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Effects of CytoReductive surgery plus hyperthermic IntraPEritoneal chemotherapy (HIPEC) *versus* CytoReductive surgery for ovarian cancer patients: A systematic review and meta-analysis

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A B S T R A C T

Background: The effects of Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) and CytoReductive Surgery (CRS) for ovarian cancer patients remain controversial.
Methods: A systematic review and meta-analysis was conducted using PubMed, Embase and Web of Science databases to investigate Overall Survival (OS), Disease Free Survival (DFS) and adverse effects between HIPEC and CRS group. Results: In our overall analysis (13 studies), patients in the HIPEC group exhibited a significantly improved OS (HR = 0.56, 95% CI = 0.41–0.76, P < 0.01) and DFS (HR = 0.61, 95% CI = 0.48–0.77, P < 0.01). Subgroup analysis revealed improved OS (HR = 0.57, 95% CI = 0.40–0.83, P = 0.04) and DFS (HR = 0.61, 95% CI = 0.47–0.80, P < 0.01) for primary ovarian cancer in favour of HIPEC group. However, recurrent ovarian cancer patients who received HIPEC exhibited only significantly improved OS (HR = 0.48, 95% CI = 0.24–0.96, P < 0.01) but not DFS (HR = 0.59, 95% CI = 0.33–1.08, P = 0.09). In addition, both significantly improved OS and DFS were also observed in patients who received HIPEC in the subgroups based on the following factors: studies published before 2015, studies with ≥100 total patients, a single drug used for HIPEC, 90-min HIPEC duration and a regimen of CRS plus HIPEC followed by chemotherapy. Moreover systematically reviewed toxicity, morbidity, mortality and long-term outcomes were tolerable after HIPEC.
Conclusions: The addition of HIPEC to CRS could significantly improve OS of ovarian cancer patients, albeit optimal drug regimen is not clear.

Introduction

Ovarian cancer is the most frequent cause of death among women with gynaecologic malignant tumours [1]. CytoReductive Surgery (CRS) and systematic chemotherapy have been the main treatments for ovarian cancer patients since the mid-1990s [2]. However, the peritoneum is most often site of involvement in ovarian cancer, given the spread of tumor cells from the ovary into the peritoneal cavity via dissemination and implantation [3]. The peritoneum is poorly reached by systemic chemotherapy due to the plasma-peritoneal barrier [4–6]. Hence, intraperitoneal delivery of chemotherapy enhances drug delivery at the peritoneal surface and may improve outcomes by eliminating residual microscopic peritoneal disease. In addition, compared with intravenous administration of chemotherapy, intraperitoneal delivery could reduce plasma toxicity [7] and increase the effect of the drug upon heating [8]. Therefore, investigators worldwide have explored the effects of CRS plus Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) for primary or recurrent ovarian cancer patients. However, the technique remains controversial because the evidence in support of HIPEC was mainly based on observational and single-arm studies.

Recently, a multicentre, randomized, open-label, phase 3 trial of interval CRS with or without HIPEC in primary ovarian cancer patients with a median follow-up of 4.7 years was published [9]. This research indicated a significant improvement of Overall Survival (OS) and Disease-Free Survival (DFS) in patients who received CRS with HIPEC (median OS: 45.7 versus 33.9 months; median DFS: 14.2 versus 10.7 months) [9]. However, a previous comparative study also demonstrated that the addition of HIPEC to CRS in patients

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with platinum-sensitive recurrent ovarian cancer does not improve survival [10]. Hence, the subgroup (i.e., primary or recurrent) that can benefit most from HIPEC remains controversial. In addition, the HIPEC (drug, timing, duration, temperature) regimens differed among investigations [11,12]. Therefore, we sought to provide comprehensive evidence in assessing the effects of HIPEC in ovarian cancer.

Based on the aforementioned factors, we aimed to quantitatively (meta-analysis) explore whether the addition of HIPEC in primary or recurrent ovarian cancer patients could improve survival outcomes (OS or DFS). Moreover, we also systematically reviewed HIPEC-related adverse events, morbidity, mortality and quality of life outcomes to provide a comprehensive evaluation of HIPEC.

Methods

Search strategy

Our systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org). A comprehensive search of published studies was performed using PubMed, Embase and the Cochrane Database (up to March 22, 2018). Language was restricted to English, and the following MeSH/main keywords were employed: “ovarian”, “HIPEC” or “hyperthermic intraperitoneal chemotherapy”. For multiple-arm comparative studies, we only extracted data from the arms that matched our eligibility criteria. In addition, the lists of references in the relevant studies were also screened for additional studies.

Inclusion and exclusion criteria

According to the PICOS criteria (Population, Intervention, Comparison, Outcomes and Study design), studies were selected in our present meta-analysis according to the following eligibility criteria. (1) Population: patients with primary or recurrent ovarian cancer; (2) intervention: HIPEC administered at any of the 5 time points (a) the time of primary treatment where optimal CRS is achieved, (b) at the time of interval debulking, (c) as a consolidation therapy after complete pathological response following initial therapy as confirmed by a second-look laparotomy, (d) at the time of first recurrence and (e) as salvage therapy; (3) comparison: CRS plus HIPEC versus CRS (both groups with or without chemotherapy); (4) outcomes: survival outcomes (OS or DFS) compared between two groups; (5) study design: comparative studies (Randomized Controlled Trials (RCTs) and observational studies).

The exclusion criteria were as follows. (1) Population: mixed patients with other cancer types; (2) intervention: patients did not undergo CRS; (3) comparison: CRS plus HIPEC versus chemotherapy alone; (4) outcomes: studies with insufficient data (without neither OS nor DFS) or lacking the outcomes of interest; (5) study design: single-arm study without a control group.

Data extraction and quality assessment of included studies

Two reviewers (Yizi Wang and Fang Ren) reviewed and assessed each of the included studies. In addition, data extraction was performed independently, and the following information was collected: first author, year of publication, study type, number of patients enrolled, age, regimens of treatment and control groups, HIPEC drugs, Complete Cytoreduction (CC) rate and survival data (OS was defined as a death event due to any cause; DFS was defined as disease recurrence or death). The Newcastle-Ottawa Scale (NOS) criterion was used to evaluate the quality of the studies included [13]. All disagreements were resolved by discussion between the two reviewers (Yizi Wang and Fang Ren).

Statistical analysis

In our systematic review and meta-analysis, the most appropriate statistic to use for evaluating primary endpoints (time-to-event outcomes) was the Hazard Ratio (HR). If studies did not provide the HR directly, we obtained an estimated HR by methods designed by Tierney [14] mainly using Kaplan-Meier curves or P values from log-rank tests and the number of observed events in each group. All analyses were performed using Stata software, version 12.0 (2011; Stata Corp., College Station, TX, USA). All the analyses in this study used a random-effects model because it provided more conservative estimates and was tailored to multicentre studies in which heterogeneity was typically present [15]. All statistical values are reported with 95% Confidence Intervals (CI), and a two-tailed P value less than 0.05 was defined as statistically significant. Subgroup analyses were conducted to further comprehensively evaluate the effects of HIPEC. Our subgroup analyses were mainly based on the following factors: study type, primary or recurrent ovarian cancer, published year, NOS scores, total patients, HIPEC drugs, HIPEC temperature, HIPEC duration, HIPEC timing and initial stage of enrolled patients. Finally, publication bias was assessed using Begg's and Egger's tests [16,17].

Results

Selected studies

Based on our search strategy, a total of 1362 published studies were identified. After the removal of duplicates, title and abstract screening and further evaluation, 13 comparative studies were included in our systematic review and meta-analysis [3,9,10,18–27]. A flow chart of the search strategies, which includes the reasons for study exclusion, is illustrated in Fig. 1. Among these included studies, two studies are randomized controlled studies, and the remaining 11 studies are observational studies. In addition, 6 studies enrolled primary ovarian cancer patients, 6 studies enrolled recurrent ovarian cancer patients and one study enrolled primary or recurrent ovarian cancer patients. In addition, 5 studies were published after 2015, and 5 studies enrolled more than 100 patients. Detailed information and quality assessment scores of the included studies are summarized in Table 1.

Overall meta-analyses of OS and DFS

In terms of OS, all of the studies except for the study of Cascales-Campos et al. provided OS data [18]. Our pooled analysis indicated that patients who received HIPEC group exhibited a significant improvement in OS compared with CRS group (HR = 0.56, 95% CI = 0.41–0.76, $P < 0.01$). In addition, 9 included studies [3,9,10,18,19,21,23–25] provided DFS data. Our pooled analysis also demonstrated that HIPEC group could significantly improve DFS in patients compared with CRS group (HR = 0.61, 95% CI = 0.48–0.77, $P < 0.01$). The overall meta-analyses of OS and DFS are presented in Fig. 2. Moreover, no publication bias was observed in terms of OS (Begg's test: P = 0.19; Egger's test: P = 0.25) or DFS (Begg's test: P = 0.75; Egger's test: P = 0.99).

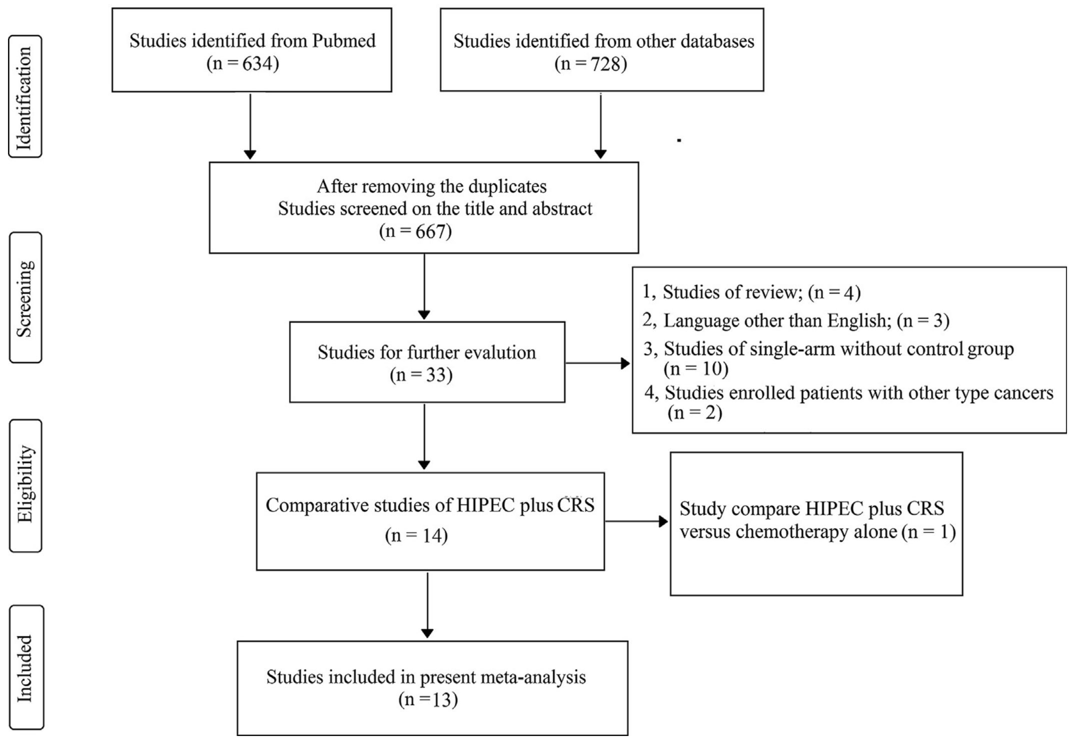

Fig. 1. Flow chart of our systematic review and meta-analysis.

Subgroup analyses

Baseline information (study type, published year, NOS, and total patients)

We conducted subgroup analyses of OS and DFS based on the study type, published year, NOS scores and total patients in included studies. Patients in the HIPEC group exhibited significantly improved OS and DFS regardless of study type or NOS scores. In addition, subgroup analysis based on studies published before 2015 demonstrated that the HIPEC group exhibited significantly improved OS and DFS when compared with CRS group. However, subgroup analysis based on studies published after or during 2015 indicated that the HIPEC group had significantly improved DFS (HR = 0.66, 95% CI = 0.49–0.89, P < 0.01) but not OS (HR = 0.67, 95% CI = 0.44–1.00, P = 0.05). Moreover, subgroup analysis of groups with ≥100 total patients demonstrated that the HIPEC group had significantly improved OS and DFS. However, subgroup analysis of groups with <100 total patients indicated that the HIPEC group exhibited significantly improved OS (HR = 0.44, 95% CI = 0.24–0.83, P = 0.01) but not DFS (HR = 0.69, 95% CI = 0.45–1.04, P = 0.08).The detailed results are presented in Table 2.

Primary versus recurrent ovarian cancer

For primary ovarian cancer patients, HIPEC group significantly improved OS (HR = 0.57, 95% CI = 0.40–0.83, P = 0.04) and DFS (HR = 0.61, 95% CI = 0.47–0.80, P < 0.01) compared with CRS group. However, for recurrent ovarian cancer patients, HIPEC group significantly improved OS (HR = 0.48, 95% CI = 0.24–0.96, P < 0.01) but not DFS (HR = 0.59, 95% CI = 0.33–1.08, P = 0.09). The detailed results are presented in Fig. 3.

HIPEC regimens (drugs, temperature, duration and timing)

We conducted subgroup analyses of HIPEC regimens based on drugs, temperature, duration and timing of HIPEC. Regarding to the number of HIPEC drugs, subgroups analysis of single drug regimens revealed that patients who received HIPEC exhibited significantly improved OS (HR = 0.52, 95% CI = 0.34–0.79, P < 0.01) and DFS (HR = 0.51, 95% CI = 0.39–0.66, P < 0.01) compared with the CRS group. In addition, subgroup analysis of two or three drugs indicated that patients who received HIPEC exhibited significantly improved OS (HR = 0.53, 95% CI = 0.35–0.80, P < 0.01) but not DFS. In terms of the type of HIPEC drugs, we found that patients who received a platinum-based HIPEC drug exhibited significantly improved DFS (HR = 0.61, 95% CI = 0.41–0.90, P < 0.01) but not OS. However, patients who received HIPEC with paclitaxel did not exhibit significant differences in survival compared with the CRS group. The detailed results are presented in Table 2.

Regarding HIPEC temperature (ranges from 40 °C to 44 °C), both subgroups of ≥43 °C or < 43 °C exhibited significant improvements in OS and DFS. In addition, our subgroup analyses indicated that patients who received HIPEC for 30 min exhibited no differences in OS and DFS compared with the CRS group. Patients who received HIPEC for 60 min exhibited significantly improved OS (HR = 0.47, 95% CI = 0.29–0.78, P < 0.01) compared with the CRS group. Meanwhile, patients who received HIPEC for 90 min exhibited significantly improved OS (HR = 0.59, 95% CI = 0.40–0.88, P < 0.01) and DFS (HR = 0.62, 95% CI = 0.47–0.81, P < 0.01) (Table 2).

What is the best timing of HIPEC? Based on the results of our subgroup analyses, immediate CRS in combination with HIPEC followed by chemotherapy exhibited both significantly improved OS (HR = 0.44, 95% CI = 0.27–0.72, P < 0.01) and DFS (HR = 0.43, 95% CI = 0.23–0.79, P < 0.01). In addition, in subgroup analysis of CRS followed by chemotherapy, patients who received HIPEC exhibited significantly improved DFS (HR = 0.53, 95% CI = 0.39–0.73, P < 0.01) but not OS (HR = 0.55, 95% CI = 0.30–1.01, P = 0.05). Moreover, we did not identify a significant difference in OS and DFS based on other timings of HIPEC (Table 2).

Table 1
Baseline characteristics of the included studies.

Author	Year	Type	Treatment arms	Number	Age	Initial stage	Primary/ Recurrent	HIPEC regimens	T °C	Duration	CC rate	OS (months or rate)	DFS (months or rate)	NOS
Spiliotis et al.	2015	RCT	CRS + HIPEC, adjuvant chemotherapy	60	mean 58	IIIc-IV	recurrent	cisplatin and paclitaxel (platinum-sensitive); doxorubicin and paclitaxel/ mitomycin (plainum-resistant)	42.50	60min	65	Mean 26.9	NA	7
			CRS, adjuvant chemotherapy	60	mean 58						55	Mean 13.4	NA	
van Driel et al.	2018	RCT	neoadjuvant chemotherapy, CRS + HIPEC, adjuvant chemotherapy	122	median 61	III	primary	cisplatin and eloxatin and mitomycin	40	90min	69	Median 45.7	Median 14.2	8
			neoadjuvant chemotherapy, CRS, adjuvant chemotherapy	123	median 63						67	Median 33.9	Median 10.7	
Le Brun et al.	2014	observational	second-line chemotherapy, HIPEC + CRS	23	NA	II-IV	recurrent	cisplatin or eloxatin or mitomycin	42	90min	65	4 years OS: 75.6%	NA	6
			second-line chemotherapy, CRS	19	NA						42	4 years OS: 19.4%	NA	
Baiocchi et al.	2016	observational	chemotherapy+/-, CRS + HIPEC	29	mean 52	I-IV	recurrent	mitomycin C and cisplatin; cisplatin and doxorubicin; cisplatin; oxaliplatin	41 −42	90min	79	Median 59.3	Median 15.8	6
			CRS	50	mean 58						77	Median 58.3	Median 18.6	
Fagotti et al.	2012	observational	CRS + HIPEC, adjuvant chemotherapy	30	median 51	I-IV	recurrent	oxaliplatin	41.5	30min	60	5 years OS: 68.4%	Median 26 Range 5-73	6
			CRS+/-, adjuvant chemotherapy	37	median 55						57	5 years OS: 42.7%	Median 15 Range 4-58	
Cascales-Campos et al.	2015	observational	CRS + HIPEC, adjuvant chemotherapy	32	mean 56	I-IV	recurrent	paclitaxel	42	NA	NA	NA	Median 21 Range 12-68	5
			CRS, adjuvant chemotherapy	22	mean 57						NA	NA	Median 22 Range 13-56	
Ceresoli et al.	2018	observational	neoadjuvant chemotherapy, CRS + HIPEC	28	mean 59	IIIc-IV	primary	cisplatin and paclitaxel	41.5	90min	93	No median reached	Median 13.96 Range 7.9 −20.01	6
			neoadjuvant chemotherapy, CRS	28	mean 62						93	Median 32.53	Median 13.23 Range 10.64 −15.81	
Gori et al.	2005	observational	CRS, chemotherapy, HIPEC	32	mean 57	IIIb-IIIc	primary	cisplatin	41 −43	60min	75	Median 64.4 Range 28-108	Median 57.1 Range 15-108	6
			CRS, chemotherapy	19	mean 58						89	Median 60.1 Range 26-120	Median 46.4 Range 15-120	
Munoz-Casares et al.	2009	observational	CRS + HIPEC, adjuvant chemotherapy	14	mean 54	IIIb-IIIc	recurrent	paclitaxel	41 −43	60min	64	5 years OS: 57%	NA	5
			CRS, adjuvant chemotherapy	12	mean 54						58	5 years OS: 17%	NA	
Kim et al.	2010	observational	CRS, chemotherapy, HIPEC	19	mean 48	Ic-IIIc	primary	paclitaxel	43 −44	90min	100	8 years OS: 84.2%	8 years PFS: 63.2%	6
			CRS, chemotherapy	24	mean 49						100	8 years OS: 25.0%	8 years PFS: 29.2%	

Table 1 (*continued*)

Author	Year	Type	Treatment arms	Number	Age	Initial stage	Primary/ Recurrent	HIPEC regimens	T °C	Duration	CC rate	OS (months or rate)	DFS (months or rate)	NOS
Mendivil et al.	2017	observational	CRS, chemotherapy, HIPEC	69	mean 60	III-IV	primary	carboplatin	41.5	90min	100	Mean 33.8	Mean 25.1	7
			CRS, chemotherapy	69	mean 63						93	Mean 33.6	Mean 20.0	
Ryu et al.	2004	observational	CRS, chemotherapy, HIPEC	57	mean 46	Ic-III	primary	carboplatin	43−44	90min	NA	5 years OS: 63.4%	Median 48.7	6
			CRS, chemotherapy	60	mean 48						NA	5 years OS: 52.8%	Median 19.8	
Warschkow et al.	2012	observational	CRS + HIPEC, adjuvant chemotherapy	21	mean 59	II-IV	primary and recurrent	cisplatin	42	90min	90	5 years OS: 72.5%	NA	6
			CRS, adjuvant chemotherapy	90	mean 65						37	5 years OS: 38.3%	NA	

RCT: Randomized Controlled Trial; CRS: CytoReductive Surgery; HIPEC: Hyperthermic IntraPeritonEal Chemotherapy; NOS: Newcastle−Ottawa Scale; CC: Complete Cytoreduction; NA: Not Applicable; T: Temperature; OS: Overall Survival; DFS: Disease-Free Survival.

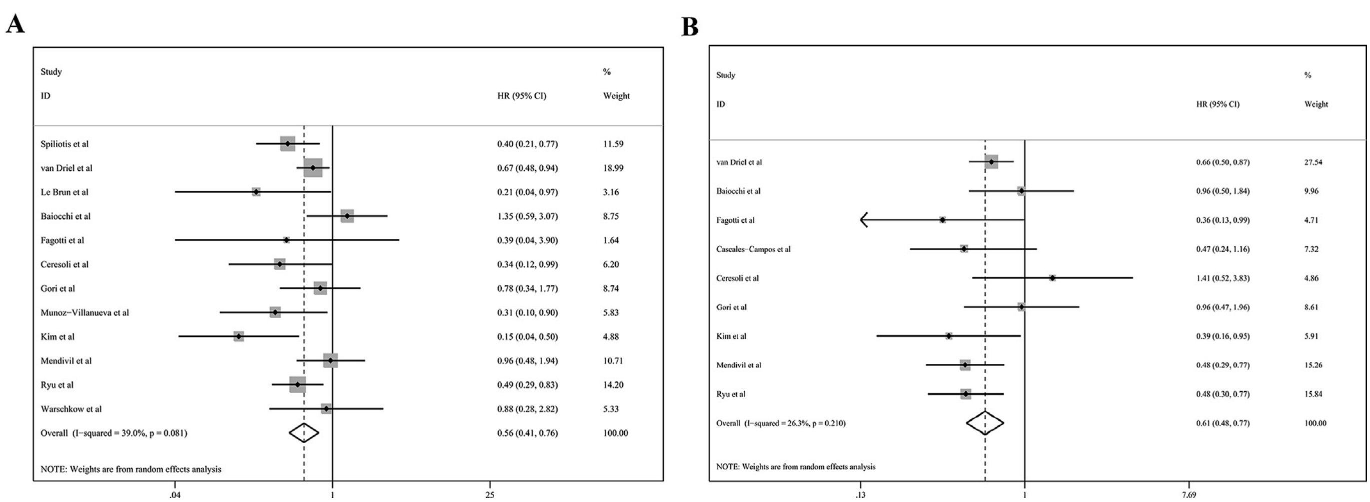

Fig. 2. Overall analyses between HIPEC plus CRS versus CRS. (A) OS; (B) DFS.

Initial stage, residual tumor and

We conducted subgroup analyses based on the initial stage of enrolled ovarian cancer patients. Our results demonstrated that HIPEC group could significantly improve OS and DFS in populations with an initial stage of III, I-III, II-IV or III-IV (Table 2). In addition, in subgroup of CC rate <15% between two groups, we also observed that HIPEC group could significantly improve OS (HR = 0.57, 95% CI = 0.39−0.83, P < 0.01) and DFS (HR = 0.66, 95% CI = 0.50−0.88, P < 0.01).

Systematic review of adverse events, morbidity, mortality and quality of life

Two included studies provided data of adverse events after receiving HIPEC [9,23]. Mendivil et al. demonstrated that all adverse events after receiving HIPEC were classified as ≤ grade 2 [23]. Among these patients, 28.9% patients had nausea, 14.4% had emesis, 31.9% had anaemia, 21.7% had neutropenia, 13% had thrombocytopenia and 5.7% had neuropathy. In addition, van Driel et al. reported no significant differences in the incidence of adverse events of any grade between the two groups [9]. In total, 25% and 27% of adverse events were classified as grade 3 or 4 in the CRS group and the HIPEC group, respectively (P = 0.76).

In addition, five included studies provided data on morbidity [10,18,21,24,25]. Cascales-Campos et al. reported no significant differences in postoperative morbidity between both groups [18]. The overall morbidity (I-IV) was 23% in the CRS group and 28% in the HIPEC group. Similar results (29% versus 25%) of postoperative morbidity were also observed in the study of Munoz-Casares [24]. Ryu et al. reported that major complications were observed in 24 of 117 (20.5%) patients and that the complication rate was increased in HIPEC patients (28.3%) but without significance [25]. Kim et al. only provided morbidity data for the HIPEC group with 7 patients (36.8%) experiencing gastrointestinal events: 1 patient had a minor leak, 4 patients had ileus and 2 patients experienced transient hepatitis [21]. However, Baiocchi et al. demonstrated that the HIPEC group included more subjects with grade III-IV morbiditythan the number inthe CRS group (34.5% versus 10.6%, P = 0.02).

Regarding postoperative mortality, seven studies presented comparative data [3,9,10,19,22,25,27]. Two studies reported no postoperative mortality in the two groups [3,22]. Baiocchi et al. and van Driel et al. reported 0% postoperative mortality in the HIPEC group. However, for the CRS group, Baiocchi et al. reported two

Table 2
Subgroup analyses of HIPEC plus CRS versus CRS in terms of OS and DFS.

Characteristics	OS Study number	HR (95% CI)	P value	Heterogeneity	DFS Study number	HR (95% CI)	P value	Heterogeneity
Study type								
RCT	2	0.56 (0.35, 0.91)	0.02	47.7%	1	0.66 (0.50, 0.87)	< 0.01	NA
Observational studies	10	0.55 (0.37, 0.83)	< 0.01	42.8%	8	0.60 (0.44, 0.81)	< 0.01	25.7%
Ovarian cancer								
Primary	6	0.57 (0.40, 0.83)	0.04	49.5%	6	0.61 (0.47, 0.80)	< 0.01	32.9%
Recurrent	5	0.48 (0.24, 0.96)	< 0.01	43.5%	3	0.59 (0.33, 1.08)	0.09	39.5%
Published year								
≥ 2015	5	0.67 (0.44, 1.00)	0.05	48.7%	5	0.66 (0.49, 0.89)	< 0.01	31.4%
< 2015	7	0.45 (0.30, 0.69)	< 0.01	17.9%	4	0.53 (0.35, 0.79)	< 0.01	21.9%
NOS scores								
≥ 7	3	0.64 (0.43, 0.95)	0.03	40.7%	2	0.60 (0.45, 0.90)	< 0.01	19.1%
< 7	9	0.50 (0.32, 0.78)	< 0.01	40.3%	7	0.63 (0.44, 0.90)	0.01	37.0%
Total patients								
≥ 100	5	0.62 (0.47, 0.80)	< 0.01	12.7%	3	0.58 (0.47, 0.72)	< 0.01	1.6%
< 100	7	0.44 (0.24, 0.83)	0.01	52.3%	6	0.69 (0.45, 1.04)	0.08	36.2%
HIPEC drugs								
Single drug	8	0.52 (0.34, 0.79)	< 0.01	33.6%	6	0.51 (0.39, 0.66)	< 0.01	0.0%
Two or three drugs	3	0.53 (0.35, 0.80)	< 0.01	32.1%	2	0.82 (0.42, 1.62)	0.58	51.5%
Platinum-based drug	6	0.60 (0.35, 1.04)	0.07	58.8%	5	0.61 (0.41, 0.90)	0.01	45.2%
Paclitaxel	3	0.54 (0.29, 1.03)	0.06	0.0%	2	0.63 (0.24, 1.63)	0.34	58.3%
HIPEC temperature								
≥ 43 °C	2	0.63 (0.46, 0.85)	< 0.01	25.9%	2	0.46 (0.30, 0.70)	< 0.01	0.0%
< 43 °C	10	0.31 (0.10, 0.97)	0.04	65.2%	7	0.66 (0.51, 0.87)	< 0.01	27.4%
HIPEC duration								
30 mina	1	0.39 (0.04, 3.90)	0.42	NA	1	0.36 (0.13, 0.99)	0.05	NA
60 min	3	0.47 (0.29, 0.78)	< 0.01	10.6%	1	0.96 (0.47, 1.96)	0.91	NA
90 min	8	0.59 (0.40, 0.88)	< 0.01	50.4%	6	0.62 (0.47, 0.81)	< 0.01	35.5%
HIPEC timing								
CRS + HIPEC, chemotherapy	4	0.44 (0.27, 0.72)	< 0.01	0.0%	2	0.43 (0.23, 0.79)	< 0.01	0.0%
NACT, CRS + HIPEC	2	0.58 (0.33, 1.00)	0.05	30.6%	2	0.82 (0.42, 1.62)	0.58	51.5%
Chemotherapy, CRS + HIPEC	2	0.61 (0.10, 3.69)	0.59	75.8%	1	0.96 (0.50, 1.84)	0.90	NA
CRS, chemotherapy, HIPEC	4	0.55 (0.30, 1.01)	0.05	58.9%	4	0.53 (0.39, 0.73)	< 0.01	12.8%
Initial stage								
III	4	0.55 (0.37, 0.80)	< 0.01	33.0%	3	0.65 (0.50, 0.83)	< 0.01	8.2%
I-III	5	0.46 (0.28, 0.74)	< 0.01	54.0%	4	0.62 (0.49, 0.78)	< 0.01	10.5%
II-IV	10	0.58 (0.43, 0.80)	< 0.01	38.7%	5	0.68 (0.52, 0.88)	< 0.01	31.8%
III-IV	8	0.52 (0.39, 0.71)	< 0.01	31.2%	5	0.64 (0.49, 0.85)	< 0.01	32.5%
Residual tumor								
CC rate available	11	0.57 (0.40, 0.80)	< 0.01	41.4%	7	0.66 (0.50, 0.88)	< 0.01	32.5%
CC rate < 15% between two groups	9	0.57 (0.39, 0.83)	< 0.01	46.5%	7	0.66 (0.50, 0.88)	< 0.01	32.5%

RCT: Randomized Controlled Trial; CRS: CytoReductive Surgery; HIPEC: Hyperthermic IntraPEritoneal Chemotherapy; NOS: Newcastle–Ottawa Scale; NA: Not Applicable; NACT: NeoAdjuvant ChemoTherapy; CC: Complete Cytoreduction.

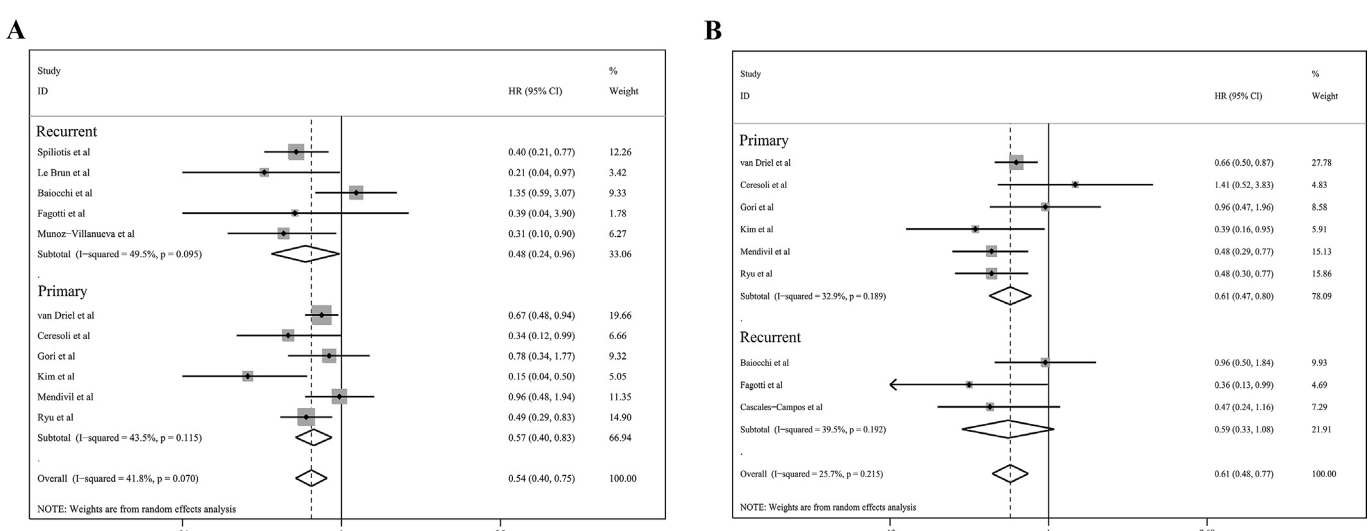

Fig. 3. Subgroup analyses in primary/recurrent ovarian cancer between HIPEC plus CRS versus CRS. (A) OS; (B) DFS.

deaths (4.3%), and van Driel et al. reported one death [9,10]. Fagotti et al. also reported no postoperative mortality in the HIPEC group, but data for the control group was not reported [19]. Warschkow et al. indicated that the causes of death were cardiac or pulmonary insufficiency in four patients, sepsis in three patients, multiorgan failure in two patients and a pulmonary embolism in one patient [27]. Moreover, Ryu et al. reported that two patients with intestinal rupture died of sepsis [25]. However, they did not present comparative data between the two groups.

Moreover, patients in the study of van Driel et al. [9] also completed the following health-related quality of life questionnaires: the European Organization for Research and Treatments of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), Quality of Life Questionnaire-OVarian Cancer Module (QLQ-OV28) and Quality of Life Questionnaire-ColoRectal Cancer Module (QLQ-CR38). No significant differences were noted between the two groups in terms of quality of life outcomes over time.

Discussion

HIPEC involves the delivery of intraperitoneal chemotherapy during surgery under hyperthermic conditions. Hyperthermia increases the sensitivity of cancer cells to the direct cytotoxic effect of chemotherapeutic agents at high temperatures and the concentration of chemotherapeutic agents that penetrate cancer tissues [28,29]. In addition, hyperthermia also induces apoptosis and activates heat-shock proteins that serve as receptors for natural killer cells, inhibit angiogenesis, and exert a direct cytotoxic effect by promoting protein denaturation [30–33]. In fact, HIPEC was first applied to gastrointestinal malignancies with peritoneal carcinomatosis at the end of the 1980s, HIPEC demonstrated significantly improved survival and a reduced recurrence rate [34–36]. Previous studies in ovarian cancer were mainly based on retrospective cohorts or single-arm trials, and Spiliotis et al. published the first RCT results of CRS plus HIPEC for current ovarian cancer patients in 2015 [26]. Recently, with the publication of results from a multicentre, open-label, phase 3 trial comparing CRS plus HIPEC to CRS for advanced ovarian cancer patients [9], the issue of HIPEC has garnered the attention of clinicians worldwide once again. Hence, we sought to provide comprehensive evidence to evaluate the effects of HIPEC in ovarian cancer patients.

Based on our overall meta-analysis results, CRS plus HIPEC significantly improved OS and DFS compared with CRS for ovarian cancer patients. In addition, our subgroup analyses based on baseline information (study type, published year, NOS scores and total patients) also supported our conclusions. Regarding subgroup analyses based on primary or recurrent ovarian cancer, our results revealed similar tendencies supporting CRS plus HIPEC; however, the subgroup of recurrent ovarian cancer exhibited no statistical significance regarding DFS. In this subgroup (DFS for recurrent ovarian cancer), all three included studies only enrolled platinum-sensitive recurrent ovarian cancer patients [10,18,19], and two studies reported no significant differences between CRS plus HIPEC versus CRS for recurrent patients. In addition, the subgroup results from RCTs also indicated that CRS plus HIPEC did not improve OS in platinum-sensitive recurrent ovarian cancer patients [26]. Hence, the effects of HIPEC in platinum-sensitive recurrent ovarian cancer patients should be further explored, and we may rely on individual data or more subgroup results from RCTs to resolve this issue.

To date, the results of HIPEC regimens remain debated. The drugs commonly used in HIPEC include cisplatin, oxaliplatin, eloxatin, carboplatin, paclitaxel and mitomycin. In fact, the choice of drug depends on its pharmacokinetic properties. The drug should be retained in the peritoneal cavity with limited systemic absorption [37]. However, we were unable to determine the best drug or combination of chemotherapy for HIPEC regimens based on our subgroup analysis given the limited number of studies with considerable heterogeneity. In addition, HIPEC temperatures in our included studies ranged from 40 °C to 44 °C, and our subgroup analyses indicated that patients with HIPEC had significantly improved OS and DFS in both the ≥43 °C and <43 °C subgroups. Moreover, the duration of HIPEC in our included studies was categorized as 30min, 60min or 90min. Our subgroup analyses demonstrated that 90min HIPEC significantly improved both OS and DFS for ovarian cancer patients. Hence, based on our results, a longer HIPEC duration may adequately achieve the full effects of chemotherapy in the peritoneal cavity. Notably, cisplatin was the most commonly used drug in our included studies, and its penetration into the adjacent tissues is potentiated by heat in both platinum-sensitive and platinum-resistance cell lines [38]. The final results of the CHIPASTIN trial (NCT02217956) indicated that the use of 70 mg/m^2 of cisplatin for greater than 60 min at 42 ±1 °C was the most appropriate regimen in initially unresectable ovarian cancer patients [39].

A major factor regarding survival in ovarian cancer is chemosensitivity. Two of our included studies only enrolled platinum-sensitive recurrent ovarian cancer patients [18,19]. Cascales-Campos et al. reported that HIPEC with paclitaxel is effective in the treatment of microscopic disease in platinum-sensitive recurrent epithelial ovarian cancer patients with microscopic residual disease after cytoreduction [18]. In addition, Fagotti et al. demonstrated that the combination of CRS and HIPEC with oxaliplatin improved survival rates in patients in the CRS group suffering from platinum-sensitive epithelial ovarian cancer recurrence [19]. In addition, Spiliotis et al. provided subgroup data forplatinum-resistant versus platinum-sensitive disease; however, they enrolled a population of mixed recurrent ovarian cancer [26]. In this study, the following HIPEC protocols were employed: cisplatin and paclitaxel were delivered for platinum-sensitive disease, and doxorubicin and paclitaxel or mitomycin were delivered for platinum-resistant disease. In platinum-sensitive disease, survival was significantly increased in the HIPEC group (26.8 versus 15.2 months, $P = 0.035$); however, this significance was not observed in the platinum-resistant group [26]. Hence, it is important to select the most appropriate HIPEC regimens for based on the chemosensitivity of ovarian cancer patients. Although we conducted subgroup analyses in terms of the drug type and number, we could still not draw a clear conclusion regarding the optimal HIPEC regimen based on currently available evidence. Therefore, future prospective studies focused on precise HIPEC regimens are needed to further clarify the relationship between chemosensitivity and ovarian cancer patient subgroups.

HIPEC can be used at various time points as summarized by Mulier et al. [40]. For primary ovarian cancer, HIPEC was commonly performed after neoadjuvant chemotherapy without previous resection (interval CRS and HIPEC) or after upfront (near) complete CRS and a full course of chemotherapy in patients with a clinically complete response (consolidation CRS and HIPEC). For recurrent ovarian cancer, HIPEC was commonly used as secondary or salvage therapy. Based on our subgroup analyses of timing, although obvious effects of HIPEC were observed, some subgroup results lacked statistical significance. In fact, the limited number of studies based on different HIPEC timings may restrict our subgroup results. In total, 89.7% patients (26/29) in the HIPEC group in the study by Baiocchi et al. [10] received chemotherapy before CRS and HIPEC. In addition, patients in study by Ceresoli et al. [3] did not receive adjuvant chemotherapy after CRS and HIPEC. These heterogeneities may impact the statistical significance in our subgroup analyses. Hence, based on currently available evidence, we could not draw a valid conclusion regarding the optimal timing of HIPEC for primary or recurrent ovarian cancer patients.

To the best of our knowledge, our systematic review and meta-analysis provides the most comprehensive evaluation of HIPEC based on comparative studies in terms of survival, toxicity, morbidity, mortality and quality of life outcomes. In addition, all potential subgroup analyses were conducted to explore the effects of HIPEC systematically. Hence, we believe our results provided valid evidence regarding the use of HIPEC in ovarian cancer patients. However, some limitations of our study should be stated. Firstly, in ovarian cancer the sequence of systemic treatment can impact by itself the prognosis both in primary either recurrent setting. Although we had tried our best to conduct subgroup analyses to explore the optimized HIPEC timing, the efficacy based on current results might be affected by the heterogeneities of included studies. Hence, our present study only provided an overall analysis on the issue of HIPEC, future studies based on individual data or prospective trials are needed to further explore this specific issue (HIPEC timing) to update our findings. Moreover, subgroups analysis performed could not totally overcome the heterogeneities of population (residual tumor, histology and stage) and treatments (timing, drugs and regimens). For example, Le Brun et al. [22] and Warshkow et al. [27] have a very large heterogeneity in CC rates and moreover higher rate is in favour to HIPEC group. Primary ovarian cancer patients with stage I disease were included in two studies [21,25]. Meanwhile, in Kim et al. [21] the large majority of patient enroled were not serous ovarian cancer but with grade of G1-2, since they are notably chemoresistant and addition of HIPEC could be of prognostic utility. However, is this the case to generalize for all the types of ovarian cancer? On the otherside, in Mendivil et al. [23] type I cancers are excluded from the study. In fact, these heterogeneities caused by study design could not be eliminated by all possible methods in our present study. Future studies based on individual data or prospective trials are needed to update our findings. Furthermore, another issue is about platinum sensitive recurrence time (6 months), in fact, using this cut off, there are patients with platinum partially sensitive and sensitive recurrence enrolled, resulting in an heterogeneity population. However, we could not obtain a crude data on this issue from the included studies or authors. Moreover, although we tried our best to provide a comprehensive analysis in terms of morbidity, however, not all the studies reported morbidity of control group (e.g. Fagotti et al. [19]). Notably, patients enrolled in the included studies have different baseline conditions and only two included studies [21,25] meet with the eligibility to a "real" (meaning $\geq 43\,^{\circ}$C and >60 min) HIPEC. Finally, we believed that HIPEC will be in the next future implented somehow at least in recurrent platinum refractory setting, but currently the evidence available should limited its use only in clinical randomized trial with a thorought selection of the patients that can't override stage, histology, peritoneal cancer index, platinum sensitiveness. Moreover, the sequence of systemic treatment can impact by itself the prognosis both in primary either recurrent setting in ovarian cancer patients.

Conclusion

The addition of HIPEC to CRS could significantly improve OS for primary and recurrent ovarian cancer patients with tolerable toxicity, morbidity, mortality and quality of life outcomes. However, the limitations for the use of HIPEC (histology, drug and timing) are still remained to further explore. Further studies based on individual data or multicentre RCTs are needed to confirm and update our findings.

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Disclosure statement

No potential conflict of interests was reported by the authors.

Conflicts of interest

All authors declare that they have no competing interests.

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