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Long-term outcomes with hyperthermic intraperitoneal chemotherapy in patients with ovarian cancer: Meta-analysis of 10 randomized trials

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Abstract

Background.

Recent trials showed that the use of hyperthermic intraperitoneal chemotherapy (HIPEC) beside cytoreductive surgery (CRS) in patients with ovarian cancers (OC) may decrease the mortality rates, but the results are still unclear. So, we aim to investigate the long-term survival and progression rates in OC patients who have undergone HIPEC.

Methods.

Recent randomized controlled trials (RCTs) that compare the use of HIPEC plus CRS vs. CRS alone in OC patients were retrieved from electronic databases up to 20 December 2024, with an updated search performed on 8 August 2025. The hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) were used to represent the pooled estimate.

Results.

A total of 10 RCTs (1,508 patients) were included in the analysis. The analysis showed that the use of HIPEC plus CRS was associated with similar overall survival (OS) (HR: 0.82, 95% CI [0.65 to 1.01], *log-rank p-value* = 0.09), and progression-free/disease-free survival (PFS/DFS) (HR: 0.80, 95% CI [0.66; 1.02], *log-rank p-value* = 0.06) compared to CRS alone at 10 years of follow-up. Subgroup analysis showed that the risk of OS and PFS was lower after applying interval surgery with neoadjuvant chemotherapy for primary tumors, but the incidence of mortality and progression was similar between the two groups after primary surgery or in recurrent tumors.

Conclusion.

Among patients with OC who underwent interval surgery, adding HIPEC to CRS had a higher OS and lower PFS/DFS, unlike primary surgery or in recurrent OC, compared with CRS alone.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related deaths among women, with approximately 1 in 78 women developing it in their lifetime (1, 2). Ovarian cancer remains one of the deadliest gynecologic cancers, primarily due to its tendency to be diagnosed at advanced stages, often with widespread peritoneal metastases (1). Up to 75% of patients have a gynecologic malignancy diagnosed when it has spread within the peritoneal cavity, as the primary site of ovarian cancer relapse is usually the peritoneum, and peritoneal carcinomatosis is a common cause of symptoms and death (3). It's often diagnosed at an advanced stage due to its insidious onset and lack of early symptoms. Standard treatment for advanced epithelial ovarian cancer includes cytoreductive surgery (CRS) followed by platinum-based systemic chemotherapy.

The high mortality rates associated with ovarian cancer, especially in patients with peritoneal metastases, underscore the urgent need for advanced therapeutic strategies. Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a promising treatment option specifically designed to combat the challenge of peritoneal metastases. HIPEC offers a more targeted and effective method for delivering chemotherapy directly to the peritoneal cavity, which may substantially enhance survival outcomes for these patients (2, 4–6). It is a single intraoperative procedure that delivers chemotherapy in a heated solution directly into the abdominal cavity after CRS. HIPEC improves the treatment of peritoneal microscopic residual disease, increases chemotherapy penetration at the peritoneal surface, and increases cancer sensitivity to chemotherapy by impairing DNA repair and apoptosis induction (3).

A previous meta-analysis that included randomized controlled trials (RCTs) showed a superior effect of HIPEC plus CRS vs. CRS in the first three years of follow-up regarding the overall survival (OS) and progression-free/disease-free survival (PFS/DFS) (7). Hence, long-term follow-up RCTs have emerged, stating the OS and PFS through five, eight, and ten years of follow-up. In this review, we intend to perform meta-analysis and time-to-event analysis from Kaplan-Meier (KM) curves for OS and PFS/DFS.

2. Methods

This systematic review and meta-analysis was conducted with adherence to the Cochrane Handbook (8) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (9). The predesigned protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration number (PROSPERO ID: CRD420251124559).

2.1 Literature search.

To evaluate the role of adding HIPEC in adults with ovarian cancers undergoing CRS to the standard care of CRS alone, we systematically searched PubMed, Embase, Cochrane Central Register of Controlled Trials databases (CENTRAL), Scopus, and Web of Science (WOS) up to 20 December 2024, with an updated search performed on 8 August 2025 without automated filters or language restrictions. The mesh terms of the HIPEC and ovarian cancers were used to formulate the search strategy for database search as follows: ("hyperthermic intraperitoneal chemotherapy" OR "HIPEC") AND ("ovarian neoplasms" OR "ovarian cancer"). The detailed search strategy is shown in **Supplementary Table 1**. A manual screening for the first 200 hits in Google Scholar was applied

using the search strategy, and the references and citations of included studies were compiled to include any additional studies that were missed from the primary search.

2.2. Eligibility criteria and study selection.

After searching in databases, EndNote 21 was used to remove the duplicates of the retrieved records. Two independent reviewers (R.N. and E.S.) screened the titles and abstracts of all articles through the Rayyan AI software. The inclusion and exclusion criteria. Subsequently, eligible studies were screened by two independent reviewers (A.I. and S.H.S.) in full text. Discrepancies during the screening process were resolved through discussion with a third reviewer (M.S.S.). The eligibility criteria are defined in the form of the PICOS format as follows:

- **Population (P)**: studies in which patients with ovarian cancers (OC), either primary or recurrent tumors, undergo CRS surgeries.
- **Intervention (I)**: HIPEC was used plus the CRS.
- **Comparison (C)**: CRS alone.
- **Outcomes (O)**: overall survival (OS) and progression-free/disease-free survival (PFS/DFS).
- **Study design (S)**: randomized controlled trials (RCTs).

RCTs not reporting the OS or PFS/DFS or focusing on acute or immediate outcomes were excluded. The Observational studies, case reports or series, conference papers (abstracts), and review articles were excluded.

2.3. Data extraction.

A standardized data-extraction sheet was developed and piloted in Google Spreadsheets. Four independent authors (M.W., M.O.A., E.R., and R.N.) extracted the data in duplicate, and discrepancies were resolved by a fifth author (M.S.S.). The items extracted included: studies' characteristics, population characteristics, and outcomes. The detailed items of each sheet are shown below: An **overview of the studies' characteristics was elaborated through extracting the** study design, year of study, country, intervention details (temperature, chemotherapy used, and dose), comparison details, inclusion criteria, follow-up period, and conclusion of the study. The patients had primary or recurrent OC; hence, the primary OC was treated either through primary surgery or interval surgery (surgery after neoadjuvant chemotherapy (NAC)). **The population characteristics were extracted by reporting the** patients' age and body mass index (BMI). **The outcomes included** overall survival (OS) and progression-free/disease-free survival (PFS/DFS) at follow-up.

2.4. Quality Assessment and certainty of evidence.

The quality of the studies included in this review was evaluated independently by two researchers (M.W. and M.O.A) utilizing the Cochrane Risk of Bias Tool (ROB-2) (10). In ROB-2, the five domains are just phrased as: 1. Bias arising from the randomization process; 2. Bias due to deviations from intended interventions; 3. Bias due to missing outcome data; 4. Bias in measurement of the outcomes; and 5. Bias in the selection of the reported results. The authors' decisions were classified as "low risk of bias", "high risk of bias," or "some concerns". Any conflicts between the two authors were resolved through discussion with a third author (M.S.S.).

The GRADE criteria were used to determine the quality of the evidence (11). In summary, the overall quality of evidence was lowered if any of the following factors are present: risk of bias in the literature, inconsistency (high heterogeneity in the estimates), indirectness, imprecision (wide 95% CIs crossing the unity or failure to reach the optimal information size), and publication bias (11). The overall quality of the evidence supporting each outcome was graded as high, moderate, low, or very low after assessing each domain of GRADE. GRADEpro GDT (GRADEpro Guideline Development Tool, McMaster University and Evidence Prime, 2024) was used to perform the GRADE assessment.

2.5 Synthesis of results and statistical analysis.

Depending on the curve approach (12) that reconstructs the individual patient data (IPD) based on the published Kaplan–Meier (KM) graphs from the included studies. The process involved two stages. In the first stage, we relied on the web plot digitizer software [Link] to get the raw data coordinates in the form of (time and probability) from the published KM plots. Subsequently, the raw data coordinates from the digitized KM plots were used to get the IPD data by using the R package IPDfromKM (version 0.1.10), concerning the numbers at risk at given time points, the corresponding total number of patients, and the total number of events (13). After finishing each study reconstruction, the reconstructed IPD for the same outcome was merged to create the final study data set for the whole reconstructed studies in the specific outcome (OS or PFS). Then, we fitted the Cox proportional hazard models and Kaplan–Meier analyses relying on the reconstructed IPD using the following R packages: survival (Version 3.2–13), survminer (Version 0.4.9), and coxph (Version 4.0.2). The Cox frailty model was applied to get the hazard ratios (HRs) with corresponding 95% confidence interval (CI) for the reconstructed IPD data set (14). To ensure that our reconstructed IPD dataset derived from KM curves was accurate enough to reproduce the original KM curves, we reviewed the reconstructed Kaplan–Meier curves for similarity with the original version. As a result of the previous step, all reconstructed curves remained within the 99% CI in comparison to the original published curves. The root mean square error and the mean and maximum absolute error were used to evaluate the similarity as well. As achieved in our analyses, the values of root mean square ≤ 0.05, mean absolute error ≤ 0.02, and maximum absolute error ≤ 0.05 indicate that the extracted data points are sufficiently well captured for subsequent analyses. In the stage of the reconstruction, we calculated the median survival or progression time if the probability was 50%. To quantify the survival or progression probability, the restricted mean survival time (RMST) was calculated, and the difference between both study arms (HIPEC + CRS versus CRS alone) was compared (15).

HRs with corresponding 95% CI were analyzed using logHR with standardized error (SE) in the pairwise meta-analysis. The random-effects model (inverse variance model) was applied for the primary analysis to adjust for the differences in characteristics of the studies. The adjusted HRs were extracted from the studies, while in studies that did not report the adjusted HRs, the crude HRs from reconstructed KM curves were used for the analysis. Because of the difference between the study populations and type of surgery, we planned to perform subgroup analyses according to the tumor type and treatment

approach (type of surgery). Statistical heterogeneity was assessed using I^2 statistics. The degree of heterogeneity was low, moderate, and high according to I^2 <25%, 25–50%, and > 50% respectively. The sensitivity leave-one-out analyses were used to determine the robustness of the obtained estimates, the effects of single study effects, and the source of heterogeneity. The results were statistically significant when p-value < 0.05. All statistical analyses were done by using R Statistical Software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager software (RevMan) version 5.2.0.

3. Results

3.1 Literature results.

The literature search revealed 3612 records. By EndNote 21, 1356 duplicates had been removed. After the title and abstract screening, only 53 studies were thought to be retrieved. Through the full-text phase, 45 articles were excluded, and eight were included. The reasons for exclusion were wrong intervention (n = 13); wrong study design (n = 12); wrong outcomes (n = 6); protocols (n = 8); and reviews (n = 6). After the manual search, citation, and reference screening, we included two other articles. This systematic review and meta-analysis included 10 RCTs (16–25). The PRISMA flowchart for study selection is shown in Fig. 1.

3.2 Characteristics of Included Studies.

A total of 10 studies (16–25) were included in the meta-analysis with 1,508 patients, 777 in the CRS + HIPEC, and 731 in the CRS alone. One study (20) was excluded from the analysis to avoid overlapping between the studies. Two studies were conducted in China, two in Spain, two studies in Korea, one in South Korea, one in the USA, and two multicenter RCTs. Eight studies used Cisplatin in the HIPEC regimen, two studies used Paclitaxel, and one used Carboplatin. A summary of included studies is shown in Table 1.

Table 1
Summary of 10 studies compared HIPEC vs. CRS in patients with ovarian cancers.

Study ID	Country/Centers	Period of enrollment	Tumor status	Stage (HIPEC + CRS/CRS)	Number of patients		HIPEC details			
					HIPEC + CRS	CRS alone	Drug	HIPEC temperature (∘C)	HIPEC duration (minutes)	Technique
Primary Tumors										
Antonio et al., 2022	Spain	March 2012 to November 2018	Primary tumor (NAC was used)	III: 33 (94.3%)/30 (83.3%) IV: 2 (5.7%)/6 (16.7%)	35	36	Cisplatin 75 mg/m²	42–43°C	60	Open
Aronson et al., 2023 / Van Driel etal., 2018	Netherlands and Belgium.	April 2007 to April 2016	Primary tumor (NAC was used)	FIGO stage III (100%)	122	123	Cisplatin 100 mg/m²	40–42°C	90	Open
Lim et al., 2022	South Korea	March2010 - January2016	Primary tumor (NAC was used)	III: 60 (65.21%)/51 (55.43%) IV: 32 (34.78%)/41 (44.56%)	92	92	Cisplatin 75 mg/m²	41.5	90	Closed
Xu et al., 2020	China	May 2013 to May 2016	Primary tumor (NAC was used)	III: 34 (77.3)/30 (68.2%) IV: 10 (22.7%)/14 (31.8%)	HIPEC: 44 HIPEC + NAC: 44	44	Cisplatin 80 mg/m²	45–48°C	60–90	Open
Recurrent tumor										
Classe et al., 2024	France, Belgium, Spain, and Canada	May2011 - May2021	Recurrent	NA	207	208	cisplatin 75 mg/m²	41 ± 1°C	60	Open or closed
Spoiliotis 2015	Greece	2006–2013	Recurrent tumor		60	60	cisplatin 100 mg/m² and paclitaxel 175 mg/m²	42.5°C	60	Closed
Zivanovic 2021	United States	February 2014 - November 2019	Recurrent tumor	NA	49	49	Carboplatin 800 mg/m²	41°C- 43°C	90	Closed
Fagotti et al., 2025	Italy	September 2012 - January 2019	Recurrent tumor	NA	82	85	Cisplatin 75 mg/m²	41.5	60	Closed
Mixed tumors										
Campos et al., 2024	Spain	August 2012 - December 2019	Mixed tumors (primary and recurrent)	III: 18 (32.7)/17 (30.4%) IV: 9 (15.4%)/3 (5.4%)	41	35	Paclitaxel 175 mg/m2	42–43 ∘C	60	Closed

3.3 Quality assessment and Certainty of evidence.

The Cochrane tool for assessing the quality of RCTs (ROB 2.0) was used to assess the quality of evidence of included studies. Out of ten, five RCTs were with “low risk” of bias in the five domains. However, the other five were with “some concerns” of bias. Three RCTs had some concerns in the second domain of deviation from intended interventions, and two had some concerns in the fifth domain. Figure 2 shows the ROB 2.0 figure and summary.

The GRADE assessment was performed using GRADE Pro, aligning with the GRADE assessment criteria of the Cochrane handbook. Both OS and PFS/DFS results were of high-quality evidence. The results of the GRADE assessment for the analyzed results are shown in **Supplementary Table 2**.

3.4 Outcomes.

3.4.1 Overall survival (OS).

Reconstruction of Kaplan-Meier (KM) curves from a total of 11 curves (nine studies) that reported the overall survival through 10 years of follow-up with 1531 patients (767 in HIPEC with CRS and 764 in CRS alone). The median survival time was higher in the HIPEC with CRS group compared to the CRS alone (median: 3.72 years; 3.68 years, respectively). The use of HIPEC besides the CRS was associated with lower mortality rates of 18% (Hazard Ratio (HR): 0.82, 95% CI [0.65 to 1.01], *log-rank p-value* = 0.09) over 10 years of follow-up, but without statistical significance (Fig. 3A). RMST was higher in HIPEC with the CRS group compared to the CRS alone group (RMST: 5.16 years; 4.56 years, respectively). The RMST difference was significant between the two groups ($RMST_{diff}$: 0.59; 95% CI: [0.24 to 0.86], p-value = 0.04) (Table 2). These results were consistent with the pairwise meta-analysis, showing that the mortality rates were similar between HIPEC plus CRS vs. CRS (HR: 0.81, 95% CI: [0.64 to 1.02], *log-rank p-value* = 0.08) with high heterogeneity (I^2= 74%) (Fig. 3B**)**. The sensitivity analysis showed that the heterogeneity was resolved after the exclusion of Campos et al 2024 (I^2= 40%), with a statistically significant reduction in mortality after using HIPEC with CRS (HR: 0.76, 95% CI [0.62 to 0.93], *log-rank p-value* = 0.008) compared to the CRS alone (**Supplementary Fig. 1)**.

Table 2
Reconstructed Values of Kaplan-Meier curves Reconstruction.

Outcome	Type of tumor and surgery	Arm	No of included curves	Event/Total of patients	Median time for OS/PF with 95% CI (years)	RMST with 95% CI	Hazard Ratio with 95% CI (p-value)	RMST Difference with 95% CI
Overall Survival (OS)	Total	HIPEC + CRS	11	449/767	3.31 (3.89; 4.67)	5.16 (4.90; 5.42)	0.82, 95% CI [0.65; 1.01], *log-rank p-value = 0.09*	0.59 (0.24; 0.86), p-value = 0.04
		CRS		491/764	3.68 (3.46; 3.95)	4.56 (4.31; 4.82)	ref	ref
	Primary surgery	HIPEC + CRS	2	70/102	3.27 (2.75; 4.46)	4.39 (3.77; 5.02)	0.99, 95% CI [0.59, 1.68], *log-rank p-value* = 0.92	-0.107 (-1.057; 0.842), p-value = 0.824
		CRS		60/93	2.85 (2.26; 4.09)	4.5 (3.79; 5.22)	ref	ref
	Interval surgery	HIPEC + CRS	4	171/235	3.86 (3.32; 4.15)	4.49 (4.11; 4.87)	0.57, 95% CI [0.43, 0.82], *log-rank p-value* < 0.001	0.98 (0.48; 1.48), p-value < 0.0001
		CRS		204/246	2.86 (2.53; 3.22)	3.51 (3.19; 3.83)	ref	ref
	Recurrent tumor	HIPEC + CRS	4	191/398	5.42 (4.84; 6.67)	5.73 (5.34; 6.11)	0.83, 95% CI [0.66; 1.04], *log-rank p-value* = 0.08	0.524 (-0.012; 1.06), p-value = 0.055
		CRS		212/402	4.72 (4.17; 5.34)	5.20 (4.83; 5.57)	ref	ref
Progression-free survival (PFS)/disease-free survival (DFS)	Total	HIPEC + CRS	8	481/619	1.33; (1.24; 1.48)	2.80 (2.54; 3.07)	0.78, 95% CI [0.60; 0.96], *log-rank p-value* = 0.02	0.42 (0.05; 0.78) p-value = 0.025
		CRS		499/616	1.13 (1.04; 1.28)	2.38 (2.13; 2.64)	ref	ref
	Interval surgery	HIPEC + CRS	3	152/191	1.33 (1.26; 1.60)	2.83 (2.45; 3.29)	0.64, 95% CI [0.53; 0.79], *log-rank p-value* < 0.001	0.88 (0.266; 1.499), p-value = 0.005
		CRS		166/202	1.03 (0.92; 1.16)	1.94 (1.545; 2.339)	ref	ref
	Recurrent tumor	HIPEC + CRS	3	271/338	1.22 (1.11; 1.35)	2.37 (2.057; 2.69)	1.01, 95% CI [0.75; 1.48], *log-rank p-value* = 0.79	-0.004 (-0.47; 0.46), p-value = 0.98
		CRS		277/342	1.11 (1.04; 1.28)	2.38 (2.04; 2.72)	ref	ref

3.4.2 Progression/Disease-free survival (PFS/DFS).

A total of eight curves pooled from six RCTs reported the PFS/DFS with 1455 patients (619 in HIPEC with CRS and 616 in CRS alone). The median free progression time was higher in the HIPEC with CRS group compared to the CRS alone group (median: 1.33 years, 1.13 years, respectively). The use of HIPEC plus CRS was associated with a similar incidence of progression compared to CRS alone (HR: 0.80, 95% CI [0.66; 1.02], *log-rank p-value* = 0.06) (Fig. 4A**)**. The RMST was higher in the HIPEC plus CRS group compared to the CRS alone group (RMST: 1.902 years, 1.835 years, respectively). The RMST difference was significant between the two groups ($RMST_{diff}$: 0.42; 95% CI [0.05 to 0.78], p-value = 0.025) (Table 2). These results were consistent with the pairwise meta-analysis, showing that the incidence of the progression was lower in the HIPEC plus CRS vs. CRS alone but without statistical significance (HR: 0.82, 95% CI: [0.64 to 1.04], *log-rank p-value* = 0.10) and with high heterogeneity (I^2= 67%) (Fig. 4B**)**. The sensitivity analysis showed that heterogeneity was moderate after the exclusion of Zivanovic et al 2021 (I^2= 51%), with a statistically significant reduction in progression rates after using HIPEC plus CRS by 25% (0.75, 95% CI: [0.61 to 0.93], *log-rank p-value* = 0.007) compared to the CRS alone (**Supplementary Fig. 2)**.

3.4.3. Subgroup and sensitivity analyses.

1. OS.

The subgroup analyses were applied according to the tumor type and treatment approach (type of surgery). After applying the interval surgery, the mortality rates were significantly reduced with HIPEC plus CRS (HR: 0.57, 95% CI [0.43 to 0.82], *log-rank p-value* < 0.001) compared to the CRS alone at 10 years follow-up (Fig. 5A**)**. The results were consistent with the pairwise meta-analysis and showed a significant reduction with low heterogeneity after interval surgery (HR: 0.57, 95% CI [0.40 to 0.80], *log-rank p-value* = 0.001, I^2 = 32%) (**Supplementary Fig. 3)**. However, there were no statistical differences in mortality rates between the two groups after primary surgeries, in recurrent tumors, or in the trial included a combined population (Fig. 5B-C, **Supplementary Fig. 3)**. There was a statistical difference between the subgroups ($P_{interaction}$ = 0.0003) (**Supplementary Fig. 3)**. The RMST difference was statistically significant between the two groups after interval surgery only ($RMST_{diff}$: 0.98; 95% CI: [0.48 to 1.48], p-value < 0.0001); however, there were similar RMST differences between the two groups after primary surgeries, in recurrent tumors, or the trial included a combined population (Table 2**).**

2. PFS/DFS.

The subgroup analyses were applied according to the tumor type and treatment approach (type of surgery). After applying the interval surgery, the progression rates were significantly reduced with HIPEC plus CRS by 36% (HR: 0.64, 95% CI [0.53 to 0.79], *log-rank p-value* = 0.001) compared to the CRS alone at 10 years follow-up (Fig. 6A**)**. The results were consistent with the pairwise meta-analysis and showed a significant reduction with low heterogeneity after interval surgery (HR: 0.63, 95% CI [0.51 to 0.78], *log-rank p-value* < 0.0001, I^2 = 0%) (**Supplementary Fig. 4)**. However, there were no statistical differences in progression rates between the two groups after primary surgeries, in recurrent tumors, or in the trial included a combined population (Fig. 6B, **Supplementary Fig. 4)**. There was a statistical difference between the subgroups ($P_{interaction}$ = 0.05) (**Supplementary Fig. 4)**. The RMST difference was statistically significant between the two groups after interval surgery only ($RMST_{diff}$: 0.88; 95% CI: [0.266 to 1.499], p-value = 0.005); however, there were similar RMST differences between the two groups after primary surgeries, in recurrent tumors, or the trial included a combined population (Table 2**).**

4. Discussion

This meta-analysis was done on ten studies involving 1364 patients with ovarian cancer (685 in HIPEC with CRS and 679 in CRS alone). A 21% lower rate of mortality and disease progression was reported after treatment with HIPEC, compared to CRS alone. Our meta-analysis had three subgroups (primary ovarian tumors treated with primary CRS, primary tumors with interval surgery, and recurrent ovarian tumors). It was reported that interval surgery for primary OC patients with HIPEC significantly decreased the mortality and progression rates. However, the mortality and progression rates of OC were not significantly reduced by the use of HIPEC with the primary CRS for primary OC and recurrent OC patients. Additionally, HIPEC at an interval CRS was linked to an increase in RMST of approximately one year compared with CRS alone. One of our included studies also noted a higher incidence of grade ≥ 3 adverse events with HIPEC. Results were heterogeneous; some analyses (e.g., Zhang (2019); Marzuqi (2025)) found survival benefits in advanced primary OC and suggested HIPEC may be cost-effective (26, 27).

For over thirty years, intraperitoneal (IP) chemotherapy has been studied due to the high incidence of IP dissemination of OC (28). Almost 75% of patients have IP metastases at the time of their initial surgery (29). The term "hyperthermic intraperitoneal chemotherapy" (HIPEC) refers to the administration of intraperitoneal chemotherapy in a hyperthermic environment during surgery. When the chemotherapeutic agent or substance is heated to an average temperature of 40°C, cancer cells become more permeable to it, increasing the agent's or substance's ability to eradicate cancer cells. In addition, hyperthermia causes apoptosis, activates heat-shock proteins that act as natural killer cell receptors, suppresses angiogenesis, and directly causes cytotoxicity by encouraging protein denaturation (30, 31). Van Driel et al. found that using HIPEC at interval debulking in the first-line scenario improved both OS and PFS (32).

In the current meta-analysis, Lim et al. 2022 (24) and Xu et al. 2020 (18) reported that the use of HIPEC, besides the primary CRS, was insignificant in reducing the mortality rates in patients with primary ovarian tumors. Additionally, there was no statistically significant difference in the RMST between the two groups. While no statistically significant difference in RMST was observed between HIPEC and CRS in the primary CRS subgroup, patients undergoing interval CRS with HIPEC demonstrated a significant improvement in RMST of approximately one year compared with CRS alone. In agreement, Yu Xia et al. (2023) (33) and Filis et al. (2022) (34) showed that, in the absence of neoadjuvant chemotherapy, the combination of HIPEC + CRS did not lead to any survival advantage. Nonetheless, Zhang et al. (2019), who used observational data, revealed that HIPEC groups outperformed groups that did not receive HIPEC treatment in terms of OS and PFS (26). Furthermore, the subgroup analysis demonstrated that HIPEC improved OS and PFS/DFS for patients with advanced primary ovarian cancers (26). This difference could be attributed to the variation in the number of included studies and the study design, which included RCTs and observational studies in their meta-analysis. This variability in findings may not only be attributed to differences in study design and the number of included studies, but also to heterogeneity in HIPEC protocols (chemotherapeutic agents, doses, and perfusion duration) and differences in the surgical setting (primary CRS vs. interval CRS).

By more effectively eradicating any remaining microscopic peritoneal illness than intravenous chemotherapy, intraperitoneal application of chemotherapy improves medication distribution at the peritoneal surface and may lead to better results (32). Therefore, HIPEC is included as an option for stage III ovarian cancer patients to interval CRS (35). In accordance, our meta-analysis, through pooling of Xu et al., 2020 (18), Lim et al., 2022 (24), Antonio et al., 2022 (25), and Aronson et al., 2023 (17), showed that the use of HIPEC with the CRS significantly lowered the mortality rates after interval surgery by 43% with primary ovarian tumors. Moreover, with the median survival time of 3.86 years, the HIPEC with CRS group surpasses the median survival time of the CRS alone, 2.86

years. RMST was also significantly higher in HIPEC with CRS compared to CRS alone (RMST: 4.94 years and 3.51 years, respectively). The ~ 33% reduction in progression rates after interval surgery reported in these three studies was consistent with the pooled PFS results across all included studies.

Similarly. Yu Xia et al. (2023) (33) and Filis et al. (2022) (34) showed that OS and PFS were markedly improved when HIPEC was combined with interval cytoreductive surgery (CRS) and neoadjuvant chemotherapy. Moreover, it was revealed that compared to cytoreductive surgery alone, women who were diagnosed with advanced ovarian cancer and underwent HIPEC + complete or optimal interval cytoreductive surgery had a higher survival time (32). Marrelli et al. (2021) recorded that six cycles of NAC, followed by CRS and HIPEC, have been linked to significant improvements in peritoneal carcinomatosis, minimal postoperative morbidity risk, and high responder survival rates (36).

On the other hand, in the present meta-analysis, the use of HIPEC with the CRS was insignificant in reducing the mortality rates and the progression rates in the recurrent tumor. In contrast to our meta-analysis, which estimated OS up to 10 years based on reconstructed KM curves, Filis et al. demonstrated 5-year OS. But both meta-analyses concluded that utilizing HIPEC for recurrent ovarian cancer does not improve survival (34). Moreover, Fagotti et al., 2025 (37) and Zhang et al., 2019 (26) reported that there was no difference in PFS between the HIPC and non-HIPEC groups. Conversely, Zhang et al. (2019) documented that HIPEC was linked to better OS for recurrent ovarian cancer (26). Additionally, Yuwen Qiet al., 2022 hypothesized that platinum-sensitive recurrent EOC patients with HRR mutations have a higher progression-free survival (PFS) when HIPEC is added to CRS as opposed to individuals without HRR (38).

H Li et al. (2023) documented the advantages of CRS plus HIPEC in the treatment of advanced ovarian cancer. However, monitoring is essential when using this co-administration in clinical settings due to a higher chance of side effects (39). This can be attributed to the intricate milieu of the peritoneal cavity; it might be difficult to deliver medications to the tumor site efficiently while avoiding healthy tissues. To this intricacy are additional variables like ascites and fluctuating blood supply (40). In agreement, Class et al. (2024), one of our included studies recorded that of the 207 patients receiving HIPEC, around 49% experienced grade 3 or greater adverse events within 60 days following surgery, compared to 27% of the patients receiving no HIPEC (3). Nonetheless, Marzuqi et al. (2025) demonstrated improvement in OS and PFS in ovarian cancer after using CRS + HIPEC, and this mix exhibits good cost-effectiveness and controllable adverse effects. However, the generalizability of results is restricted by the variability of study designs, variances in patient groups, and differences in HIPEC protocols (27).

Strengths, Limitations, and Recommendations

A thorough search strategy was carried out using various databases, which led to the discovery of numerous records, one of the study's strengths. However, there are some limitations to our study, one of which is the small number of included trials. Moreover, one of the main limitations is that reliable pooled estimates of time-to-event outcomes are limited by the majority of studies' failure to present adjusted HRs. Additionally, after assessing the quality of RCTs, five of the 10 RCTs were found to have "some concerns." Three RCTs had some concerns in the domain of deviation from intended interventions, and two had some concerns in the domain of the "selection of the reported result". This suggests a possibility of reporting bias, in which the authors might have overestimated the efficacy of the intervention by reporting only statistically significant results. Despite these methodological issues, the GRADE evaluation graded the overall quality of evidence for both Overall Survival (OS) and Progression-Free/Disease-Free Survival (PFS/DFS) as high. Consequently, future studies should strive to conduct larger, better-designed randomized controlled trials with strict adherence to intervention protocols and open reporting. Our results would help in making the optimal treatment decision for ovarian cancer and could be used as a reference for future research.

Clinical implications

Current guidelines state that HIPEC may be considered for selected patients with stage III epithelial ovarian cancer who receive neoadjuvant chemotherapy followed by interval cytoreductive surgery (41). ASCO's 2025 update adds that HIPEC can be offered to some medically fit patients at the time of interval surgery and notes the resource demands of this approach (41). European consensus guidance reports no consensus on HIPEC at interval surgery in newly diagnosed disease (42). The same document states that HIPEC is not recommended during cytoreductive surgery for relapsed disease and recommends that care should be concentrated in expert centers (42). These positions align with our subgroup findings that benefit appears confined to the interval surgery setting rather than primary debulking or recurrence.

5. Conclusion

When HIPEC is used in addition to CRS, the rate of mortality and disease progression decreases compared to CRS alone. In addition to HIPIC, interval surgery is optimal to reduce the mortality and progression rates for primary OC patients. These observations emphasize how crucial it is to give chemotherapy before surgery if we want to employ HIPEC.

Declarations

Ethics approval and consent to participate.

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Consent for publication.

Not applicable

Clinical trial number

Not applicable

Competing Interests.

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Author Contribution

Idea conceptualization and preparation of the framework (M.S.S), Methodology and data extraction (M.S.S. M.W., D.M.G., M.O.A., R.N.A.E., E.R., and R.N.A.E.), Software and formal analysis (M.S.S.) Writing the original draft (M.S.S., D.M.G., M.A.A., and R.N.A.E.) Reviewing and writing the second draft (M.S.S., A.F.G., U.A.N.)

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Availability of data and materials.

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Figures

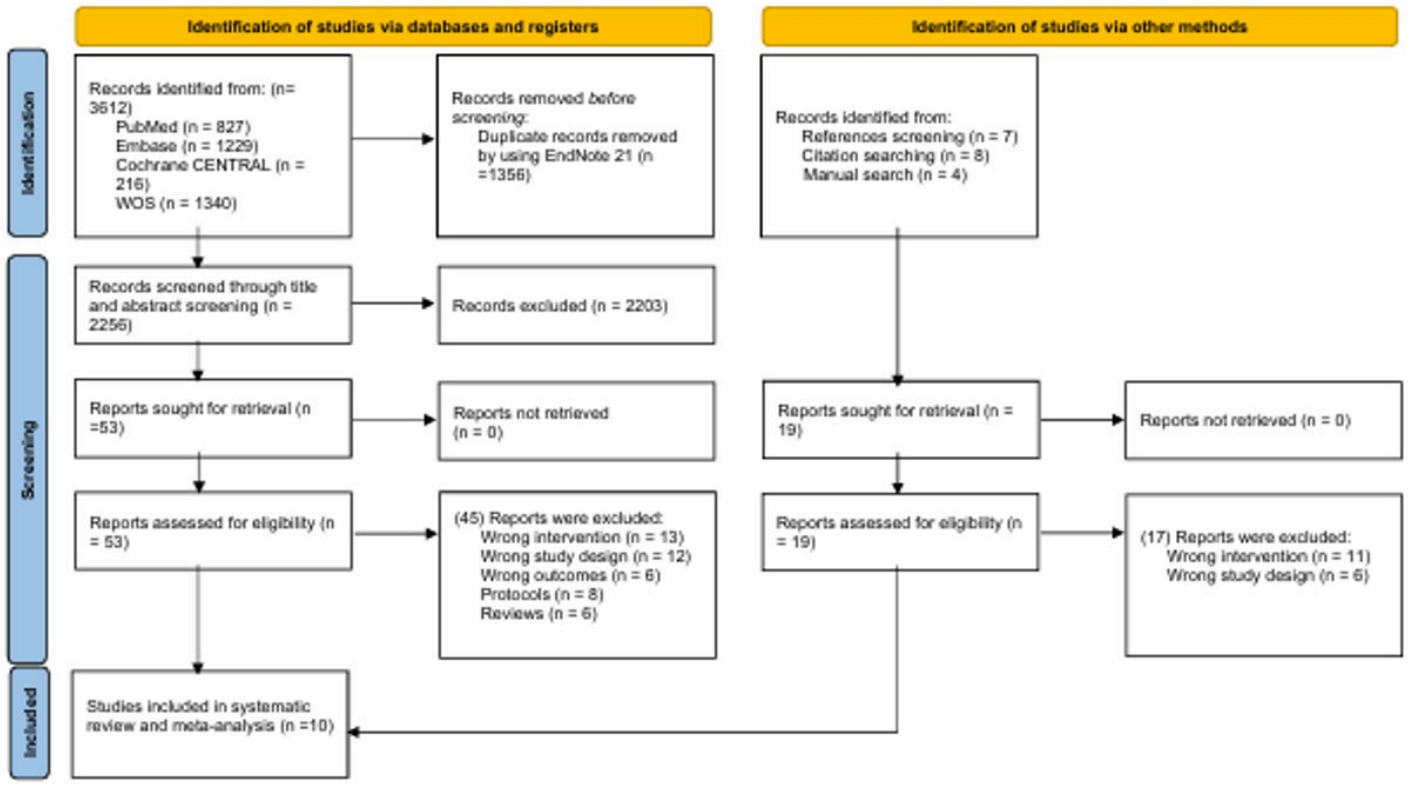


Figure 1

PRISMA Flowchart for the study selection process.

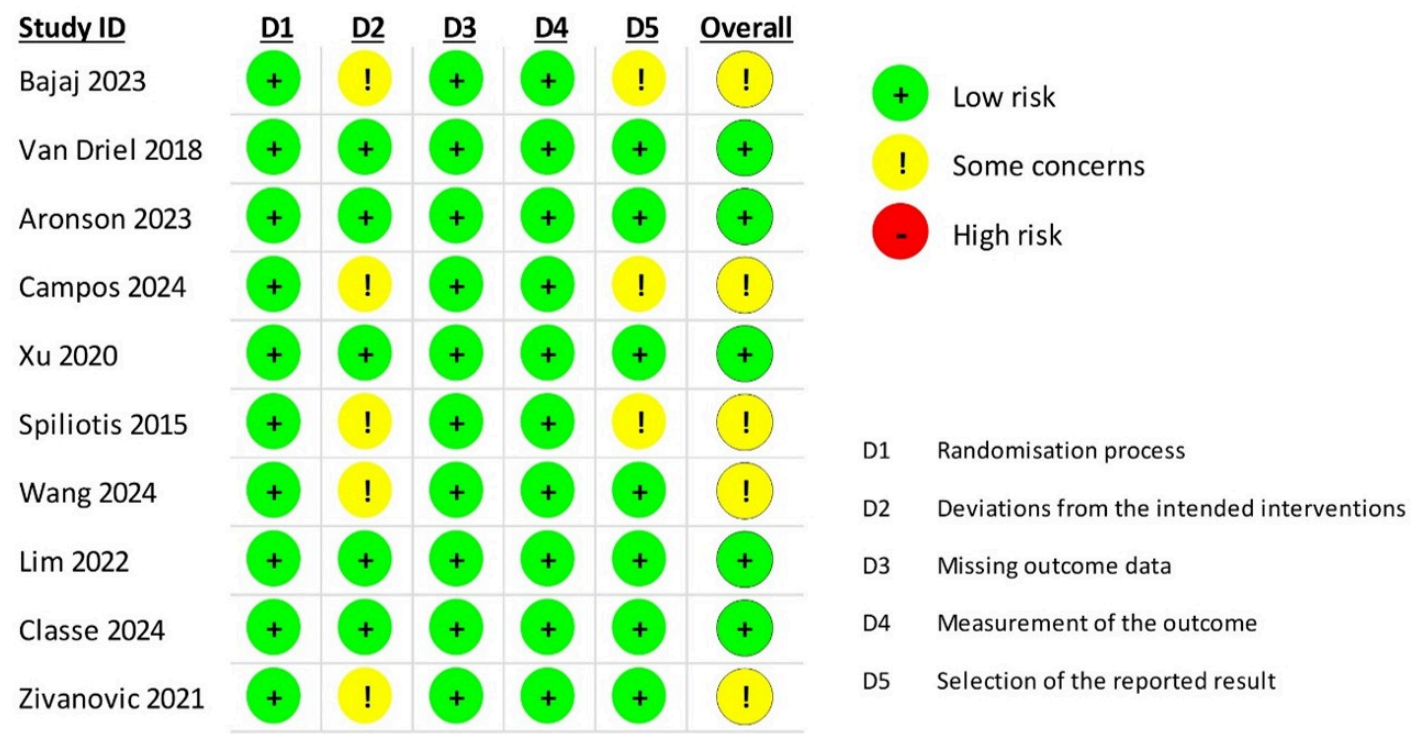


Figure 2

ROB 2.0 Graph for Quality Assessment of included studies.

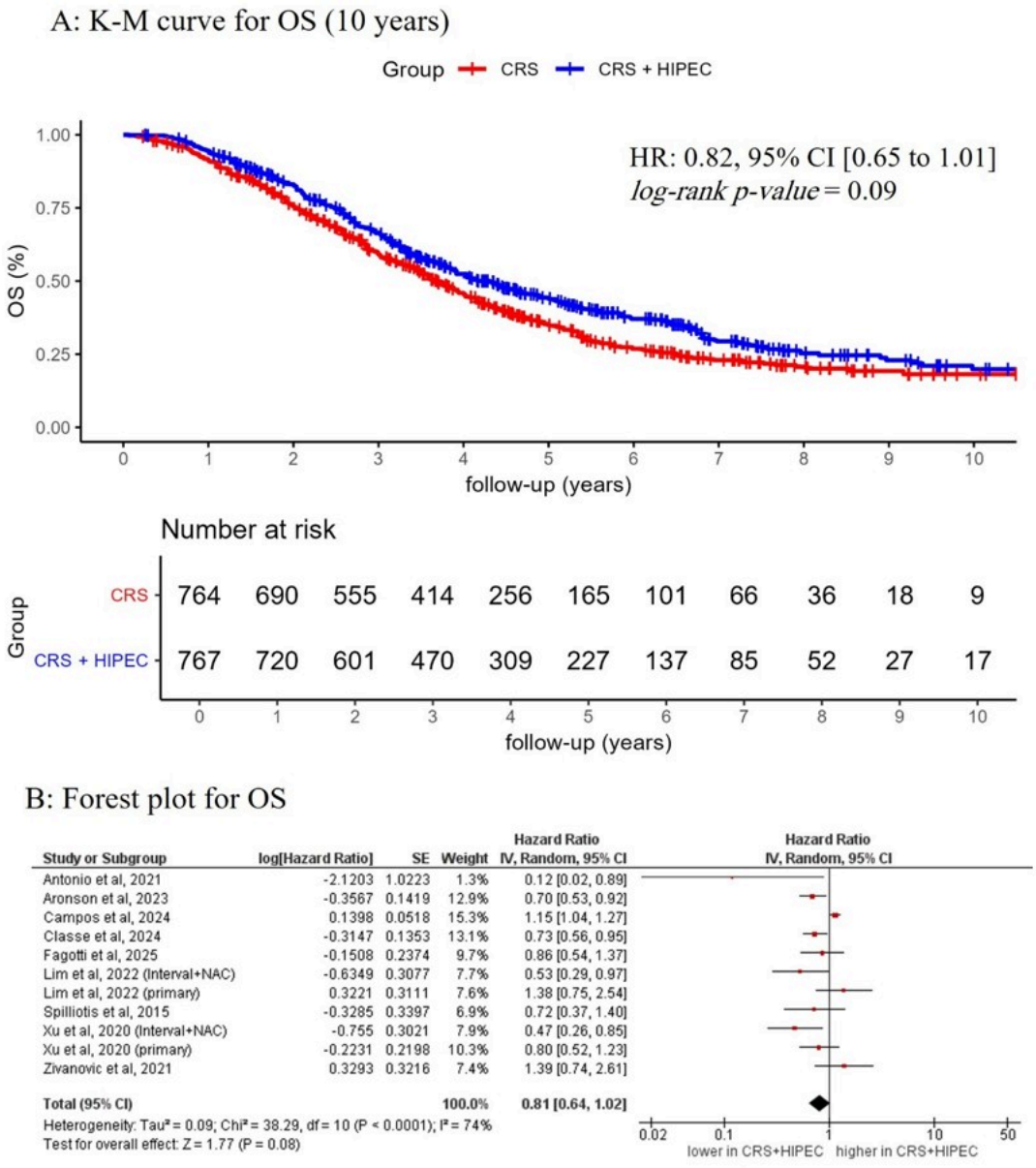


Figure 3

(A) Reconstructed Kaplan-Meier for Overall Survival (follow-up through 10 years) (B) Forest Plot meta-analysis for Overall Survival (follow-up through 10 years)

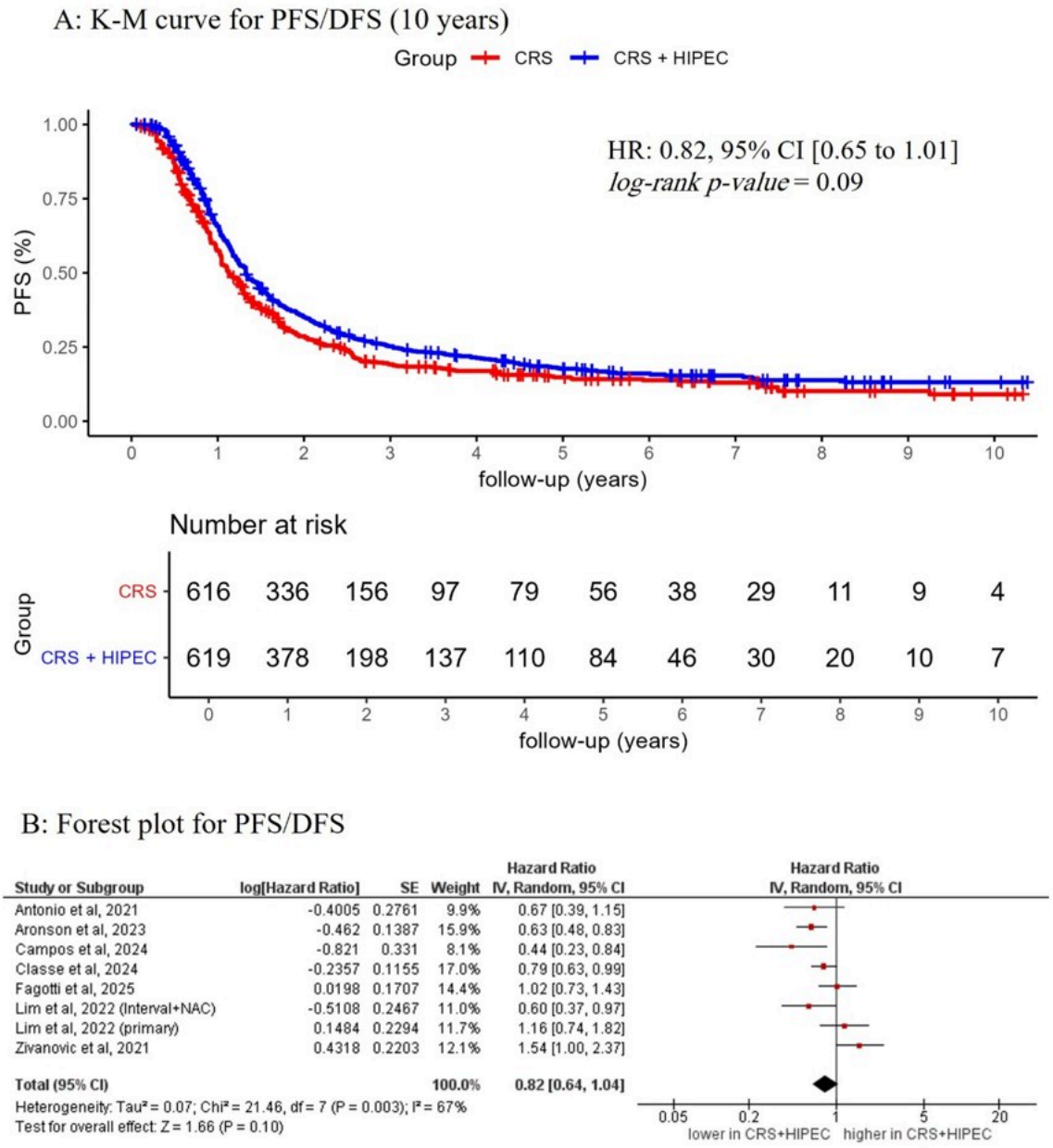


Figure 4

(A) Reconstructed Kaplan-Meier for progression/disease-free survival (PFS/DFS) (follow-up through 10 years) (B) Forest Plot meta-analysis for progression/disease-free survival (PFS/DFS) (follow-up through 10 years)

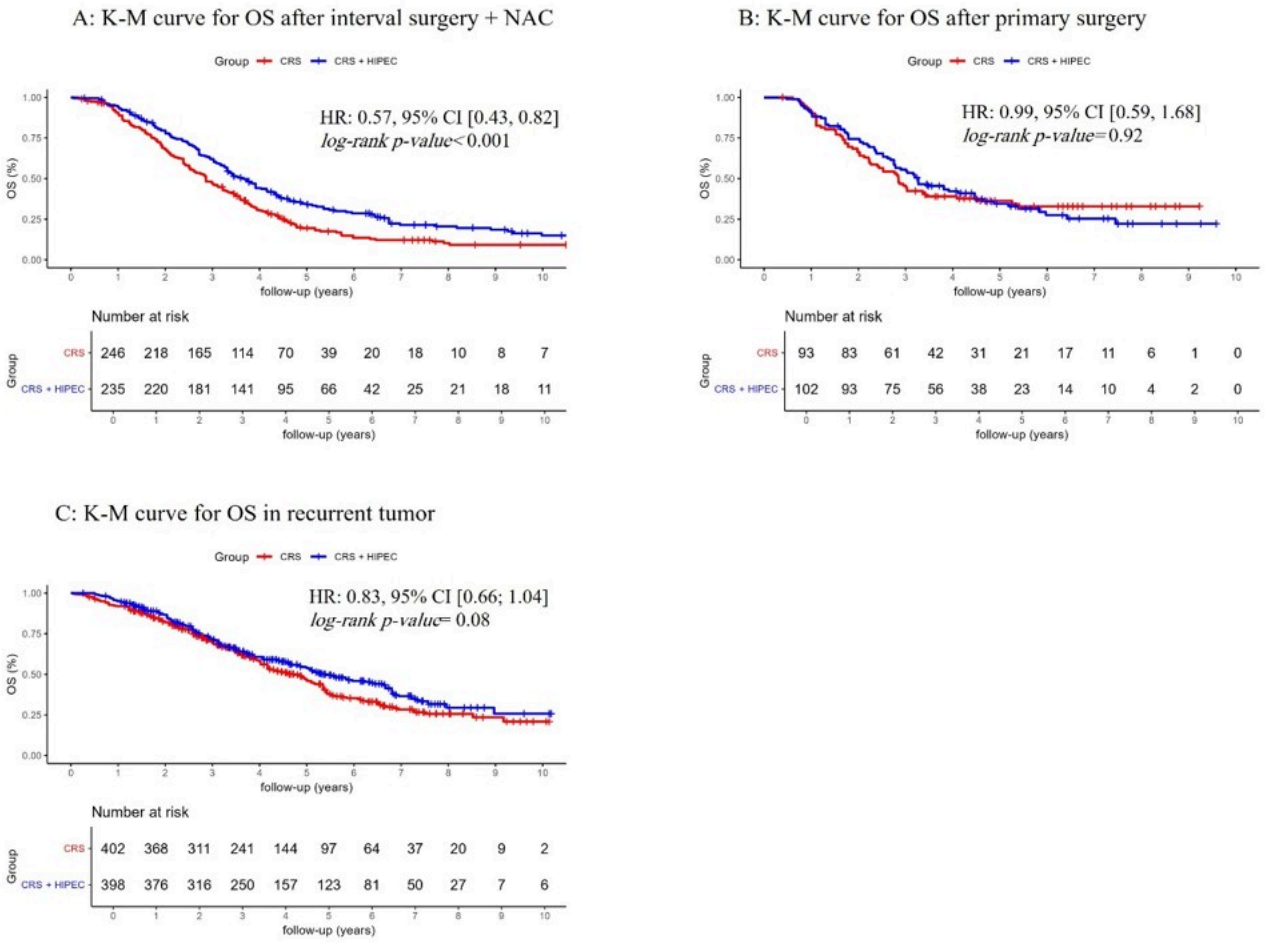


Figure 5

(A) Reconstructed Kaplan-Meier for Overall Survival after Interval surgery + Neoadjuvant chemotherapy (NAC), (B) Reconstructed Kaplan-Meier for Overall Survival after Primary surgery, and (C) Reconstructed Kaplan-Meier for Overall Survival after surgery in recurrent tumors.

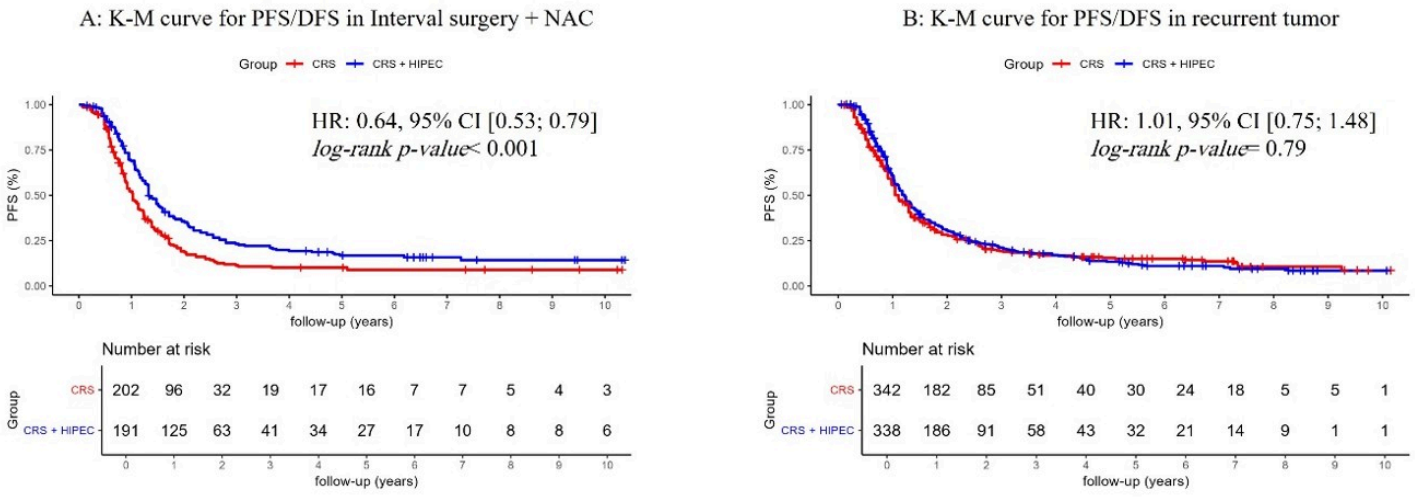


Figure 6

(A) Reconstructed Kaplan-Meier for progression/disease-free survival (PFS/DFS) after Interval surgery + Neoadjuvant chemotherapy (NAC), and (B) Reconstructed Kaplan-Meier for progression/disease-free survival (PFS/DFS) after surgery in recurrent tumors.

Supplementary Files

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- SupplementaryMaterials.docx