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Article

Prolonged survival in epithelial ovarian cancer patients: Efficacy and safety of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy

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Abstract: Objective: To investigate the effects of Cytoreductive surgery (CRS) combined with Hyperthermic intraperitoneal chemotherapy (HIPEC) on the clinical efficacy and safety of Epithelial ovarian cancer (EOC) patients. **Methods:** We selected 120 EOC patients treated in the Affiliated Cancer Hospital of Guangzhou Medical University during July 2010 to July 2020 as retrospective case-control study subjects. They were divided into 60 cases in the observation group (CRS and HIPEC) and 60 cases in the comparison group (CRS) according to the principle of balanced clinicopathological characteristics. Adverse effects and prognosis-related factors, Overall survival (OS) and safety were analyzed in the two groups. **Results:** The results of multifactorial Cox regression analysis showed that CC score [P = 0.013, HR (95%CI) = 2.153 (1.014−7.638)], postoperative chemotherapy cycle [P = 0.045, HR (95%CI) = 2.056 (2.004−6.730)], and treatment method [P = 0.025, HR (95%CI) = 2.409 (1.000−5.814)], lymph node status P = 0.019, [HR (95%CI) = 1.221 (1.032−10.136)], and ascites volume P = 0.034, [HR (95%CI) = 2.459 (1.072−5.643)] were independent influences on overall survival. **Conclusions:** CRS and HIPEC prolonged overall survival in patients with recurrent EOC with a high safety profile.

Keywords: epithelial ovarian cancer; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; overall survival

1. Introduction

As a gynecologic malignancy, epithelial ovarian cancer (EOC) is known for its high malignancy and poor prognosis, and is the leading cause of death in patients with gynecologic tumors [1]. In recent years, the incidence of EOC has continued to rise. Globally, about 200,000 new cases of EOC are diagnosed each year, and up to 60% of these patients eventually die tragically [2]. Due to the hidden location of the ovaries, deep in the pelvis, and the lack of effective screening and early diagnostic tools, more than 70%–80% of women have advanced disease at the time of diagnosis, with a recurrence rate of up to 50% [3]. For EOC, standard treatment consists of an initial Cytoreductive surgery (CRS) combined with a platinum-based combination regimen [4]. However, the outcome of EOC is influenced by several factors, including the thoroughness of the surgery, the chemotherapy regimen, and the mode of drug delivery [5]. Despite achieving satisfactory CRS, peritoneal implantation metastases and microscopic or occult lesions often persist on the peritoneal surface, leading to high recurrence rates and limited survival outcomes [6].

The current main treatment strategy for recurrent EOC consists of either another CRS followed by adjuvant chemotherapy, or adjuvant chemotherapy only [7].

However, these approaches face limitations, particularly in addressing platinum-resistant disease and achieving durable disease control. This highlights a critical need for innovative therapeutic strategies that can enhance tumor clearance, delay disease progression, and improve overall survival. Most scholars now agree that once EOC recurs, treatment goals should focus on prolonging the patient's life as much as possible, delaying disease progression, controlling tumor-related symptoms, and reducing side effects during treatment [8]. Controversy exists within the field of gynecologic oncology regarding secondary CRS for recurrent EOC. However, the general opinion is that only those patients who have an isolated lesion that can be completely resected, have a recurrence interval of more than one year after the initial chemotherapy, are free of ascites, are young, in good physical condition, can tolerate surgery and strongly desire it, are likely to benefit from secondary CRS [9].

Over the past three decades, the international oncology community has extensively studied advanced or recurrent EOC with CRS combined with HIPEC and has concluded that this approach improves survival in patients with recurrent EOC peritoneal cancer [10]. This integrated approach combines surgical removal of visible tumors with the intraperitoneal administration of heated chemotherapeutic agents to target microscopic residual lesions, leveraging the synergistic effects of hyperthermia and chemotherapy. For example, a prospective randomized controlled phase II clinical study found that CRS and HIPEC significantly enhanced survival in patients with EOC compared to treatment with CRS alone [11]. Despite encouraging results from several studies, there remains a lack of large-scale, region-specific evidence, particularly in China, to validate the efficacy and safety of this approach and establish it as a standard treatment. Specifically, in developed countries such as Europe and the United States, HIPEC has not yet become the standard treatment for EOC. The International Congress of Peritoneal Cancer recommended HIPEC as a treatment option for EOC peritoneal cancer [12]. Relatively few cases have been studied using CRS and HIPEC for the treatment of recurrent EOC in China, so this treatment has not yet been widely recognized and clinically applied [13].

To address these gaps, this study retrospectively evaluates the impact of CRS combined with HIPEC on clinical efficacy, safety, and prognosis in patients with recurrent EOC treated at a cancer center in China. By providing comprehensive data on survival outcomes and prognostic factors, this study aims to offer valuable insights to guide future clinical practice and improve treatment strategies for this high-mortality disease.

2. Materials and methods

2.1. Study subjects

We collected clinicopathologic data of 60 patients with recurrent epithelial EOC who received CRS and HIPEC from July 2010 to July 2020 in the Affiliated Cancer Hospital of Guangzhou Medical University. The clinicopathologic data of 60 patients with recurrent epithelial EOC who underwent CRS at the Affiliated Cancer Hospital of Guangzhou Medical University during the same period were collected according to the main inclusion criteria, exclusion criteria, and the principle of balanced clinicopathologic features. The patients were divided into Observation

group (CRS and HIPEC) and Comparison group (CRS). All patients had complete clinicopathologic data and follow-up information. The screening process for the inclusion of patients is shown in **Figure 1**.

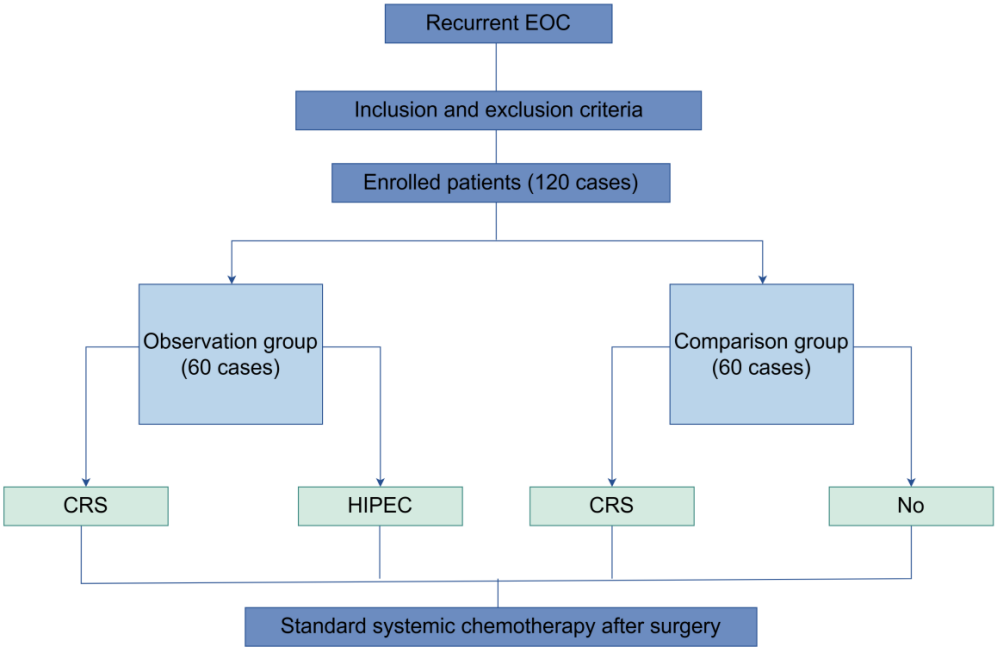


Figure 1. Patient screening process for inclusion (By Figdraw, ID: IAOIW414ef).

2.2. Exclusion inclusion criteria

Inclusion criteria: patients with Karnofsky Performance Status (KPS) score greater than 50, patients with good general condition and mobility. The age range of the patients was between 20 and 75 years old. The patient's peripheral blood leukocyte count is not less than 3.5×10^9/L, platelet count is not less than 80×10^9/L, and hemoglobin concentration is not less than 90×10^{12}/L. The patient's hepatic and renal functions are basically normal, and he can tolerate surgical treatments and intra-operative chemotherapy, and the level of total bilirubin is not more than twice the upper limit of normal, and the concentration of blood creatinine is not more than 1.5 mg/dL. the patient's cardiorespiratory function is normal. Patients with previous surgical diagnosis of epithelial EOC or diagnosis of epithelial EOC at the time of initial treatment by ovarian tumor aspiration cytology or laparoscopic exploratory biopsy were eligible for this study, and patients had a life expectancy of at least 3 months. The study protocol was approved by the Ethics Committee of Guangzhou Medical University Cancer Hospital.

Exclusion criteria: age less than 20 years or more than 75 years were excluded. Exclusion of distant metastases such as liver and lungs or extensive retroperitoneal lymph node metastases found in preoperative examination. Obvious abnormalities in blood routine, liver and kidney functions were excluded. Moderate to severe contracture of the small bowel mesentery was excluded. Exclude preoperative evaluation that the patient could not tolerate the procedure. Exclude those who could not complete satisfactory tumor CRS with preoperative imaging suggesting intestinal

obstruction, intraoperative tumor in close relationship with the mesentery, or nodules with a diameter of > 5 cm visible on the surface of the peritoneum or mesentery.

2.3. Methods

All patients underwent open laparotomy under general anesthesia, and the surgical incision was located in the midline of the abdomen, extending from the subxiphoid process (or 5 cm above the umbilicus) to the pubic symphysis. After opening the abdomen, the peritoneum was explored from the diaphragmatic surface to the pelvic peritoneum to assess the degree of tumor invasion and the extent of the peritoneal carcinomatosis index (PCI), and to record the size and location of the tumor, the amount of ascites, and its nature. Radical resection was performed in patients who were able to completely resect the tumor, while in patients who were unable to completely resect the tumor, maximal CRS was performed as far as possible and cytoreductive scoring (CC scoring) was performed. The operation of CRS followed the method of Prof. Sugerbaker of the Washington Cancer Center, which consisted of two parts: peritoneal resection and visceral resection. (**Figure 2**).

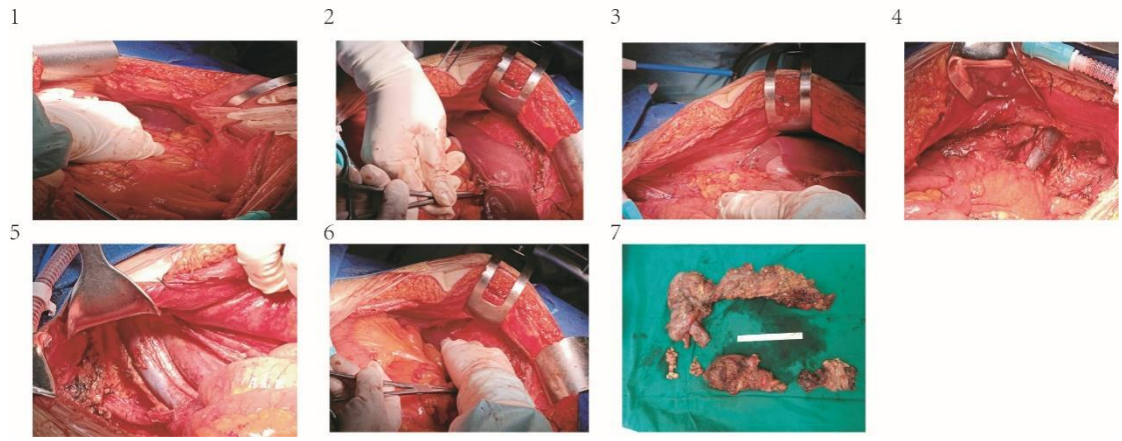


Figure 2. Procedure of CRS. (**(1)** Separation of the adhesion between liver and diaphragm; **(2)** remove lumps on the surface of the liver; **(3)** disconnect the diaphragm from the peritoneum; **(4)** complete hysterectomy of bilateral adnexa, rectum and sigmoid; **(5)** no tumor remains were found after pelvic organ resection; **(6)** remove pelvic lymph nodes; **(7)** complete specimens were obtained after CRS).

After the surgery was completed, HIPEC chemotherapy was started. All patients completed 2–3 HIPEC within 7 d after the completion of CRS, and we used BR-TRG-I I type body cavity heat perfusion therapy system manufactured by Guangzhou BORI Medical Technology Co. Two inlet tubes were placed under the septum muscle on both sides and two outlet tubes were placed in the right and left iliac fossa before closing the abdomen after tumor reduction surgery. The perfusate consisted of 3500mL of normal saline, which was used to prepare the chemotherapy solution. For the first session, paclitaxel (135 mg/m^2) or docetaxel (75 mg/m^2) was administered, while for the second session, cisplatin (75–100 mg/m^2) was used. If a third session was performed, only saline without chemotherapy drugs was used. The chemotherapy solution was heated in the perfusion system to a target temperature of 43 ℃ before being infused into the abdominal cavity. To ensure precise temperature control, the perfusion system continuously monitored the temperature at the inflow

and outflow points, maintaining a range of 42.5 ℃–43.5 ℃ throughout the procedure. This temperature was chosen to optimize the cytotoxic effects on cancer cells while minimizing damage to normal tissues. The treatment duration for each HIPEC session was 60–90 min, during which the chemotherapy solution was circulated uniformly within the abdominal cavity. The procedure also involved manual agitation of the abdomen to ensure even distribution of the chemotherapy agent.

In addition to the standard CRS procedures, this study incorporated a rigorous patient selection process using matched clinicopathological characteristics to reduce baseline heterogeneity between the CRS and CRS + HIPEC groups. This retrospective design ensured that the observed differences in survival outcomes were more likely attributable to the intervention itself rather than confounding factors. Furthermore, we implemented standardized HIPEC protocols, including precise control of perfusion temperature (43 ℃), chemotherapeutic agent concentrations, and perfusion durations (60–90 min). These factors have been inconsistently reported in prior studies, potentially leading to heterogeneity in reported outcomes. By standardizing these parameters, our study provides a more robust framework for evaluating the efficacy and safety of HIPEC in EOC patient.

2.4. Statistical methods

The Observation group and Comparison group conducted 1:1 tendency score matching to balance baseline characteristics, ensuring comparability and reducing selection bias. Missing data, such as incomplete follow-up information, were addressed using multiple imputation techniques. This method allowed us to estimate missing values based on observed data patterns, thus minimizing potential bias introduced by missingness. Sensitivity analyses were conducted to confirm the robustness of the results after imputation. The common method deviation test and the normality test were carried out on the data. The database was established with Excel software, and after logical verification, it was imported into SPSS26.0 software for data analysis. Counting data is expressed as integers or percentages, x^2 tests are used for comparison between groups, and rank sum tests are used for ordered variables. The measurement data were represented by mean ± standard deviation; the data meeting the normal distribution were presented by two-independent sample t test; if the data did not meet the normal distribution, the Mann-WhitneyU rank sum test was presented for statistical analysis. For the survival analysis, we utilized the Kaplan-Meier method to estimate OS, the Log-rank test was used to compare survival distributions between groups, and Cox proportional risk model was used to analyze independent prognostic factors affecting survival outcomes. To address truncated data, we ensured that the last follow-up date was clearly defined, and censoring was properly accounted for. Median follow-up time was calculated using the reverse Kaplan-Meier method, ensuring an accurate representation of follow-up duration. To account for potential risks affecting survival, particularly death from causes other than ovarian cancer, we performed survival analysis using the Cox proportional hazards model. This model allowed us to estimate the hazard ratios for relevant prognostic factors, providing insights into how various factors influence the survival

probabilities of ovarian cancer patients. This approach offers a comprehensive understanding of survival outcomes by evaluating the relationship between prognostic factors and the time to event, although it does not account for competing risks. *P*-value < 0.05 indicates a statistically significant difference.

3. Results

3.1. Comparison of patients' clinical data

The mean age of the Observation group and the Control group was similar (54.6 vs 54.8 years) and there was no statistically significant difference in age between the two groups (P = 0.711). The mean values of KPS were also similar in both groups (77.9 vs. 78.02) and there was no statistical difference between the two groups (P = 0.833). The mean value of ascites volume was also similar in both groups (1321.19 mL vs 1332.21 mL) and there was no statistical difference between the two groups (P = 0.569). There was also no statistical difference in the distribution of the two groups in terms of histologic type (P = 0.976). There was also no statistical difference in the distribution of tumor growth site, differentiation, platinum sensitivity, bowel resection, number of organs removed, targeted therapy, immunotherapy, and lymph node status between the two groups. The difference in comparison was not statistically significant *P*-value > 0.05. see **Table 1**.

Table 1. Comparison of clinical data between the two groups {$\bar{x}$sd, [n (%)]}.

	Observation group (60)	**Comparison group (60)**	t/x^2	***P*-value**
Age (years)	54.6 ± 2.8	54.8 ± 3.1	0.370	0.711
Karnofsky (KPS)	77.90 ± 3.21	78.02 ± 3.03	0.210	0.833
Ascites volume (mL)	1321.19 ± 102.21	1332.21 ± 109.19	0.570	0.569
Histologic type			0.210	0.976
Plasmacytoid adenocarcinoma	49	50		
Mucinous adenocarcinoma	5	5		
Endometrioid carcinoma	3	2		
Clear cell carcinoma	3	3		
Previous Tumor Reduction			1.045	0.307
No	19	14		
Yes	41	46		
Tumor Site			0.186	0.666
Unilateral Ovary	15	13		
Bilateral Ovary	45	47		
Degree of differentiation			0.240	0.624
Highly differentiated	9	11		
Moderately/Lowly Differentiated	51	49		
Platinum sensitivity			0.745	0.388
Sensitive	44	48		
Resistant	16	12		

Table 1. (*Continued*).

	Observation group (60)	**Comparison group (60)**	t/x^2	***P*-value**
Bowel resection			0.034	0.855
Yes	28	27		
No	32	33		
Number of organs removed			0.256	0.880
0	13	14		
1-3	26	27		
4-7	11	9		
Targeted therapy			1.534	0.215
Yes	41	47		
No	19	13		
Immunotherapy			0.058	0.810
Yes	10	11		
No	50	49		
Lymph node status			0.051	0.822
Positive	48	47		
Negative	12	13		

3.2. Single factor analysis affecting overall survival

The P values between CC0-1 and CC2-3 groups were all less than 0.05, indicating that the status of residual cancer had a significant impact on overall survival. Patients with CC0-1 may have better overall survival than patients with CC2-3. The P values between the CRS and HIPEC and CRS groups were all less than 0.05, indicating that the treatment had a significant impact on overall survival. CRS and HIPEC may provide better overall survival for patients. The P values between the postoperative chemotherapy cycle ≥ 6 weeks and the postoperative chemotherapy cycle < 6 weeks were less than 0.05, indicating that the postoperative chemotherapy cycle had a significant impact on overall survival. The P values between the groups of ≤ 1000 mL and > 1000 mL were all less than 0.05, indicating that the amount of abdominal water had a significant impact on the overall survival. The P values between the positive and negative groups were all less than 0.05, indicating that the lymph node status had a significant impact on overall survival. Patients with negative lymph nodes may have better overall survival. Although the *P*-values of factors such as age, degree of differentiation, pathological type, PCI, bowel resection, platinum sensitivity, targeted therapy, and immunotherapy showed no significant association in the table (*P*-value > 0.05), these factors may still be potentially important across different studies or larger sample sizes. See **Table 2**.

Table 2. Analysis of single factors affecting overall survival.

	Observation group (60)			**Comparison group (60)**		
	OS	**95%CI**	***P*-value**	**OS**	**95%CI**	***P*-value**
Age (years)			0.073			0.062
< 60 years	52.18	12.189–108.103		52.21	12.190–108.113	
≥ 60 years	12.20	8.209–115.901		12.19	8.213–115.109	
Degree of differentiation			0.105			0.185
Highly differentiated	26.14	19.125–33.103		25.24	19.115–29.113	
Moderately/lowly differentiated	42.26	14.218–90.118		41.108	14.79–31.108	
Pathologic type			0.132			0.147
Plasma adenocarcinoma	12.30	5.108–18.132		11.26	3.128–19.152	
Mucinous adenocarcinoma	19.12	8.117–29.127		18.07	9.277–39.173	
Other	30.20	24.109–65.211		30.20	20.129–75.101	
PCI			0.146			0.213
PCI ≤ 15	30.20	20.120–40.010		28.10	20.0–40.130	
PCI > 15	22.18	1.201–46.103		21.14	1.100–46.210	
CC			0.018			0.019
CC0-1	12.18	19.24–56.022		11.18	7.104–56.220	
CC2-3	10.20	18.219–41.011		12.20	8.309–41.011	
Bowel Resection			0.081			0.079
With Bowel Resection	48.18	16.102–89.214		45.29	15.012–89.124	
Without bowel resection	36.14	3.114–49.284		38.54	3.501–49.034	
Platinum sensitivity			0.128			0.098
Sensitive	9.16	1.106–41.206		11.26	1.6–41.096	
Resistant	8.42	49.063–67.621		18.12	49.3–67.110	
Treatment			0.017			0.010
CRS and HIPEC	21.61	3.184–67.28		19.06	7.904–79.128	
CRS	21.30	4.126–57.54		20.07	1.206–89.534	
Postoperative chemotherapy cycles			0.012			0.026
≥ 6 weeks	25.10	10.210–184.210		31.15	10.0–172.103	
< 6 weeks	14.74	9.4–129.405		45.13	9.114–178.324	
Ascites volume			0.007			0.016
≤ 1000 mL	31.19	2.190–70.424		29.68	3.510–68.424	
> 1000 mL	22.12	5.265–30.381		13.78	4.215–26.471	
Lymph node status			0.003			0.013
Positive	37.62	8.317–324.415		21.56	8.197–298.253	
Negative	41.36	2.285–181.239		17.29	2.815–170.921	
Targeted therapy			0.173			0.263
yes	45.18	8.189–79.017		31.81	18.219–89.612	
No	39.23	2.154–84.045		24.20	25.642–69.551	
Immunotherapy			0.534			0.672
Yes	21.36	14.138–88.418		21.6	4.418–98.324	
No	27.21	17.421–67.468		27.6	7.284–69.678	

3.3. Multivariate Cox regression analysis of overall survival

We conducted a multivariate Cox regression analysis on the overall survival of patients, and the results showed that CC score, postoperative chemotherapy cycle, treatment method, lymph node status and abdominal water volume were significant factors affecting overall survival. CC score [P = 0.013, HR (95%CI) = 2.153 × (1.014−7.638)], postoperative chemotherapy cycle [P = 0.045, HR (95%CI) = 2.056 × (2.004−6.730)], treatment method [P = 0.025, HR (95%CI) = 2.409 × (1.000−5.814)], lymph node status P = 0.019, [HR (95%CI) = 1.221 × (1.032−10.136)] and abdominal water volume P = 0.034, [HR (95%CI) = 2.459 × (1.072−5.643)] were all independent risk factors affecting overall survival. As shown in **Table 3**.

Table 3. Cox regression analysis of multiple factors affecting overall survival.

	X^2	*P*-value	HR	95%CI
CC score	9.174	0.013	2.153	1.014–7.638
Postoperative chemotherapy cycle	2.767	0.045	2.056	2.004–6.730
Treatment method	3.820	0.025	2.409	1.000–5.814
Lymph node status	6.304	0.019	1.221	1.032–10.136
Abdominal water volume	4.507	0.034	2.459	1.072–5.643

3.4. Survival analysis

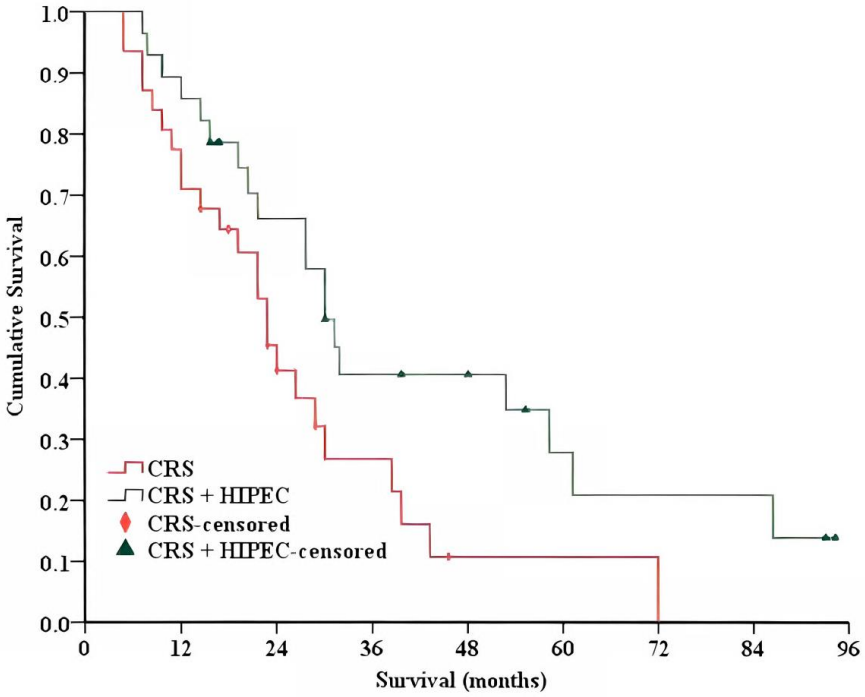


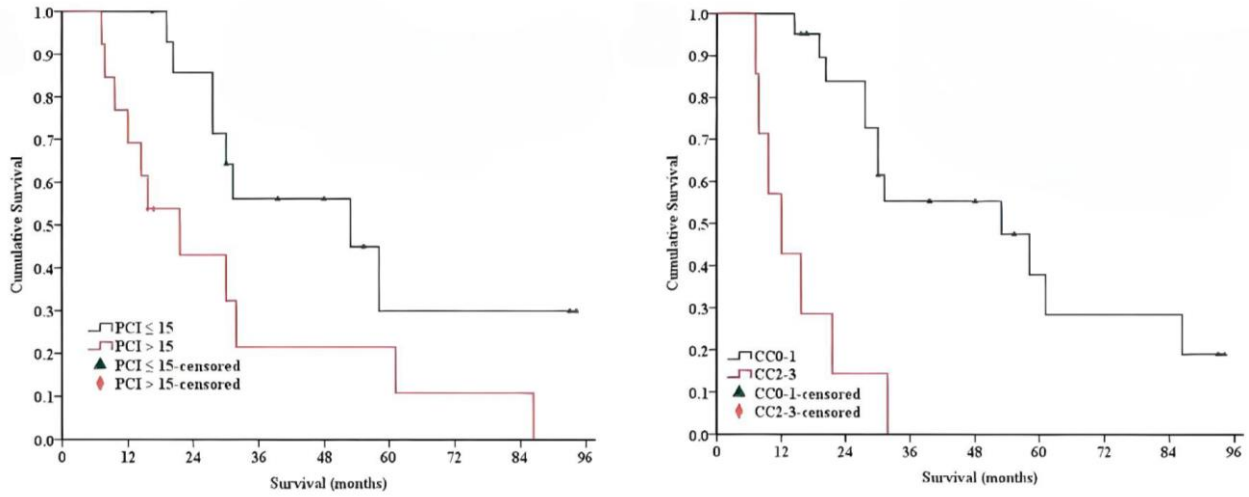
Figure 3. Comparison of survival analysis between the two groups.

Observation group patients were followed for an average of 43 months, during which 49 patients died and 11 were still alive. The average follow-up time in the Comparison group was 46 months, of which 53 died and seven survived. The follow-up time of both groups was sufficient, and the data were mature, suitable for

statistical analysis. The median overall survival (OS) of the Observation group and Comparison group were 30 months (95%CI = 21.3−31.3) and 22.8 months (95%CI = 8.2−22.6), respectively, with significant difference between the two groups (P = 0.017). Survival in the Observation group was 36.9 percent longer than in the control group. The 1-year, 3-year and 5-year survival rates were 86.8%, 51.6%, 41.6% and 69.0%, 33.5% and 23.8%, respectively. See **Figure 3**.

3.5. Subgroup analysis of patient survival

After we performed a subgroup analysis of the overall survival of the two groups based on different clinicopathologic factors, we observed the following results: in the Observation group, the median overall survival of patients with a PCI value of no more than 15 was 49.8 months (95 CI = 0.972~108.213), whereas the median overall survival of patients with a PCI value of more than 15 was 23.6 months (95%CI = 10.214~32.238), and this difference was statistically significant (P = 0.021). For CC0-1 resected patients, the median overall survival reached 52.8 months (95%CI = 14.138~90.348), while the median overall survival for CC2-3 resected patients was 12.0 months (95%CI = 5.278~18.132). In terms of platinum sensitivity, the median overall survival was 32.0 months (95%*CI* = 6.215~57.261) for sensitive patients and 33.8 months (95%CI = 25.215~34.415) for resistant patients, with no significant difference between them (P = 0.133). Our median overall survival in the Comparison group was 21.8 months (95%CI = 16.213~29.413) for patients with PCI value up to 15, while the median overall survival for patients with PCI value more than 15 was 12.0 months (95%CI = 8.319~15.201), and the difference was not statistically significant (P = 0.251).The median overall survival was 27.4 months (95%CI = 19.325~33.123) for CC0-1 resected patients and 9.4 months (95%CI = 5.1~11.7) for CC2-3 resected patients, again a non-significant difference (P = 0.127). However, in terms of platinum sensitivity, the median overall survival was 23.0 months (95%CI = 18.128~29.311) in sensitive patients compared to 7.9 months (95%CI = 2.415~11.239) in resistant patients, a difference that was statistically significant (P = 0.001). See **Figure 4**.



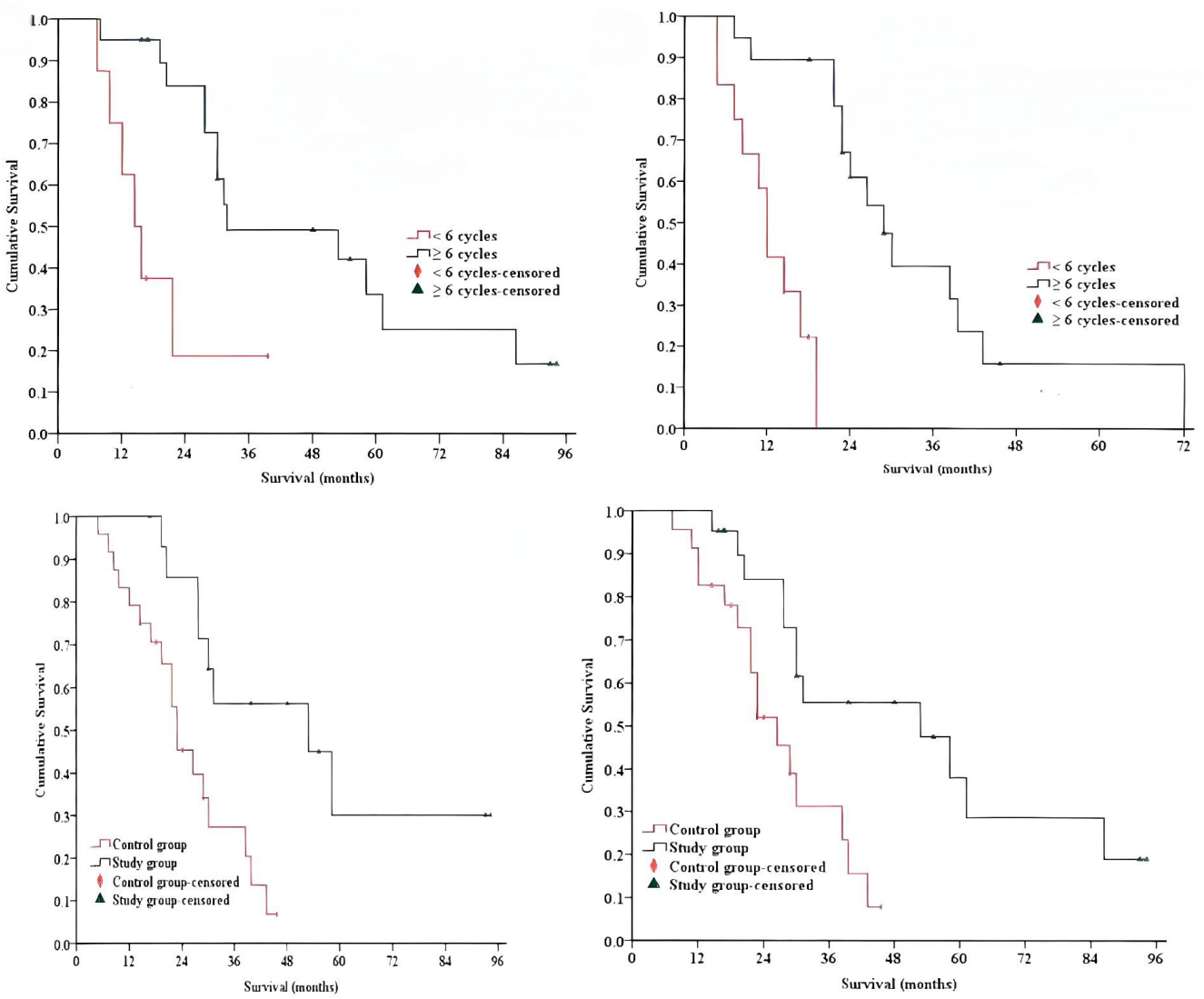


Figure 4. Subgroup analysis of patient survival.

4. Discussion

The combination of CRS with HIPEC represents a novel approach in the treatment of advanced and recurrent EOC [14], particularly in the Chinese population, where its application remains underexplored. While previous international studies have demonstrated the survival benefits of CRS + HIPEC, few have specifically focused on its use in a Chinese cohort, where variations in healthcare access, patient demographics, and tumor biology may influence outcomes. Our study addresses this gap by providing region- specific evidence on the clinical efficacy and safety of this approach. This integrated protocol provides a new treatment pathway for certain patients with peritoneal cancer [15]. CRS with HIPEC first removes as much of the tumor as possible through surgery, and then injects a heated mixture of chemotherapeutic drugs into the patient's peritoneal cavity, taking advantage of the different temperature tolerances of cancer cells and normal tissue [16]. The high temperature not only directly destroys the tumor cells, but also enhances the effect of the chemotherapeutic drugs and removes the cancer cells by mechanical flushing [17]. This treatment combines the advantages of surgical removal of the

tumor and regional hyperthermic chemotherapy, which helps to improve survival time for certain patients with peritoneal metastatic cancer.

We performed a multifactorial Cox regression analysis of the factors affecting the overall survival of the patients, and the results showed that CC score, postoperative chemotherapy cycle, treatment method, lymph node status, and ascites volume were significant factors affecting overall survival.CC score, postoperative chemotherapy cycle, treatment method, lymph node status, and ascites volume were independent risk factors affecting overall survival. There is more literature similar to our study. It has been documented that in a comprehensive analysis of 895 patients, the median overall survival of EOC patients treated with HIPEC ranged from 22 to 64 months, and the median disease-free survival ranged from 10 to 57 months [18]. In patients who achieved ideal tumor reduction, the median overall survival was even extended to 29 to 66 months. These patients achieved three-year survival rates of 35 to 63%, while five-year survival rates ranged from 12 to 66%. Scholars have also explored the potential impact of treatment with CRS combined with HIPEC on survival at different time points during the natural progression of EOC [19]. A retrospective case-control study of patients with stage Ic EOC who were treated with CRS plus HIPEC was conducted and compared over time with patients treated with CRS only [20]. The results of the study showed that the survival of the CRS plus HIPEC Observation group was prolonged by 20% compared to the CRS alone Observation group. Multifactorial analysis showed that intraoperative HIPEC treatment was an independent factor affecting prognosis. Many studies have reported that CRS plus HIPEC for recurrent EOC improves survival [21,22]. Two prospective non-randomized trials compared the effect of CRS plus HIPEC versus CRS treatment alone on survival [23,24]. A randomized controlled phase I clinical study of CRS plus HIPEC for recurrent EOC was also reported in the literature [25]. This study included 60 patients with first recurrence of EOC after first-line treatment in FIGO phase II/IV who received CRS plus HIPEC and postoperative adjuvant chemotherapy, and compared them with 60 patients with recurrent EOC who received only CRS and postoperative adjuvant chemotherapy during the same period. The above reports in the literature are similar to the results of our study.

In patients with EOC who relapse within six months of completing platinum-based first-line adjuvant chemotherapy, this condition is usually associated with platinum resistance. Patients with platinum-resistant EOC tend to have rapid disease relapse and progression due to poor response to chemotherapy, leading to a poorer prognosis. Thermotherapy was found to significantly enhance the cytotoxic effects of cisplatin, an effect that was equally valid for cisplatin-resistant and sensitive cells. Continuous action at a temperature of 43 °C for 60 min reversed cisplatin resistance, although the exact molecular mechanism is unclear. Intraoperative HIPEC utilizing cisplatin, combined with the synergistic effect of thermotherapy and cisplatin, can enhance cytotoxicity in platinum-resistant or sensitive patients [26]. The study showed that the median overall survival of platinum-resistant and sensitive patients was 48 and 52 months, respectively. A study by Greek scholars came to a similar conclusion; in the Observation group, the mean survival times of platinum-sensitive and drug-resistant patients were 26.8 and 26.6 months, respectively, whereas in patients who received CRS only, the mean survival times of sensitive and drug-

resistant types were 15.2 and 10.2 months, respectively [27]. This suggests that HIPEC is of significant benefit in patients with recurrent EOC, especially in the platinum-resistant type. CRS plus HIPEC is a complex and time-consuming procedure, and the necessary peritoneal resection and visceral resection to achieve complete tumor reduction may increase the risk of serious perioperative adverse events. A systematic review by Australian scholars noted that the incidence of grade III adverse events was 0%–40% and grade IV adverse events was 0%–15% when CRS plus HIPEC was used to treat advanced or recurrent EOC, and that common postoperative adverse events included intestinal obstruction, intestinal leakage, hemorrhage, incisional infection, and pleural effusions [28]. A specialized study by Spanish scholars found lower rates of perioperative disability and mortality with CRS plus HIPEC for EOC peritoneal carcinomatosis [29].

The results of this study provide valuable insights into the long-term efficacy of CRS + HIPEC. The median OS in the CRS + HIPEC group was 36.9% longer than in the CRS-only group, with a significant improvement in 1-year, 3-year, and 5-year survival rates. This suggests that CRS + HIPEC not only improves short-term outcomes but also provides durable survival benefits for patients with recurrent EOC. Furthermore, subgroup analysis indicates that the therapeutic effect is more pronounced in patients with low peritoneal cancer index (PCI) scores and complete cytoreduction (CC0-1), highlighting the importance of patient selection in achieving optimal outcomes. Compared with other treatment options, such as secondary CRS followed by systemic chemotherapy, CRS + HIPEC offers distinct advantages. Systemic chemotherapy alone often fails to control peritoneal metastases effectively due to limited drug penetration into the peritoneal cavity. In contrast, HIPEC delivers high concentrations of chemotherapeutic agents directly to the peritoneal surface, leveraging hyperthermia to enhance cytotoxicity and improve drug efficacy. For patients with platinum-resistant disease, CRS + HIPEC also shows promise in overcoming chemotherapy resistance, providing a therapeutic option for a subgroup with limited treatment alternatives.

In terms of methodological innovation, our study adopted a rigorous retrospective case-control design with propensity score matching to minimize selection bias—a limitation often encountered in previous studies on this topic. Moreover, the use of standardized HIPEC protocols ensures greater reproducibility and reliability of our findings compared to studies with variable regimens. In addition, this study uniquely analyzed the impact of prognostic factors, such as CC score, ascites volume, and lymph node status, on overall survival in patients undergoing CRS + HIPEC. While these factors have been examined individually in prior research, our study integrates them into a comprehensive multivariate Cox regression model, providing new insights into how these variables interact to influence patient outcomes. This approach highlights not only the overall efficacy of CRS + HIPEC but also identifies subgroups of patients who may derive the most benefit from this treatment. Finally, our findings suggest that CRS + HIPEC may improve survival even in patients with platinum-resistant disease, a population with historically poor outcomes. This observation is particularly significant as it underscores the potential of HIPEC to overcome platinum resistance, an area that warrants further investigation into the underlying molecular mechanisms.

Despite its promising results, our study has several limitations that warrant discussion. First, the retrospective nature of the study and the relatively small sample size (60 patients in each group) may introduce potential selection bias, despite our efforts to match clinicopathological characteristics. A larger, prospective randomized controlled trial would be ideal to validate these findings and ensure their generalizability. Second, the follow-up period, while sufficient for evaluating median OS, may not fully capture the long-term efficacy and potential late complications of CRS + HIPEC. Future studies should include extended follow-up to assess the durability of survival benefits and the incidence of late adverse events. Third, the study population is limited to a single center in China, which may restrict the extrapolation of results to other regions with different healthcare systems, patient demographics, and clinical practices. Comparative studies across multiple centers and geographic regions would provide a more comprehensive understanding of the applicability of CRS + HIPEC in diverse settings. Lastly, while our analysis included key prognostic factors such as CC score, ascites volume, and lymph node status, other potentially important variables, such as molecular and genetic markers, were not evaluated. Incorporating these factors into future research may provide deeper insights into the mechanisms underlying the observed treatment benefits and identify biomarkers for patient stratification.

5. Conclusion

In conclusion, the combination of CRS and HIPEC can significantly improve the overall survival of patients with recurrent EOC. This combination therapy can more effectively control disease progression and provide patients with a better prognosis than traditional chemotherapy approaches. The safety profile of CRS and HIPEC is also relatively high. While there are some risks associated with any surgery and chemotherapy, the risks of these treatments are comparable to those of surgery and chemotherapy for other types of cancer. Many patients tolerate these treatments well and recover well from them. CRS and HIPEC are effective treatments for recurrent EOC and can significantly prolong a patient's overall survival while maintaining a high safety profile. By providing standardized treatment protocols, rigorous methodological approaches, and region-specific data, this study contributes valuable evidence to the evolving landscape of CRS + HIPEC in recurrent EOC. It highlights not only the survival benefits of this approach but also its potential to address longstanding challenges in EOC management, such as platinum resistance and residual peritoneal disease. However, further research is needed to confirm these findings, explore long-term outcomes, and refine patient selection criteria to maximize the therapeutic potential of this combined approach.

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Ethical approval: The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University. Ethical number: GYZL-XW-2024 (016). Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

Short name	Full name
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
EOC	Epithelial ovarian cancer
OS	Overall survival
KPS	Karnofsky Performance Status
PCI	Peritoneal cancer Index
CC	Cell reduction score

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