Hyperthermic intraperitoneal chemotherapy (HIPEC) for the management of primary advanced and recurrent ovarian cancer: a systematic review and meta-analysis of randomized trials

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Introduction: Ovarian cancer is the most lethal gynecologic malignancy. Although treatment with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promising results, its role remains elusive. The aim of this study was to assess the comprehensive randomized evidence for the use versus non-use of HIPEC in primary and recurrent ovarian cancer. Materials and methods: The Medline, Embase and Cochrane databases, as well as the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) conference abstracts of the last 5 years, were scrutinized in January 2022 for randomized, controlled trials that studied the use of HIPEC in ovarian cancer. Overall survival (OS), disease-free survival (DFS) and progression-free survival, as well as post-operative morbidity were the outcomes of interest. This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

Results: Six randomized, controlled trials that randomized 737 patients were included in our analysis; of these, four studies (519 patients) were in primary and two (218 patients) in recurrent settings. In primary ovarian cancer, the combination of HIPEC with interval CRS and neoadjuvant chemotherapy significantly improved the 5-year OS [393 patients, risk ratio (RR) = 0.77; 95% confidence interval (CI) 0.67-0.90; P value = 0.001] and DFS (hazard ratio = 0.60; 95% CI 0.41-0.87; P value = 0.008) compared with standard treatment alone. In the absence of neoadjuvant chemotherapy, the use of HIPEC + CRS was not associated with any survival advantage (126 patients, 4-year OS, RR = 0.93; 95% CI 0.57-1.53; P value = 0.781), but the sample size was smaller in this subset. Use of HIPEC in recurrent ovarian cancer did not provide any survival advantage (5-year OS: 218 patients, RR = 0.85; 95% CI 0.45-1.62; P value = 0.626). The risk for grade ≥3 adverse events was similar between HIPEC and no HIPEC (RR = 1.08; 95% CI 0.98-1.18; P value = 0.109).

Conclusions: In primary ovarian cancer the combination of HIPEC with interval CRS and neoadjuvant chemotherapy is a safe option that significantly improved 5-year OS and DFS. Its use in other settings should continue to be considered investigational.

Key words: ovarian cancer, hyperthermic intraperitoneal chemotherapy, HIPEC, cytoreductive surgery, primary CRS, interval CRS

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy. In 2022, it is estimated that 19 880 new cases of ovarian cancer will be diagnosed in the United States and 12 810 deaths will occur from this disease.¹ Approximately 75% of ovarian cancer patients are diagnosed in the advanced setting, when the disease has already predominantly spread in the peritoneal cavity.¹ Thus, the research for potentially curative therapeutic strategies is essential.

In primary stage III ovarian cancer the importance of radical reduction of the comprehensive tumor burden with cytoreductive surgery (CRS) is established and has been proved to provide curative, overall and progression-free survival (PFS) benefits.³⁻⁶ Accordingly, the optimal therapy for primary advanced (stage II-IV) ovarian cancer consists of
CRS followed by adjuvant platinum-based chemotherapy and biological treatments.7,8

The theory that intraperitoneal chemotherapy could be effective against microscopic seeding, tumor cell entrapment and peritoneal carcinomatosis in ovarian cancer paved the way for several randomized trials, some of which showed beneficial results, while also being accompanied by toxicities.9-13 The 2021 guidelines suggest intraperitoneal chemotherapy, as an option, only for optimally debulked (<1 cm residual disease), stage II-III selected epithelial cancer types.4 Hyperthermic intraperitoneal chemotherapy (HIPEC) holds a series of advantages over intraperitoneal chemotherapy, since it requires a single administration that is being delivered at a special timing, following a complete CRS, when all peritoneal surfaces are exposed to the chemotherapy, while also leveraging the effect of hyperthermia (41-43°C for 30-120 min) to increase the cytotoxicity of chemotherapeutic drugs.14-16 Of note, complete cytoreduction remains the cornerstone of advanced ovarian cancer treatment and the potential additional benefit for the use of HIPEC following CRS as combination therapy has arisen as an interesting concept that has yet to be clarified.

Currently, the plethora of meta-analyses studying the efficacy of HIPEC in gynecological malignancies rely mainly on cohort studies.17-20 We therefore carried out a systematic review in order to scrutinize and estimate the comprehensive available level I evidence for use versus no use of HIPEC in advanced primary and recurrent ovarian cancer.

MATERIALS AND METHODS

Search and selection

The Medline, Cochrane and Embase databases, as well as European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) congress abstracts were systematically searched in January 2022 for randomized, controlled trials (RCTs) comparing the use of HIPEC treatment with any other therapy in patients with ovarian cancer. The search in Medline was updated in April 2022. The search algorithm contained: (ovarian) AND (neoplasm* OR cancer* OR tumor*) AND (HIPEC OR IPHP OR IHC OR CHPP OR hyperthermic OR hyperthermic intraperitoneal chemotherapy OR hyperthermic intraperitoneal perfusion OR intraperitoneal hyperthermic chemoperfusion OR continuous hyperthermic peritoneal perfusion) AND (random*). This study was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.21

Two independent investigators (PF, NF) screened all studies identified in our search by titles and abstracts for eligibility. Any article identified as having the potential to fulfill our inclusion criteria underwent full-text evaluation. If agreement on eligibility was not reached between the two investigators, a third investigator (DM) was involved to evaluate the article. Database searches were supplemented by using citation analysis of those eligible. The eligibility was defined by the PICO framework: Population (P): patients with primary or recurrent ovarian cancer; Intervention (I): Hyperthermic Intraperitoneal Chemotherapy (HIPEC); Comparison (C): treatment without HIPEC; Outcomes (O): Overall survival, disease-free survival, Progression-free survival, Post-operative morbidity. Studies that did not fulfill the above-mentioned criteria, such as cohort and case-control studies, or were not published in English language were excluded.

Data extraction

The data extraction was carried out by two authors (PF, GM) who filled in a pre-piloted extraction form independently. Any disagreement was resolved by consensus. Multiple records reporting on the same trial were excluded. In case of double reporting data in conference abstracts and article publications, only the data from the publication, the highest level of evidence was taken into account. The data extraction included: first author, year of publication, chronological period of the study recruitment, study population, number of patients, experimental and control arm therapy details, HIPEC technique, median follow-up, median overall survival (OS), median progression-free survival (PFS) in months, survival and PFS rates, number of deaths and number of disease progression incidences, as well as rates of grade ≥3 adverse events occurrence after surgery (according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0).

Outcomes

The primary outcome of interest is the OS of patients with primary advanced and recurrent ovarian cancer treated with HIPEC versus treatment without HIPEC, which is also measured at different time points of follow-up (1-, 2-, 3-, 4-, 5-year OS). Secondary outcomes are disease-free survival (DFS) for primary and PFS for recurrent ovarian cancer measured at consecutive time points, as well as post-operative morbidity.

Statistical analysis and risk of bias

Risk ratios (RRs) of OS were characterized by the proportion of patient deaths as indicated from each study’s reported survival rates, whereas those for DFS and PFS were calculated according to the proportion of disease progression events. The rates of post-operative morbidity in the two groups were used to calculate the corresponding RR. Because the rates of interest were minimally reported in the articles, Engauge Digitizer (https://markummitchell.github.io/engauge-digitizer/) was used to calculate the OS and PFS rates from the Kaplan—Meier curves at 1, 2, 3, 4 and 5 years. Additionally, a heterogeneity P value was calculated to assess the differences by year. These findings were compared with the corresponding data when they were directly reported in the articles and showed complete validity (± no more than one patient). When the rates were directly reported in the articles, then these estimates were taken into consideration for the analysis. As expected, this technique of measuring the rates at different time points was not feasible when assessing conference abstracts, so in this case we only considered the measures of interest that were directly mentioned. For each outcome, a random-
effects model was used, utilizing the inverse variance method, to compare the RRs and 95% confidence intervals (CIs) between patients who did and did not receive HIPEC. An RR <1 will indicate a protective impact of HIPEC, whereas an RR >1 will indicate reduction in OS or PFS from the use of HIPEC compared with no use. Statistical heterogeneity was assessed using the $I^2$ statistic. Statistical significance was indicated from a $P$ value <0.05. Due to the small number of included trials, we did not perform an evaluation of small study effects and publication bias. All statistical analyses were carried out in Stata version 14 (Stata Corp, College Station, TX). Risk of bias assessed by the RoB 2 tool: a revised Cochrane risk of bias tool for randomized trials.

RESULTS

The review flow chart is described in Figure 1. Electronic searches identified 162 hits in Medline, 360 in Embase and 170 in Cochrane. These hits were screened by title and abstract, complemented by additional screening of ESMO congress 2017-2021 and ESMO gynecological cancers 2021 congress abstracts, as well as ASCO 2017-2022 and ASCO gynecologic oncology/women cancer 2018-2021 congress abstracts. After full-text evaluation of 11 articles, the search ultimately yielded a total of six eligible studies, five RCTs published in peer-reviewed journals and one RCT from conference abstract. Five studies were excluded due to not being randomized and due to researching outcomes unrelated to our analysis. The eligible studies were conducted in South Korea, Spain, USA, the Netherlands, Greece and three of them were multicenter. Overall 737 patients were randomized across six trials; among these four studies (519 patients) concerned the experimental use of HIPEC in primary ovarian cancer and two (218 patients) its investigational use in recurrent settings. Table 1 summarizes the characteristics of the included RCTs. All studies were randomized in 1 : 1 fashion, five studies described the type of randomization and three studies described the method of randomization concealment and four studies provided details for withdrawals. Risk of bias assessed by the RoB 2 tool is provided in Supplementary Figure S1,

Figure 1. Review flow chart.
ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.
| Author | Year of publication period | Recruitment period | HIPEC group (n) | Control group (n) | Experimental arm | Control arm | Median follow-up (months) | Median OS (months) | Median PFS (months) |
|--------|---------------------------|-------------------|----------------|------------------|----------------|------------|--------------------------|------------------|-----------------|
| **Primary ovarian cancer** | | | | | | | | | |
| Lim (NACT) | 2022 | 2010-2016 | 34 | 43 | Cisplatin 75 mg/m² | 90 | 41.5 | Carboplatin and paclitaxel (+NACT) | Carboplatin and paclitaxel (+NACT) | 69.4 | 61.8/48.2 | 17.4/15.4 |
| Lim | 2022 | 2010-2016 | 58 | 49 | Cisplatin 75 mg/m² | 90 | 41.5 | Carboplatin and paclitaxel | Carboplatin and paclitaxel | 69.4 | 71.3/— | 23.9/29.7 |
| Campos | 2022 | 2012-2018 | 35 | 36 | Cisplatin 75 mg/m² | 60 | 42-43 | Carboplatin and paclitaxel (+NACT) | Carboplatin and paclitaxel (+NACT) | 32 | 52/45 | 18/12 |
| Van Driel | 2018 | 2007-2016 | 122 | 123 | Cisplatin 100 mg/m² | 90 | 40 | Carboplatin and paclitaxel (+NACT) | Carboplatin and paclitaxel (+NACT) | 56.4 | 45.7/33.9 | 14.2/10.7 |
| Diaz-Montes | 2018 | 2014-2018 | 10 | 9 | Carboplatin 800 mg/m² | 90 | — | Carboplatin and paclitaxel | I.V. paclitaxel/I.p. cisplatin/I.p. paclitaxel | — | — | — |
| **Recurrent ovarian cancer** | | | | | | | | | |
| Zivanovic | 2021 | 2014-2019 | 49 | 49 | Carboplatin 800 mg/m² | 90 | 41-43 | Carboplatin and paclitaxel or gemcitabine or doxorubicin | Carboplatin and paclitaxel or gemcitabine or doxorubicin | 39.5 | 52.5/59.7 | 12.3/15.7 |
| Spiliotis | 2014 | 2006-2013 | 60 | 60 | Cisplatin 100 mg/m² and paclitaxel 175 mg/m² or doxorubicin 35 mg/m² and (paclitaxel 175 mg/m² or mitomycin 15 mg/m²) | 60 | 42.5 | Systemic chemotherapy | Systemic chemotherapy | — | 26.7/13.4 (mean) | — |

C, control group; H, HIPEC group; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials.
available at https://doi.org/10.1016/j.esmoop.2022.100586. Overall, two trials in primary ovarian cancer indicated a low risk of bias and one raised some concerns due to a lack of information for the evaluation of selection of the reported results. In recurrent ovarian cancer both trials presented a high risk of bias. The study by Zivanovic et al. showed deviations from the protocol with regards to the intended statistical analyses, while the study by Spiliotis et al. raised concerns regarding the statistical analyses and reporting of outcomes, as also described elsewhere.

HIPEC in primary ovarian cancer

Four trials studied the use of HIPEC in primary ovarian cancer including a total of 519 patients (259 in intervention and 260 in control group). In two of these studies, CRS and HIPEC were preceded by neoadjuvant chemotherapy, and in another one of these studies, CRS and HIPEC were preceded by neoadjuvant intervention and in control group). In two of these ovarian cancer including a total of 519 patients (259 in

FIGURE 2. Forest plots of 5-year overall survival (OS) and 5-year disease-free survival (DFS) for the use versus no use of HIPEC in the treatment of primary ovarian cancer with interval cytoreduction following neoadjuvant chemotherapy (POC, interval CRS + NACT).

Cl, confidence interval; HIPEC, hyperthermic intraperitoneal chemotherapy.
HIPEC in recurrent ovarian cancer

Two trials \(^{24,26}\) studied the use of HIPEC in recurrent ovarian cancer including a total of 218 patients (109 in intervention and 109 in control group). No OS benefit was evidenced for the use versus no use of HIPEC at any time point analyzed and despite the fact that some beneficial effect may be argued at the first year of follow-up, this benefit did not reach statistical significance (\(RR = 0.29; 95\% \, CI \, 0.08-1.10; \, P = 0.068\)). (Table 2, Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100586).

Regarding PFS in patients with recurrent ovarian cancer, the data for risk analyses were only available from the Zivanovic et al.\(^{5,24}\) trial. Despite the fact that the number of patients analyzed was small (98 patients randomized, 49 patients in each arm) it is evidenced that the use of HIPEC may be associated with an 18% increase in the risk of disease progression or death, that reached statistical significance and stabilized from the third year of follow-up (Table 2, Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2022.100586). Nonetheless, considering the small number of patients included in the trial, no firm conclusion can be driven in this setting, and the use of HIPEC is to be considered experimental unless new data will be available from future trials.

**Toxicities**

Five studies\(^{22-25,27}\) with a total of 617 patients (308 in intervention and 309 in control group) provided data on grade \(\geq 3\) adverse events, the most common of which can be summarized in the following: electrolyte disturbance, anemia, decrease of neutrophils, decrease of white blood cells, abdominal pain, infection and ileus. The risk for occurrence of grade \(\geq 3\) adverse events (of any type) was similar between the intervention and control groups (143/308 patients in the HIPEC group and 130/309 patients in the control group), with a non-significant trend against the use of HIPEC (any setting considered) (\(RR = 1.08; 95\% \, CI \, 0.98-1.18; \, P = 0.109\) (Figure 3, Table 2). More specifically, the risk of grade \(\geq 3\) adverse events in primary ovarian cancer (\(RR = 1.08; 95\% \, CI \, 0.98-1.18; \, P = 0.120, \, n = 4\) (Figure 3, Table 2) did not significantly differ from the risk in recurrent ovarian cancer (\(RR = 1.20; 95\% \, CI \, 0.57-2.51; \, P = 0.629, \, n = 1\) (Figure 3, Table 2). Regarding post-operative mortality, three studies reported zero post-operative deaths in both groups,\(^{22,24,27}\) one study reported one death in each group,\(^{23}\) and one study reported one death only in the control group,\(^{25}\) indicating that the use of HIPEC does not negatively affect post-operative mortality compared with treatment without HIPEC.

**DISCUSSION**

A recent umbrella review of meta-analyses, involving data mainly from cohort studies, highlighted that HIPEC research
in ovarian cancer seems promising and underscored the need of evidence from prospective randomized trials.35

This is the first systematic review and meta-analysis that depicts the available level I evidence data for the use versus no use of HIPEC in patients with ovarian cancer. Only randomized trials were included, many of which were recently published, and the two different settings of advanced primary ovarian cancer and recurrent ovarian cancer were separately analyzed, both for safety and efficacy.

In primary advanced ovarian cancer treated with interval CRS following neoadjuvant chemotherapy, our analyses on approximately 400 randomized patients showed that the use of HIPEC can significantly improve OS and DFS, and with a durable long-term (at 5 years) reduction of 23% in the risk of death when compared with treatment without HIPEC.

Our analyses also suggested that in advanced primary ovarian cancer, the use of upfront HIPEC immediately after CRS may not provide some additional OS or DFS benefits. Only ~100 randomized patients were included in the analyses, however, and thereafter we cannot exclude the presence of outcome differences between its use versus non-use will be revealed in future larger RCTs. Of note, in a 2019 meta-analysis of cohort studies, HIPEC significantly improved OS and PFS in patients with primary ovarian cancer compared with patients who did not receive HIPEC,27 thus our analyses from available randomized data shrink the magnitude of potential survival benefit (if any) for HIPEC use in this setting. Nonetheless, it should be highlighted that currently there is no published RCT that exclusively studies the use of HIPEC in primary ovarian cancer after CRS without neoadjuvant chemotherapy, and that the analyzed randomized patients in our study for this setting represent a subset of patients from the study by Lim et al.,22 where HIPEC was used both upfront and after as neoadjuvant treatment. Consequently results in this setting should be interpreted with caution until larger, properly planned, multicenter randomized studies are available.

The reason why use of HIPEC after neoadjuvant chemotherapy provides some benefit whereas its upfront use does not, may stem from the possibility of patients/drug selection in the neoadjuvant phase. Firstly, potentially chemoresistant patients are not eligible candidates to undergo upfront surgery due to extreme regional disease extension, as well as comorbidities, and patients who progressed or remained stable after induction chemotherapy would probably never undergo CRS and would have never been randomized. In this vision, only chemosensitive patients will receive HIPEC with drug sensitivity having already been tested in the neoadjuvant regimen. Secondly, for those patients resistant to neoadjuvant regimens but fit for surgery, the use of HIPEC after neoadjuvant treatment failure will provide the opportunity to switch the drugs to other non-cross-resistant chemotherapeutical compounds during the hyperthermic treatment.

It may also be speculated that the potential benefits of neoadjuvant chemotherapy include higher rates of complete cytoreduction, reduced blood loss during surgery and postoperative morbidity, better quality of life, as well as testing the response to upfront therapy.30 A meta-analysis, however, reported inferior survival for the neoadjuvant chemotherapy

| Group and grade >3 adverse events | Treatment | Control | Risk ratio (95% CI) | Weight |
|----------------------------------|-----------|---------|-------------------|--------|
| Primary OC                       |           |         |                   |        |
| Lim et al.22 2022 (NACT)         | 86/92     | 80/92   | 1.08 (0.98-1.18)  | 92.25  |
| Antonio et al.22 2022            | 10/35     | 10/36   | 1.03 (0.49-2.16)  | 1.53   |
| Van Driel et al.23 2018          | 32/122    | 30/123  | 1.08 (0.70-1.65)  | 4.57   |
| Diaz-Montes et al.24 2018        | 3/10      | 0/9     | 6.36 (0.37-108.56)| 0.11   |
| Subgroup, DL                    | 131/259   | 120/260 | 1.08 (0.98-1.18)  | 98.45  |
| (I² = 0.0%, P = 0.877)           |           |         |                   |        |
| Recurrent OC                     |           |         |                   |        |
| Zivanovic et al.25 2021          | 12/49     | 10/49   | 1.20 (0.57-2.51)  | 1.55   |
| Subgroup, DL                    | 12/49     | 10/49   | 1.20 (0.57-2.51)  | 1.55   |
| (I² = 0.0%, P = .)               |           |         |                   |        |
| Heterogeneity between groups: P = 0.775 |     |         |                   |        |
| Overall, DL                     | 143/308   | 130/309 | 1.08 (0.98-1.18)  | 100.00 |
| (I² = 0.0%, P = 0.808)           |           |         |                   |        |

Figure 3. Forest plot of the risk for occurrence of grade ≥3 adverse events from the use versus no use of HIPEC in the treatment of primary ovarian cancer and recurrent ovarian cancer.

CI, confidence interval; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; OC, ovarian cancer.

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approach.\textsuperscript{37} Two later randomized trials came to contradict this result.\textsuperscript{38-40} Nonetheless, it is implied that neoadjuvant chemotherapy does not offer any clear benefit and should be reserved for patients with advanced ovarian cancer who are not deemed eligible for upfront surgery due to poor performance status, comorbidities, old age or low probability of complete cytoreduction and would potentially benefit from its combination with interval debulking surgery.\textsuperscript{8}

Regarding the use of HIPEC in recurrent ovarian cancer, our study indicates that the available randomized evidence from \(~\sim\) 200 patients analyzed is not solid enough, thus no firm conclusion can be made and the data are stated here only as a point of reference. Zivanovic et al.\textsuperscript{24} and Spiliotis et al.\textsuperscript{26} both studied the effect of CRS plus HIPEC on the treatment of recurrent ovarian cancer. The two studies reported contradictory results, where Zivanovic et al. did not support the use of HIPEC, whereas Spiliotis et al. presented data in favor of HIPEC. While critically appraising these results, it is crucial to keep in mind the limitations mentioned by Zivanovic et al., as well as the drawbacks of the Spiliotis et al. trial,\textsuperscript{41} which could be partially expected since it was the earliest published RCT. A 2020 meta-analysis of cohort studies comparing the use versus no use of HIPEC in recurrent ovarian cancer reported that HIPEC in addition to CRS and chemotherapy significantly improved OS.\textsuperscript{18} It should be pointed out, however, that the influence on the outcomes of patients with recurrent ovarian cancer is multifactorial, depending on the time interval from the last chemotherapy, the disease-free interval, the success of cytoreduction and the residual disease, the existence of peritoneal carcinomatosis synchronously to the recurrence, the performance status, as well as the potential accompanying gene mutations.\textsuperscript{42-45} Larger data from randomized patients in properly planned, multicenter studies are thereafter needed before giving firm conclusions. Nonetheless, a cautious approach is to be kept in scheduling future trials in this clinical setting, since randomized data from the analysis of Zivanovic et al.\textsuperscript{24} evidenced a statistical 18\% increase in the risk of disease progression or death among patients receiving HIPEC.

About 20\% of primary ovarian tumors are naturally platinum-resistant and most recurrences will develop resistance over time.\textsuperscript{6} Even though Zivanovic et al.\textsuperscript{24} exclusively included platinum-sensitive patients, Spiliotis et al.\textsuperscript{26} recruited and independently analyzed platinum-resistant patients with recurrent ovarian cancer. Results for this population were encouraging, but they should be weighted by the real limitations of the study. Nonetheless, a series of cohort studies have also been supportive for the use of HIPEC in addition to optimal CRS in this population that is characterized by poorer prognosis.\textsuperscript{36-38} Moving forward, properly planned randomized trials are essential in order to clarify the possible benefits of HIPEC in chemoresistant ovarian cancer and potentially introduce a reliable therapeutic approach for this specific patient population.

HIPEC has constantly been criticized for the relatively high rates of complications and toxicities with potential risk for death and long-term severe sequel from the procedure, overshadowing HIPEC potential benefits.\textsuperscript{49-51} Two retrospective studies, each involving \(\sim\) 1100 patients, with \(\sim\) 20 years of experience, reported that HIPEC was associated with grade \(\geq\) 3 morbidity rates of 9.6\% and 20\% and 30-day mortality rates of 1.5\% and 2.2\%, respectively.\textsuperscript{52,53} The most common complications reported were anastomotic leaks, bowel perforations, hematological complications and infections. Conversely, our results (from 617 randomized patients) indicate at level I evidence that HIPEC is a safe therapeutic modality, in any setting of ovarian cancer, with a similar risk of grade \(\geq\) 3 adverse events and risk of early death events compared with cytoreduction without HIPEC. The observed absence in toxicity between HIPEC use versus no use may probably stem from the fact that the scrutinized randomized studies were carried out in institutions with long HIPEC experience. Data from literature suggest that the rate of post-operative morbidity and mortality may be correlated with the experience of the clinical centers that perform the technique.\textsuperscript{46,52,53} Thus, in experienced centers, HIPEC should be considered safe both for clinical practice and research applications.

Our study has limitations. The designs of the included RCTs were not homogenous, the patient accrual was not satisfactory and very little information for survival and PFS rates were directly reported in the articles. Thus, we relied on calculations assisted by a software program to make full use of all the available randomized evidence. Moreover, although we consider the distinguishing we made in the trial by Lim et al.\textsuperscript{22} scientifically necessary, as well as needed for a side by side comparison of treatments that have not been compared until now, neoadjuvant chemotherapy was given in selected patients which may have been a source of bias. Furthermore, although the inclusion of information from conference abstracts contains well-known caveats due to the lack of the available information, any level I evidence on such uncharted topics should not be neglected. Currently 22 RCTs are examining the effectiveness of HIPEC and CRS in the management of primary or recurrent ovarian cancer, however, and their results are eagerly awaited, especially since some of them (NCT037772028, NCT04280185, NCT03842982, NCT01376752) are expected to recruit a large number of participants ranging from 200 to 540 patients.\textsuperscript{54} The true bottleneck of HIPEC research and subsequently of the interpretation of the results of published trials is the sub-optimal study protocols and the not complete presentation of the data. The heterogeneity in HIPEC protocols was evident in our study, since three trials used cisplatin,\textsuperscript{22,23,25} two trials used carboplatin,\textsuperscript{24,27} and Spiliotis et al.\textsuperscript{26} used more than one drug as the HIPEC regimen.

**Conclusion**

Overall, promising current evidence exists for the use of HIPEC following interval CRS with neoadjuvant chemotherapy for primary ovarian cancer and more RCT evidence is needed to evaluate the use of HIPEC in other settings. Complete cytoreduction followed by systemic chemotherapy remains the treatment mainstay. Among patients
who cannot undergo upfront CRS and need neoadjuvant chemotherapy, the use of CRS followed by HIPEC is a proper option and is now documented to be effective and safe.

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DISCLOSURE
The authors have declared no conflicts of interest.

DATA SHARING
All data generated or analysed during this study are included in this published article (and its supplementary information files).

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