrinks the tumor volume, facilitates subsequent tumor remov-

al, and reduces the risk of surgery, postoperative complications, and recurrence⁹. It has been widely reported that HIPEC neoadjuvant chemotherapy combined with CRS for advanced or recurrent ovarian cancer¹⁰. However, their results vary, and disputes exist regarding the efficiency of HIPEC and its benefit on the survival of ovarian cancer patients. To this end, this study was performed to investigate the safety and efficacy of HIPEC combined with CRS in the treatment of advanced or recurrent ovarian cancer, in order to offer a point of reference for clinical treatment.

Materials and Methods

Literature Search Strategy

An electronic search of databases, including PubMed, Embase, Cochrane, Medline, and Web of Science, was performed from inception to April 1, 2023, to collect controlled studies on HIPEC combined with CRS administered for advanced ovarian cancer. The search was conducted using Mesh phrases such as “hyperthermic intraperitoneal chemotherapy”, “HIPEC”, “ovarian tumor”, and “ovarian cancer”. Taking the PubMed database search as an example, the detailed search strategy is shown in Table I. Secondary screening of citations for the retrieved literature was also carried out to avoid missing literature.

This meta-analysis was conducted and reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist. This meta-analysis’s registration number is INPLASY202360020 (<https://www.inplasy.com>).

Inclusion and Exclusion Criteria of the Literature

Inclusion criteria: 1) participants with a pathological diagnosis of ovarian cancer; 2) study design was randomized controlled, case-control, or retrospective study matched for basic information; 3) all patients were treated with CRS; 4) both participants receiving HIPEC and those not receiving HIPEC

were included; (5) clinical outcome including at least one of DFS, OS, and hazard ratio (HR) and 95% confidence interval (CI) were also calculated.

Exclusion criteria: animal studies, reviews, case reports, conference abstracts, and unavailability of the specified data extraction.

Data Extraction and Literature Quality Assessment

Data extraction included basic information from the literature and outcome indicators. The basic information included the first author’s name, year of publication, mean age, cancer stage, treatment modality, and follow-up time. Endpoints included DFS, OS, and AEs with their HR and 95% CIs. DFS was defined as the length of time from treatment initiation to disease progression, and OS was defined as the length of time from surgery intervention to death. The Risk of Bias tool provided in the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane, Oxford, London, UK) was used to assess the quality of the included literature in seven dimensions: random sequence generation, concealment of random assignment, blinding of investigators and participants, incomplete and selective reporting of outcome data, relevance of the obtained outcome data, and other potential sources of bias. For each aspect, the study quality assessment was classified as “low risk”, “uncertain risk”, and “high risk”.

Literature screening, data extraction, and literature quality assessment were performed independently by two investigators, and standardized forms were used for data extraction. Discrepancies in data extraction were resolved through discussions with a third investigator. Should data be incomplete or other problems be encountered during data extraction, we contacted the authors by phone or email for additional information.

Statistical Analysis

The R language SURVIVAL package and meta-package (Lucent Technologies Corp., Mount Jasmine, NJ, USA) were used to analyze the data and plot the relevant graphics. HR and OR, with

Table I. PubMed database search strategy.

Search	Query
#1	(HIPEC[Title/Abstract]) OR (Hyperthermic intraperitoneal chemotherapy [Title/Abstract])
#2	(Ovarian cancer[Title/Abstract]) OR (Ovarian tumors[Title/Abstract])
#3	#1 and #2

their 95% CI, were used to assess survival data and categorical data outcomes. The I^2 test was used to analyze the heterogeneity of the included literature, where $I^2 < 50\%$ suggested the absence of significant heterogeneity between studies, and a fixed-effects model was used for analysis; $I^2 \geq 50\%$ suggested the existence of significant heterogeneity between studies, and subgroup analysis was performed. If I^2 remained $\geq 50\%$ after subgroup analysis, a random effects model was used for analysis. Publication bias was assessed for each combined study group using funnel plots and further assessed using Egger's test. A $p < 0.05$ was considered a statistically significant difference.

Results

Basic Characteristics of the Included Literature

A total of 759 pieces of literature were found by computer search, and 569 pieces were coarsely included after excluding 131 pieces of duplicate

literature and 59 pieces of irrelevant studies, reviews, case reports, and non-clinical studies. After reading the abstracts, we excluded 36 studies with no specified data or no specified intervention method, 3 studies with no access to raw data, and 7 case reports, and finally included 12 studies¹¹⁻²² with a total of 1,622 participants, including 694 cases in the control group and 928 cases in the study group. The PRISMA flowchart is shown in Figure 1, and the basic characteristics of the included literature are shown in Table II.

Literature Quality Evaluation

Of the 12 included RCTs, 8^{11-15,17-19} mentioned "randomized grouping" with low risk, and 4^{16,20-22} were retrospective analyses but were matched for basic information with an unclear risk. No concealment of random assignment was mentioned in all included studies. Confined to informed consent for treatment, only data analysts were blinded. Six studies^{11-13,15,17,22} described participants' withdrawal. A bar chart of the quality evaluation of the literature is shown in Figure 2.

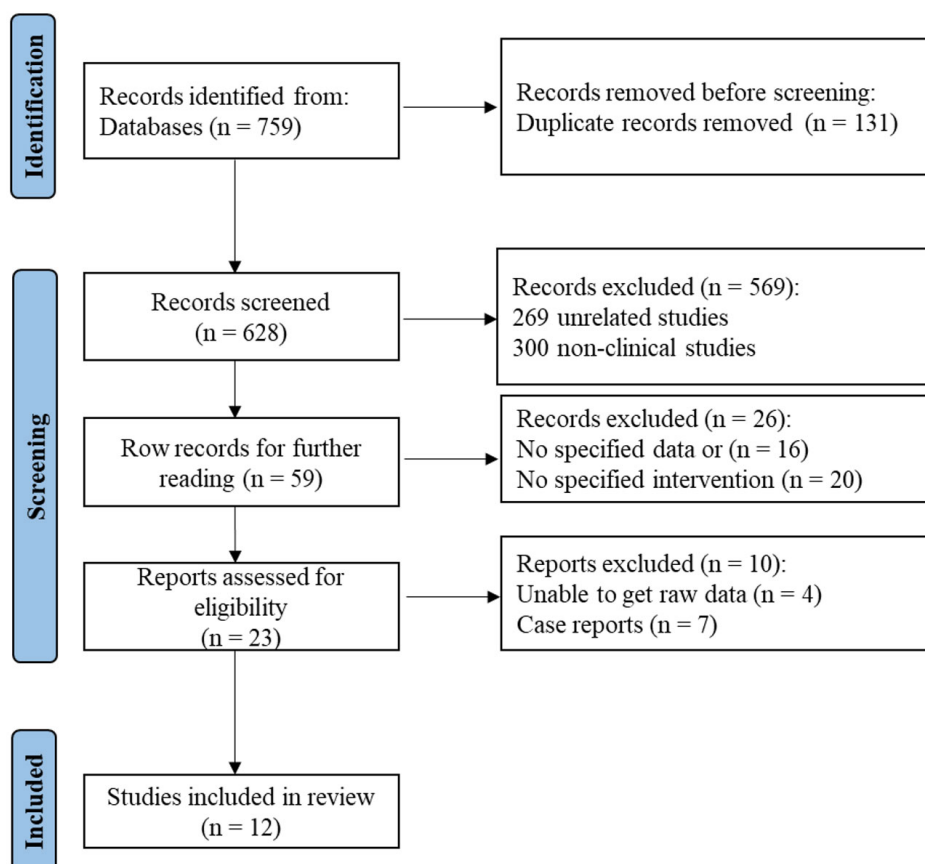


Figure 1. PRISMA flowchart.

Table II. Basic characteristics of the included literature.

Author	Year	FIGO stage	Enrollments	Number of patients		Outcome
				HIPEC	non-HIPEC	
van Driel et al ¹¹	2018	III	Treatment-naïve	123	112	DFS, OS, AEs
Yu et al ¹²	2023	Unstated	Treatment-naïve and recurrent	33	33	AEs
Antonio et al ¹³	2022	III and IV	Treatment-naïve	36	35	DFS, AEs
Kim et al ¹⁴	2010	Ic to IIIc	Secondary cytoreduction	24	19	DFS, OS
Lim et al ¹⁵	2022	III and IV	Treatment-naïve	92	92	DFS, OS, AEs
Lei et al ¹⁶	2020	III	Treatment-naïve	159	425	DFS, OS, AEs
Zivanovic et al ¹⁷	2021	Platinum sensitive	Secondary cytoreduction	49	49	DFS, OS, AEs
Baiocchi et al ¹⁸	2016	Platinum sensitive	Secondary cytoreduction	50	29	OS
Muñoz-Casares ¹⁹ et al	2009	III	Secondary cytoreduction	12	14	OS
Ceresoli et al ²⁰	2018	IIIc, IV	Treatment-naïve	28	28	DFS, AEs
Le Brun et al ²¹	2014	II to IV	Treatment-naïve	19	23	OS
Mendivil et al ²²	2017	III and IV	Secondary cytoreduction	69	69	DFS

Hyperthermic intraperitoneal chemotherapy (HIPEC), disease-free survival (DFS), overall survival (OS), and adverse events (AEs).

Forest Plot for Meta-Analysis

Forest plot of DFS

Of the 12 included studies, 8^{11,13-17,20,22} reported DFS outcomes, and the results of the heterogeneity analysis showed significant heterogeneity ($I^2=52%$), which was analyzed using a random-effects model with a pooled HR of 0.70 (95% CI: 0.58, 0.84). Considering significant heterogeneity between studies, subgroup analysis was performed based on participants undergoing primary

(treatment-naïve) and secondary cytoreduction. The results of the intra-subgroup heterogeneity analysis showed significant heterogeneity within treatment-naïve subgroup studies ($I^2=74%$), and an HR of 0.77 (95% CI: 0.64, 0.93) was observed after random effects model analysis. There was no significant heterogeneity within the Secondary cytoreduction subgroup of studies ($I^2=0%$), and the HR was 0.54 (95% CI: 0.40, 0.74) when analyzed using a fixed-effects model. The forest plot of the DFS outcome is shown in Figure 3.

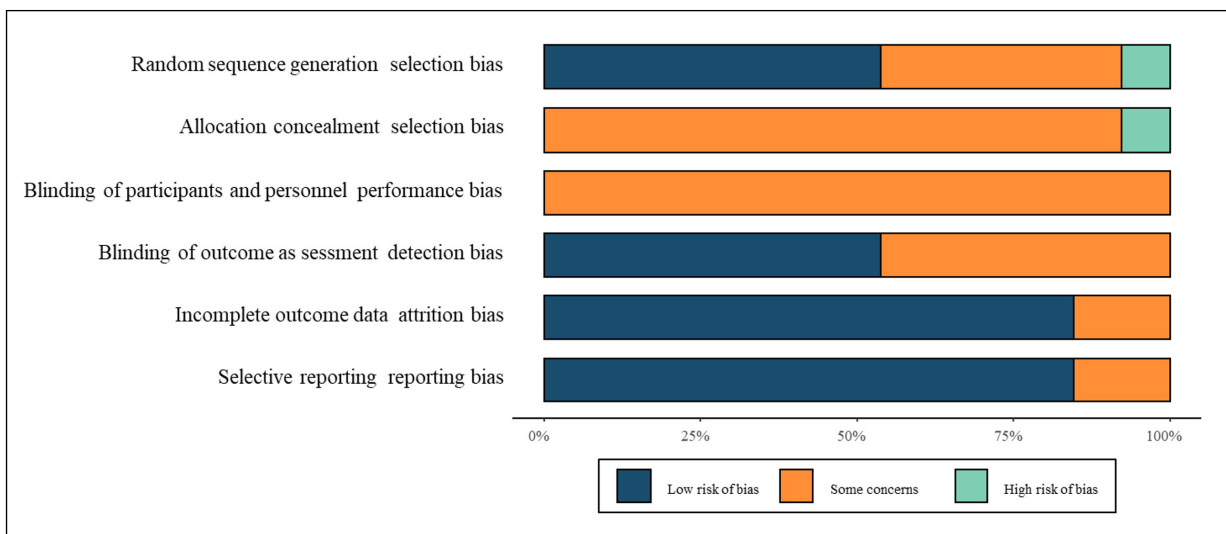


Figure 2. Evaluation of the quality of the included literature.

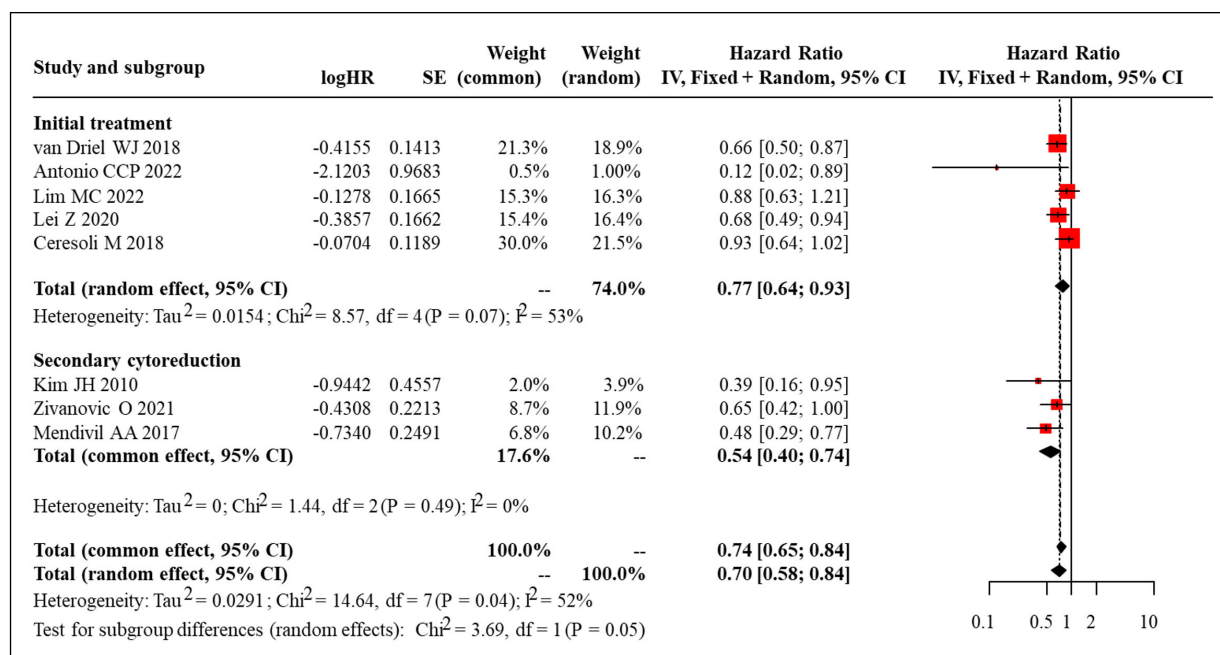


Figure 3. Forest plot of the DFS outcomes.

Forest plot of OS

A total of 8^{11,14-19,21} of the 12 included studies reported OS outcomes and the heterogeneity analysis showed no significant heterogeneity (I²=47%), with a pooled HR of 0.63 (95% CI: 0.52, 0.77) when an-

alyzed using a fixed-effects model. The HR was 0.67 (95% CI: 0.54, 0.83) for the treatment-naïve subgroup and 0.47 (95% CI: 0.29, 0.77) for the secondary cytoreduction subgroup. The forest plot of OS outcomes is shown in Figure 4.

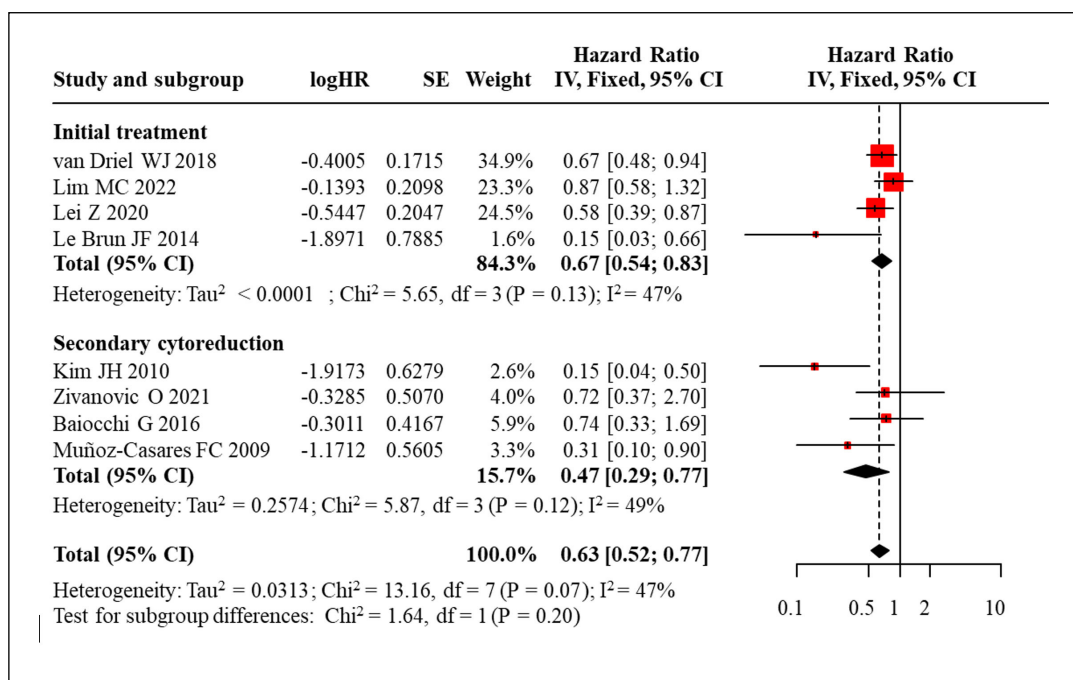


Figure 4. Forest plot of OS outcomes.

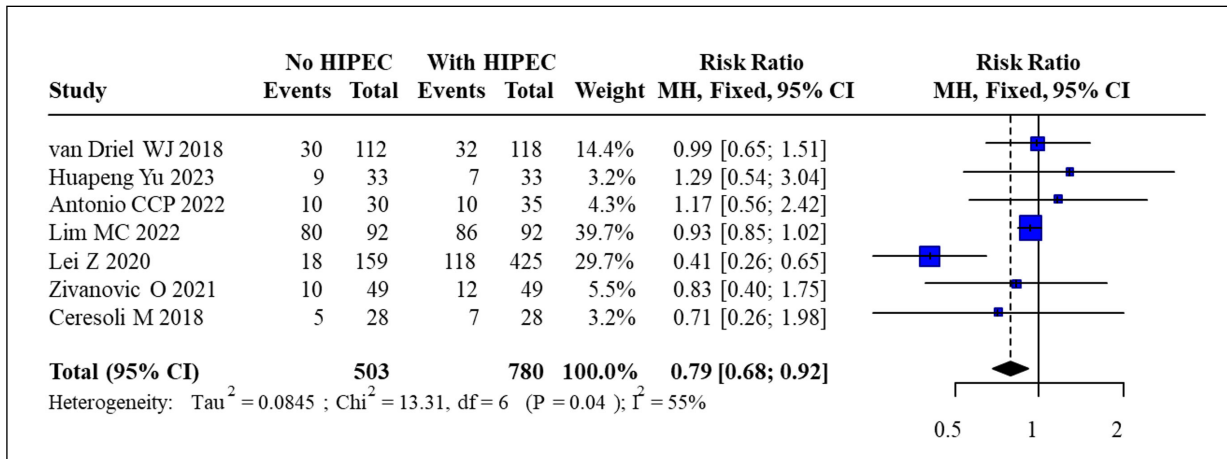


Figure 5. Forest plot of adverse events.

Forest plot of adverse events

Data related to grade III or higher AEs were extracted and analyzed to further examine the safety differences between different treatment modalities. A total of 7 articles^{11-13,15-17,20} reported the incidence of grade III or higher AEs, and the heterogeneity analysis showed significant heterogeneity ($I^2=55\%$) with a pooled OR of 0.79 (95% CI: 0.68, 0.92) obtained by the random effects model analysis. The forest plot of adverse events is presented in Figure 5.

Assessment of Publication Bias of Included Studies

Funnel plots were used to evaluate the publication bias of the included literature, and the funnel plots of OS and AEs were significantly asymmetrical, suggesting a possible publication bias. This publication bias may be attributed to the small number of the included studies, which is less than 10. The funnel plot of publication bias is shown in Figure 6.

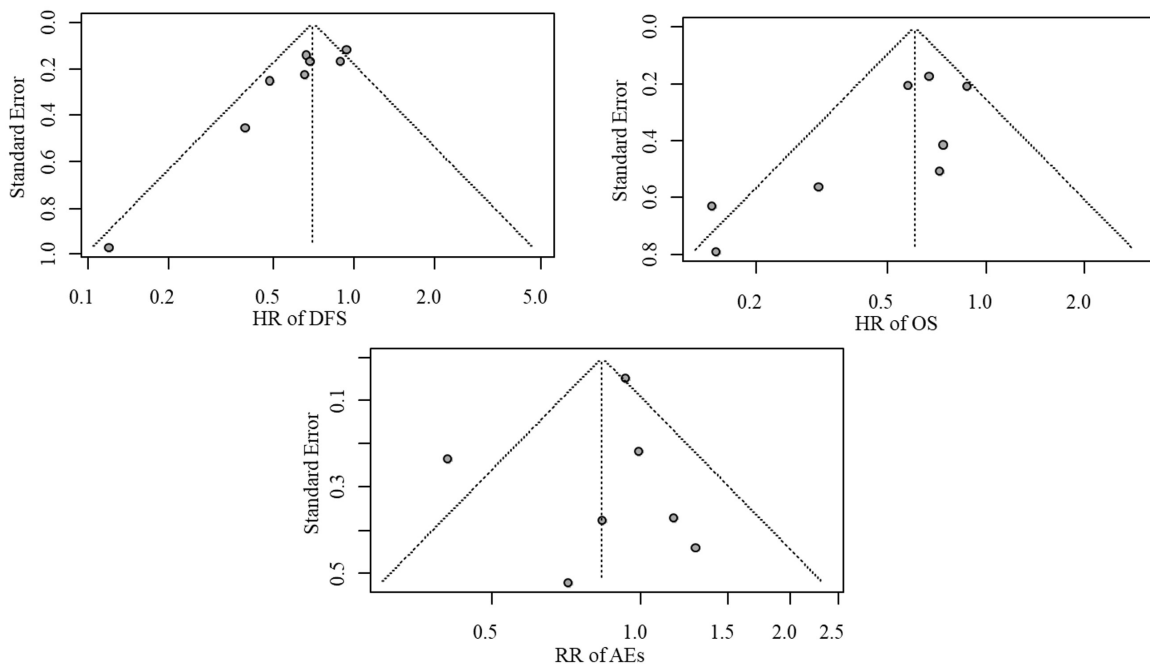


Figure 6. Funnel plot of publication bias.

Discussion

The results of the current meta-analysis found a significantly improved progression-free survival and overall survival but an increased risk of adverse events of patients with advanced ovarian cancer after incorporating HIPEC into the standardized care of CRS. Further subgroup analysis suggested that CRS plus HIPEC is less effective in improving the DFS and OS of treatment naïve patients than those with secondary surgery; however, the difference was statistically insignificant.

CRS is the standard first-line treatment for advanced ovarian cancer to facilitate subsequent tumor removal, followed by chemotherapy with paclitaxel and/or platinum-based chemotherapy²³. Despite the good response to treatment in about 70% of women, most patients relapse within the following 3 years²⁴. HIPEC refers to the combination of thermotherapy on top of peritoneal chemotherapy. Intraperitoneal chemotherapy uses the blood-peritoneal barrier to obtain higher drug concentrations on the peritoneal surface, with the addition of thermotherapy to enhance the thermal effect of chemotherapeutic agents²⁵. HIPEC, a strategy combining maximal cytoreductive surgery with regional chemotherapy, has been suggested for the care of advanced ovarian cancer. Unlike intraperitoneal chemotherapy, HIPEC is administered during CRS to avoid the side effects of postoperative intraperitoneal chemotherapy⁸. HIPEC produces direct cytotoxic effects due to high temperature, leading to the denaturation of cellular proteins, inducing vasodilation, and facilitating the entry of cytotoxic drugs into ovarian tumors²⁶. The large sample size prospective randomized controlled trial OVHIPEC¹¹ demonstrated that combining HIPEC in CRS was safe to improve recurrence-free survival and overall survival in patients with stage III ovarian cancer who were otherwise ineligible for stage I cytoreductive surgery, due to the extent of their disease. The OVHIPEC-2 trial²⁷ is currently underway to determine if HIPEC has a similar effect in primary CRS, and the results are still unavailable.

Complications and toxic reactions are the main concerns that limit the use of HIPEC. It has been suggested that HIPEC has a potential risk of death and risk of serious long-term sequelae. The majority of the literature included in the present study found no significant effect of HIPEC on the rate of grade III or higher adverse events. However, the results of our meta-analysis showed a risk of grade III+ adverse events of 0.79 (95% CI: 0.68,0.98) without the administration of HIPEC

compared with the use of HIPEC. Therefore, it is particularly important to understand how to reduce the incidence of adverse events. Evidence suggests that postoperative morbidity and mortality may be related to the treatment experience of the patient's clinical center²⁸. Experienced centers deem HIPEC to be safe for both clinical practice and research applications^{29,30}.

Most of the ongoing trials are conducted on women with primary ovarian cancer, where cisplatin is the most used HIPEC agent, followed by paclitaxel. According to ESMO guidelines, HIPEC is excluded from the standard of care for first-line treatment and its use should be limited to well-designed randomized controlled trials³⁰. To date, there are no standard guidelines for specific patient populations and ovarian tumor histology to determine the benefits of HIPEC. Furthermore, no standardized chemotherapeutic drug regimens are available, nor are there guidelines on treatment duration and temperature for the clinical implementation of HIPEC³¹.

Despite the interesting findings reported in this meta-analysis, large sample size prospective randomized control group studies are required to validate the findings. The sample sizes of the included studies in this study were small, and some of the studies^{16,20-22} were retrospective and matched studies with a low level of evidence.

Conclusions

The benefits of CRS plus HIPEC for the management of advanced ovarian cancer are significant but also associated with an increased risk of adverse events. Thus, clinical use of this co-administration requires caution.

Ethics Approval

Not applicable.

Informed consent

Not applicable.

Funding

None.

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Authors' Contributions

Liao Lanjin is responsible for the research concept, research design, definition of knowledge content, literature research, clinical research, experimental research, data collection, data analysis, statistical analysis, and manuscript preparation. Li Hui is responsible for the definition of knowledge content, literature research, clinical research, experimental research, data collection, data analysis, statistical analysis, and manuscript preparation. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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