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Effect of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on epithelial ovarian, fallopian tube, and peritoneal cancer: An institutional review of outcomes and its clinical implications

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Abstract:

BACKGROUND: Ovarian, fallopian tube, and peritoneal cancer patients with advanced-stage diagnosis or recurrences spread to the peritoneal surface of the abdomen. Hyperthermic intraperitoneal chemotherapy (HIPEC) can penetrate and eradicate tumors that are microscopic up to those with a diameter of 2.5 cm from the peritoneal surface following cytoreductive surgery (CRS).

OBJECTIVES: The study aimed to determine the efficacy and safety of CRS with HIPEC versus CRS alone for patients with epithelial ovarian, fallopian tube, and peritoneal cancer.

MATERIALS AND METHODS: This retrospective cohort study included 50 patients (20 patients underwent CRS + HIPEC, while 30 patients underwent CRS alone). Records of these patients from January 2014 to June 2020 were reviewed, tabulated, and analyzed.

RESULTS: The difference in recurrence rate between CRS with HIPEC and CRS alone was not statistically significant (50% vs. 43%, $P = 0.774$). The median time to recurrence was 10 and 9 months, respectively ($P = 0.636$). Five percent in the HIPEC group succumbed to the disease, while 13% died in the CRS alone group ($P = 0.636$). More post-operative complications were noted in the HIPEC group (45% vs. 10%, $P = 0.007$), but among these, only 2 cases had grade 3 to 4 complications (10%). The addition of HIPEC in the management of these patients resulted in a longer operative time (360 vs. 240 min, $P < 0.001$) and postoperative hospital stay (8 vs. 6 days, $P = 0.026$). There were no intra- or peri-operative mortalities in both groups.

CONCLUSION: CRS with HIPEC and CRS alone showed similar time to recurrence and recurrence rate. CRS with HIPEC had low risk of grade 3-4 complications and may still be considered as a treatment option for advanced, progressive, and recurrent epithelial ovarian, fallopian tube, and peritoneal cancer.

Keywords:

Cytoreductive surgery, fallopian cancer, hyperthermic intraperitoneal chemotherapy, ovarian cancer, peritoneal cancer

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Introduction

Ovarian, fallopian tube, and peritoneal cancers are gynecologic malignancies associated with the highest mortality among all gynecologic cancers in the world. In 2018, 5069 new cases were identified in the Philippines, which translates to a

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6.4% mortality caused by ovarian cancer. In 2020, at the Philippine General Hospital Cancer Institute, there were a total of 108 new cases of ovarian malignancy, 34% of which were diagnosed on initial consult as stage III-IV or recurrent disease. Eight percent of the new cases (9 patients) expired within the year.[1]

Standard therapy with surgery or debulking surgery and platinum-based chemotherapy remains the most effective treatment for these gynecologic malignancies. Particularly in the advanced stage of the disease or recurrence, maximum effort is given to achieve zero residual disease through surgery followed by chemotherapy. Residual disease after cytoreductive surgery (CRS) for advanced ovarian cancer is defined by the diameter of the largest remaining tumor. Since this is one of the most important prognostic factors, complete cytoreduction (R0) must be the objective during surgery. Nevertheless, R0 cytoreduction may be challenging in some instances, and standard surgical procedures may fail to remove the entire tumor burden, including nonvisible remaining disease.[2,3] In most cases of primary and recurrent ovarian cancer, the peritoneum is the primary site of spread and failure.[4] Thus, there is a need to assess local treatment strategies apart from peritonectomy.

Combination treatment with intravenous (IV) and intraperitoneal chemotherapy has been shown to prolong overall survival after primary CRS among patients with stage III ovarian cancer.[5] Delivery of intraperitoneal chemotherapy at the end of surgery enhances drug delivery at the peritoneal surface and may improve outcomes by eliminating residual microscopic peritoneal disease more efficiently than IV administration of chemotherapy.

Previous trials that compared six cycles of intraperitoneal chemotherapy plus IV chemotherapy with IV chemotherapy alone after complete or optimal primary CRS showed that survival was 16 months longer after exposure to chemotherapy at the peritoneal surface than after intravenous chemotherapy alone.[6] Nevertheless, the uptake of postoperative IV chemotherapy plus intraperitoneal chemotherapy in clinical practice is limited by increased side effects, including catheter-related complications, and the inconvenience of administering therapy intraperitoneally.

Intraperitoneal chemotherapy during surgery that can be delivered under hyperthermic conditions is termed hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC is usually applied immediately following the peritonectomy procedure with the aim of directly delivering a heated cytotoxic drug to the peritoneal surface of the abdomen. Hyperthermia increases the penetration of chemotherapy at the peritoneal surface and increases the sensitivity of the cancer to chemotherapy by impairing DNA repair. Hyperthermia also induces apoptosis and activates heat-shock proteins that serve as receptors for natural killer cells, inhibit angiogenesis, and have a direct cytotoxic effect by promoting the denaturation of proteins.[7] While CRS removes macroscopic disease, the purpose of HIPEC is to eradicate the microscopic disease from the peritoneal surface. CRS is performed first through a traditional open approach. The treatment rationale is that HIPEC can penetrate and eradicate tumors up to a diameter of 2.5 cm, so that any cancer left should be smaller than this for HIPEC to be most effective. After which, chemotherapeutic agents heated to 40 to 41.5°C are infused for up to 1.5 h.[4]

Currently, available data are equivocal with regard to the efficacy of HIPEC in the treatment of advanced primary and recurrent ovarian, fallopian tube, and peritoneal cancer.

In 2013, one of the initial practice-changing research, the French multicenter retrospective cohort study of 566 patients (FROGHI) showed results wherein for advanced and recurrent epithelial ovarian cancers (EOC), curative therapeutic option combining optimal CRS and HIPEC may be considered depending on the peritoneal cancer index (PCI) as it may achieve long term survival in patients with a severe prognosis disease even in patients with chemoresistant disease.[8] Some centers have proposed using HIPEC after neoadjuvant chemotherapy (NACT) in a primary setting. A comparative Spanish study of 87 patients, 52 of whom were HIPEC paclitaxel patients (23 primary and 29 post-NACT), found that HIPEC was associated with prolonged progression-free survival (PFS) in the HIPEC group. All patients had complete CRS with no visible residual disease (CC0). In the control group, respectively, the PFS was 66%, 33%, and 18%, and in the HIPEC arm, the PFS was 81%, 67%, and 63% at 1, 2, and 3 years ($P < 0.01$).[9] One of the first meta-analyses[10] showed that among patients with primary EOC, the median, 1-, 3-, and 5-year overall survival rates are 46.1 months, 88.2%, 62.7%, and 51%. This systemic review of published trials identified 9 comparative studies reporting an improvement in survival following CRS + HIPEC (± chemotherapy) compared with CRS alone (± chemotherapy).

Among the initial randomized controlled trials (RCTs) providing evidence for HIPEC in recurrent disease, the findings revealed a significant difference in mean survival, with 26.7 months observed in the HIPEC-treated group compared to 13.4 months in those who did not receive HIPEC.[11] This was followed by the results of

the first RCT for HIPEC for primary ovarian cancer published in 2018 by Van Driel (OVHIPEC). To date, this is the best evidence that a single administration of HIPEC given at the time of CRS for ovarian cancer may achieve significant benefits in terms of survival without excess morbidity or loss of quality of life. The addition of HIPEC to interval CRS for the treatment among patients with stage III epithelial ovarian cancer resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects. In the intention-to-treat analysis, the median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. At a median follow-up of 4.7 years, 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died (hazard ratio, 0.67; 95% confidence interval [CI], 0.48 to 0.94; $P = 0.02$). The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, $P = 0.76$) 7. Van Driel's study indicates that the addition of HIPEC to complete or optimal interval CRS resulted in longer median recurrence-free survival, by 3.5 months, and longer median overall survival, by 11.8 months, than surgery alone.[7] A nephroprotective treatment (sodium thiosulfate) was also administered, the pathophysiology of which was not specified in the study. More than 90% of patients have completed six complete cycles of IV chemotherapy in both arms. It should be noted that this is a different patient population as all are not immediately resectable.

Altogether, up until recently, most of the evidence for HIPEC in the treatment of advanced ovarian cancer was based on large retrospective series,[2,8,12] small non-randomized prospective studies[13,14] and a few randomized trials.[7,11] However, these available studies are difficult to interpret and compare due to the heterogeneity of the study groups.

In contrast to the Van Driel study, an RCT from Korean showed contrasting results. Lim's study included 184 women with stage III and IV ovarian cancer and HIPEC failed to show a significant difference in 5-year survival.[15] Results showed 2-year PFS was 43.2% and 43.5% and 5-year PFS was 20.9% and 16.0% in HIPEC and control group, respectively ($P = 0.569$). Five-year OS was 51.0% and 49.4% in the HIPEC and control group, respectively ($P = 0.574$). The survival analysis did not show the statistical superiority of the HIPEC arm. Moreover, an RCT from Memorial Sloan Kettering showed no benefit in favor of HIPEC for recurrent ovarian cancer.[16] This was followed by the PRODIGE 7[17] for colorectal cancer which also showed no benefit.

Be that as it may, international consensus has not regarded HIPEC as a reference treatment outside clinical trials. HIPEC is currently only indicated by the National Comprehensive Cancer Network guidelines for administration in the interval debulking setting, in patients with stage III disease.[18] There is currently no indication in the recurrent setting or after primary debulking surgery. Despite the results of the Van Driel study, one of the concerns with the patient selection in OVHIPEC is since 90% of the patients are able to undergo upfront debulking. The remainder would be 6% of the patients who received NACT. Hence overall, in the patient journey with advanced stage III/IV epithelial cancer, the eligible patients for the OV HIPEC were only 5%.[19] In addition, the data on recurrent disease show conflicting results. Nevertheless, the combination of CRS+HIPEC seems to be an interesting therapeutic option in view of the latest data in the literature.

In addition, in the included studies, only Van Driel reported information about adverse events between HIPEC arm and non-HIPEC arm. There were no significant differences in complications between the two groups. Mendivil[20] also reported a similar situation of toxicity and complications in HIPEC therapy. Morbidity following CRS + HIPEC has been reported to be between 12% and 33%. The majority of complications are more likely due to the aggressive CRS rather than HIPEC, particularly with respect to bowel complications (anastomotic insufficiencies and bowel fistula sepsis). However, the addition of HIPEC is often associated with renal impairment and hematological toxicity due to transient bone marrow suppression.

For years, centers have pursued comprehensive CRS combined with HIPEC for the management of peritoneal surface malignancies. This combined approach is the standard of care for the management of some rare peritoneal diseases such as pseudomyxoma peritoneum or peritoneal mesothelioma but is also recommended as a curative approach for selected patients with colorectal carcinomatosis.[8]

Thus, due to the equivocal data for ovarian, fallopian tube, and peritoneal cancer, the therapeutic option with HIPEC offered to patients is always discussed, especially in the clinical application in a local setting.

Standard of care for advanced epithelial ovarian cancer patients (institutional practice)

In the study institution, patients with advanced epithelial cancer who cannot achieve complete cytoreduction during the first surgery are advised NACT for 3–4 cycles. Subsequently, a physical examination is done, and imaging is requested to determine if interval debulking surgery (IDS) could be performed. Chest and/or

abdominopelvic computed tomography scan is often done for these high-risk tumors and with clinical suspicion of extensive disease.

Candidates for CRS + HIPEC are screened based on the criteria cited in the 2023 Society of Gynecologic Oncologists of the Philippines (SGOP) Clinical Practice Guidelines: Among patients with Stage III EOC, HIPEC may be an additional option to complete primary or optimal interval CRS. Based on the Peritoneal Surface Oncology Group International (PSOGI),[21] there are five criteria relevant to the indication to perform HIPEC include: (1) whether it is a primary tumor or recurrent disease; (2) whether the tumor is resectable (no or residual tumor masses of ≤2.5 mm); (3) absence of distant metastases; (4) epithelial histology; and (5) PCI <21 (most important criterion in the decision). In the guidelines of the SGOP, for advanced and recurrent EOC, CRS + HIPEC may be considered as a curative treatment depending on the PCI as it may achieve long-term survival in patients with a severe prognosis disease even in patients with chemoresistant disease.[22]

HIPEC was formally adopted by the Section of Gynecologic Oncology as an option for managing advanced-stage ovarian cancer in 2014. The cases are often done with the supervision of gynecologic oncology and colorectal surgery consultants who underwent training in HIPEC. Since then, a total of 26 cases for ovarian cancer, 11 cases for peritoneal cancer, 1 case for cervical cancer, and 1 case for endometrial cancer have undergone HIPEC. The surgical procedure for CRS often involves total hysterectomy with bilateral salpingo-oophorectomy, peritonectomy or peritoneal biopsies, and total omentectomy. Additional procedures performed were bowel resections, resection of tumor implants (bowel/liver), appendectomy, and lymphadenectomy.

However, despite that HIPEC may offer curative treatment in cases of advanced and recurrent EOC, financial constraints are often a hindrance. It could be a cost-prohibitive procedure as out-of-pocket spending could reach approximately PhP90,000, if there are no subsidies available. However, for advanced EOC patients who opt not to undergo HIPEC, the course of treatment involves CRS followed by adjuvant IV chemotherapy.

Patients were then advised to follow-up 2 weeks after the surgery and then resumed adjuvant chemotherapy (ACT) after 3–4 weeks from surgery. The standard adjuvant treatment in the form Carboplatin (area under the curve 5) – Paclitaxel (175 mg/m^2) every 3 weeks for the same number of cycles given before CRS are given. Follow-up after ACT was done every month for the first 3 months and every 3 months for the first 2 years with CA 125 monitoring.

Significance of the study

HIPEC outcomes of overall survival and progression-free period from the international studies remain equivocal. Ergo, HIPEC as a treatment option for advanced epithelial ovarian cancer will primarily depend on the local experience, focusing on the efficacy and safety of its application.

It is imperative to gather Philippine data, especially since this procedure can be associated with increased cost and out-of-pocket spending for the patient, intensive care unit (ICU) admissions and increased length of hospital stay. Subsequently, administrative and financial support to sustain the practice is will depend of evidence-based medicine. In a resource-limited setting, socioeconomic factors are factored in by gynecologic oncologists in their treatment planning.

The present study aims to present the local oncologic outcomes of patients who underwent HIPEC in a Tertiary National Cancer Referral Center. A review of the efficacy and safety of HIPEC will give us an overview of the impact of the integration of this treatment into our current practice. The results from this study may steer future undertakings and even influence guidelines impacting health policy in relation to advanced epithelial ovarian cancer management.

General and specific objectives

Objectives

General objectives

To determine the efficacy and safety of CRS and HIPEC followed by IV chemotherapy versus CRS and IV chemotherapy alone for patients with epithelial ovarian cancer

Specific objectives

1. To document the baseline characteristics of patients who underwent HIPEC
2. To determine the efficacy of CRS and HIPEC followed by IV chemotherapy (RR, PFS, OS) versus CRS and IV chemotherapy alone for patients with epithelial ovarian cancer
3. To determine the safety of HIPEC (during and after, medical and nonmedical, toxicity) versus CRS and IV chemotherapy for patients with epithelial ovarian cancer
4. To determine surgical-prognostic factors associated with the efficacy of HIPEC (stage, residual tumor, histologic type)

Materials and Methods

Study design and setting

This is a single-center, retrospective cohort study through chart review of the patients who underwent

CRS, with and without HIPEC, followed by IV chemotherapy at the UP-Philippine General Hospital, a tertiary research and training hospital, from January 2014 to June 2020.

Study population

The epithelial ovarian, fallopian tube, and peritoneal cancer patients diagnosed to have primary advanced stage III and IV, recurrent and progressive disease who underwent CRS, with and without HIPEC were included in this study. Patients with cervical or uterine primary gynecologic malignancies or non-epithelial ovarian cancers were excluded.

Data collection

Ninety-three patients met the inclusion criteria: 39 from the CRS + HIPEC group and 54 from the CRS group. Of these, only 50 patients were included in the study (20 from the CRS + HIPEC group, and 30 from the CRS group). A total of 43 patients were excluded (19 from the CRS + HIPEC group, 24 from the CRS group) because of uterine primary malignancy, nonepithelial histology, and missing intraoperative and admitting records, with a retrieval rate of 74%.

Demographic and clinical data were noted for each patient including age, gravidity, parity, body mass index, medical comorbidities, and performance status based on the Eastern Cooperative Oncology Group (ECOG) scoring. Histopathologic results such as primary organ of involvement (ovary, fallopian tube, and peritoneum), histologic type, grade, and lymphovascular space invasion were also recorded, including the stage of disease according to the International Federation of Gynecologic Oncology (FIGO)[23] system. Disease characteristics such as tumor classification (primary, recurrent, or progressive), NACT agent used, and number of cycles received were likewise noted.

Intraoperative data recorded included the PCI,[24] a diagnostic and prognostic tool that is a sum of scores in thirteen abdominal regions [Figure 1]. Each receives a score of 0–3 based on the largest tumor size in that region. Total scores range from 0 to 39. Higher scores indicate more widespread and/or larger tumors in the peritoneal cavity. Completeness of cytoreduction (CC) assessed by measuring the size of the residual peritoneal implants following surgery was noted as well and scored as follows: CC0, no residual disease; CC1, residual nodules measuring <2.5 mm; CC2, residual nodules measuring between 2.5 mm and 2.5 cm; or CC3, residual nodules greater than 2.5 cm.[13]

Other perioperative and postoperative outcomes were recorded: laboratory results (hemoglobin, hematocrit, platelet, electrolytes, CA 125), complications, adverse events and ICU admission. The Clavien–Dindo classification [Figure 2] was utilized in grading the post-operative complications.[25] The operative time, blood loss, intraoperative blood transfusions, and length of hospital stay were recorded and tabulated.

Follow-up data included duration of follow-up, cycles of ACT, any relapse, with relapse location and date of death. Data on recurrence-free survival and overall survival were censored at the date of the last contact documented for the patients who remained alive and had no evidence of disease.

Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median, and interquartile range for nonnormally distributed continuous variables, and mean and standard deviation for normally distributed continuous variables. Independent Sample T-test, Mann–Whitney U, and Fisher's Exact/Chi-square test were used to determine the difference of mean, rank, and frequency, respectively, between CRS + HIPEC versus CRS group. All statistical tests were two-tailed tests. Shapiro–Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA is statistical software package developed by StataCorp. for data manipulation, visualization, statistics, and automated reporting.

Results

A total of 50 patients were included in this study, 20 from the CRS + HIPEC group and 30 from the CRS-only group. The comparisons of demographic and clinical profiles between the two groups are summarized in Table 1. The median age of the patients under the CRS + HIPEC group was 60.35 ± 9.58, and 48.9 ± 11.21 for those who underwent CRS alone. Older patients with poorer performance scores were identified in the CRS + HIPEC group ($P < 0.001$ and 0.012, respectively). Nevertheless, all patients had a performance score of ECOG 0-2. There was no statistical difference in the histologic diagnosis ($P = 0.505$), tumor grade ($P = 0.277$), stage at diagnosis ($P = 1.000$), primary organ of origin ($P = 0.108$) and comorbidities ($P = 1.000$ for hypertension, 0.143 for diabetes, 0.740 for others) between the two groups. Most of the cases were primary tumors: 65% from the CRS + HIPEC group and 86% from the CRS alone group. There was a significantly higher proportion of recurrent cases for which CRS + HIPEC was performed (35%) compared to those for which CRS alone was done (7%)

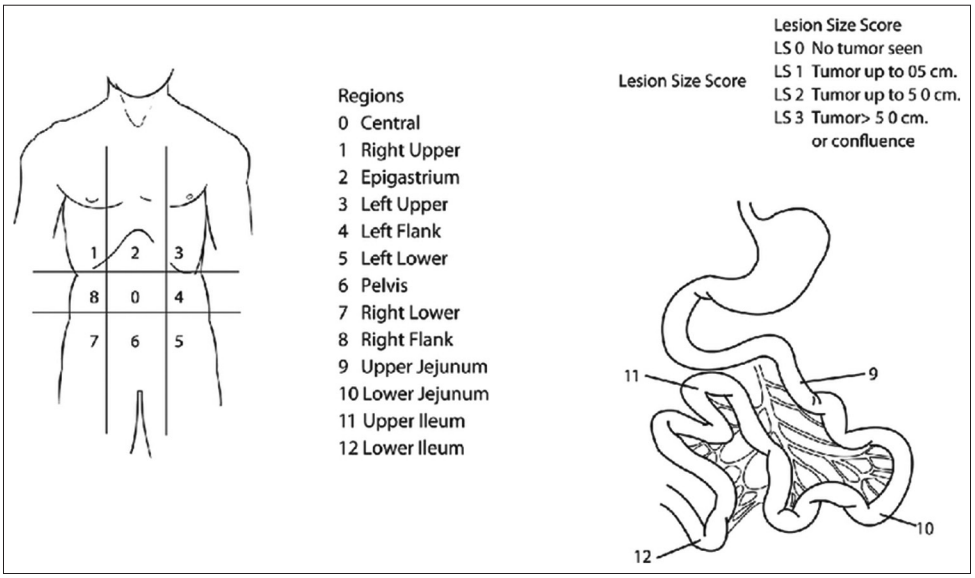

Figure 1: Peritoneal cancer index[24]

Figure 2: Clavien-dindo classification

Degree	Definition
I	Any deviation from the normal postoperative course without need of intervention beyond the administra- tion of anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and psychical therapy
II	Complication requiring pharmacological treatment with other medicines beyond the ones used for complica- tions of degree I
III	Complications requiring surgical, endoscopic, or radio- logical intervention
III-a	Intervention without general anesthesia
III-b	I Intervention under general anesthesia
IV	Life-threatening complication requiring admission to intensive care unit
IV-a	Uniorgan dysfunction (including dialysis)
IV-b	Multiorgan dysfunction
V	Death

(P = 0.021). The seven cases of recurrence in the former group were stage IIIC/IVB disease. Nevertheless, it is important to note that 65% (13 patients) of the CRS + HIPEC cases were front-line therapy for primary advanced ovarian, fallopian tube, and peritoneal cancer: 5 as first look surgery, and 8 as IDS.

The surgical information and treatment characteristics are summarized in Table 2. Ureteral stenting and stomas were more frequently performed in patients who underwent CRS with HIPEC (both have $P < 0.001$). There was no significant difference in blood loss (425 mL in the CRS + HIPEC group versus 750 mL in the CRS group, P = 0.211) or intraoperative transfusions (P = 0.315) received. The duration of the operation was significantly longer in the CRS + HIPEC group with a mean of 360 min, in contrast to the CRS-only group with 240 min ($P < 0.001$).

The chemotherapy agents used in the HIPEC regimen were often Cisplatin-based: Cisplatin alone or in combination with Doxorubicin and/or Ifosfamide with Mesna (55%). Mitomycin-C (with and without Doxorubicin,) and Ifosfamide with Mesna were also utilized. Five patients were given Sodium thiosulfate as part of the chemotherapy regimen. All HIPEC procedures had a 90-min perfusion period. The HIPEC regimens are summarized in Table 3.

The PCI scores were significantly higher among the patients who only underwent CRS (median for CRS + HIPEC: 10; median for CRS: 15, P = 0.023). CC was statistically significant, as all patients in the CRS + HIPEC group had complete cytoreduction ($P < 0.001$). Ten (10) patients in the CRS group did not achieve zero residual.

Post-operatively, CRS + HIPEC patients had lower platelet counts but did not reach thrombocytopenic levels (P = 0.021). Creatinine was noted to be higher in this group as well (P = 0.042). There was no significant difference between CRS + HIPEC and CRS alone groups, in terms of the decrease in the hemoglobin and hematocrit levels (P = 0.181 and 0.330, respectively). Potassium level increased in the CRS group post-operatively (P = 0.006). There was no significant change in the magnesium levels pre- and post-operatively in either group. Both electrolytes, however, were within normal limits. A comparison of preoperative and post-operative laboratories showed a significant decrease in albumin (P = 0.007) and a significant increase in creatinine (P = 0.008) in the CRS + HIPEC group.

More post-operative complications were noted in the CRS + HIPEC group (45% vs 10%, P = 0.007), but only 2 cases had grade 3 to 4 complications. The grade 3

Table 1: Demographic and clinical profile

	HIPEC + CRS (*n*=20), *n* (%)	CRS (*n*=30), *n* (%)	*P*
Age	60.35±9.58	48.9±11.21	<0.001
BMI	22.89±3.98	21.19±6.16	0.393
Performance score (ECOG)			0.012
0	12 (60)	26 (86.67)	
1	7 (35)	2 (6.67)	
2	1 (5)	0	
Unknown	0	2 (6.67)	
Histopathology results			0.505
Serous carcinoma	12 (60)	17 (56.67)	
Adenocarcinoma	5 (25)	3 (10)	
Mucinous cystadenocarcinoma	0	3 (10)	
Clear cell carcinoma	1 (5)	2 (6.67)	
Endometrioid adenocarcinoma	0	2 (6.67)	
Others	2 (10)	2 (6.67)	
Unknown	0	1 (3.33)	
FIGO grade			0.277
Grade 0	0	1 (3.33)	
Grade 1	0	4 (15.38)	
Grade 2	1 (12.5)	0	
Grade 3	7 (87.5)	23 (76.67)	
Unknown	0	2 (6.67)	
Stage			1.000
Stage I	0	1 (3.33)	
Stage II	1 (6.25)	1 (3.33)	
Stage III	11 (68.75)	18 (60)	
Stage IV	4 (25)	8 (26.67)	
Unknown	4 (25)	2 (6.67)	
Lymphovascular space invasion			0.374
Positive	6 (30)	13 (43.33)	
Negative	13 (43.33)	15 (50)	
Unknown	1 (3.33)	2 (6.67)	
Follow-up/postsurgical care agent			0.555
Carboplatin-paclitaxel	7 (100)	22 (73.33)	
None	0	4 (13.33)	
Unknown	13	4 (13.33)	
Postsurgical cycles	5 (3–5)	3 (2–3)	0.012
Comorbidities			
Hypertension	4 (20)	5 (25)	1.000
Diabetes	4 (20)	1 (3.33)	0.143
Others	4 (20)	8 (26.67)	0.740
None	8 (40)	6 (20)	
Classification of primary tumor			0.021
Primary	13 (65)	26 (86.67)	
Recurrent	7 (35)	2 (6.67)	
Progression	0	2 (6.67)	
Primary organ			0.108
Ovary	14 (70)	27 (90)	
Peritoneal	4 (20)	1 (3.33)	
Fallopian tube	2 (10)	2 (6.67)	
Neoadjuvant treatment (agent)			0.444
None	8 (40)	12 (40)	
Carboplatin- paclitaxel	9 (45)	16 (53.33)	
Others	1 (5)	2 (6.67)	
Unknown	2 (10)	0	
Number of cycles	5 (4–6)	4 (3–5)	0.115

Contd...

Table 1: Contd...

	HIPEC + CRS (*n*=20), *n* (%)	CRS (*n*=30), *n* (%)	*P*
Postoperative laboratories			
Hemoglobin	126 (106–139)	120 (108–131)	0.181
Hematocrit	0.38 (0.33–0.43)	0.37 (0.35–0.41)	0.330
Platelet	206 (161–260)	260 (192–427)	0.021
Na	142 (137–145)	137 (136–142)	0.055
K	3.8 (3.5–4.5)	4.1 (3.6–4.3)	0.425
Mg	0.82 (0.71–0.92)	0.72 (0.62–0.73)	0.004
Albumin	22 (19–25)	24.5 (18–28)	0.546
Creatinine	79 (58–120)	58 (47–71)	0.042
Tumor markers (CA 125)			
Preoperative	228 (108–1000)	215 (36.4–738)	0.601
Postoperative	33.7 (18.78–121)	84.5 (20–342)	0.253

CA 125: Cancer antigen 125, ECOG: Eastern Cooperative Oncology Group, CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy, FIGO: International Federation of Gynecologic Oncology

Table 2: Surgical information and treatment characteristics

	HIPEC + CRS (*n*=20), *n* (%)	CRS (*n*=30), *n* (%)	*P*
PCI	10 (5.5–12)	15 (9–20)	0.023
Complete cytoreduction score	0	0 (0–4)	<0.001
Ureteric stenting done	17 (85)	3 (10)	<0.001
Duration of OR (min)	360 (300–383)	240 (215–255)	<0.001
Chest tube thoracostomy	1 (5)	0	0.400
Stoma	11 (55)	2 (6.67)	<0.001
Operative outcomes			
EBL (mL)	425 (300–600)	750 (500–1000)	0.211
Intraoperative transfusion (PRBC)	0 (0–1)	0 (0–2)	0.315
Postoperative complications	9 (45)	3 (10)	0.007
Grade of complication			
Grade I	2 (22.22)	0	1.000
Grade II	5 (55.56)	3 (100)	
Grade III	1 (11.11)	0	
Grade IV	1 (11.11)	0	
ICU	4 (20)	0	0.021
Number of days postoperative stay	8 (7–13)	6 (4–9)	0.026
Adjuvant chemo			0.001
Unknown	12 (60)	28 (93.33)	
Carboplatin - paclitaxel	7 (35)	1 (3.33)	
Others	1 (5)	1 (3.33)	
Recurrence	10 (50)	13 (43.33)	0.774
Time to recurrence (months)	10 (7–16.5)	9 (6–11)	0.636
Site of recurrence			0.029
Multiple sites	6 (30)	1 (33.33)	
Isolated site	2 (10)	3 (10)	
Unknown site	12 (60)	26 (86.67)	
Postoperative follow-up (months)	10.5 (1–16)	10.5 (2.5–22.5)	0.340
Expired	1 (5)	4 (13.33)	0.636

ICU: Intensive care unit, PRBC: Packed red blood cell, EBL: Estimated blood loss, PCI: Peritoneal cancer index, OR: Odds ratio, CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy

complication was due to an intra-abdominal abscess. The patient with grade 4 complication experienced hemorrhage, and acute kidney injury, and underwent hemodialysis.

ICU admission was more frequent in the CRS + HIPEC group (P = 0.021). The median postoperative hospital stay was also longer (8 days vs. 6 days, P = 0.026). There were no intraoperative or perioperative deaths in either groups with CRS or CRS+HIPEC.

Median time to recurrence was similar in both treatment arms, 10 months for CRS + HIPEC (7 to 16.5 months) and 9 months for CRS (6 to 11 months). There was

no statistical difference in the number of patients with recurrence (50% for CRS + HIPEC and 43% for CRS alone). All cases in the CRS group were interval debulking surgeries.

Postsurgery, patients' median follow-up time was 10.5 months in both groups. There was no statistical difference between the two groups with regard to the number of patients who succumbed to the disease during this time (P = 0.636).

There was only 1 mortality documented in the CRS + HIPEC group, and 4 mortalities in the CRS-only group, for a total of 10% for all the subjects, hence analysis of survivor function was consolidated. Survivor function is the probability of survival of the patients at a given point in time [Table 4 and Figure 3]. From the date of surgery to last follow-up, the probability of survival of all patients at 23 months was 88.89% (95% CI: 43%–98%), at 25 months was 77.78% (95% CI: 36 to 94%), at 35 months was 51.85% (95% CI: 8%–84%), and at 47 months was 25.93% (95% CI: 1%–67%).

Discussion

This retrospective study included 50 patients with ovarian, fallopian tube, and peritoneal cancer who underwent CRS with or without HIPEC from January 2014 to June 2020. In 2014, the Gynecologic Oncology Committee of FIGO revised the staging to incorporate ovarian, fallopian tube, and peritoneal cancer in the same system. Histologic, molecular, and genetic evidence shows that as many as 80% of tumors that were classified as high-grade serous carcinomas of the ovary or peritoneum may have originated in the fimbrial end of the fallopian tube. These new data support the view that high-grade serous ovarian, fallopian tube and peritoneal cancers should be considered collectively.[23]

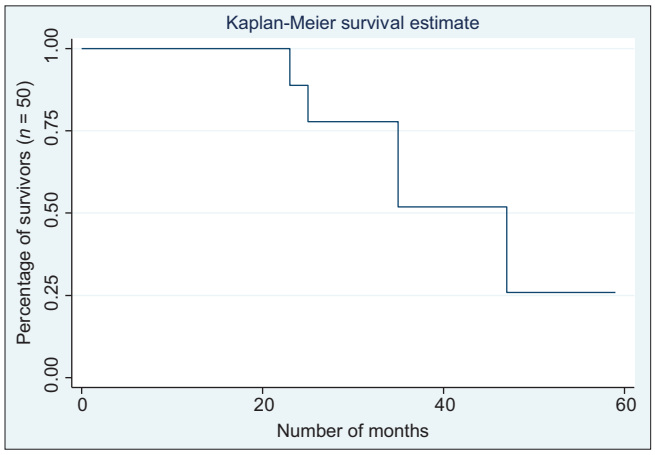

Figure 3: Survival curve of advanced stage or recurrent ovarian, fallopian tube, and cancer patients who underwent cytoreductive surgery with or with hyperthermic intraperitoneal chemotherapy from date of surgery to last follow-up

CRS + HIPEC was formally adopted by the Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, UP-PGH as an option for managing advanced-stage and recurrent ovarian cancer since 2014. In the 2023 guidelines of the Society of Gynecologic Oncologists of the Philippines,[22] for advanced and recurrent epithelial ovarian cancer, CRS with HIPEC may be considered as a curative treatment depending on the PCI as it may achieve long-term survival even in patients with a poor prognosis or those with chemo-resistant disease. These procedures were performed by a multidisciplinary team that included gynecologic oncology, colorectal surgery, urology, anesthesiology, medical oncology, and may also include the thoracovascular surgery service.

The present study showed a median time to recurrence of 10 months in the combined treatment of CRS with HIPEC. This value is lower than the findings of Van Driel who cited a median recurrence-free survival of 14.2 months[7] in the surgery-plus-HIPEC group. It should be noted that the current study has a different patient population. Patient selection may play a role since among patients with recurrent disease, CRS+HIPEC was more commonly performed (7 out of 9) than CRS alone (2 out of 9). In addition, among the 39 patients with primary disease, two-thirds underwent CRS alone. The shorter median time to recurrence found in this study can thus be attributed to the greater number of patients having a poorer prognosis who belonged to the CRS+HIPEC group. Moreover, the positive results by Van Driel can be secondary to their IDS) cases which were only represented in 8 patients or 40% of the present HIPEC cohort.

Table 3: Hyperthermic intraperitoneal chemotherapy regimen (*n*=20)

Chemotherapy	Frequency (%)
Cisplatin	5 (25)
Cisplatin - doxorubicin	2 (10)
Cisplatin - ifosfamide + mesna	4 (20)
Mitomycin C	1 (5)
Doxorubicin + mitomycin C	2 (10)
Ifosfamide + mesna	1 (5)
Unknown	5 (25)
Sodium thiosulfate (given concurrent with other chemotherapy)	5 (25)

Table 4: Survivor function

Time (months)	Expired	Survivor function	95% CI
23	1	0.8889	0.43–0.98
25	1	0.7778	0.36–0.94
35	1	0.5185	0.08–0.84
47	1	0.2593	0.01–0.67

CI: Confidence interval

The CRS-only group had a higher median PCI score of 15 versus only 10 in the HIPEC group. There is no established PCI cutoff for gynecologic disease. Nevertheless, both groups had PCI <21, which was the recommended cutoff by the PSOGI to prognosticate resectability.[26] However, the limits of PCI especially in gynecologic disease would be the spread to the pelvic side walls which precludes complete resection despite PCI < 21.

There was no significant difference in the histology between both cohorts. In contrast, the Van Driel study included cases of carcinosarcoma and clear cell carcinomas in their CRS arm which tend to have poorer prognosis, while the CRS+HIPEC arm had low-grade and mucinous histologic types which tend to have a better prognosis. The poorer histologies in the CRS arm and the less aggressive histologies in the CRS+HIPEC arm may have impacted the difference in outcomes.

Moreover, institutional practice for patients with advanced disease, with no contraindications to primary surgery, often undergoes cytoreductive debulking alone followed by IV chemotherapy (86%, 26 patients). Even if CRS+HIPEC may offer curative treatment in cases of advanced and recurrent EOC, logistic and financial concerns also influence the utilization of HIPEC since the machine is requisitioned from a private group, necessitating advanced planning and permits. It proves to be an expensive procedure, particularly within the charity setting, with out-of-pocket costs potentially reaching around PhP 90,000 in the absence of available subsidies.

As this study aimed to characterize the utilization of HIPEC in the country, future studies are needed to better ascertain the use of HIPEC in primary or interval debulking versus cases with recurrent or progressive disease. The initial out-of-pocket cost of HIPEC might mitigate, in the long run, additional cycles of chemotherapy for progressive or recurrent disease, in light that immunotherapy is not readily available. In this study, the number of chemotherapy cycles is lower in post-CRS patients (P = 0.012) probably because this cohort had less number of recurrent and progressive disease cases compared to the CRS + HIPEC group.

With regards to morbidity and mortality, the results of this study showed better outcomes for CRS + HIPEC compared to the published literature. There were only 2 cases with grade 3 to 4 complications, accounting for 10% of the population cohort. In the retrospective study conducted by Bakrin, overall morbidity was 31% and mortality was 0.5%. Leukopenia, intra-abdominal hemorrhage, and an anastomotic leak occurred in 11.6%, 3%, and 2.4% respectively.[8] OVHIPEC reported the information about adverse events between HIPEC arm and non-HIPEC arm. The percentage of patients who had grade 3 or 4 adverse events was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P = 0.76).[7] Morbidity following CRS + HIPEC has been reported to be between 12% and 33%.[2,7] The percentage of grade 3 and 4 HIPEC complications in the present study (10%) was even lower than those in the surgery alone group cited in the Van Driel study (27%). The addition of HIPEC is associated with renal impairment and hematological toxicity due to transient bone marrow suppression often associated with the chemotherapy administration component of the procedure.[27] In this study, the grade 1-2 complications were due to anemia, ileus, and acute kidney injuries as reflected in a higher postoperative serum creatinine. Although none of the patients became thrombocytopenic, patients belonging to the CRS + HIPEC group were found to have lower platelet counts, which may be indicative of transient bone marrow suppression. Furthermore, expected complications of anemia were not seen in this study, as reflected by post-operative hemoglobin and hematocrit being within normal limits for both groups. This could probably be attributed to the extent of the CRS, better patient selection, low PCI median of only 10, and optimization of all preoperative laboratory parameters.

Ureteral stenting was part of the institution's initial practice for HIPEC, ergo more cases in the CRS + HIPEC group underwent stenting. The percentage of patients who underwent a colostomy or an ileostomy after surgery was also significantly higher in the CRS+HIPEC arm. This difference in the rate of colostomy or ileostomy could reflect the surgeons' preference. However, there is no evidence to suggest that the rate of anastomotic leakage after bowel surgery is higher among patients who underwent HIPEC after CRS.

Majority of complications were more likely due to the aggressive CRS rather than HIPEC, particularly in terms of bowel complications. The grade 3 complication was due to an intraabdominal abscess, which has been reported in 4.8% of HIPEC cases. The nature or causative nature of the infection in patients treated with CRS + HIPEC usually had received multicycle chemotherapy. Some of these patients may have poor physical condition and are at high risk of adverse events after invasive multi-organ resection. In addition, HIPEC drugs can not only kill residual tumor cells in patients' abdominal cavities, but also have drug toxicity and immunosuppressive effects, making patients potentially at high risk for postoperative infection. The grade 4 complication was due to intraoperative blood loss which led to acute kidney injury, subsequently warranting hemodialysis. This could reflect one of the main limitations of HIPEC as it is only performed when the surgery was classified as

complete (no visible residual disease, R0), which would necessitate extensive surgery and could be associated with an increase in morbidity and mortality as reported in literature. Nevertheless, morbidity and mortality have improved considerably in HIPEC expert centers. Retrospective studies conducted between 2005 and 2011 showed a complication rate of 33% and a 30-day mortality rate of 2.3%.[21] The current study demonstrated no mortality during the perioperative period.

ICU stay was more frequent in the CRS + HIPEC group as part of the initial practice when HIPEC was being started, where all patients were co-managed by colorectal surgery and admitted in the Surgical ICU postoperatively. On the other hand, there is no dedicated gynecologic ICU; hence, patients who underwent CRS alone were directly transferred directly to the gynecologic wards. The longer postoperative stay for the CRS + HIPEC patients may be due to the higher ICU admissions and the presence of Grade 3 and 4 complications in this cohort.

Multiple studies have described different methods and protocols for HIPEC.[14,27] There were differences in techniques, equipment used, protection mechanisms, and training. In international studies, the type of chemotherapy, temperature, and duration of treatment are very heterogeneous. Platinum salts, most often cisplatin, oxaliplatin, or carboplatin, are generally used because of its capacity to induce DNA adducts in tumors, thereby rendering majority of the epithelial ovarian and peritoneal cancers platinum-sensitive. These are also reflected in the local setting [Table 3], where Cisplatin was often incorporated in the regimen together with other chemotherapy drugs such as Doxorubicin or Ifosfamide (with Mesna). Some regimens took into account the risks for nephrotoxicity, and sodium thiosulfate was administered. The most frequent (25%) regimen used was Cisplatin alone over a 90-min infusion time which was also the regimen utilized in the Van Driel study.[7]

After a median follow-up of 10.5 months, there was only 1 mortality documented in the CRS + HIPEC group, and 4 mortalities in the CRS-only group, hence analysis of survivor function was consolidated for all subjects. For all ovarian, fallopian tube, and peritoneal cancer patients who underwent CRS with and without HIPEC, survival at approximately 2 years was 77.78%–88.89%. This decreases to 51.85% at approximately 3 years, and to 25.93% at 4 years [Table 4]. This study is in accordance with the prevailing 5-year survival rates of 20%–30% for advanced ovarian cancer.

Given the nature of the study, investigators were limited to the small number of patients who underwent CRS with HIPEC from January 2014 to June 2020 and the available information from the database and chart reviews. Selection bias for patients who underwent HIPEC may have also affected the results of the study. Nevertheless, the results of this study gave an overview of how CRS + HIPEC was integrated in the past 7 years of gynecologic oncology practice in the national cancer referral center in the Philippines and the nuances which might have contributed to its impact on clinical outcomes.

CRS + HIPEC may still be a treatment option for advanced, recurrent, and progressive epithelial ovarian, fallopian tube, and peritoneal cancer given its 10-month median recurrence-free interval, comparable recurrence rate to CRS alone, and low complication risks. Prospective studies are warranted to better define clear population groups and to measure the impact of HIPEC in primary versus recurrent or progressive gynecologic malignancies. Future studies are needed to define PCI thresholds and chemotherapy regimens for HIPEC concerning the whole multimodal treatment strategy.

Conclusion

This retrospective cohort study aimed to determine the efficacy and safety of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) versus CRS alone for patients with epithelial ovarian, fallopian tube, and peritoneal cancer. CRS with or without HIPEC had similar time to recurrence and recurrence rates. CRS with HIPEC had a low risk of grade 3-4 complications and may still be considered as a treatment option for advanced, progressive and recurrent epithelial ovarian, fallopian tube, and peritoneal cancer.

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Authorship contributions
Onglao - Conceptualization, methodology, analysis, investigation, writing - original draft, visualization.

Luna - Conceptualization, methodology, writing - review and editing, supervision.

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Conflicts of interest
There are no conflicts of interest.

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