Selection of patients with ovarian cancer who may show survival benefit from hyperthermic intraperitoneal chemotherapy

A systematic review and meta-analysis

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Abstract

Background: The use of hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery has been extensively studied in patients with peritoneal carcinomatosis from various malignancies. However, the effectiveness of HIPEC for ovarian cancer is still controversial. Therefore, we performed this meta-analysis to identify patients with ovarian cancer who can obtain survival benefit from HIPEC.

Methods: Articles regarding HIPEC in the MEDLINE, EMBASE, and Cochrane Library were searched till December 2018. In total, 13 case-control studies and two randomized controlled trials were included in this meta-analysis. We investigated the effect of HIPEC on disease-free survival (DFS) and overall survival (OS), and performed subgroup analyses based on the study design, adjustment of confounding variables, and quality of the study.

Results: HIPEC improved both DFS (hazard ratio [HR], 0.603; 95% confidence interval [CI], 0.513–0.709) and OS (HR, 0.640; 95% CI, 0.519–0.789). In cases of primary disease, HIPEC improved DFS (HR, 0.580; 95% CI, 0.476–0.706) and OS (HR, 0.611; 95% CI, 0.376–0.992). Subgroup analyses revealed that HIPEC did not improve OS but improved DFS of patients with residual tumors ≤1 cm or no visible tumors. In cases of recurrent disease, HIPEC was associated with better OS (HR, 0.566; 95% CI, 0.379–0.844) but not with DFS. Subgroup analyses also revealed similar tendencies. However, HIPEC improved DFS of patients with residual tumors ≤1 cm or no visible tumors, while it improved OS of only those with residual tumors ≤1 cm.

Conclusions: HIPEC may improve DFS of patients with ovarian cancer when residual tumors were ≤1 cm or not visible. It may also improve OS of only patients with recurrent disease whose residual tumors were ≤1 cm.

Abbreviations: CI = confidence interval, DFS = disease-free survival, FIGO = Federation of Gynecology and Obstetrics, HIPEC = hyperthermic intraperitoneal chemotherapy, HR = hazard ratio, IDS = interval debulking surgery, NAC = neoadjuvant chemotherapy, NOS = Newcastle-Ottawa Scale, OS = overall survival, RCT = randomized controlled trial.

Keywords: hyperthermic intraperitoneal chemotherapy, meta-analysis, ovarian cancer
1. Introduction

Peritoneal carcinomatosis develops in more than 80% of patients with advanced ovarian cancer, resulting in a 5-year survival rate of <50%. In terms of the biologic aspect of intraperitoneal dissemination of tumors, peritoneal carcinomatosis is considered the terminal status of cancers, resulting in poor prognosis. However, there is no effective method for treating peritoneal carcinomatosis from various malignancies, with an improvement in the survival rate and reduction in the recurrence rate. Compared to conventional intraperitoneal chemotherapy, HIPEC has several advantages, even showing synergistic effects. Hyperthermia itself has direct cytotoxicity on tumors and increases the penetration of chemotherapeutic drugs and drug concentration at the peritoneal surface. Moreover, HIPEC can decrease catheter-related complications observed after conventional intraperitoneal chemotherapy because it is conducted in a single session.

Till date, only 2 randomized controlled trials (RCTs) have evaluated the effect and safety of HIPEC for ovarian cancer. Spiliotis et al reported that HIPEC resulted in survival benefit for patients with recurrent ovarian cancer. However, that study had limitations considering the randomization process and the definition of the end-points, both of which affect the interpretation of the results. In the other RCT performed by van Driel et al, better disease-free survival (DFS) and overall survival (OS) were observed in patients treated with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) and HIPEC, compared to those treated with NAC followed by IDS alone. However, the small sample size resulted in an intergroup difference of only 15 deaths, and the different effects of HIPEC among centers make it hard to justify the practical application of HIPEC in the clinical setting. Moreover, a previous meta-analysis did not provide the exact pooled hazard ratios (HRs) associated with HIPEC for evaluating the effect.

Thus, precise knowledge regarding the exact impact of HIPEC on the prognosis of ovarian cancer is still needed, owing to the heterogeneity in the study population, such as primary or recurrent disease, and the extent of cytoreductive surgery among the previous studies. In particular, the identification of patients with ovarian cancer who can benefit from HIPEC will allow for the implementation of individualized treatment. For this purpose, we performed a meta-analysis to investigate the effect of HIPEC on the survival of patients with ovarian cancer.

2. Methods

2.1. Search strategy and selection criteria

This meta-analysis was conducted in accordance with the recommendations per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies investigating the effect of HIPEC on the prognosis of ovarian cancer were identified via a literature search of the MEDLINE, EMBASE, and Cochrane Library, from when recording began up to December 2018. Our overall search strategy included the following terms for HIPEC (“hyperthermic intraperitoneal chemotherapy” or “HIPEC” or “intraperitoneal”), ovary (“ovarian” or “ovary”), and cancer (“cancer” or “carcinoma” or “neoplasm” or “malignancy”, or “tumor”). Details about the search strategy are shown in Supplementary Table 1, http://links.lww.com/MD/D497.

We included relevant studies that met the following criteria: studies that included patients with epithelial ovarian cancer; study designs included RCT, case-control, and 2-arm cohort studies; and comparison of DFS or OS between patients who underwent HIPEC and those who did not receive it. However, we excluded the following studies: review articles, case reports, editorials, and letters to the editor; studies that had no data of survival or did not meet the selection criteria; and non-English literature.

As the present meta-analysis was performed based on previously published studies, thus no ethical approval and patient consent are required.

2.2. Selection of studies

Two authors (SKK and SJP) independently screened the eligibility of all studies retrieved from the database according to the predetermined selection criteria. The third author (HSK) resolved any disagreement between the 2 authors after discussion. A total of 11,728 studies were identified, and we excluded 3615 duplicates. We excluded 7972 studies because of the following reasons: non-English literature (n = 381), non-original articles (n = 1275), studies on other cancers (n = 1613), translational studies (n = 1477), animal studies (n = 1082), studies on other treatment modalities (n = 1866), and studies dealing with other issues (n = 278). In addition, we excluded 126 non-relevant articles after assessing the full-text articles. Finally, 13 case-control studies and 2 RCTs with 1314 patients were included in the meta-analysis (Fig. 1).

2.3. Data extraction

Two authors (SKK and EJL) independently extracted the data, and any discrepancies were addressed by a joint re-evaluation of the article with the third author (HSK). The following data were extracted from each study for the meta-analysis: author; year of publication; country in which the study was performed; study design; disease status (primary disease, platinum-sensitive and platinum-resistant recurrence); the International Federation of Gynecology and Obstetrics (FIGO) stage; histology; grade; age; numbers of patients who received HIPEC and who did not receive it; drugs and methods of HIPEC; the extent of cytoreductive surgery (or residual tumor size after cytoreductive surgery); follow-up period; DFS and OS; and HRs with 95% confidence intervals (CIs).

For the study with only the HR and P value of the Cox proportional hazards model, we estimated the 95% CI mathematically. If patients treated with HIPEC were regarded as the reference group, the HRs were inverted and 95% CIs were subsequently calculated. In case of studies in which the risk parameters were not presented with specific numbers, we could obtain the estimated risks with 95% CIs by analyzing survival curves according to the statistical procedure described by Tierney et al.

2.4. Quality assessment

The methodological quality of the 13 case-control studies were evaluated based on the Newcastle-Ottawa Scale (NOS). The NOS includes eight items over three dimensions: selection,
Figure 1. The search strategy and number of studies identified for inclusion in this meta-analysis.
comparability, and exposure with a maximum of 4, 2, and 3 points, respectively. In this meta-analysis, 11 of 13 case-control studies scored 8 showing “high quality”, whereas the other 2 studies scored 6 showing “low quality” (Supplementary Table 2, http://links.lww.com/MD/D498).

2.5. Statistical analysis

Pooled HRs with 95% CIs were calculated in all studies, and heterogeneity was assessed by using the Higgins $I^2$ value that represented the percentage of the total variance in the summary estimate owing to inter-study heterogeneity rather than chance.\textsuperscript{129} A value of $> 50\%$ was considered to have substantial heterogeneity, and we used the random effects model with the DerSimonian and Laird method. When the $I^2$ value was $\leq 50\%$, we used the fixed effect model with the Mantel–Haenszel method. In the fixed effect model, each study was weighted by the inverse of its variance.

Subgroup meta-analyses were performed based on the study design, adjustment of confounding variables, and quality of the study. To identify the publication bias, funnel plots were used, where each study’s HR and standard error of the log HR were plotted on the X-axis and Y-axis, respectively. We observed symmetric funnel plots, implying no publication bias in this meta-analysis. The Egger test results also showed the absence of publication bias (Supplementary Figure 1, http://links.lww.com/MD/D499).

All statistical analyses were performed with Comprehensive Meta-analysis Version 2.0 (Biostat Inc., Englewood, NJ), and a $P < 0.05$ was considered statistically significant. All statistical tests were two-sided.

3. Results

3.1. Effect of HIPEC on survival by study design

The characteristics of the 13 case-control studies and two RCTs including 1,314 patients are shown in Table 1. Potential confounding variables such as age, FIGO stage, histology, grade, and residual tumor size at the first surgery were adjusted in most of the studies. In all the studies, HIPEC improved both DFS (HR, 0.603; 95% CI, 0.513–0.709) and OS (HR, 0.640; 95% CI, 0.519–0.789; Fig. 2A). On subgroup analyses confined to the case-control studies, HIPEC improved DFS (HR, 0.575; 95% CI, 0.471–0.702)\textsuperscript{14,17,18,20,22–26} and OS (HR, 0.613; 95% CI, 0.398–0.944; Fig. 2B).\textsuperscript{114–19,21,22,24–26}

3.2. Effect of HIPEC on survival by disease status

For cases of primary disease, five studies including 630 patients showed that HIPEC was associated with better DFS (HR, 0.580; 95% CI, 0.476–0.706)\textsuperscript{19,14,17,20,26} and 5 studies including 591 patients also showed that HIPEC was associated with improved OS (HR, 0.611; 95% CI, 0.376–0.992; Fig. 2C).\textsuperscript{19,14,17,18,21,22,24–26}

When we performed subgroup analyses according to the study design, FIGO stage, and adjustment of confounding variables, HIPEC showed a favorable effect on DFS, whereas it failed to improve OS. However, HIPEC showed a favorable effect on OS for advanced, stage III-IV disease (HR, 0.748; 95% CI, 0.563–0.994; Table 2).\textsuperscript{19,15,26}

For cases of recurrent disease, 5 studies including 357 patients did not show improved DFS after HIPEC (HR, 0.644; 95% CI, 0.395–1.049).\textsuperscript{18,22–25} In particular, all these 5 studies targeted
platinum-sensitive recurrent disease. On subgroup analyses according to the study design and quality of study, HIPEC failed to improve DFS. However, HIPEC showed better DFS after adjusting confounding variables (Table 3).

In terms of OS of patients with recurrent disease, 7 studies including 491 patients showed survival benefit after HIPEC (HR, 0.566; 95% CI, 0.379–0.844; Fig. 2D).

Figure 2. Effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on survival by study design: (A) all studies; (B) case-control studies, and by disease status: (C) primary disease; (D) recurrent disease.
variables, HIPEC was consistently associated with better OS (Table 3).

### 3.3. Effect of HIPEC on survival by the extent of cytoreductive surgery

HIPEC significantly prolonged the DFS of patients with residual tumors ≤1 cm after cytoreductive surgery (HR, 0.488; 95% CI, 0.389–0.612)\(^{14,17,18,20,22,23,25,26}\) and in those with no visible tumor (HR, 0.486; 95% CI, 0.377–0.628)\(^{14,17,20,22,23,25,26}\). These results were also observed on subgroup analyses according to disease status, quality of the study, and adjustment of confounding variables (Table 4).

However, HIPEC did not increase OS of patients with no visible tumor (HR, 0.564; 95% CI, 0.310–1.027)\(^{15,17,19,21,22,25,26}\) despite the improvement of OS of those

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### Table 2

Subgroup analyses for evaluating the effect of hyperthermic intraperitoneal chemotherapy on the survival of patients with primary disease.

| Subgroup                | No. of studies | HR   | 95% CI         | Heterogeneity | Model used |
|-------------------------|----------------|------|---------------|---------------|------------|
| **Disease-free survival** |                |      |               |               |            |
| Study design            |                |      |               |               |            |
| Case-control            | 4              | 0.508 | 0.383–0.672   | .90           | 0.0%       | Fixed effect |
| Stage                   |                |      |               |               |            |
| III-IV disease          | 3              | 0.600 | 0.480–0.749   | .49           | 0.0%       | Fixed effect |
| Adjustment              |                |      |               |               |            |
| Age, stage, neoadjuvant chemotherapy | 3   | 0.600 | 0.480–0.749   | .49           | 0.0%       | Fixed effect |
| Age, stage, histology, neoadjuvant chemotherapy | 2 | 0.609 | 0.479–0.775 | .25          | 24.0%       | Fixed effect |
| Age, stage, grade, neoadjuvant chemotherapy, ECOG | 2 | 0.505 | 0.349–0.732 | .71           | 0.0%       | Fixed effect |
| **Overall survival**    |                |      |               |               |            |
| Study design            |                |      |               |               |            |
| Case-control            | 4              | 0.563 | 0.265–1.196   | .01           | 72.5%      | Random effects |
| Stage                   |                |      |               |               |            |
| III-IV disease          | 3              | 0.748 | 0.563–0.994   | .17           | 44.5%      | Fixed effect |
| Adjustment              |                |      |               |               |            |
| Age, stage, histology   | 3              | 0.748 | 0.563–0.994   | .17           | 44.5%      | Fixed effect |
| Age, stage, grade       | 2              | 0.972 | 0.443–2.137   | .14           | 53.2%      | Random effects |
| Age, stage, neoadjuvant chemotherapy | 2 | 0.911 | 0.439–1.890 | .06          | 70.9%      | Random effects |

ECOG = Eastern Cooperative Oncology Group performance status.

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### Table 3

Subgroup analyses for evaluating the effect of hyperthermic intraperitoneal chemotherapy on the survival of patients with recurrent disease.

| Subgroup                          | No. of studies | HR   | 95% CI         | Heterogeneity | Model used |
|-----------------------------------|----------------|------|---------------|---------------|------------|
| **Disease-free survival**         |                |      |               |               |            |
| Study design                      |                |      |               |               |            |
| Case-control                      | 5              | 0.644 | 0.395–1.049   | .02           | 64.6%      | Random effects |
| Quality of study (NOS)            |                |      |               |               |            |
| 8                                 | 3              | 0.702 | 0.390–1.592   | .01           | 81.1%      | Random effects |
| Drug resistance                   |                |      |               |               |            |
| Platinum-sensitive                |                |      |               |               |            |
| Age, stage                        | 4              | 0.489 | 0.395–1.049   | .02           | 64.6%      | Random effects |
| Age, stage, grade                 | 2              | 0.526 | 0.300–0.922   | .74           | 0.0%       | Fixed effect |
| Age, stage, ECOG                  | 2              | 0.510 | 0.312–0.833   | .85           | 0.0%       | Fixed effect |
| Overall survival                  |                |      |               |               |            |
| Study design                      |                |      |               |               |            |
| Case-control                      | 6              | 0.593 | 0.390–0.902   | .10           | 46.1%      | Fixed effect |
| Quality of study (NOS)            |                |      |               |               |            |
| 8                                 | 5              | 0.454 | 0.226–0.912   | .08           | 52.1%      | Random effects |
| Drug resistance                   |                |      |               |               |            |
| Platinum-sensitive                |                |      |               |               |            |
| Age, stage                        | 5              | 0.616 | 0.402–0.945   | .13           | 41.7%      | Fixed effect |
| Overall survival                  |                |      |               |               |            |
| Study design                      |                |      |               |               |            |
| Case-control                      | 6              | 0.593 | 0.390–0.902   | .10           | 46.1%      | Fixed effect |
| Quality of study (NOS)            |                |      |               |               |            |
| 8                                 | 5              | 0.454 | 0.226–0.912   | .08           | 52.1%      | Random effects |
| Drug resistance                   |                |      |               |               |            |
| Platinum-sensitive                |                |      |               |               |            |
| Age, stage                        | 5              | 0.616 | 0.402–0.945   | .13           | 41.7%      | Fixed effect |

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.
with residual tumors ≤1 cm after cytoreductive surgery (HR, 0.591; 95% CI, 0.431–0.811).\cite{14-19,21,22,23,26} On subgroup analyses, HIPEC was effective for patients with recurrent disease who had residual tumors ≤1 cm after cytoreductive surgery (HR, 0.493; 95% CI, 0.315–0.773; Table 5).\cite{16,18,19,21,22,25}

### 4. Discussion

The current meta-analysis provides further evidence that HIPEC may be associated with better survival of patients with ovarian cancer, and suggests how we can select patients with ovarian cancer who will benefit from HIPEC after cytoreductive surgery.

Considering the DFS, HIPEC was associated with better prognosis in patients with primary disease, whereas it failed to increase DFS of patients with recurrent disease. However, subgroup analyses revealed that HIPEC increased DFS of patients with residual tumors ≤1 cm and no visible tumor, regardless of primary or recurrent diseases. These results suggest that HIPEC may be effective for all patients with primary ovarian cancer, whereas its effect may be limited for those who underwent

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### Table 4

**Effect of hyperthermic intraperitoneal chemotherapy on disease-free survival by the extent of cytoreductive surgery.**

| Residual tumor ≤1 cm | No. of studies | HR           | 95% CI            | Heterogeneity | Model used |
|----------------------|----------------|--------------|-------------------|---------------|------------|
| All studies          | 8              | 0.488        | 0.389–0.612       | >.99          | Fixed effect |
| Primary disease      | 4              | 0.470        | 0.349–0.656       | .93           | Fixed effect |
| Age, stage, grade, neoadjuvant chemotherapy, ECOG | 2              | 0.505        | 0.349–0.732       | .71           | Fixed effect |
| Recurrent disease    | 4              | 0.493        | 0.359–0.690       | .96           | Fixed effect |
| Quality of study (NOS) | 8              | 3            | 0.303–0.661       | .94           | Fixed effect |
| Adjustment           | Age, stage, residual tumor size after surgery | 2 | 0.484 | 0.324–0.723 | .72 | Fixed effect |
| All studies          | 6              | 0.486        | 0.377–0.628       | .99           | Fixed effect |
| Primary disease      | 3              | 0.486        | 0.345–0.685       | .81           | Fixed effect |
| Age, stage, grade, neoadjuvant chemotherapy, ECOG | 2              | 0.505        | 0.349–0.732       | .71           | Fixed effect |
| Recurrent disease    | 3              | 0.487        | 0.332–0.713       | .88           | Fixed effect |
| Quality of study (NOS) | 8              | 2            | 0.300–0.713       | .91           | Fixed effect |
| Adjustment           | Age, stage, grade | 2 | 0.526 | 0.300–0.922 | .74 | Fixed effect |

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.

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### Table 5

**Effect of hyperthermic intraperitoneal chemotherapy on overall survival by the extent of cytoreductive surgery.**

| Residual tumor ≤1 cm | No. of studies | HR           | 95% CI            | Heterogeneity | Model used |
|----------------------|----------------|--------------|-------------------|---------------|------------|
| All studies          | 10             | 0.591        | 0.431–0.811       | .06           | Fixed effect |
| Primary disease      | 4              | 0.590        | 0.255–1.362       | .02           | Random effects |
| Age, stage, grade, histology | 2 | 0.443 | 0.443–2.137 | .14 | Random effects |
| Recurrent disease    | 6              | 0.403        | 0.315–0.773       | .39           | Fixed effect |
| Quality of study (NOS) | 8              | 4            | 0.230–0.676       | .44           | Fixed effect |
| Adjustment           | Age, stage, residual tumor size after surgery | 3 | 0.378 | 0.204–0.702 | .57 | Fixed effect |
| All studies          | 7              | 0.564        | 0.310–1.027       | .02           | Random effects |
| Primary disease      | 3              | 0.563        | 0.179–1.770       | .01           | Random effects |
| Age, stage, grade, histology | 2 | 0.972 | 0.443–2.137 | .14 | Random effects |
| Recurrent disease    | 4              | 0.525        | 0.308–0.894       | .22           | Fixed effect |
| Quality of study (NOS) | 8              | 3            | 0.230–1.220       | .30           | Fixed effect |
| Adjustment           | Age, stage, residual tumor size after surgery | 2 | 0.522 | 0.110–2.465 | .11 | Random effects |

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.
optimal cytoreduction (residual tumors ≤1 cm and no visible tumor) for recurrent disease. The survival benefit from HIPEC in primary disease is in line with the RCT of van Driel et al in which HIPEC increased DFS of patients with ovarian cancer who received NAC followed by IDS.[9] After NAC, hidden tumors might still exist despite gross evaluation and optimal cytoreduction after IDS.[10] However, HIPEC may control both biologically residual and hidden tumors, resulting in a favorable prognosis.

For patients with recurrent ovarian cancer, improvement of DFS after HIPEC was observed only in those who achieved optimal cytoreductive surgery in this study. This limitation might have originated owing to the different biological properties of recurrent tumors because they commonly show drug resistance to chemotherapy.[31] Moreover, the penetration depth of chemotherapeutic drugs in HIPEC is limited to a few millimeters only.[32] Accordingly, the role of cytoreductive surgery may be particularly important for recurrent ovarian cancer, and optimal cytoreduction should be performed before the implementation of HIPEC because of drug resistance and limited penetration depth of the drugs used in HIPEC.

In terms of OS, HIPEC improved the prognosis in both primary and recurrent diseases. However, the effect of HIPEC was not observed in patients with primary disease who had residual tumors ≤1 cm or no visible tumors. In cases of primary disease, most of the tumors are naïve to systemic chemotherapy. In addition, we have to keep in mind that HIPEC has treatment-related complications as well.[33] Therefore, HIPEC might be unnecessary for patients with primary disease if optimal cytoreductive surgery is achieved and completion of planned cycles of adjuvant chemotherapy is expected.

The current meta-analysis showed that HIPEC did not increase OS of patients with recurrent ovarian cancer who had no visible tumor after cytoreductive surgery. However, the effect of HIPEC on OS could be expected in those who had residual tumors ≤1 cm after cytoreductive surgery. We do not know the exact reason, but one it is possible that HIPEC can increase the response of drug-resistant tumor cells to systemic chemotherapy. Previous studies have suggested that drug-resistant tumor cells with high amount of heat-shock proteins became more susceptible to the effect of hyperthermia[34] and epigenetic alterations induced by hyperthermic chemoperfusion altered the responsiveness to platinum agents.[35]

Nevertheless, this meta-analysis had some limitations. First, the different types of drugs used in HIPEC among the studies may result in bias. Second, the toxicity or adverse events of HIPEC were not evaluated. Third, most studies in this meta-analysis were retrospective studies except for the 2 RCTs.

Despite these limitations, the results of the current meta-analysis suggest the strong relationship between HIPEC and better survival of patients with primary or recurrent ovarian cancer. In particular, the results of this meta-analysis are significant, as they indicate which patients with ovarian cancer may benefit from cytoreductive surgery and HIPEC. However, additional relevant clinical trials are needed to select the appropriate patients and to demonstrate the effect of HIPEC on their prognosis in the near future.

Author contributions

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