Complications of HIPEC for ovarian cancer surgery: evaluation over two time periods

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ABSTRACT

Objective Cytoreductive surgery in conjunction with hyperthermic intraperitoneal chemotherapy (HIPEC) is being explored in the upfront, interval, and recurrent setting in patients with ovarian cancer. The objective of this systematic review was to assess the rate of complications associated with HIPEC in epithelial ovarian cancer surgery over two time periods.

Methods This study was registered in PROSPERO (CRD42022328928). A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Ovid/Medline, Ovid/Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials were searched from January 2004 to April 2022. We included studies reporting on patients with advanced primary or recurrent epithelial ovarian cancer who underwent cytoreductive surgery and HIPEC. We evaluated two different time periods: 2004–2013 and 2014–2022. A random-effects meta-analysis was used to produce an overall summary. Subgroup analyses were planned according to recruited period for each specific complication type. Heterogeneity was assessed using the I² statistic.

Results A total of 4928 patients were included from 69 studies for this systematic review; 19 published from 2004–2013, and 50 published from 2014–2022. No significant differences were found between the two time periods in terms of blood transfusions (33% vs 51%; p=0.46; I²=95%) overall gastrointestinal complications (15% vs 21%; p=0.36; I²=98%), infectious diseases (16% vs 13%; p=0.62; I²=93%), overall respiratory complications (12% vs 12%; p=0.88; I²=91%), overall urinary complications (6% vs 12%; p=0.06; I²=94%), or thromboembolic events (5% vs 3%; p=0.25; I²=63%). Also, no differences were found in intensive care unit (ICU) admissions (89% vs 28%; p=0.06; I²=99%), reoperations (8% vs 7%; p=0.50; I²=37%), or deaths (3% vs 3%; p=0.77; I²=57%).

Conclusions Our review showed that overall complications have not changed over time for patients undergoing HIPEC in the setting of primary or recurrent ovarian cancer. There was no decrease in the rates of ICU admissions, reoperations, or deaths.

INTRODUCTION

Ovarian carcinoma is the most common cause of death from gynecologic malignancies in the United States, accounting for 12,810 deaths in 2022.1 Complete cytoreduction remains the most important independent prognostic factor in advanced epithelial ovarian cancer.2 3 Hyperthermic intraperitoneal chemotherapy (HIPEC) has been evaluated in the setting of primary, interval, and recurrent surgery in patients with ovarian cancer.4–8

Van Driel et al4 published a multicentric randomized clinical trial comparing surgery with surgery plus HIPEC at the time of interval cytoreduction. This study showed a benefit for HIPEC in progression-free survival and overall survival. Zivanovic et al6 published a phase II study to evaluate HIPEC with carboplatin in the recurrent setting after secondary cytoreductive surgery. No differences were found in overall survival when comparing HIPEC with surgery. Lim et al8 published a randomized trial comparing surgery with surgery plus HIPEC after primary or interval cytoreductive surgery. This trial did not show a benefit in progression-free or overall free survival in the HIPEC group. There is still a lack of prospective data on the benefit of HIPEC in the upfront setting, and results from the ongoing OVHiPEC-2 (NCT03772028) are awaited.

HIPEC has been associated with significant morbidity, ranging from 11.7–47%.6 8 10 11 Rates of post-operative mortality vary from 0–21.6%.6 8 12 13
Original research

There are no data that compile rates of complications related to HIPEC during cytoreductive surgery over the course of implementation of HIPEC in gynecologic oncology. The goal of this review was to assess the rate of complications related to HIPEC in women with advanced ovarian cancer undergoing cytoreductive surgery over two different time periods.

METHODS

Information Sources and Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to conduct this systematic review, and the protocol was registered in PROSPERO (CRD42022328928). We performed a systematic search, including the Ovid/Medline, Ovid/Embase, Cochrane Library, Scopus, and Web of Science databases from January 2004 to April 2022. Search structures were tailored to each database by a medical research librarian (KJK), and searches were restricted to humans and the English language. All studies were included, except for case reports, conference material, and editorials. The full search strings for all databases can be found in online supplemental file 1. Four authors were contacted for information, but we only obtained responses from two.

Selection Process

Covidence was used to screen the citations. Two of the investigators (BNS, DV-C) independently screened the titles and abstracts, and studies were retrieved for full-text review. The investigators (BNS, DV-C) then independently screened full-text articles. Disagreements were resolved by consensus and by seeking the opinion of a third reviewer (RP).

Eligibility Criteria

Inclusion criteria were patients with newly diagnosed epithelial advanced ovarian cancer (International Federation of Gynecology and Obstetrics (FIGO) 2018 stages III–IV) or recurrent epithelial ovarian cancer (any initial stage) that underwent cytoreductive surgery (interval or upfront) followed by HIPEC (any agent at any concentration and duration). Open and closed techniques were included. Patients could receive any other treatment such as anti-angiogenic therapy, intraperitoneal chemotherapy, adjuvant or neoadjuvant chemotherapy, or target therapies if complications of any grade related to HIPEC were specified. Studies that included other tumors were included only if the data for ovarian epithelial cancer could be extracted separately.

Exclusion criteria were studies performed before 2004, and studies including patients aged <18 years, cytoreductive surgery by minimally invasive surgery, pregnancy, or non-epithelial ovarian tumors. Conference abstracts were excluded. When two or more manuscripts were published by the same authors or same data source, only the most recent or more relevant manuscript was included.

Figure 1 PRISMA 2020 flow diagram. FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy.
were considered at high risk of bias.19 No separate analysis was 
≥7 were defined as low risk of bias, while studies with a score <7 

Quality Assessment
Studies were assessed for quality of methodology following the 
Newcastle-Ottawa Scale.18 The analysis was done independently 
by two authors (BNS, EG-T). Studies with a Newcastle-Ottawa Score 
≥7 were considered as low risk of bias, while studies with a score <7 
were considered at high risk of bias.19 No separate analysis was 
performed exclusively for those with low risk of bias.

Statistical Analysis
The analysis was performed using the R Core Team 2022 version 
4.2.2, using the estimated proportions and obtained by direct 
method, to generate a pooled estimator together with its respective 
95% confidence interval (CI). Heterogeneity was assessed using the 
I² statistic, and the presence of a value >40% for this test was 
considered substantial. A random-effects meta-analysis was used to 
produce an overall summary. Subgroup analyses were planned 
according to recruited period (2004–2013 and 2014–2022). We started data extraction in 2004, 
leaving enough time to consider the learning curve in ovarian cancer 
surgery and HIPEC administration, and chose two equal periods 
for evaluating trends in rates of complications. The rate of each 
complication of any grade was defined as the ratio of patients who 
underwent HIPEC. 

RESULTS
Study Selection
We retrieved 1175 articles for review. Of these, 69 met all the 
criteria for inclusion. This led to the inclusion of 4928 patients. The 
PRISMA flow diagram shows the review process (Figure 1). We 
excluded 102 studies of which one was a prospective randomized 
trial20 (online supplemental table 1). The most common reasons 
for exclusion were: no report of specific complication types (n=34, 
33.3%), inclusion of several types of cancers without a breakdown 
of data for ovarian cancer (n=18, 17.6%) and the same cohort of 
patients (n=14, 13.7%).

Risk of Bias
According to the Newcastle-Ottawa scale, 17 studies were assessed 
as having a low risk of bias, while 52 were judged to have a high 
risk of bias (online supplemental table 2).

Study Characteristics
Sixty-nine studies were published between 2004 and 2022. Nineteen 
studies were published from 2004–2013,6 11 21–37 and 50 from 
2014–2022.4 5 7–9 12 13 15 38–80 Twenty-six articles reported data 
on primary advanced ovarian cancer, 17 reported data on cancer 
recurrence, and 26 reported data on both. Eighteen studies (26%) 
did not specify epithelial cancer subtypes. Data on specific compli-
cations are provided below, and information regarding the studies 
that published on that given complication may be found in online 
supplemental table 3.

Thromboembolic Events
Frequency of all thromboembolic events was 3% (95% CI 2 to 5; 
I²=63%). For 2004–2013 the frequency was 5% (95% CI 2 to 11;

Data Extraction and Analysis
Relevant information was retrieved from selected studies indepen-
dently by two authors (BNS, EG-T). We resolved any disagree-
ments by discussion or consulting other authors (PTR). The two 
investigators extracted data in an established form. The rate of 
complications of any grade was assessed for two different periods: 
2004–2013 and 2014–2022. We started data extraction in 2004, 
5 years after the first publication related to HIPEC complications. We 
left enough time to consider the learning curve in ovarian cancer 
surgery and HIPEC administration, and chose two equal periods 
for evaluating trends in rates of complications. The rate of each 
complication of any grade was defined as the ratio of patients who 
had at least one complication of any grade to the total number of 
patients who underwent HIPEC.

Table 1
<table>
<thead>
<tr>
<th>Events</th>
<th>No of studies</th>
<th>No of participants</th>
<th>No of events (%)</th>
<th>Period 2004–2013, frequency (95% CI; I²)</th>
<th>Period 2014–2022, frequency (95% CI; I²)</th>
<th>P value for subgroup differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall thromboembolic</td>
<td>22</td>
<td>1841</td>
<td>65 (3.5)</td>
<td>5% (2 to 11; 13%)</td>
<td>3% (2–5%); 65%</td>
<td>0.25</td>
</tr>
<tr>
<td>Overall gastrointestinal</td>
<td>66</td>
<td>4865</td>
<td>1272 (26.1)</td>
<td>15% (10 to 21; 82%)</td>
<td>21% (10–34%); 99%</td>
<td>0.36</td>
</tr>
<tr>
<td>Overall infectious</td>
<td>56</td>
<td>3901</td>
<td>682 (17.5)</td>
<td>16% (8 to 24; 80%)</td>
<td>13% (8–19%); 94%</td>
<td>0.62</td>
</tr>
<tr>
<td>Overall respiratory</td>
<td>38</td>
<td>3017</td>
<td>317 (10.5)</td>
<td>12% (7 to 19; 74%)</td>
<td>12% (7–17%); 93%</td>
<td>0.88</td>
</tr>
<tr>
<td>Overall urinary</td>
<td>44</td>
<td>3806</td>
<td>389 (10.2)</td>
<td>6% (4 to 8; 21%)</td>
<td>12% (6–19%); 96%</td>
<td>0.06</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>12</td>
<td>613</td>
<td>295 (48.1)</td>
<td>33% (2 to 75; 96%)</td>
<td>51% (31–71%); 94%</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Raw proportions (in the main text we show the pooled proportions which were calculated using a random-effect model, and therefore, it may not reflect the raw proportions in this table).

CI, confidence interval.

I² statistic, and the presence of a value >40% for this test was 
considered substantial. A random-effects meta-analysis was used to 
produce an overall summary. Subgroup analyses were planned 
according to recruited period (2004–2013 and 2014–2022). We started data extraction in 2004, 
leaving enough time to consider the learning curve in ovarian cancer 
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for evaluating trends in rates of complications. The rate of each 
complication of any grade was defined as the ratio of patients who 
had at least one complication of any grade to the total number of 
patients who underwent HIPEC.

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Studies were assessed for quality of methodology following the 
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by two authors (BNS, EG-T). Studies with a Newcastle-Ottawa Score 
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I² statistic, and the presence of a value >40% for this test was 
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produce an overall summary. Subgroup analyses were planned 
according to recruited period (2004–2013 and 2014–2022) for 
each complication type. A sensibility analyses was also calculated 
for all complications type. Publication bias was evaluated by 
visual inspection of funnel plots and quantified applying the Egger's 
regression model. Two-tailed p value of<0.05 was statistically 
significant.

RESULTS
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did not specify epithelial cancer subtypes. Data on specific compli-
cations are provided below, and information regarding the studies 
that published on that given complication may be found in online 
supplemental table 3.

Thromboembolic Events
Frequency of all thromboembolic events was 3% (95% CI 2 to 5; 
I²=63%). For 2004–2013 the frequency was 5% (95% CI 2 to 11;
Gastrointestinal Events
Overall frequency of all gastrointestinal events was 20% (95% CI 11 to 29; I²=98%). For 2004–2013, the frequency was 15% (95% CI 10 to 21; I²=82%), and for 2014–2022 it was 21% (95% CI 10 to 34; I²=99%). In the subgroup analysis, no differences were found (p=0.36) (Table 1).

Anastomotic Leak/Intestinal Fistula
Overall frequency of this complication was 4% (95% CI 3 to 6; I²=65%). In the subgroup analysis, no differences were found (p=0.25) (Table 1).

Ileus/Bowel Obstruction
The overall frequency of ileus/bowel obstruction was 6% (95% CI 4 to 8; I²=78%). For 2004–2013, the frequency was 5% (95% CI 2 to 9; I²=28%), and for 2014–2022 it was 6% (95% CI 3 to 9; I²=83%). In the subgroup analysis, no differences were found (p=0.72) (online supplemental file 2).

Sepsis/Septic Shock
Frequency of sepsis/shock septic was 3% (95% CI 2 to 5; I²=46%). For 2004–2013 the frequency was 6% (95% CI 2 to 11; I²=52%), and for 2014–2022 it was 2% (95% CI 1 to 4; I²=28%). In the subgroup analysis, no differences were found (p=0.055) (online supplemental file 2).

Overall Respiratory
Frequency of respiratory events was 12% (95% CI 8 to 16; I²=91%). For 2004–2013 the frequency was 12% (95% CI 7 to 19; I²=74%), and for 2014–2022 it was 12% (95% CI 7 to 17; I²=93%). In the subgroup analysis, no differences were found (p=0.88) (Table 1).

Pleural Effusion
Frequency of pleural effusion was 10% (95% CI 6 to 14; I²=77%). For 2004–2013 the frequency was 10% (95% CI 5 to 17; I²=71%), and for 2014–2022 it was 9% (95% CI 5 to 14; I²=80%). In the subgroup analysis, no differences were found (p=0.80) (online supplemental file 2).

Overall Urinary
Overall frequency urinary events was 10% (95% CI 6 to 14; I²=94%). For 2004–2013 the frequency was 5% (95% CI 2 to 10; I²=0%), and for 2014–2022 was 4% (95% CI 2 to 7; I²=73%). In the subgroup analysis, no differences were found (p=0.03) (online supplemental file 2).

Kidney Injury
Overall frequency of kidney injury was 8% (95% CI 5 to 10; I²=79%). For 2004–2013, the frequency was 6% (95% CI 4 to 10; I²=37%), and for 2014–2022 it was 8% (95% CI 5 to 12; I²=83%). In the subgroup analysis, no differences were found (p=0.06) (Table 1).

Deaths
Overall frequency of deaths was 3% (95% CI 2 to 4; I²=57%). For 2004–2013, the frequency was 3% (95% CI 1 to 5; I²=47%), and for 2014–2022 it was 3% (95% CI 1 to 5; I²=63%). No significant differences were found (p=0.77) (Figure 2).

Reoperations
Overall frequency of reoperations was 7% (95% CI 6 to 9; I²=37%). For 2004–2013, the frequency was 8% (95% CI 5 to 11; I²=20%), and for 2014–2022, it was 7% (95% CI 5 to 9; I²=43%). No significant differences were found (p=0.50) (Figure 3).

Intensive Care Unit Admission
Overall frequency of intensive care unit (ICU) admission was 49% (95% CI 20 to 79; I²=99%). For 2004–2013, the frequency was 89% (95% CI 34 to 100; I²=98%), and for 2014–2022 it was 28% (95% CI 30 to 63; I²=99%). No significant differences were found (p=0.06) (Figure 4).

Intra-abdominal Infection/Peritonitis
Frequency of this complication was 4% (95% CI 3 to 6; I²=65%). For 2004–2013 the frequency was 4% (95% CI 2 to 7; I²=0%), and for 2014–2022 it was 4% (95% CI 2 to 7; I²=73%). In the subgroup analysis, no differences were found (p=0.96) (online supplemental file 2).

Blood Transfusion
Frequency of blood transfusions overall was 45% (95% CI 26 to 64; I²=95%). For 2004–2013 it was 33% (95% CI 2 to 75; I²=96%), and for 2014–2022 it was 51% (95% CI 31 to 71; I²=94%). In the subgroup analysis, no differences were found (p=0.087) (online supplemental file 2).

Overall Infectious
Overall frequency of infectious complications was 14% (95% CI 10 to 19; I²=93%). For 2004–2013, the frequency was 16% (95% CI 8 to 24; I²=80%), and for 2014–2022 it was 13% (95% CI 8 to 19; I²=94%). In the subgroup analysis, no differences were found (p=0.62) (Table 1).

Hemorrhage
Overall frequency of hemoperitoneum/gastrointestinal bleeding was 3% (95% CI 2 to 4; I²=44%). For 2004–2013, the frequency was 4% (95% CI 3 to 6; I²=0%), and for 2014–2022 it was 3% (95% CI 2 to 4; I²=50%). This difference was significant (p=0.015) (online supplemental file 2).

Overall Urinary
Overall frequency urinary events was 10% (95% CI 6 to 14; I²=94%). For 2004–2013 the frequency was 5% (95% CI 2 to 10; I²=0%), and for 2014–2022 was 4% (95% CI 2 to 7; I²=73%). In the subgroup analysis, no differences were found (p=0.03) (online supplemental file 2).

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Frequency of this complication was 4% (95% CI 3 to 6; I²=65%). For 2004–2013 the frequency was 4% (95% CI 2 to 7; I²=0%), and for 2014–2022 it was 4% (95% CI 2 to 7; I²=73%). In the subgroup analysis, no differences were found (p=0.96) (online supplemental file 2).
Readmissions

The overall frequency of readmissions was 11% (95% CI 6 to 18; I²=57%). Articles included in the first period did not include data for readmissions (online supplemental file 2).

DISCUSSION

Summary of Main Results

Complications related to HIPEC did not change over the two time periods evaluated, except for hemoperitoneum, which was lower in the second period. There was a decrease in both sepsis and ICU admission rates over the course of the time evaluated; however, these differences were not statistically significant. Readmissions or death rate did not decrease when comparing the two time periods. The most common associated event was blood transfusion in 45% (95% CI 26 to 64) of patients.

Results in the Context of Published Literature

In a previous literature review by Chiva et al., grade 3–4 adverse events with HIPEC were 19% in primary surgery and 25% in recurrent surgery. Mortality was 0–7% which was similar to our review. However, their review was different from ours, as we accounted for complications of any grade, and we did not separate complications for primary and recurrent surgery. A meta-analysis by Bouchard-Fortier showed that with primary surgery plus HIPEC, grade 3–4 complications were 34%, and the proportion for reoperation was 8%. In our review, the reoperation frequency was similar. The proportion for death was 1%. Another meta-analysis found that mortality was 1.8% after HIPEC, which was very similar to our results. The authors found that rate of grade 3–4 complications for primary and recurrent ovarian cancer was 31.3% and 26.2%, respectively. These meta-analyses lacked information on type of overall and specific complications, and did not assess changes over time. Regarding cytoreductive surgery without HIPEC, one comparative study reported that 26.7% of patients developed surgical complications; of which, 11.1% died and 14.4% needed a second operation. Another comparative study by Bhatt et al. reported 29.8% grade 3–4 post-operative morbidity, and 2.2% mortality in the surgery alone group.
Original research

Regarding specific complications assessed in this review, as we included studies which used different regimens of chemotherapy, we found that the overall frequency of hemoperitoneum was lower than in some studies which only used oxaliplatin. The CHIPOVAC study, used oxaliplatin during ovarian cancer surgery and was closed prematurely due to the high rate of hemoperitoneum. In a study evaluating HIPEC use with oxaliplatin, Fagotti et al concluded that hemorrhage was the most frequent treatment toxicity at 28%, compared with 0–3% in patients without HIPEC administration.

In our study, frequency of anastomotic leak was 4%, which was lower than in a meta-analysis that evaluated rate of anastomotic leak after bowel resection during cytoreductive surgery for ovarian cancer in patients with and without ostomy. That study included 2719 patients and showed an anastomotic leak rate of 8%. In that meta-analysis, however, the authors did not stratify for use of HIPEC, and only included patients with bowel resections. In our review, we included patients with and without bowel resections, which could be why we had a lower rate of anastomotic leaks. Moreover, frequency of anastomotic leak in patients without HIPEC is reported to be 0–2%. 4 5 7 15

Renal failure has been a frequent adverse outcome of HIPEC with cisplatin; however, thiosulfate may prevent it in certain cases. 4 6 7 8 In our review, kidney injury was 8%. Nevertheless, we recognize the heterogeneity in type of chemotherapy agent and use of thiosulfate among studies. Bakrin et al reported an incidence of kidney injury of 8% after HIPEC. These results differ from those of Angeles et al, who reported an incidence of 48.4%, and those of Sin et al, who described an incidence of nephrotoxicity of 40.4%. 8 9 These differences in the incidence of renal failure may be due to the fact that the authors do not always report a concise definition of acute and chronic kidney injury. Renal failure in patients without HIPEC is estimated to be around 0–6%. 5 15 46

Strengths and Weaknesses

The main strength of this review is its rigorous criteria for methodology for data collection. We have a pre-registered protocol with a complete search strategy, specified selection criteria, and a pre-defined process for data analysis. Also, this is the first review published in the literature which analyses complications derived from HIPEC comparing two time periods. In addition, we performed strict analysis of study methodology using established quality assessment tools.

Our review is limited for several reasons. The retrospective nature of most studies, with potential selection and publication bias, must be considered. The inclusion of reports over a prolonged period with the significant heterogeneity in the type of chemotherapy used, the dose of treatment, the delivery techniques, and indications for the procedure as the performance bias. Of note, over the time period of our study, incidence of perioperative complications and chemotherapy-related complications were not analysed in our systematic review. In addition, most of the studies were at high risk of bias according to the Newcastle-Ottawa scale, and several studies included in this analysis were retrospective single-arm and did not account for potential confounding variables.

In addition, we did not perform an analysis of only the studies with low risk of bias. Many articles did not report specific complications or ovarian cancer data separately, and values were not balanced for type of surgery. Also, we included only articles published in the English language, we could have missed some relevant references published in other languages. Moreover, one needs to consider the migration bias, which may be produced by the fact that our study comprises a total period of 18 years. Lastly, we also recognize that the high risk of biases and heterogeneity as well as the inclusion of any grade of complications impacts the validity of the findings. However, this is a standard weakness of this type of study.

Implications for Practice and Future Research

HIPEC should be offered to patients only in the context of clinical trials for the upfront setting and recurrent setting, and patients should be informed about the type and frequency of complications derived from this technique. We await the results of large multicentric prospective randomized trials in determining the frequency and types of complications.

CONCLUSIONS

The rate of complications for cytoreductive surgery and HIPEC in the setting of advanced ovarian cancer is not negligible, and has not varied over the years. Most of the literature on HIPEC for the treatment of ovarian cancer is derived from retrospective studies with high risk of bias. Complications and their definitions are also variable among these studies.

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Original research


