



Hyperthermic Intraperitoneal Chemotherapy as a Treatment for Epithelial Ovarian Cancer

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Abstract

Treatment by cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been an option for selected patients with peritoneal carcinomatosis. This study aims to evaluate the impact of HIPEC in epithelial ovarian cancer (EOC). A retrospective observational cohort study including 48 EOC patients treated and followed up between 2012 and 2016. Thirty-seven cases were treated by CRS only, while 11 cases were treated by CRS and HIPEC. The study was performed at National Cancer Institute (NCI)—Cairo University. There was no statistically significant difference regarding overall survival or disease-free survival between the group of EOC patients treated by CRS only and the one treated by CRS and HIPEC. Presence of ascites and histological types (serous/non-serous) were the significant independent variables related to overall survival. Presence of ascites was the only independent variable associated with a significant relation to disease-free survival. No statistically significant impact of HIPEC in treatment of EOC was found in this study.

Keywords Epithelial ovarian cancer (EOC) · Peritoneal carcinomatosis · Peritoneal cancer index (PCI) · Cytoreductive surgery (CRS) · Hyperthermic intraperitoneal chemotherapy (HIPEC)

Introduction

Epithelial ovarian cancer (EOC) is the most lethal type among all types of gynecological malignancies. Up to 75% of EOC

present with advanced stage with peritoneal carcinomatosis or distant metastasis [1].

It has been shown that treatment by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy

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(HIPEC) is associated with improved survival rates in advanced and recurrent ovarian cancer, compared to treatment by CRS only [2]. In this study, the aim is to investigate the potential benefit of HIPEC in EOC and independent variables with potential significant prognostic impacts.

Patients and Methods

This is a retrospective observational cohort study performed at National Cancer Institute (NCI)—Cairo University including 48 cases with EOC treated and followed up between 2012 and 2016. Inclusion criteria were stage II and III EOC patients with good performance status, adequate hepatic and renal functions, and associated with peritoneal nodules on surgical exploration, while exclusion criteria were those with poor general condition, metastatic disease, disease progression on neoadjuvant chemotherapy (if given), or those who had incomplete CRS (CC score 2 or 3).

Surgical intervention included total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal cytology/ascitic cytology, and pelvic peritonectomy in addition to removal of all extra pelvic peritoneal nodules and any enlarged lymph nodes, if present. The goal of the surgery was to achieve a complete cytoreduction with eradication of every tumor deposit (to achieve CC score 0 and 1). PCI was assessed during surgical exploration and documented in every case associated with peritoneal nodule presence.

HIPEC was performed after CRS using closed technique. Thermal probes were positioned to monitor the

inflow and outflow temperature. The abdomen was perfused with 4–6 l of isotonic saline at a flow rate of 900–1000 ml/min and a peritoneal temperature of 40–42 °C for 60 min. The used chemotherapeutic agent was cisplatin, at a dose of 200 mg/m². After the procedure, the abdomen was closed after insertion of four suction drains. In case of associated intestinal resection and anastomosis, intra-abdominal chemotherapy was administrated after the performance of intestinal anastomosis. Low anterior resection was performed in three cases.

After the discharge of patients, they were followed up after 3 months, then regularly every 6 months with abdominal and pelvic CT scans, serum CA 125, CBCs, and renal and liver function tests. The median follow-up period was 26 months. All patients were assessed according to their operative complications, overall survival, and disease-free survival. Overall survival was calculated as the length of time between diagnosis of the disease and the last point of time the patients were still alive. Disease-free survival was calculated as the length of time between the surgical treatment of the disease and time of first manifestation of recurrence or death.

The study was approved by the ethical committee of NCI. Clinical data were collected from hospital medical records and investigations' reports, recorded in a standard database form, evaluated and analyzed by the authors. For this type of study (retrospective study), formal consent is not required.

Data were analyzed using SPSS win statistical package version 23. Numerical data were expressed as mean, standard deviation (SD), median, and range, as appropriate. Qualitative data were expressed as frequency and percentage. Survival

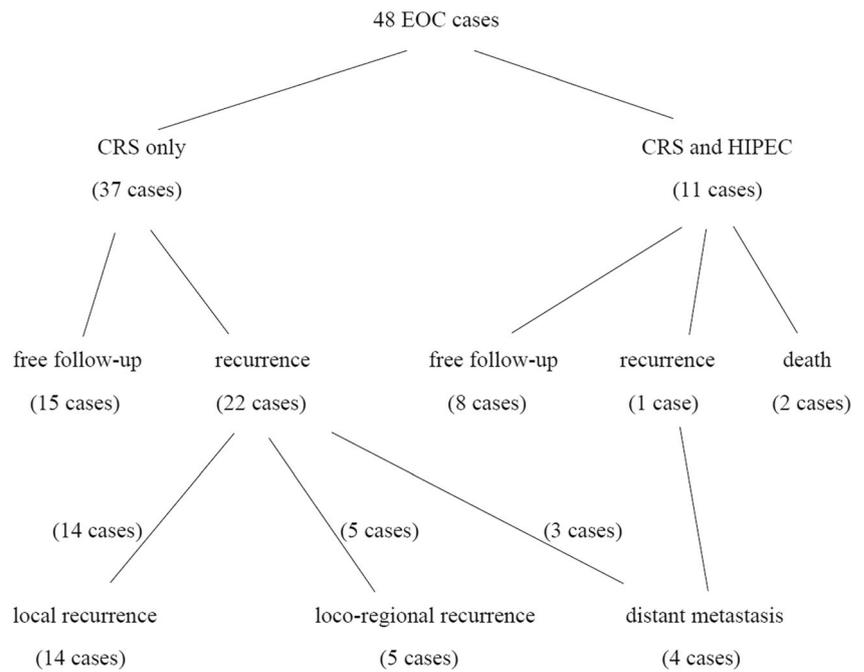
Table 1 Patients' and tumor's characteristics

Characteristics	CRS only for primary disease <i>N</i> = 37 (%)	CRS and HIPEC for primary disease <i>N</i> = 11 (%)	<i>P</i> value
Age (year)			
Median (range)	52 (24–69)	57 (35–64)	0.713
Histological type			
Serous	31 (83.8%)	10 (90.9%)	
Non-serous	6 (16.2%)	1 (9.1%)	0.557
Stage			
II	24 (64.9%)	2 (18.2%)	
III	13 (35.1%)	9 (81.8%)	0.006*
PCI median (range)	6 (2–12)	7 (3–16)	0.351
Ascites			
Present	22 (59.5%)	5 (45.5%)	
Absent	15 (40.5%)	6 (54.5%)	0.411
Neoadjuvant chemotherapy			
Given	13 (35.1%)	10 (90.9%)	0.001*
Not given	24 (64.9%)	1 (9.1%)	

PCI peritoneal cancer index

*Significant

Fig. 1 Patients’ flow diagram. A diagram illustrating patients flow after surgical intervention (either CRS only or CRS and HIPEC) illustrating free follow-up or incidence of recurrence or postoperative death



analysis was done using Kaplan-Meier method. Comparison between two survival curves was done using log-rank test. Multivariate analysis was done by Cox regression model to test for the independent prognostic effect of statistically significant variables on univariate level with calculating the hazard ratio and its 95% confidence interval. *P* value ≤ 0.05 was considered significant, and all tests were two-tailed.

Results

A total number of 48 patients with EOC were treated and followed up during the period of the study. Surgical interventions were CRS for 37 cases and CRS and HIPEC for 11 cases. Patients’ and tumor’s characteristics are demonstrated in Table 1 with significant differences regarding disease stage (II/III) and neoadjuvant chemotherapy (given/not given) between the two groups of EOC; one of them was treated by CRS only, and the other one was treated by CRS and HIPEC.

During the follow-up, local recurrence (peritoneal carcinomatosis) occurred in 14 cases among those who were treated by CRS only (37.8%), while it did not occur in cases treated by CRS and HIPEC. Patients’ flow is demonstrated in Fig. 1.

The average surgical duration was 4 h for CRS only and 5 h for CRS and HIPEC. All cases, treated by CRS only, were transferred to the ward postoperatively and were discharged within 3 weeks after the surgery.

Postoperatively, all cases treated by CRS and HIPEC were admitted to ICU, with an ICU stay length ranging between 2

to 10 days (average 3 days for cases with no postoperative morbidities). In case of having a smooth postoperative course without any operative complications, the average hospital stay length was 2 weeks.

Postoperative complications occurred in three cases after CRS and HIPEC; one case died from pulmonary embolism, one case developed renal failure, and one case developed wound infection. While postoperative complications occurred in four cases after CRS only; two cases developed wound infection, one case developed chest infection and one case developed DVT.

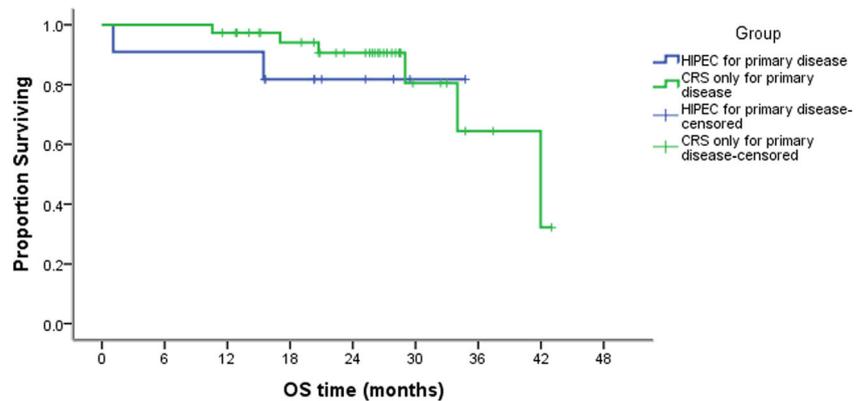
Total number of postoperative deaths due to surgical complications was two cases after CRS and HIPEC; one case died from pulmonary embolism and one case developed acute renal failure after CRS and HIPEC and died 5 months after the surgery. Postoperative death due to surgical complications did not occur in cases treated by CRS only.

By univariate analysis between different variables and overall survival, presence of ascites was statistically

Table 2 Multivariate analysis of prognostic factors associated with lower overall survival

Prognostic factor	Hazard ratio (HR)	95% CI for HR	<i>P</i> value
Non-serous histological types			
Present	6	1.643–21.803	0.007
Absent	1		
Ascites			
Present	7	1.521–31.941	0.012
Absent	1		

Fig. 2 Impact of HIPEC on overall survival (OS) (P value 0.559). There was no statistically significant difference regarding overall survival between the group of EOC patients treated by CRS only and the other group of those treated by CRS and HIPEC



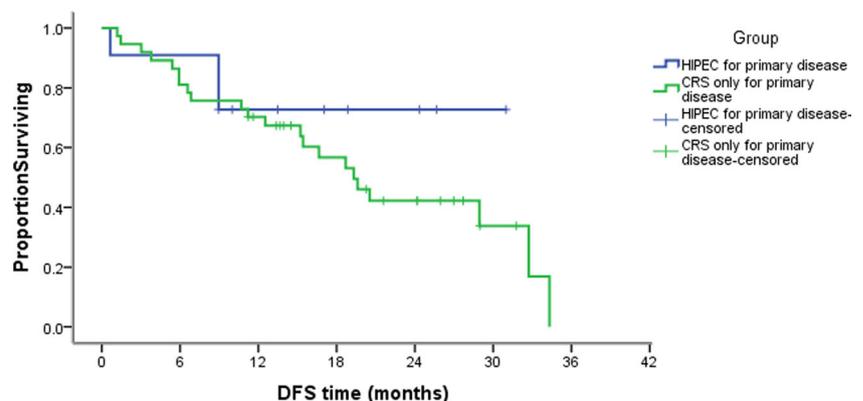
significantly associated with a poor impact on overall survival (P value 0.002). Regarding histological types of EOC, non-serous types were associated with a statistically significant poor overall survival compared to serous type (P value 0.001). Multivariate analysis showed that presence of ascites and non-serous histological types were both associated with a statistically significant reduced overall survival (Table 2).

By univariate analysis between different variables and disease-free survival, presence of ascites was the only variable having a statistically significant relation with disease-free survival (P value 0.013). Other variables such as age, stage, and neoadjuvant chemotherapy were not statistically significantly associated with overall survival or disease-free survival.

The median overall survival for the group of EOC patients treated by CRS only was 42 months and that for the group of EOC patients treated by CRS and HIPEC was not reached. The median disease-free survival for the group of EOC patients treated by CRS only was 19.5 months and for the group of EOC patients treated by CRS and HIPEC was not reached.

In this study, there was no statistically significant difference between the group of EOC patients treated by CRS only and the group of EOC patients treated by CRS and HIPEC regarding overall survival (P value 0.559) or disease-free survival (P value 0.316) (Figs. 2 and 3).

Fig. 3 Impact of HIPEC on disease-free survival (DFS) (P value 0.316). There was no statistically significant difference regarding disease-free survival between the group of EOC patients treated by CRS only and the other group of those treated by CRS and HIPEC



Discussion

In this study, there was no statistically significant impact of HIPEC on overall survival or disease-free survival in EOC. In a study including 87 patients with primary EOC (52 patients were treated by CRS and HIPEC and 35 patients were treated by CRS only), the addition of HIPEC was associated with a significant improved disease-free survival in patients with well and moderately differentiated tumors [3].

Another study, including 111 patients with primary and recurrent ovarian cancer (90 patients were treated by CRS only and 21 patients were treated by CRS and HIPEC), did not detect a statistically significant benefit of HIPEC administration [4].

A systematic review and meta-analysis, including 37 studies about the role of HIPEC in treatment of primary and recurrent EOC, concluded that the addition of HIPEC to CRS was associated with an improved overall survival [2]. A recent randomized clinical trial, including 245 stage III EOC patients, concluded that addition of HIPEC to CRS resulted in improved disease-free survival and overall survival compared to CRS alone and is not associated with higher rate of side effects [5].

A study, including 42 cases of EOC (15 as primary disease and 27 as recurrent disease), concluded that HIPEC is a

promising option for EOC regarding overall survival and disease-free survival [6]. Another study, including 61 patients with EOC (31 as primary disease and 30 as recurrent disease), concluded that treatment of EOC with CRS and HIPEC is associated with good results regarding morbidity and survival [7].

In conclusion, presence of ascites and histological type of EOC were associated with a statistically significant impact on overall survival, while presence of ascites was the only factor associated with a statistically significant impact on disease-free survival. However, local recurrence, in the form of peritoneal carcinomatosis, was observed in 37.8% of EOC cases treated by CRS only, while it did not occur in cases treated by CRS and HIPEC. No statistically significant impact of HIPEC regarding overall survival or disease-free survival was found.

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Compliance with Ethical Standards

The study was approved by the ethical committee of NCI. Clinical data were collected from hospital medical records and investigations' reports, recorded in a standard database form, evaluated and analyzed by the authors. For this type of study (retrospective study), formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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