Original Article

Secondary cytoreductive surgery with and without hyperthermic intraperitoneal chemotherapy for recurrent ovarian cancer

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Background: Secondary cytoreductive surgery (CRS) can afford promising results in patients with recurrent ovarian cancer; however, the impact of hyperthermic intraperitoneal chemotherapy (HIPEC) remains unclear. We compared the outcomes of secondary CRS combined with and without HIPEC in patients with recurrent ovarian cancer.

Methods: We retrospectively evaluated patients with recurrent ovarian cancer who underwent secondary CRS, with or without HIPEC (n=46), at the Yonsei Cancer Center between January 2006 and February 2021. Of the 46 included patients, 20 underwent secondary CRS-plus-HIPEC, while 26 underwent secondary CRS without HIPEC (henceforth referred to as secondary CRS-only).

Results: Of the 46 patients, 84.8% and 89.1% had undergone optimal surgery and platinum-based chemotherapy, respectively, as the initial treatment before the first relapse. Overall, 32.6% of patients received maintenance therapy, such as bevacizumab or polyadenosine diphosphate ribose polymerase inhibitors. The median follow-up period was 15.9 months. The median progression-free survival (PFS) was 32.7 and 25.1 months in the secondary CRS-plus-HIPEC and secondary CRS-only groups, respectively; however, both groups failed to reach the median overall survival (OS). Based on the Kaplan-Meier analysis, there was no difference in PFS (P=0.587) or OS (P=0.239) between the two groups. We identified patients with epithelial ovarian cancer and found that the median PFS was 25.1 months in the secondary CRS-only group; this was not achieved in the secondary CRS-plus-HIPEC group (P=0.244).

Conclusions: In patients with recurrent ovarian cancer, secondary CRS with HIPEC did not improve survival when compared with CRS without HIPEC. However, on subgrouping patients with epithelial ovarian cancer, the addition of HIPEC to secondary CRS tended to improve PFS.

Keywords: Recurrent ovarian cancer; cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); epithelial ovarian cancer

Submitted Jul 14, 2023. Accepted for publication Nov 02, 2023. Published online Dec 22, 2023.
doi: 10.21037/gs-23-293
View this article at: https://dx.doi.org/10.21037/gs-23-293

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Introduction

Ovarian cancer is a lethal malignant gynecological cancer known to impact women (1). Optimal cytoreductive surgery (CRS) followed by platinum-based chemotherapy is considered the standard of treatment for advanced ovarian cancer (2,3). In addition, the administration of maintenance therapy with drugs such as bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors is gradually increasing (4). However, approximately 60–80% of patients with advanced-stage ovarian cancer experience relapse after complete remission, even after optimal primary treatment (5,6).

Recurrent ovarian cancer typically relies on systemic chemotherapy. However, recent research has revealed that CRS followed by chemotherapy can achieve improved survival outcomes when compared with those with chemotherapy alone (7), thereby highlighting the critical role of secondary CRS. Previous randomized clinical trial suggested a benefit for hyperthermic intraperitoneal chemotherapy (HIPEC) in recurrent ovarian cancer (8), but this publication raised multiple questions including methodological and statistical issues, randomization process, unclear end point definition, hamper the interpretation of results (9). In patients with ovarian cancer, improved progression-free survival (PFS) and overall survival (OS) have been documented in patients who underwent HIPEC during interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) (10,11). In patients with peritoneal metastasis arising from gastric cancer, CRS plus HIPEC was found to improve OS and recurrence-free survival when compared with CRS alone (12). In the CRS plus HIPEC and CRS alone groups, the authors reported 5-year OS rates of 19.87% and 6.43% (P=0.005), respectively, along with recurrence-free survival rates of 17.05% and 3.76% (P=0.001) (12). However, regarding the implementation of secondary CRS in patients with recurrent ovarian cancer, comparisons of HIPEC outcomes have not been reported.

The objective of the present study was to compare survival outcomes in patients with recurrent ovarian cancer who underwent secondary CRS with and without HIPEC. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-293/rc).

Highlight box

Key findings

- Hyperthermic intraperitoneal chemotherapy (HIPEC) could be valuable in patients with recurrent epithelial ovarian cancer.

What is known and what is new?

- In patients with recurrent ovarian cancer, cytoreductive surgery (CRS) after chemotherapy is more beneficial than chemotherapy alone. However, whether HIPEC could further improve survival in patients with recurrent ovarian cancer remains debatable.
- In this retrospective trial, there was no difference in progression-free survival and overall survival (OS) between patients who underwent secondary CRS with HIPEC and those who underwent secondary CRS alone.

What is the implication, and what should change now?

- Although HIPEC did not improve OS, it could benefit patients with recurrent epithelial ovarian cancer. A longer follow-up period and larger sample size may help clarify the role of CRS in combination with HIPEC in patients with recurrent epithelial ovarian cancer.

Methods

Study population

This retrospective study was conducted at Yonsei Cancer Center of Severance Hospital in South Korea between January 2006 and February 2021. We compared the outcomes of patients who underwent secondary CRS combined with HIPEC (secondary CRS-plus-HIPEC group) and those who underwent secondary CRS alone (secondary CRS-only group) in the first-relapse ovarian cancer group. Eligible patients were those diagnosed with ovarian, fallopian tubal, or peritoneal cancer who underwent primary debulking or IDS and had a history of recurrence. *Figure 1* presents a flowchart of the patients. All patients were initially diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) stage. Most patients received platinum-based systemic chemotherapy after debulking surgery. All patients underwent CRS to remove visible tumors. The complexity of the procedures used during CRS was classified in accordance with previously published protocols as low [surgical complexity score (SCS) 1 to 3], intermediate (SCS 4 to 7), or high (SCS ≥8) (13). Complete resection was defined as the removal of all residual tumors, and optimal CRS was defined as a residual tumor measuring <1 cm. Patients who did not undergo surgery after the first recurrence but underwent subsequent surgery were excluded from the study inclusion.

HIPEC was performed using the open technique, and peritoneal fluid perfusion was performed for 90 min.

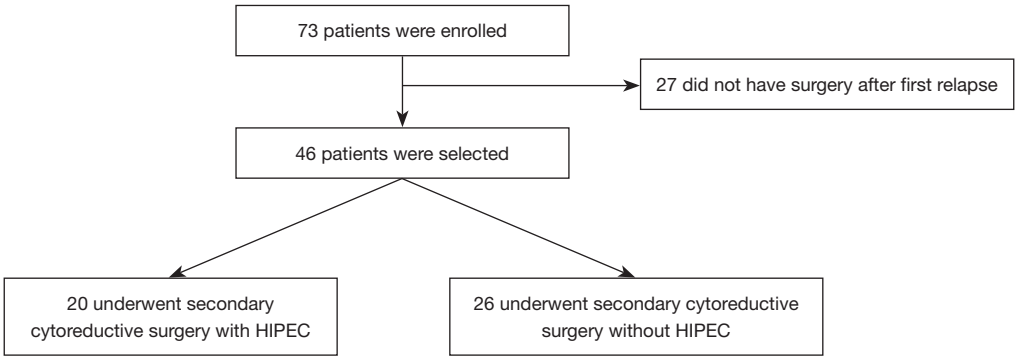


Figure 1 Flow chart of patient enrollment. HIPEC, hyperthermic intraperitoneal chemotherapy.

Chemotherapy was performed using cisplatin (100 mg/m^2) or paclitaxel (175 mg/m^2), which was diluted in 3 L of a 1.5% dextrose solution for peritoneal dialysis. Initially, 3 L of heated perfusion solution was infused into the abdominal cavity at a rate of 800–1,000 mL/min through the inflow tube using a Belmont Hyperthermic Pump (Belmont Instrument Corporation, Billerica, MA, USA). Three intra-abdominal thermometers (one positioned in the pelvis and two in the diaphragm area) were used to monitor the temperature within the abdominal cavity during the infusion, maintained at 42 ℃ constantly (14,15).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Institutional Review Board at Severance Hospital, Yonsei University Health System, Seoul, Korea (IRB number: 4-2023-0443). Informed consent for this retrospective study was waived.

Outcomes

PFS was defined as the time from the date of disease progression to death from any cause. Progression of disease was clinically defined using the Response Evaluation Criteria in Solid Tumors, version 1.1 (16), or based on an increased CA 125 level exceeding the upper limit of the normal range. OS was defined as the time from diagnosis to death from any cause. Survival data were censored at the last contact or follow-up for surviving patients.

Statistical analysis

The Kaplan-Meier method and log-rank test were used to estimate and compare survival between the CRS-plus-HIPEC and CRS-only groups. Additional subgroup analysis (in epithelial ovarian cancer only) was performed using the Kaplan-Meier method and log-rank test. Statistical significance was set at $P<0.05$, and all statistical analyses were conducted using the SPSS statistical software (version 21.0; IBM Corp., Armonk, NY, USA).

Results

Patients

Between January 2006 and February 2021, 73 patients underwent CRS after recurrence at Yonsei Cancer Center. Of the 73 patients, 46 underwent CRS after the first recurrence. The secondary CRS-plus-HIPEC and secondary CRS-only groups comprised 20 and 26 patients, respectively. There were no significant differences in patient characteristics, including age, FIGO stage, histologic type, *BRCA* mutation, recurrence site, and chemotherapy regimen, between the two groups (*Table 1*). In both groups, the recurrence locations in the abdominal cavity were similar, there was no difference in surgical procedures, and surgery was performed optimally according to the recurrence sites. Of the 46 patients, most (89.1%) received platinum-based chemotherapy during the initial treatment prior to the first recurrence. Overall, 32.6% of patients received maintenance therapy with drugs such as bevacizumab or PARP inhibitors.

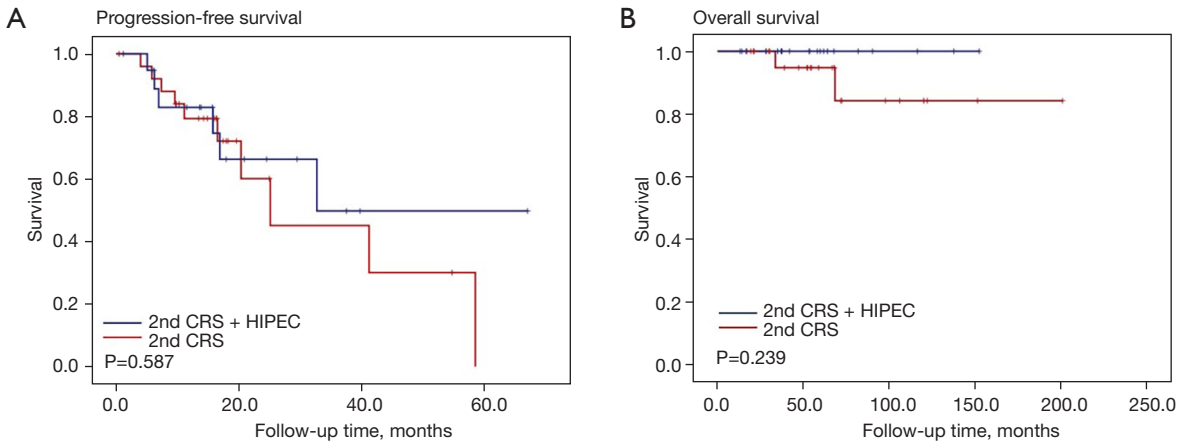
Outcomes

Of the 46 patients, 20 (43.5%) were assigned to the secondary CRS-plus-HIPEC group and 26 (56.5%) to the secondary CRS-only group. The median follow-up duration from recurrence to the last follow-up was 15.9 months. The

Table 1 Baseline characteristics of patients (N=46)

Variables	2nd CRS with HIPEC (N=20)	2nd CRS without HIPEC (N=26)	P value
Age (years), median [IQR]	54.75 [38–69]	50.23 [22–62]	0.134
FIGO stage			0.696
I	5 (25.0%)	5 (19.2%)	
II	1 (5.0%)	2 (7.7%)	
III	10 (50.0%)	16 (61.5%)	
IV	4 (20.0%)	3 (11.5%)	
Histologic type			0.415
EOC	15 (75.0%)	22 (84.6%)	
Others	5 (25.0%)	4 (15.4%)	
BRCA mutation			0.439
BRCA1/2	9 (45.0%)	12 (46.2%)	
Wild type	6 (30.0%)	11 (42.3%)	
Unknown	5 (25.0%)	3 (11.5%)	
Site of recurrence			0.348
Intraperitoneal	14 (50.0%)	11 (36.7%)	
Lymph node	5 (17.9%)	5 (16.7%)	
Visceral	6 (21.4%)	3 (10.0%)	
Others (thoracic, extraperitoneal)	3 (10.7%)	11 (36.7%)	
Surgical complexity score groups			0.341
Low (≤3)	16 (80.0%)	21 (80.8%)	
Intermediate (4–7)	3 (15.0%)	5 (19.2%)	
High (≥8)	1 (5.0%)	0	
Residual disease, n (%)			0.745
No	19 (95.0%)	25 (96.2%)	
<1 cm	1 (5.0%)	1 (3.8%)	
Previous first therapy			
Platinum based	16 (80.0%)	25 (96.2%)	0.249
Others	1 (5.0%)	0	
No therapy	3 (15.0%)	1 (3.8%)	
Previous maintenance			
Bevacizumab	1 (5.0%)	1 (3.8%)	0.849
PARP inhibitor	0	4 (15.4%)	0.066
Therapy after 2nd CRS			
Platinum based	16 (80.0%)	23 (88.5%)	0.257
Others	2 (10.0%)	0	
No therapy	2 (10.0%)	3 (11.5%)	
Maintenance after 2nd CRS			
Bevacizumab	2 (10.0%)	2 (7.7%)	0.783
PARP inhibitor	5 (25.0%)	6 (23.1%)	0.880

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; FIGO, International Federation of Gynecology and Obstetrics; EOC, epithelial ovarian cancer; PARP, poly (ADP-ribose) polymerase.



	2nd CRS	2nd CRS + HIPEC	Log rank P
Events	10	6	
Median PFS	25.1 m	32.7 m	0.587

	2nd CRS	2nd CRS + HIPEC	Log rank P
Events	2	0	
Median OS	Not reached	Not reached	0.239

Figure 2 Kaplan-Meier curves of PFS and OS according to HIPEC in patients who underwent secondary CRS (A,B). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PFS, progression-free survival; OS, overall survival.

median PFS was 32.7 and 25.1 months in the secondary CRS-plus-HIPEC and secondary CRS-only groups, respectively. The median OS was not achieved in either group. The Kaplan-Meier analysis revealed that HIPEC did not significantly impact PFS (P=0.587) or OS (P=0.239) (*Figure 2*). Of the 46 patients, 37 (80.4%) had epithelial ovarian cancer. Of these 37 patients, 15 (40.5%) were in the secondary CRS-plus-HIPEC group, and 22 (59.5%) were in the secondary CRS-only group.

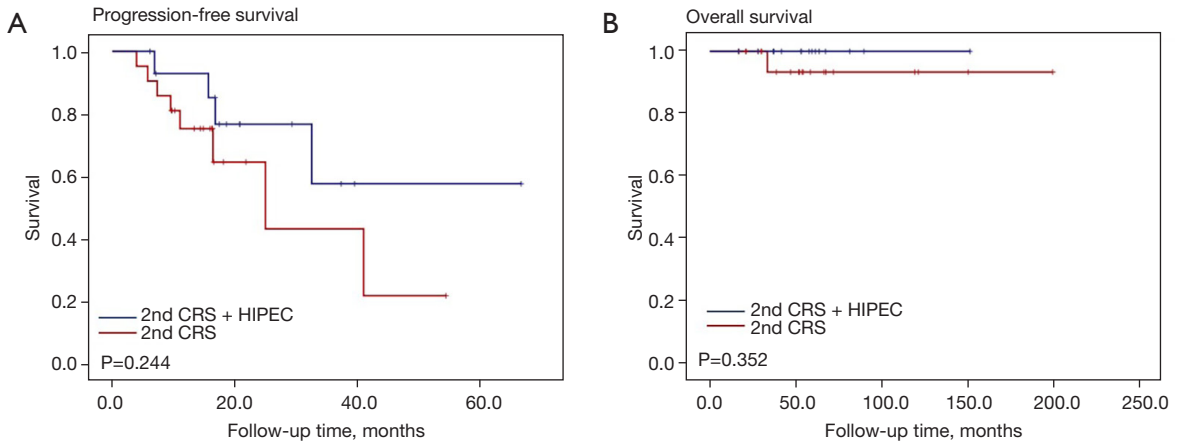
In the subgroup analyses of epithelial histologic type ovarian cancer, the median PFS was not reached in the secondary CRS-plus-HIPEC group and was 25.1 months in the secondary CRS-only group. The median OS was not achieved in either group. Based on the Kaplan-Meier analysis, HIPEC did not significantly impact PFS (P=0.244) and OS (P=0.352) (*Figure 3*). Of the 46 patients, 41 (89.1%) received platinum-based chemotherapy after primary cytoreduction. Of these 41 patients, 36 (87.8%) patients were sensitive to the initial platinum treatment. The median time to recurrence (defined as the time from the date of last chemotherapy done to first recurrence) was 27.4 months in platinum-sensitive group. In patients with platinum-sensitive recurrent, 32 (88.9%) patients experienced secondary platinum-sensitive recurrence. Most of the platinum-sensitive patients were still platinum-sensitive after secondary CRS with or without HIPEC.

Discussion

In the present study, we evaluated whether incorporating HIPEC into CRS has prognostic relevance in patients with recurrent ovarian cancer. In patients with recurrent ovarian cancer who underwent secondary CRS, HIPEC had no benefits in terms of PFS or OS. However, when analyzing a subgroup of patients with epithelial ovarian cancer, the addition of HIPEC to secondary CRS showed a greater tendency to improve PFS; no favorable tendency was observed in terms of OS.

A randomized study (7) has reported that CRS with systemic chemotherapy could improve OS when compared with systemic chemotherapy alone in patients with recurrent ovarian cancer; however, the trial was limited to complete macroscopic resections. Of the 407 patients, 206 were assigned to the surgery and chemotherapy groups and 201 to the chemotherapy-alone group. The CRS and chemotherapy group had a longer median OS than the chemotherapy-alone group (53.7 *vs.* 46.0 months, P=0.02). In another randomized trial, the PFS results revealed the benefits of adding secondary CRS to chemotherapy (17). Therefore, secondary CRS is an important treatment, similar to systemic chemotherapy, and complete resection is an important prognostic factor.

It is necessary to think about the feasibility of minimally invasive surgery like laparoscopic or robotic surgery when



	2nd CRS	2nd CRS + HIPEC	Log rank P
Events	8	4	
Median PFS	25.1 m	Not reached	0.244

	2nd CRS	2nd CRS + HIPEC	Log rank P
Events	1	0	
Median OS	Not reached	Not reached	0.352

Figure 3 Kaplan-Meier curves of PFS and OS according to HIPEC in patients who underwent secondary CRS in the subgroup analyses of epithelial ovarian cancer (A,B). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PFS, progression-free survival; OS, overall survival.

doing secondary CRS. The performance of minimally invasive surgery can be confirmed in previous studies on the safety and availability of minimally invasive surgery for optimal cytoreduction (18). However, since this is possible in localized recurrent ovarian cancer, which is a case of recurrence on a single nodule or single organ site (19), it would be meaningful to do the minimally invasive surgery in such a specific case. The BRCA status can be selection criterion in the application of CRS and HIPEC on patients with recurrent ovarian cancer. In recurrent ovarian cancer, BRCA status did not have a significant association with PFS after salvage lymphadenectomy (20), but after hepatic resection, PFS was significantly favorable (21). Therefore, we believe that the BRCA status can help us decide whether to apply cytoreduction and HIPEC.

HIPEC plays an important role in the treatment of advanced primary ovarian cancer. HIPEC was reportedly effective only in patients who underwent IDS after recent NAC (10). Hyperthermia can activate systemic immune responses by stimulating proteins that are immune modulators involved in innate and adaptive immune responses. In addition, HIPEC can activate proteins, thereby inducing the maturation of dendritic cells to enhance antitumor responses (22). The role of HIPEC in patients with recurrent ovarian cancer has been actively studied in recent years. In platinum-sensitive recurrent ovarian cancer, the use of CRS plus HIPEC with oxaliplatin (460 mg/m^2) represents a safe treatment that can substantially influence survival rates when compared with chemotherapy alone or surgery plus standard chemotherapy (median disease-free survival and OS of 24 and 38 months, respectively) (23). However, this was a retrospective study with a small sample size, and oxaliplatin was used instead of cisplatin, which is mainly used in HIPEC of ovarian cancer patients. Spiliotis *et al.* (8) have reported the effectiveness of CRS with HIPEC followed by subsequent second- or third-line systemic chemotherapy in patients with recurrent ovarian cancer. The authors compared survival outcomes between the CRS followed by HIPEC and CRS-only groups. CRS with HIPEC significantly improved survival in patients with recurrent ovarian cancer (mean survival 26.7 *vs.* 13.4 months, P<0.006). However, this study raised multiple questions, including unclear end point definition, statistical analysis, and randomization process.

In the present study, we detected no significant difference in survival between the CRS-plus-HIPEC and CRS-only groups. Recently, maintenance therapies such as bevacizumab or PARP inhibitors have been used after CRS, followed by chemotherapy in advanced/recurrent ovarian cancer. Treatment with PARP inhibitors was shown to

exert considerable survival benefits in primary or recurrent ovarian cancer, particularly in patients with *BRCA* mutations or similar genes associated with a defect in DNA repair, known as homologous recombination deficiency (24-27). Moreover, bevacizumab could improve PFS in patients with recurrent ovarian cancer (28-30). However, in the GOG 213 trial, the lack of survival benefit in the secondary CRS group, compared with the chemotherapy-only group, was attributed to treatment with bevacizumab (31). In the current study, 33% of patients received maintenance therapy after secondary CRS with or without HIPEC, which might partially explain the lack of any difference in survival rates between the CRS-plus-HIPEC and CRS-only groups.

This retrospective study has several limitations. First, the sample size was small, given the limited number of patients. Second, the follow-up period was short; therefore, a longer follow-up period could elucidate a relevant outcome. Notably, HIPEC could exert potential benefits in patients with recurrent epithelial ovarian cancer. Our study did not perform further analysis by subdividing patients according to *BRCA* mutation or homologous recombination deficiency. Accordingly, treatment outcomes might differ significantly between the two groups, although we did not detect any statistical difference between the two groups.

Further studies are needed to determine whether CRS and HIPEC can exert benefits following second, third, and subsequent recurrences. A longer follow-up period and larger sample size should be considered to comprehensively clarify the observed findings in patients with recurrent epithelial ovarian cancer who undergo secondary CRS with or without HIPEC.

Conclusions

In the current retrospective study, secondary CRS with HIPEC did not improve survival when compared with CRS without HIPEC in patients with recurrent ovarian cancer. However, when assessing a subgroup of patients with epithelial ovarian cancer, the addition of HIPEC to secondary CRS tended to improve PFS. Thus, HIPEC may be beneficial in patients with epithelial ovarian cancer.

Acknowledgments

Funding: This study was supported by a grant from the Industry-Academic Cooperation Foundation, Yonsei University, Shin Poong Pharmaceutical Co. Ltd. (No. 2022-31-1712).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-293/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-293/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-293/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-293/coif). All authors receive article processing charges from Shin Poong Pharmaceutical Co. Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Institutional Review Board at Severance Hospital, Yonsei University Health System, Seoul, Korea (IRB number: 4-2023-0443). Informed consent for this retrospective study was waived.

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Cite this article as: Lee D, Lee J, Park H, Lee YJ, Lee JY, Nam EJ, Kim SW, Kim S, Kim YT. Secondary cytoreductive surgery with and without hyperthermic intraperitoneal chemotherapy for recurrent ovarian cancer. Gland Surg 2023;12(12):1696-1704. doi: 10.21037/gs-23-293