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Original Article

Hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer

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ABSTRACT

Background: To investigate outcomes and morbidity of patients undergoing secondary cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in recurrent ovarian cancer.

Materials and methods: Between April 2014 and January 2019, a total of 51 recurrent ovarian cancer patients receiving secondary CRS and HIPEC were retrospectively reviewed.

Results: Among the 51 patients, median peritoneal cancer index score was 13 (range 3–34), and completeness of cytoreduction (CC) score of 0/1 was achieved in 41 patients (78.8%). Regimen of HIPEC included cisplatin and paclitaxel in 39 (75%) cases. The median follow-up duration of survivors was 20.2 months. Sixteen (30.8%) patients remained free of recurrence after HIPEC. The median progression-free survival (PFS) and overall survival (OS) were 11.8 months and 34.5 months respectively. Multivariate analysis showed previous chemotherapy <2 lines (HR 0.24, 0.11–0.52; $p = 0.001$), chemotherapy-free interval ≥6 months (HR 0.19, 0.09–0.37; $p < 0.001$) and CA125 < 35 U/mL before HIPEC (HR 0.133, 0.021–0.0832; $p = 0.031$) were good prognostic factors for PFS. CC0/1 was not significant in multivariate analysis. The most common grade 3/4 toxicity was anemia (17.3%), pleural effusion (11.5%) and renal insufficiency (5.7%). Patients with age ≥50, peritoneal carcinomatosis index (PCI) ≥ 11, operation time ≥10 h and diaphragm surgery had significantly higher incidence of pleural effusion.

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Conclusions: The current study showed adding HIPEC to secondary CRS might prolong PFS especially in patients with previous chemotherapy <2 lines, chemotherapy-free interval ≥6 months and CA125 < 35 U/mL before HIPEC.

At a glance commentary

Scientific background on the subject

Secondary cytoreductive surgery (CRS) for recurrent ovarian cancers inside abdominal cavity does not prolong overall survivals compared to chemotherapy with or without bevacizumab. HIPEC can synergize the cytotoxic effects of hyperthermia and accelerating the efficacy of intraperitoneal chemotherapy. HIPEC with CRS was proved to have longer overall survivals in primary ovarian cancer than CRS alone.

What this study adds to the field

For patients with recurrent ovarian cancer, our current study showed adding HIPEC to secondary CRS might prolong progression-free survivals, especially in patients with following prognostic factors: previous chemotherapy < 2 lines, chemotherapy-free interval ≥ 6 months and CA125 < 35 U/mL before HIPEC.

Ovarian cancer is one of the most prevalent gynecologic cancers, with nearly 22,000 new-onset cases and 14,000 deaths in the United States in 2015 [1]. In Taiwan, there are nearly 1500 new cases and 650 deaths per year [2]. About 70% of patients with ovarian cancer obtain complete response after debulking surgery and adjuvant chemotherapy, but around 70% of them suffer from recurrent disease. The major treatment for recurrent ovarian cancer is chemotherapy and subsequent maintenance therapy. Most of the recurrent ovarian cancers present with intraperitoneal tumors or carcinomatosis. Several studies of intraperitoneal chemotherapy suggested better survival results than conventional intravenous route [3,4]. Elevation of body temperature had been used to treat cancer since ancient times. The cancer-killing effect of hyperthermia might result from heat-induced necrosis, protein inactivation, changing of tumor cytoskeletal structures, disruption of cell motility and intracellular signal transduction [5,6]. There is no consensus on the temperature of hyperthermia. Urano et al. showed that thermal enhancement of cytotoxicity of chemotherapeutic agents was maximized at the temperatures of 40.5–43 °C [7].

Hyperthermia-enhanced anti-cancer effect of radiotherapy and chemotherapy involves inhibition of homologous recombination repair of double-strand DNA breaks, preventing cells from repairing sub-lethal damage [8]. Hyperthermia treatments include local, regional and whole-body approaches. In among, hyperthermic intraperitoneal chemotherapy (HIPEC) during cytoreduction surgery (CRS) became more acceptable treatment with evidence of better prognosis.

HIPEC at 42–43 °C synergizes the cytotoxic effects of hyperthermia and accelerating the efficacy of intraperitoneal chemotherapy [9]. A randomized-controlled study by Spiliotis showed that patients with recurrent ovarian cancer undergoing secondary CRS and HIPEC had better median overall survival (OS) than those without HIPEC (26.7 versus 13.6 months) [10]. Another 3 retrospective studies by Casecales-Campos [11], Le Brun [12], Safra [13] also demonstrated better outcome in patients receiving additional HIPEC for salvage surgery.

The aim of our study was to review the therapeutic response and associated toxicities of HIPEC for patients with recurrent ovarian cancer receiving secondary CRS in Chang Gung Memorial Hospital at Linkou.

Materials and methods

Patient and study design

This study retrospectively analyzed data of patients with recurrent epithelial ovarian cancers, including origins of ovary, fallopian tube and peritoneum who received HIPEC during secondary CRS in the Linkou branch of Chang Gung Memorial Hospital from April 2015 to January 2019. The study was approved by the local ethics committee (IRB No. 201800797B0). We retrieved clinical data from electric medical charts. Peritoneal carcinomatosis index (PCI) score and completeness of cytoreduction (CC) score were recorded during surgery based on previous articles [14,15].

Patients must have intraperitoneal recurrence and no other distant metastasis defined by computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET). All the pre-operational surveys and treatment plans were discussed in a weekly multidisciplinary conference composed of gynecological oncologists, diagnostic radiologists, radiation oncologists, pathologists and nuclear medicine physicians. All the intraperitoneal lesions and enlarged nodes must be possibly removed to an expectation of complete cytoreduction as judged by pre-operative image study to fit criteria of secondary CRS and HIPEC. Peritonectomy was done in patients with intraperitoneal tumor seedings. Resection of diaphragmatic nodules, liver nodules, peritonectomy, bowel resection, ureter tumor, and bladder procedures were done in cooperation with general surgeon, proctologist, and urologist, and were done before HIPEC. Reanastomosis of resected bowels, colostomy, and ileostomy were done after completion of HIPEC. Regimen of adjuvant chemotherapy were selected according to physician's judgment.

Primary endpoints of the current study were progression-free survival (PFS) and OS. The definition of PFS was the interval between HIPEC date to the time of disease progression

or death. The OS was calculated since HIPEC date to the time of death. Status of disease was determined by RECIST criteria [16] and CA125 criteria of GCIG (Gynecologic Cancer InterGoup) [17]. Chemotherapy-free interval (CFI) was defined as interval between the last date of previous chemotherapy and the date of recent relapse before CRS.

HIPEC protocols and regimens

HIPEC was performed immediately after CRS. We used a closed-system machine (Performer HT, Rand, Italy) with heating system and adjustable flow rate to provide adequate intraabdominal circulation at a static flow. The regimens of chemotherapy for HIPEC were cisplatin (75 or 90 mg/m^2) plus paclitaxel (135 or 175 mg/m^2), cisplatin plus doxorubicin, cisplatin, mitomycin-C and gemcitabine as demonstrated in Table 1. During setting up of intraabdominal circulation system, the chemotherapeutic drug was diluted into 6 L with peritoneal dialysis fluid. We kept a volume of 2 L time body surface area (BSA) to distend abdominal cavity to ensure smooth circulation of chemotherapy drug in it, and remained the other fluid in the extracorporeal system. Four thermal sensors were placed at liver/diaphragm space, cul-de-sac, inflow site, and outflow site to monitor the temperature of therapeutic fluid between 42 °C and 43 °C. The circulation system included two tubes of infusion and 2 for outflow connecting to the HIPEC machine. Pressure monitoring was done by 6 transducers that are attached at various locations within the disposable extracorporeal circuit. Total duration of intraabdominal chemotherapy was 90 min. The intraabdominal chemotherapeutic fluid was evacuated by rinsing procedure at the end of HIPEC.

Safety and toxicity

All associated adverse effects were recorded until 30 days after operation. The toxicity grading was evaluated based on the Common Terminology Criteria for Adverse Events version 5.0 [18].

Statistical analysis

Both PFS and OS were analyzed by Kaplan–Meier curves. The differences in PFS and OS among groups were evaluated with log-rank tests. Univariate and multivariate Cox regression analysis were used to evaluate the relationship between parameters and survival data. Descriptive statistics were used to summarize the demographic characteristics, and Chi-square test was used to analyze categorical data. *The P values less than 0.05* were considered as statistically significant.

Results

From April 2015 to January 2019, 51 patients accepted HIPEC after secondary CRS, including 1 patient undergoing 2 times, in our hospital. The median follow-up time among the survivors was 20.2 months. As shown in Table 1, the median age at HIPEC was 53.9 years (range 35.3–77.8), and the median body mass index (BMI) was 24.2 (range 18.7–42.6). High grade

Table 1 Patient characteristics.

Characteristics	N (%)
Patients	51
HIPEC treatment	52
Median age at HIPEC (range)	53.9 (35.3–77.8)
Median BMI (range)	24.2 (18.7–42.6)
Histology	
HGSC	33 (63.5)
LGSC	1 (1.9)
Endometrioid	8 (15.4)
Mucinous	1 (1.9)
Clear cell	3 (5.8)
Mixed	1 (1.7)
Others	5 (9.6)
Initial FIGO stage	
1A/1B	4 (7.7)
1C	4 (7.7)
2	3 (5.8)
3	33 (63.5)
4	6 (11.5)
NA	2 (3.8)
Previous lines of chemotherapy	
0 or 1	23 (44.2)
≥2	29 (55.8)
Chemotherapy-free interval	
Median months (range)	8.3 (0.1–74.0)
Initial platinum sensitivity	
Platinum sensitive	37 (71.2)
Platinum resistant	13 (25.0)
NA	2 (3.8)
PCI score	
Median (Range)	13 (3–34)
Upper abdomen alone, N (%)	4 (7.7)
Lower abdomen alone, N (%)	11 (21.2)
Upper and lower abdomen, N (%)	30 (57.7)
Missing data, N (%)	7 (13.4)
Diaphragm surgery	20 (38.5)
Bowel resection	29 (55.8)
Small intestinal resection	3 (5.8)
Large intestinal resection	13 (25)
Small and large intestinal resection	13 (25)
Bowel anastomosis	23 (44.2)
Intestinal stoma	15 (28.8)
OP time (CRS + HIPEC)	
Median hours (Range)	10.3 (5.1–16.3)
HIPEC regimen	
Cisplatin + paclitaxel	39 (75)
Cisplatin + doxorubicin	2 (3.8)
Cisplatin	4 (7.7)
Mitomycin-C (+/− doxorubicin)	6 (11.5)
Gemcitabine	1 (1.9)
CC score after CRS	
0	27 (51.9)
1	19 (36.5)
2	5 (9.6)
3	1 (1.9)
ICU stay	20 (38.5)
Median days in ICU (Range)	3 (2–8)
Median hospitalization days (Range)	17 (5–60)
Interval to next chemotherapy	
Median days (Range)	31 (12–149)

Abbreviations: HIPEC: hyperthermic intraperitoneal chemotherapy; BMI: body mass index; HGSC: high-graded serous carcinoma; LGSC: low-graded serous carcinoma; FIGO: The International Federation of Gynecology and Obstetrics; NA: not applicable; PCI: peritoneal cancer index; OP: operation; CRS: cytoreductive surgery; CC score: completeness of cytoreduction score; ICU: intensive care units.

serous carcinoma accounted for 63.5% of patients. The median PCI score was 11 (range 3–34) and the median operation time was 10.3 h (range 5.1–16.3). The operation time was defined as the period between incision to closure of abdominal wall. The percentage of patients undergoing diaphragmatic surgery and bowel resection were 38.3% and 55.8% respectively. Thirty-seven patients were platinum-sensitive and 13 patients were platinum-resistant. Nearly 75% of HIPEC regimen was cisplatin plus paclitaxel. CRS to CC0, CC1 and CC0/1 were achieved in 51.9%, 36.5% and 88.4% of operations respectively. Due to long operation time, 38.5% of patients were transferred to intensive care unit (ICU) after operation, and the median ICU stay was 3 days (range 2–8). The median hospitalization was 17 days (range 5–60), and the median time to next chemotherapy was 1 month. Forty patients (76.9%) accepted post-operative chemotherapy, with a median cycle of 5 (range 1–8). The median PFS and OS were 11.8 months (95% CI 6.2–17.3 months) and 34.5 months (95% CI 11.7–57.3) respectively [Fig. 1]. The PFS rate at 12 and 24 months were 48.4% and 18.7%. The survival rate at 12 months, 24 months, and 36 months were 74.6%, 58.5%, and 43.8% respectively. For patients with first recurrence, the median PFS and OS were 22.3 and 41.3 months respectively. In the 46 patients of CC0/1, platinum-sensitive patients had longer PFS (15.2 months vs 3.8 months, $p < 0.001$) and OS (41.3 months vs 10.6 months, $p < 0.001$) than platinum-resistant ones.

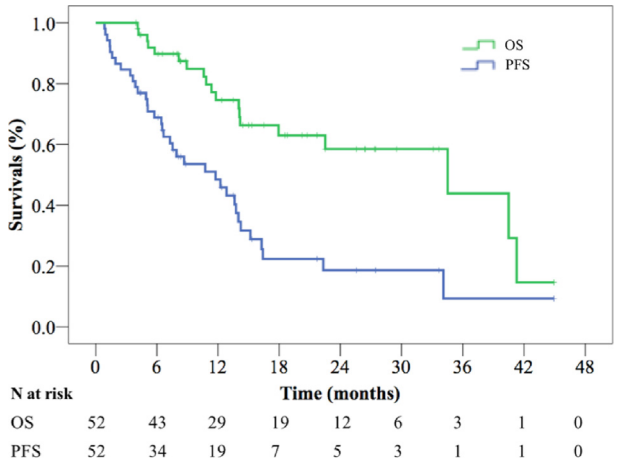

Fig. 1 PFS and OS curve of patients. PFS: progression-free survivals, OS: overall survivals.

Table 2 showed univariate and multivariate analysis. Univariate analysis showed CC 0 (HR 0.469, 95% CI 0.239–0.919; $p = 0.027$), previous line of chemotherapy 0/1 (HR 0.235, 95% CI 1.106–0.523; $p < 0.001$), and CFI ≥6 months (HR 0.185, 95% CI 0.093–0.369; $p < 0.001$) were good prognostic factors for PFS, while age, body mass index (BMI), operation time, different PCI score, bowel resection, diaphragmatic surgery, and grade of non-hematologic toxicity had no significance in our patients. Further multivariate analysis demonstrated CFI ≥6 months (HR 0.042, 95% CI 0.011–0.16; $p < 0.001$), previous line of chemotherapy 0/1 (HR 0.1, 95% CI 0.024 to 0.407; $p = 0.001$), and CA125 < 35 U/ml (HR 0.133, 95% CI 0.021–0.832; $p = 0.031$) were good prognostic factors.

Twenty-eight (56%) patients did not have subsequent intraperitoneal recurrence after HIPEC, and their PFS was 16.3 months. In the intraperitoneal recurrence-free patients, 7 of them were heavily pretreated with average 2 lines of previous chemotherapy.

Table 3 listed adverse events including hematologic and non-hematologic toxicity. There was no grade 5 toxicity. Most

Table 3 Adverse events of HIPEC.

	≥ G3	Any grade
Hematologic toxicity	12 (23.1)	46 (88.5)
Anemia	9 (17.3)	45 (86.5)
Neutropenia	2 (3.8)	6 (11.5)
Thrombocytopenia	1 (1.9)	6 (11.5)
Non-hematologic toxicity	11 (21.2)	31 (59.6)
Venous thrombosis	0	1 (1.9)
Pleural effusion	6 (11.5)	20 (38.5)
Renal impairment	3 (5.7)	18 (34.6)
Wound healing defective	1 (1.9)	5 (9.6)
GI perforation	1 (1.9)	2 (3.8)
Fistula	1 (1.9)	3 (5.7)
Abscess	1 (1.9)	2 (3.8)

Abbreviations: G3: grade 3; CHF: congestive heart failure; GI: gastrointestinal.

Table 2 Univariate and multivariate analysis of PFS.

		Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age	≥60	1.147 (0.535–2.455)	0.725	0.418 (0.136–1.289)	0.129
BMI	≥25	0.485 (0.232–1.016)	0.055	0.365 (0.132–1.01)	0.052
OP time (hr)	≥10	1.026 (0.523–2.013)	0.939	0.457 (0.158–1.325)	0.149
PCI score	≥12	1.547 (0.749–3.194)	0.238	2.209 (0.911–5.359)	0.08
Bowel resection	yes	1.065 (0.55–2.062)	0.852	2.578 (0.881–7.549)	0.084
Diaphragm surgery	yes	0.743 (0.378–1.462)	0.39	0.425 (0.17–1.062)	0.067
CC score	<1	0.469 (0.239–0.919)	0.027	1.801 (0.614–5.285)	0.284
NH G3 at least	yes	1.102 (0.495–2.451)	0.812	2.769 (0.929–8.25)	0.068
Prior chemo lines	<2	0.235 (0.106–0.523)	<0.001	0.1 (0.024–0.407)	0.001
Chemotherapy-free interval	≥6 months	0.185 (0.093–0.369)	<0.001	0.042 (0.011–0.16)	<0.001
CA-125 (U/mL)	<35	0.357 (0.125–1.015)	0.053	0.133 (0.021–0.832)	0.031

Abbreviations: PFS: progression-free survivals; HR: hazard ratio; CI: confidence interval; BMI: body mass index; OP: operation; hr: hour; PCI: peritoneal cancer index; CC score: completeness of cytoreduction score; NH: non-hematologic toxicity; G3: grade 3; Chemo: chemotherapy.

common hematologic toxicity was anemia accounting for 86.5% of total patients, and 17.3% of them were grade 3/4. Non-hematologic toxicity occurred in 59.6% of patients, including pleural effusion (38.5%), renal function impairment (34.6%), and poor wound healing (9.6%). The incidence of grade 3/4 non-hematologic toxicity was 21.2% including pleural effusion (11.5%) and renal function impairment (5.7%).

Patients with age ≥50, PCI ≥11, operation time ≥10 h and diaphragm surgery had statistically significant higher incidence of pleural effusion [Table 4]. The renal toxicity was not related to age, BMI, PCI score, operation time, bowel surgery, diaphragmatic operation, CA125 level, and cisplatin use during HIPEC (Appendix table A).

Discussion

Patients with advanced ovarian cancers have high recurrent rate over 70% after primary cytoreductive surgery and adjuvant chemotherapy [19]. Those with recurrent diseases suffer from subsequent recurrences almost without exception. The PFS shortens along with the recurrent times, with median interval of 10.2, 6.4, 5.6, 4.4 and 4.1 months after 1st, 2nd, 3rd, 4th and 5th recurrence respectively [20]. There is an unmet need for better measures to prolong PFS after salvage chemotherapy for recurrent disease, and hoping for longer OS. Among them, combining anti-angiogenesis drug and switching to poly ADP-ribose polymerase (PARP) inhibitor for maintenance therapy are effective strategy [21–24]. Use of dose-dense chemotherapy is another option suggested in a retrospective study [25]. Secondary debulking surgery is not a regular option for recurrent ovarian cancer because the survivals benefit was still needed to be validation since different results had been reported before [24,26,27]. However, intraperitoneal carcinomatosis is incurable and finally becomes refractory to chemotherapy. HIPEC is a kind of intraperitoneal chemotherapy to kill small or nonvisible cancerous implants theoretically.

Table 4 Parameters of pleural effusion toxicity.

	Any grade N (%)	*p* value	≥ G3 N (%)	*p* value
Age		0.005		0.351
<50	2 (11.8)		1 (5.9)	
≥50	18 (51.4)		5 (14.3)	
BMI		0.499		0.397
<20	1 (25.0)		1 (25.0)	
≥20	19 (39.6)		5 (10.4)	
PCI		0.023		0.063
<11	3 (18.8)		0	
≥11	16 (53.3)		6 (20.0)	
OP time (hr)		0.042		0.506
<10	5 (22.7)		3 (13.6)	
≥10	15 (50.0)		3 (10.0)	
Bowel OP		0.220		0.157
No	7 (30.4)		1 (4.3)	
Yes	13 (44.8)		5 (17.2)	
Diaphragm OP		0.001		0.144
No	6 (18.8)		2 (6.3)	
Yes	14 (70.0)		4 (20.0)	
Cisplatin		0.247		0.180
Yes	16 (35.6)		4 (8.9)	
No	4 (57.1)		2 (28.6)	
CA125		0.485		0.146
<35	8 (34.8)		1 (4.3)	
≥35	11 (39.3)		5 (17.9)	

Abbreviations: G3: grade 3; BMI: body mass index; PCI: peritoneal cancer index; OP: operation; hr: hour.

Several articles showed that adding HIPEC to secondary CRS had better results than conventional treatment for advanced and recurrent ovarian cancer [12,13,28,29]. The French retrospective study by Bakrin et al. reported median OS up to 45.7 months in patients with recurrent ovarian cancer after secondary CRS and HIPEC [30]. A prospective phase 3 study comparing the survivals between secondary CRS with/without HIPEC in first recurrent ovarian cancer by Spiliotis et al. showed significantly better survival in HIPEC group (26.7 months vs. 13.4 months, $p < 0.006$) [10]. For our patients with first recurrence, the median PFS and OS were 22.3 and 41.3 months respectively, and the data was longer than Spiliotis et al.'s result. More than half of our patients (53.8%) were repeatedly recurrent ovarian cancers and heavily pretreated. In our entire cohort, the median PFS and OS were 11.8 months and 34.5 months respectively which were comparable to that of previous studies [31,32].

Complete cytoreduction to CC0 is invariably the most dominant factor of longer survival in many studies [10,33–36]. The current study also showed that patients of CC0 had longer PFS than those with CC1 or more. This result encourages HIPEC for recurrent ovarian cancer with small intraperitoneal nodules that escape detection of image studies and revelation of tumor marker surveillance. The reason why CC0 was a significantly good prognostic factor in the univariate study, but not in the multivariate study might be the small case number. The lower CA125 level, < 35 U/ml, standing out as a good prognostic factor in our univariate study might be explained with its association with small tumor burden. Although it was also reported in previous study, if CA125 could be used as a selection criterion for CRS plus HIPEC needs more evidence for validation. Previous studies found that among the patients accepting CRS plus HIPEC, OS was not different between platinum-sensitive and platinum-resistant cohorts [10,30,31]. Our study still showed a significant worse survival for platinum-resistant patients.

Intraperitoneal spreading is the major cause of ascites, abdominal distention and bowel obstruction and also is the reason of treatment failure after its repeated occurrences. In our cohort, 23 (44.2%) patients did not have subsequent intraperitoneal recurrence after HIPEC and chemotherapy, and obtained a longer PFS benefit (HR: 0.20, 95% CI 0.09–0.46, $p = 0.001$). The similar results were also shown in the study of Ceresoli et al. [37]. Our study disclosed better survival results in patients with less lines of prior-chemotherapy or longer CFI and suggested early intervention of secondary CRS plus HIPEC to recurrent ovarian cancer. We suggest using pre-operative selection criteria of AGO-DESKTOP [38] or Chi's [39] study to increase the possibility of cytoreduction to CC0 and subsequent HIPEC procedures.

The morbidity and mortality might come from the long anesthesia time, extensive surgery, or hyperthermic effect and intraabdominal chemotherapy of HIPEC. A systemic review reported that HIPEC-related morbidity rate occurred in

20%–66% of patients, and mortality rates was 0–12% [40]. Besides, another study reported multi-discipline teamwork model can improve the major complications rate of HIPEC [41]. The severest and most common morbidity in the current study was pleural effusion (38.5%), which was associated with age over 50 ($p = 0.005$), PCI score ≥11 ($p = 0.023$), operation time ≥10 h ($p = 0.042$), and diaphragmatic surgery ($p = 0.001$). These factors can be used to identify patients at high risk and do more post-operative pulmonary care or delayed extubation. Transient renal impairment occurred in 34.6% of our patients, without significant associated factor. This result suggests that surveillance of renal function and supportive care should last longer after HIPEC. The reasons why our patients had higher non-hematologic toxicity than that reported in the literatures might be more re-recurrence and severer disease of high PCI score (median 13, range 3–34) [11,29,31,32,34,36].

This is a retrospective study of patients of inconsistent clinical situations in a single center. Although the sample size is limited, it is a real-world data to provide patients an option of salvage therapies.

Conclusions

The current retrospective study showed adding HIPEC to secondary CRS might prolong PFS and decrease the percentage of subsequent intraperitoneal recurrence in patients with CFI ≥6 months, CA125 < 35 U/ml, previous line of chemotherapy <2 and optimal cytoreduction to CC 0, especially those with first recurrence.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2021.10.003.

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