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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic factors of early recurrence after complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Abstract

BACKGROUND

Although cytoreductive surgery (CRS) and hyperthermic intraperitoneal

chemotherapy (HIPEC) offer the potential for long-term survival in peritoneal carcinomatosis, outcomes following CRS/HIPEC vary significantly.

AIM

To identify the clinical factors associated with progression-free survival (PFS) after complete CRS/HIPEC in patients with colorectal/high-grade appendiceal, ovarian, and gastric cancers.

METHODS

We retrospectively evaluated the risk of recurrence within 1 year after CRS/HIPEC and its impact on overall survival (OS) in patients recruited between 2015 and 2020. Logistic regression models were used to assess the prognostic factors for the risk of recurrence within 1 year. Kaplan–Meier survival curves and Cox proportional hazards models were used to evaluate the association between recurrence and OS.

RESULTS

Of the 80 enrolled patients, 39 had an unfavorable PFS (< 1 year) and 41 had a favorable PFS (≥ 1 year). Simple logistic models revealed that the patients with a completeness of cytoreduction score of 0 (CC-0) or length of CRS ≤ 6 h had a favorable PFS [odds ratio (OR) = 0.141, P = 0.004; and OR = 0.361, P = 0.027, respectively]. In multiple logistic regression, achieving CC-0 was the strongest prognostic factor for a favorable PFS (OR = 0.131, P = 0.005). A peritoneal cancer index score > 12 was associated with a lower rate of achieving CC-0 (P = 0.027). The favorable PFS group had a significantly longer OS (median 81.7 mo *vs* 17.0 mo, P < 0.001).

CONCLUSION

Achieving CC-0 was associated with a lower early recurrence rate and improved long-term survival. This study underscores the importance of selecting appropriate candidates for CRS/HIPEC to manage peritoneal carcinomatosis.

Key Words: Peritoneal metastasis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Predictor; Recurrence

Core Tip: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can extend survival in peritoneal carcinomatosis, but outcomes vary. This study examined factors affecting progression-free survival (PFS) after CRS/HIPEC in patients with colorectal, high-grade appendiceal, ovarian, and gastric cancers. Evaluating the results of 80 patients from 2015-2020 showed that those with a completeness of cytoreduction score of 0 (CC-0) or surgery duration ≤ 6 h had better PFS. Achieving CC-0 was the key predictor of favorable PFS and longer overall survival. The study highlights the importance of patient selection for optimal CRS/HIPEC outcomes.

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INTRODUCTION

Peritoneal carcinomatosis is a devastating condition often managed with systemic therapy or supportive care. However, extensive cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a promising treatment, offering the potential for long-term survival and even cure in select patients[1]. HIPEC involves the infusion of chemotherapeutic drugs into the peritoneal cavity at a temperature of 41 °C-43 °C for 60-90 min following optimal CRS. This localized administration targets microscopic residual cancer cells, with both chemotherapy and hyperthermia contributing to the therapeutic effect[2]. Nevertheless, CRS/HIPEC is an aggressive treatment associated with significant side effects[3]. Identifying patients who are likely to respond favorably to CRS/HIPEC and benefit from this intensive approach remains a major challenge.

Complete cytoreduction is considered to be the most crucial prognostic factor in CRS/HIPEC, and various clinical indicators have been investigated to determine optimal patient selection to achieve this goal. The completeness of cytoreduction score (CC score) is evaluated after CRS, with cytoreduction score of 0 (CC-0) indicating the absence of peritoneal seeding, CC-1 denoting nodules persisting after cytoreduction measuring less than 0.25 cm, CC-2 representing nodules between 0.25 cm and 2.50 cm, and CC-3 indicating nodules larger than 2.50 cm[4]. Advanced imaging techniques have been shown to enhance the preoperative evaluation of completeness of cytoreduction and predict surgical outcomes[5].

Even when achieving complete cytoreduction, the outcomes following CRS/HIPEC can still vary significantly. For example, 1-year mortality and recurrence rates of 13% and 35%, respectively, have been reported after CRS/HIPEC in patients with colon cancer[6,7]. In gastric cancer patients, a systematic review reported recurrence rates in those undergoing CRS/HIPEC ranging from 10% to 27%[8], and a meta-analysis of CRS/HIPEC in patients with epithelial ovarian cancer showed significant improvements in overall survival (OS) [hazard ratio (HR) = 0.5] and progression-free survival (PFS) (HR = 0.57)[9]. While CRS/HIPEC may contribute to longer survival in patients with peritoneal carcinomatosis, some patients fail to achieve favorable outcomes, and the outcomes cannot be reliably predicted even with complete cytoreduction. Several studies have explored preoperative predictors of recurrence after CRS/HIPEC, including well-established factors such as low peritoneal cancer index (PCI)[4,10]. A study involving 52 patients with colorectal cancer reported a median PFS of 229 d, with high-grade primary tumor (≥ 3) identified as an independent risk factor for worse outcomes[11]. Lymph node (LNs) metastasis or the number of positive LNs has also been associated with poorer outcomes in patients with appendiceal and colorectal cancers[12,13]. Predictors of worse PFS in patients with recurrent ovarian cancer include platinum resistance, more than one relapse prior to HIPEC, presence of ascites, ≥ 2 lines of prior chemotherapy, chemotherapy-free interval < 6 mo, and CA-125 level > 35 U/mL[14,15]. However, these studies have been limited by small sample sizes and variations in the degree of cytoreduction. Moreover, complete cytoreduction is often defined as achieving CC-0 or CC-1, with CC-1 tumor nodules believed to be penetrable by intracavitary chemotherapy, making them eligible for complete cytoreduction when HIPEC is used[4]. Therefore, there remains a need for comprehensive studies investigating PFS outcomes and relevant predictors in patients who have achieved complete cytoreduction.

The aim of this retrospective cohort study was to investigate the clinical factors associated with recurrence after complete cytoreduction and HIPEC in patients with colorectal/high-grade appendiceal, ovarian, and gastric cancers presenting with peritoneal carcinomatosis.

MATERIALS AND METHODS

Study design and patient population

From April 2015 to August 2020, a total of 205 patients underwent HIPEC procedures at Chang Gung Memorial Hospital, Chiayi, Taiwan. All patients were discussed in a multidisciplinary team meeting prior to CRS/HIPEC. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (202001607A3). All personal information has been removed by de-identification, so that specific persons and their identities cannot be re-identified or be linked to other database. In accordance with the Declaration of Helsinki, this study did not increase the risk of participants, and the requirement for patient consent was waived by the IRB.

The inclusion criteria were as follows: (1) Patients with primary or recurrent colorectal/high-grade appendiceal cancer, gastric cancer, or ovarian cancer with peritoneal carcinomatosis who underwent curative-intent salvage CRS/HIPEC; (2) patients in whom CRS achieved CC-0 or CC-1; and (3) patients with resectable extraperitoneal oligometastasis. The exclusion criteria were as follows: (1) Patients undergoing palliative HIPEC to control ascites without curative intent; (2) patients receiving adjuvant HIPEC who did not have peritoneal carcinomatosis; (3) patients with primary ovarian cancer who achieved a clinical response after neoadjuvant chemotherapy; (4) patients who underwent repeated CRS/HIPEC procedures (≥ 2 times); (5) patients planned for curative-intent CRS/HIPEC but who had a CC score ≥ 2; and (6) patients who were lost to follow-up.

Surgery and HIPEC technique

The surgical procedures and HIPEC were performed by members of the multidisciplinary team. Preoperative PCI scores were evaluated using multidetector computed tomography (CT) and/or magnetic resonance imaging (MRI), and intraoperative assessments were performed using laparoscopy or laparotomy exploration. Extraperitoneal LNs were removed if preoperative imaging indicated positive involvement. After CRS, the CC score was assessed. HIPEC was delivered using the closed method with a Performer™ HT (RanD Biotech, Medolla, Italy). The perfusate used for HIPEC included a mixture of normal saline and pentastarch (Haes-steril, 60 mg/mL, Meda, Sweden) 10% (3:1), or Dianeal® PD4 peritoneal dialysis solution 1.5% dextrose (Baxter) when using oxaliplatin-based regimens. The perfusate was administered at a dose of 2 L/m^2 of body surface area. Chemotherapy was initiated after achieving an intra-abdominal temperature of 43 °C, and the duration of HIPEC was 30, 60, or 90 min depending on the regimen. The choices of chemotherapy regimen and HIPEC duration were based on the specific cancer type, disease status, and relevant references. The HIPEC regimens were as follows: (1) For colorectal cancer or pseudomyxoma peritonei: mitomycin 40 mg (30 mg at time 0; 10 mg at 60 min) over 90 min; or intraperitoneal oxaliplatin (460 mg/m^2) and intravenous 5-FU 1 h before, for 30 min; (2) For platinum- sensitive recurrent ovarian cancer: cisplatin 50-100 mg/m^2 and/or paclitaxel 175 mg/m^2 over 60 min; (3) For platinum-resistant recurrent ovarian cancer: doxorubicin 35 mg/m^2 and mitomycin 15 mg/m^2 over 60 min; and (4) For gastric cancer: mitomycin 15 mg/m^2 and cisplatin 50 mg/m^2 over 60 min; doxorubicin 12.5 mg/m^2 and cisplatin 50 mg/m^2 over 60 min; or mitomycin 40 mg (30 mg at time 0; 10 mg at 60 min) over 90 min. The intraperitoneal chemotherapy drugs were drained out after completing HIPEC[16].

Clinical data collection and follow-up strategy

Data on patient characteristics, operative details, postoperative outcomes, and pathology were recorded by the case manager and evaluated by the multidisciplinary team committee. Postoperative complications were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Follow-up evaluations were conducted at our institution or the patient's referring outside institution, with outside medical records obtained and reviewed. Follow-up CT/MRI scans were performed at 3-6 mo after surgery, upon recurrence of clinical symptoms, or when tumor marker levels increased. Survival and relapse information was recorded from medical records and/or the case manager's record system. The patients were followed from the date of CRS/HIPEC until disease progression. If no progression occurred during the study period, the patients were censored at their last follow-up appointment.

Statistical analysis

Descriptive statistics were reported as mean ± SD, median with minimum and maximum, or frequency with percentage, as appropriate. Potential prognostic variables included age, sex, primary cancer site, LN involvement, CC score, PCI, and number of visceral resections. LN involvement was defined as the involvement of extraperitoneal LNs and recorded dichotomously as wither present or absent. If no LNs were removed, the number of positive LNs was considered to be zero. The association between the receipt of systemic chemotherapy and PFS was also examined. Both pre-HIPEC salvage chemotherapy (within 6 mo before HIPEC) and post-HIPEC salvage chemotherapy (within 6 mo after HIPEC) were recorded as either having received or not received.

The follow-up period was from 1 April 2015 to 31 March 2023. The primary outcome was PFS < 1 year or PFS ≥ 1 years, where PFS was defined as the time from CRS/HIPEC to the first radiographic or pathologic evidence of new or enlarging intra- or extraperitoneal lesions or death, whichever occurred first. Differences in patient characteristics between the favorable and unfavorable groups were compared using a two-sample *t*-test, Mann–Whitney *U*-test or χ^2 test. Crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for all variables using simple logistic regression, and explanatory variables with a *P* value < 0.1 were considered in multiple logistic regression analysis. The final model included baseline characteristics such as age and sex, and significant explanatory variables selected by sequentially removing covariates with a *P* value > 0.05. To examine the impact of recurrence on OS, which was defined as the time from CRS/HIPEC to death, we used Kaplan–Meier curves, log rank tests, and adjusted HRs calculated from Cox proportional hazards models. All tests were two-sided, and a *P* value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, version 23.0, IBM Corp., Armonk, NY, United States).

RESULTS

Patient characteristics and perioperative details

The patient enrollment flowchart is shown in Figure 1. Of the initial 205 procedures performed at the hospital from April 2015 to August 2020, 12 were excluded due to having undergone repeated HIPEC procedures. Among the remaining 193 patients, 113 were further excluded from the analysis for the reasons shown in Figure 1, including not having the specified cancer type, receiving adjuvant or palliative HIPEC, not achieving CC-0/1, non-disease-related deaths before recurrence, and loss to follow-up. As a result, the final analysis included 80 patients. Of these patients, 42 had colorectal cancer, 22 had recurrent ovarian cancer (11 platinum-sensitive and 11 platinum-resistant), 12 had gastric cancer, and 1 had appendiceal high-grade adenocarcinoma. These 80 patients formed the basis for further analysis and investigation of outcomes related to the CRS/HIPEC procedure.

The patients were divided into two groups based on their PFS outcomes: a favorable PFS group (PFS ≥ 1 year; *n* = 41) and an unfavorable PFS group (PFS ≤ 1 year; *n* = 39). The demographics of the patients are shown in Table 1. The distributions of cancer type, previous chemotherapy, and extraperitoneal lesions did not differ significantly between the two groups. However, there was a significant difference in histological grade (*P* = 0.02), with the unfavorable PFS group having a higher proportion of grade 3 disease [24/39 (61.5%) *vs* 21/41 (51.2%)].

Comparisons between the two groups regarding perioperative factors are shown in Table 2. In terms of CC score, only 25 of the 39 patients (64%) in the unfavorable PFS group achieved CC-0, compared to 38 of the 41 patients (93%) in the favorable PFS group, and the difference was significant (*P* = 0.002). Analysis of recurrent patterns also revealed a significant difference between the two groups, with a higher incidence of extraperitoneal recurrence (30/39, 76.9%) in the unfavorable PFS group compared to the favorable PFS group (10/41, 24.4%) (*P* < 0.001).

Prognostic factors for recurrence after CRS/HIPEC

Simple logistic regression was conducted to identify the potential prognostic factors for the likelihood of recurrence within 1 year. As presented in Table 3, the patients who achieved a CC score of 0 and those who had a length of CRS of ≤ 6 h had the lower risk of recurrence within 1 year (OR = 0.141, *P* = 0.004; and OR = 0.361, *P* = 0.027, respectively). For the non-significant covariates, there was a trend toward a favorable PFS with a PCI score of ≤ 7 (OR = 0.444, *P* = 0.078) and no pre-HIPEC chemotherapy (OR = 2.529, *P* = 0.075). Cancer type, previous systemic chemotherapy, extraperitoneal metastasis, surgical method, and bowel resection were not associated with recurrence. Furthermore, the multiple logistic regression model revealed that achieving a CC score of 0 during CRS was significantly associated with a favorable PFS (adjusted OR = 0.130, *P* = 0.005) (Table 4). We further analyzed the association between PCI score and CC score, and found that 85% (51/60) of the patients with a PCI score ≤ 12 achieved CC-0, compared to only 60% (12/20) of those with a PCI score > 12 (*P* = 0.027). Given that HIPEC procedures were more frequently performed for gastrointestinal cancers than for recurrent ovarian cancer in clinical practice, and given the distinct behaviors of these cancer types, we stratified the cancer types into two subgroups: recurrent ovarian cancer and gastrointestinal cancers (including gastric cancer, colorectal cancer, and appendiceal cancer). These subgroups were incorporated into the multiple logistic regression

Table 1 Demographic and clinical data of the study population

Characteristic	All	< 1 yr group, *n* = 39	≥ 1 yr group, *n* = 41	*P* value
Age in yr				
mean ± SD	55.21 ± 11.48	52.74 ± 12.36	57.56 ± 10.18	0.060
Median (mix, max)	58 (22, 74)	56 (22, 73)	59 (36, 74)	0.102
Sex				
Male	27 (33.7)	15 (38.5)	12 (29.3)	0.480
Female	53 (66.3)	24 (61.5)	29 (70.7)	
BMI in kg/m^2				
mean ± SD	24.20 ± 3.98	24.05 ± 4.22	24.34 ± 3.77	0.746
Hypertension	23 (28.8)	11 (28.2)	12 (29.3)	1.000
Diabetes mellitus	16 (20.0)	8 (20.5)	8 (19.5)	1.000
Clinical presentation				
Primary	35 (43.7)	18 (46.2)	17 (41.5)	0.822
Recurrence	45 (56.3)	21 (53.8)	24 (58.5)	
Ascites presentation	2 (2.5)	1 (2.6)	1 (2.4)	1.000
Previous systemic therapy				
Never	20 (25.0)	8 (20.5)	12 (29.3)	0.443
1st line or more	60 (75.0)	31 (79.5)	29 (70.7)	
Extraperitoneal oligometastasis				
Liver	13 (16.3)	7 (17.9)	6 (14.6)	0.767
Lung	3 (3.8)	1 (2.6)	2 (4.9)	1.000
Extraperitoneal LN	3 (3.8)	1 (2.6)	2 (4.9)	1.000
Skin	4 (5.0)	3 (7.7)	1 (2.4)	0.353
Vagina	2 (2.5)	1 (2.6)	1 (2.4)	1.000
Cancer types				0.540
Colorectal	42 (52.5)	22 (56.4)	20 (48.8)	
Ovary	22 (27.5)	9 (23.1)	13 (31.7)	
Platinum-sensitive	11 (13.8)	3 (7.7)	8 (19.5)	
Platinum-resistance	11 (13.8)	6 (15.4)	5 (12.2)	
Gastric	12 (15.0)	7 (17.9)	5 (12.2)	
Appendix, high grade	4 (5.0)	1 (2.6)	3 (7.3)	
Histology grade				0.020[a]
1	10 (12.4)	1 (2.6)	9 (22.0)	
2	25 (31.3)	14 (35.9)	11 (26.8)	
3	45 (56.3)	24 (61.5)	21 (51.2)	

[a]$P < 0.05$.

Data are *n* (%) unless otherwise indicated. BMI: Body mass index; LN: Lymph node; SD: Standard deviation.

model. The subgroup analysis of gastrointestinal cancers demonstrated that achieving a CC score of 0 during CRS was significantly associated with favorable PFS (adjusted OR = 0.046, $P = 0.008$). However, in the subgroup of recurrent ovarian cancer, the use of pre-HIPEC chemotherapy was significantly associated with unfavorable outcomes (adjusted OR = 22.932, $P = 0.042$), whereas achieving a CC score of 0 was not significantly associated with outcomes (adjusted OR = 0.239, $P = 0.332$).

Table 2 Perioperative details and outcomes

Characteristic	All	< 1 yr group, *n* = 39	≥ 1 yr group, *n* = 41	*P* value
Surgical method				
Laparoscopy	11 (13.7)	5 (12.8)	6 (14.6)	1.000
Laparotomy	69 (86.3)	34 (87.2)	35 (86.4)	
Preoperative PCI	7.99 ± 5.97	9.08 ± 6.52	6.95 ± 5.26	0.112
CC score				
0	63 (78.8)	25 (64.1)	38 (92.7)	0.002[a]
1	17 (21.2)	14 (35.9)	3 (7.3)	
Residual lesion				
Small bowel	6 (7.5)	4 (10.3)	2 (4.9)	
Large bowel	1 (1.3)	1 (2.6)	0	
Major vessels	3 (3.8)	3 (7.7)	0	
Peritoneum	7 (8.8)	6 (15.4)	1 (2.4)	
Pre-HIPEC chemotherapy[1]	41 (51.3)	24 (61.5)	17 (41.5)	0.080
Response to pre-HIPEC chemotherapy				0.121
Complete remission	0	0	0	
Partial remission	15 (18.8)	8 (20.5)	7 (17.1)	
Stable disease	6 (7.5)	1 (2.6)	5 (12.2)	
Progression disease	16 (20.0)	11 (28.2)	5 (12.2)	
CRS time in min	338.60 ± 144.80	365.50 ± 135.10	313.10 ± 150.80	0.106
Visceral organ resections				
Liver	6 (7.5)	3 (7.7)	3 (7.3)	1.000
Lung wedge resection	3 (3.8)	1 (2.6)	2 (4.9)	1.000
Small bowel	23 (28.8)	13 (33.3)	10 (24.4)	0.461
Large bowel	45 (56.3)	25 (64.1)	20 (48.8)	0.184
Uterus and adnexa[2]				
TH-BSO	7 (13.2)	2 (8.3)	5 (17.2)	0.433
BSO	3 (5.6)	1 (4.2)	2 (6.9)	1.000
HIPEC duration in min				0.603
30, oxaliplatin-based	18 (22.4)	10 (25.6)	8 (19.5)	
60	31 (38.8)	16 (41.0)	15 (36.6)	
90, mitomycin c	31 (38.8)	13 (33.3)	18 (43.9)	
HIPEC regimens				
Cisplatin-based	22 (27.5)	13 (33.3)	9 (22.0)	0.319
Non-cisplatin-based	58 (72.5)	26 (66.7)	32 (78.0)	
Post-HIPEC chemotherapy[3]	70 (87.5)	35 (89.7)	35 (85.4)	0.738
Any postoperative complication ≥ grade 3	7 (8.8)	4 (10.3)	3 (7.3)	0.709
AKI	1 (1.3)	0	1 (2.4)	
Bowel perforation	4 (5.0)	4 (10.3)	0	
Others	2 (2.5)	0	2 (4.9)	
Recurrent site				< 0.001[a]
Extraperitoneal	23 (28.8)	18 (46.2)	5 (12.2)	

Intraperitoneal	26 (32.5)	9 (23.1)	17 (41.5)
Both	17 (21.3)	12 (30.8)	5 (12.2)
No recurrence	14 (17.5)	0	14 (34.1)

[a]$P < 0.05$.
[1]Within 6 mo before hyperthermic intraperitoneal chemotherapy (HIPEC).
[2]Female only.
[3]Within 6 mo after HIPEC.
Data are *n* (%) or mean ± standard deviation. AKI: Acute kidney injury; BSO: Bilateral salpingo-oophorectomy; CC: Completeness of cytoreduction; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal cancer index; TH-BSO: Total hysterectomy with bilateral salpingo-oophorectomy.

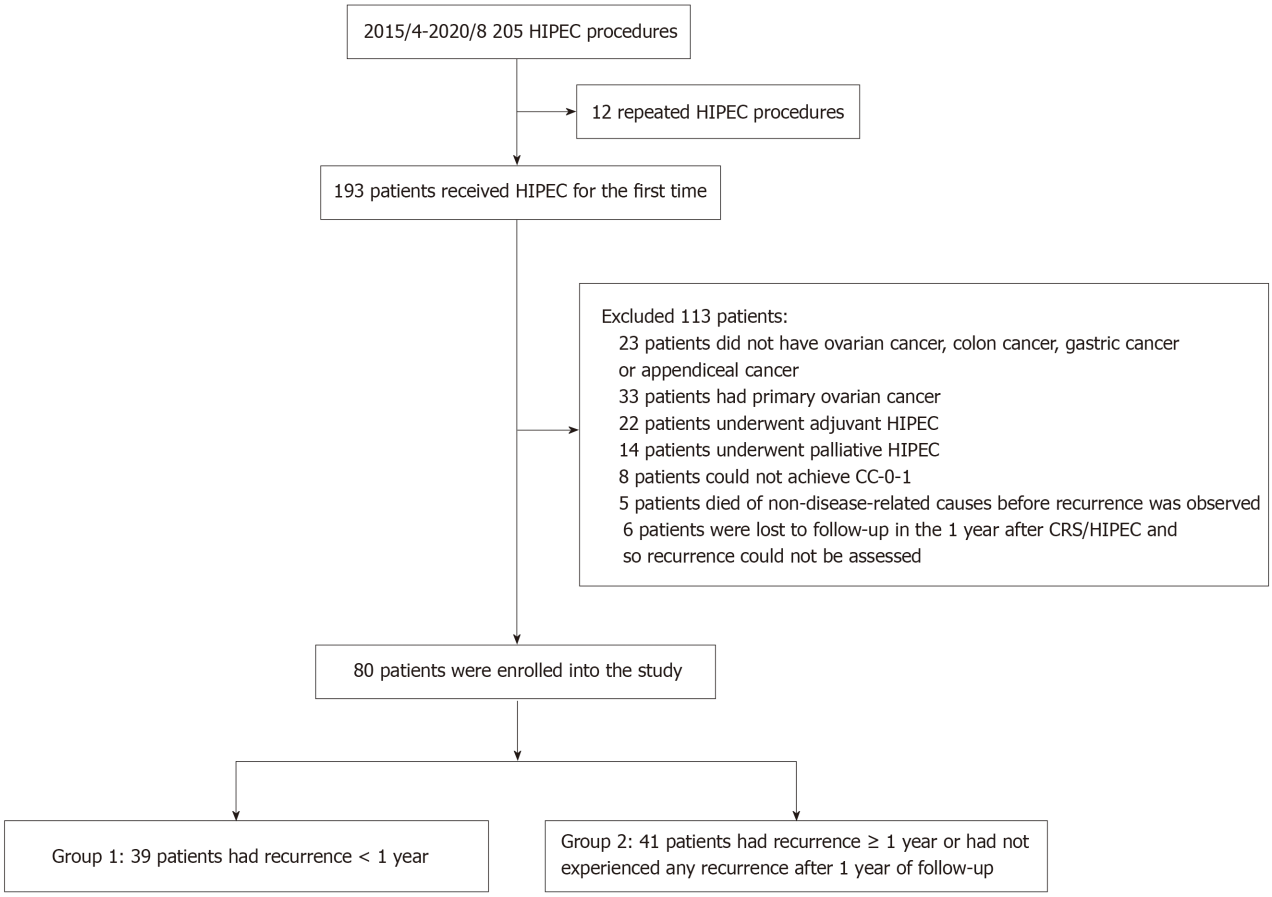

Figure 1 Patient enrollment and study population flowchart. Eighty patients met the inclusion and exclusion criteria and were categorized into two groups: Group 1 included 39 patients with recurrence within 1 year, and Group 2 included 41 patients with recurrence after more than 1 year or no recurrence during the follow-up period. CC: Completeness of cytoreduction; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

Follow-up and survival analysis

The median follow-up duration was 44.5 mo. In the overall cohort, the median PFS and OS after primary CRS/HIPEC were 12.3 mo (95%CI: 9.2-15.5 mo) and 37.0 mo (95%CI: 26.1-47.9 mo), respectively. The favorable PFS group had a significantly longer OS compared to the unfavorable PFS group (81.7 mo *vs* 17.0 mo, $P < 0.001$) (Figure 2). This was confirmed in a Cox model, which revealed that the unfavorable PFS group had a significantly shorter survival time than the favorable group after adjusting for age, sex, and CC score (adjusted HR = 4.853, $P < 0.001$).

Among the patients with a potential 3-year follow-up period (those who underwent CRS/HIPEC before 31 March 2020, if alive), 23 were still alive, of whom 9 were alive with disease (AWD) and 14 had no evidence of disease (NED). Among the 9 patients who were AWD, only 3 belonged to the unfavorable PFS group (1 had platinum-sensitive recurrent ovarian cancer, and 2 had colorectal cancer). Among the 14 patients with NED, 10 remained recurrence-free after CRS/HIPEC, including 5 with recurrent ovarian cancer (3 patients were platinum-sensitive and had one episode of recurrence, while 2 patients were platinum-resistant and had four and five episodes of recurrences prior to this CRS/HIPEC procedure), and the other 5 had colon cancer. Notably, all 10 patients without recurrence (among the 14 patients with NED) achieved CC-0 CRS. The 3-year PFS rate was 12.98%, and the 3-year OS rate was 29.87% (23/77). In contrast, in the

Table 3 Analysis of the risk of recurrence within 1 year using a simple logistic regression model

Parameter	Crude OR (95%CI)	*P* value
Age in yr		
≥ 55	0.546 (0.222, 1.343)	0.188
< 55	1.000	
Sex		
Female	0.662 (0.261, 1.681)	0.386
Male	1.000	
Previous systemic therapy		
Any	1.603 (0.574, 4.482)	0.368
Never	1.000	
Clinical presentation		
Primary	1.210 (0.500, 2.931)	0.673
Recurrence	1.000	
Cancer type		
Ovary	0.646 (0.239, 1.746)	0.389
GI	1.000	
CC score		
0	0.141 (0.037, 0.541)	0.004[a]
1	1.000	
PCI score		
1-7	0.444 (0.180, 1.095)	0.078
8-39	1.000	
HIPEC regimen		
Cisplatin	1.778 (0.657, 4.809)	0.257
Non-cisplatin	1.000	
HIPEC duration in min		
≤ 60	1.565 (0.632, 3.879)	0.333
90	1.000	
Extraperitoneal oligometastasis		
Any	1.071 (0.401, 2.830)	0.890
None	1.000	
Surgical method		
Laparoscopy	0.858 (0.239, 3.077)	0.814
Laparotomy	1.000	
Histology grade		
Grade 1/2	0.656 (0.270, 1.597)	0.353
Grade 3	1.000	
Pre-HIPEC chemotherapy[1]		
Yes	2.259 (0.922, 5.532)	0.075
No	1.000	
Post-HIPEC chemotherapy[2]		
Yes	1.500 (0.389, 5.781)	0.556

No	1.000	
CRS time in h		
≤ 6	0.361 (0.146, 0.892)	0.027[a]
> 6	1.000	
Bowel resection		
Yes	2.143 (0.858, 5.351)	0.103
No	1.000	

[a]*P* < 0.05.
[1]Within 6 mo before hyperthermic intraperitoneal chemotherapy (HIPEC).
[2]Within 6 mo after HIPEC.
CC: Completeness of cytoreduction; CI: Confidence interval; CRS: Cytoreductive surgery; GI: gastrointestinal cancers, including gastric, colorectal and appendiceal cancers; HIPEC: Hyperthermic intraperitoneal chemotherapy; OR: Odds ratio; PCI: Peritoneal cancer index.

Table 4 Analysis of the risk of recurrence within one year using a multiple logistic regression model

Parameters	Overall	*P* value	Ovarian cancer	*P* value	GI cancers	*P* value
	Adjusted OR		Adjusted OR		Adjusted OR	
Age in yr						
≥ 55	0.496	0.157	0.097	0.114	0.528	0.293
< 55	1.000		1.000		1.000	
Sex						
Female	1.091	0.872	-		0.566	0.375
Male	1.000		-		1.000	
CC score						
0	0.130	0.005[a]	0.239	0.332	0.046	0.008
1	1.000		1.000		1.000	
Pre-HIPEC chemotherapy						
Yes			22.932	0.042[a]	-	
No			1.000		-	
Platinum-response[1]						
Resistant			7.133	0.153	-	
Sensitive			1.000		-	

[a]*P* < 0.05.
[1]Adjusted for platinum-response only in the subgroup of ovarian cancer.
CI: Confidence interval; CC: Completeness of cytoreduction; GI: gastrointestinal cancers, including gastric, colorectal and appendiceal cancers; HIPEC: Hyperthermic intraperitoneal chemotherapy; OR: Odds ratio.

unfavorable PFS group, 22 patients experienced recurrence within 6 mo, and 15 patients died of the disease within 1 year.

DISCUSSION

In this study, we aimed to identify the prognostic factors for PFS in patients who underwent CRS/HIPEC. The results showed that 51.25% (41/80) of the patients with peritoneal carcinomatosis had a PFS ≥ 1 year, and the 3-year PFS rate was 12.98% (10/77) after strict cytoreduction and HIPEC. The patients with a better PFS also had a significantly better OS. CC-0 was found to be a major prognostic factor for prolonged PFS.

To ensure that the study population was primarily comprised of those with stage IV peritoneal carcinomatosis, patients with primary ovarian cancer and carcinomatosis were excluded due to their relatively good response to systemic chemotherapy and the lack of convincing randomized control trials regarding the indication for CRS/HIPEC[17].

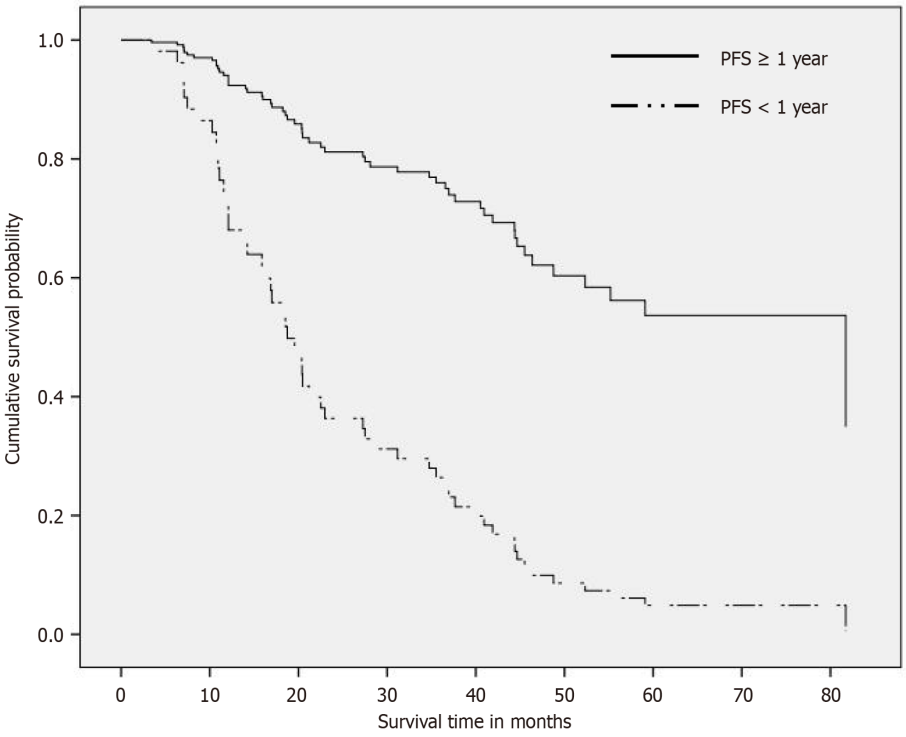

Figure 2 Kaplan–Meier analysis of overall survival comparing patients in the progression-free survival < 1-year group and progression-free survival ≥ 1-year group. The favorable progression-free survival (PFS) group had a significantly longer overall survival compared to the unfavorable PFS group.

Peritoneal carcinomatosis is associated with a poor prognosis and worse outcomes compared to other metastatic sites. A median OS of 5-11 mo has been reported in patients with gastric cancer and peritoneal carcinomatosis[18], and a median OS of 15-24 mo has been reported in patients with colon cancer and peritoneal carcinomatosis, even in those who receive systemic chemotherapy[19]. In addition, OS of around 5-17 mo has been reported in patients with recurrent ovarian cancer depending on the line of therapy and chemotherapy-sensitive or resistant status[20]. Long-term survival is rare in patients with peritoneal carcinomatosis. However, the OS rate in the present study was better compared to previous studies that only included patients receiving systemic therapy. This suggests that aggressive CRS/HIPEC in selected patients has clinical value in the treatment of this challenging disease.

Previous studies on CRS/HIPEC outcomes have often included patients with varying cytoreduction statuses (CC-0 to CC-3), and concluded that CC-0 and CC-1 represent complete cytoreduction. While CC score is a common factor associated with CRS/HIPEC outcomes[4], some studies have suggested that CC score is not a strong prognostic factor[12,21]. In the present study, strict cytoreduction to achieve CC-0 was the strongest prognostic factor, particularly in gastrointestinal cancers, consistent with findings from the CYTO-CHIP study[10]. A PCI score ≤ 7 showed a trend toward a favorable PFS in simple regression analysis, but it was not a significant predictor in the multiple logistic regression model, due to its correlation with the CC score. Although the PCI score did not directly affect patient prognosis, a PCI score > 12 was associated with a lower rate of achieving CC-0. Furthermore, better PFS was associated with better OS. Notably, all 10 patients who were progression-free for more than 3 years without any recurrence events had a CC score of 0. These findings suggest that all efforts should be made to achieve CC-0, and that peritoneal minimal residual tumors on non-vital organs should not be left to chance. Considering our results, we further suggest that in patients with a preoperative imaging PCI score > 12, clinicians should be aware of the potential challenges in achieving CC-0 and may consider incorporating diagnostic laparoscopy before proceeding with CRS. For patients with potential CC-1, especially those with diffuse small bowel lesions or critical major vessel invasion, prioritizing systemic therapy to reduce tumor burden or considering novel therapy combinations (such as immunotherapy or pressurized intraperitoneal aerosolized chemotherapy) may be beneficial, particularly if they have received multiple lines of treatment before CRS/HIPEC. When involving vital organs, repeated HIPEC for CC-1 patients can also be considered[22,23]. Of the 17 patients with CC-1 in this study, 9 had unavoidable diffuse small miliary seeding of the bowel and major vessel involvement. However, the remaining 8 patients with large bowel or peritoneal miliary residual tumors should have been approached more proactively. These 8 patients were early cases at our institution, when the surgical experience and peritonectomy skills were not as advanced.

Approximately 5%-15% of patients with colorectal, gastric, and ovarian cancers present with oligometastasis. Resection of extraperitoneal lung or liver oligometastases and extraperitoneal LNs may improve survival and achieve curative intent[24]. A systematic review of patients with colorectal cancer with peritoneal and limited liver metastasis reported a 3-year survival rate of 34% with CRS/HIPEC and local liver treatment[25]. Resection of oligometastases and lymphadenectomy have also been associated with improved OS, with a reported survival of 35.2 mo and 5-year survival rate of 22%

in patients with gastric cancer[26,27]. For patients with a low PCI score who have the potential to achieve CC-0, peritoneal carcinomatosis can be treated as a local disease with CRS/HIPEC, and vigorous resection of extraperitoneal metastases may be feasible. In this study, 12 patients underwent resection of extraperitoneal metastases during CRS/HIPEC, and all had a PFS > 1 year. However, due to distant metastatic disease, perioperative systemic therapy was encouraged to control the disease[25,27].

Systemic chemotherapy has been demonstrated to have limited efficacy in treating peritoneal dissemination compared to hematogenous spread[28]. In the present study, the use of post-HIPEC chemotherapy did not show a significant association with PFS in simple regression analysis. Similarly, the association between pre-HIPEC chemotherapy and PFS in overall population was not statistically significant, although there was a trend indicating potentially worse PFS with the use of chemotherapy before HIPEC. However, the use of pre-HIPEC chemotherapy was significantly associated with unfavorable outcomes in recurrent ovarian cancer. Recurrent ovarian cancer is characterized by repeated relapses[29]. Patients who received pre-HIPEC chemotherapy often had a more extensive tumor burden, which may be associated with shorter subsequent PFS. Therefore, postoperative chemotherapy and maintenance therapy are particularly important[29]. Notably, for patients with peritoneal carcinomatosis resulting from LN-positive colorectal carcinoma, perioperative systemic chemotherapy has been associated with increased OS and PFS[30]. It has been hypothesized that LN metastasis may arise from hematogenous spread[31].

In selected patients, minimally invasive procedures are equally effective and more tolerable. For patients with limited peritoneal disease (PCI < 10), laparoscopic CRS/HIPEC has been reported as a feasible and safe approach for curative treatment, potentially reducing postoperative complications[32]. In ovarian cancer, the laparoscopic approach is also considered safe, despite ongoing debate regarding its oncologic advantages[33]. In the present study, laparoscopic CRS/HIPEC did not impact PFS, consistent with previous evidence.

There are several strengths to this study. First, the study population was restricted to patients with curative intent and complete cytoreduction only, which reduced heterogeneity arising from incomplete surgery or potentially palliative cases. While CC score is commonly associated with prognosis, we found that achieving CC-0 was the only significant factor contributing to prolonged PFS. Second, the long follow-up period enhances the validity of our PFS results. Finally, the study significantly benefited from the presence of a well-established multidisciplinary program specifically designed for peritoneal malignancies. This program ensured consistent and standardized quality of care during the perioperative period.

CONCLUSION

Achieving CC-0 was a significant prognostic factor of recurrence in patients undergoing CRS/HIPEC. A PCI score > 12 was associated with a lower likelihood of achieving CC-0. Our results show that a favorable PFS can have a substantial impact on OS and long-term prognosis for patients with challenging peritoneal malignancies. It is crucial to explore novel therapeutic strategies for managing potential residual disease after CRS. Our findings offer valuable guidance for clinicians in decision-making regarding patient management. Future research to improve preoperative evaluations and the selection of patients who may be able to achieve CC-0 is also warranted.

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FOOTNOTES

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