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Secondary Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS+HIPEC) for Recurrent Epithelial Ovarian Cancer (EOC): Indian Experience

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Abstract

Background: Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has been proposed as treatment for recurrent epithelial ovarian carcinoma. We evaluated the outcomes of CRS +HIPEC in recurrent epithelial ovarian cancers, in Indian patients.

Method: In this prospective non-randomized study between February 2013 and January 2015, 26 patients with advanced recurrent EOC, with no extra-abdominal disease treated with secondary CRS+HIPEC in a tertiary care cancer institution, Southern India, were analyzed. Belmonte® hyperthermia (HIPEC) pump with cisplatin 100 mg/m^2, 41.5°C to 43°C for 90 minutes, in platinum sensitive cases and doxorubicin 15 mgs/m^2 + cisplatin 75 mg/m^2 in platinum resistant cases was used.

Result: Among twenty six patients 18 were upfront and 8 were post chemotherapy. Median peritoneal carcinomatosis Index was 9.5 (Range: 3-19). The extent of cytoreduction associated with longer hospital stay ($p < 0.001$), delayed gastrointestinal recovery ($p=0.039$), infections ($p=0.036$), and Acute Respiratory Distress Syndrome ($p=0.041$). Completeness of cytoreduction score CC0 achieved in 24 and CC1 in 2 patients. Bowel resection required in 34.6%. Diaphragm stripping was required in 30.7% with resection in 7.6%. Median hospital stay was 12 days (range: 10-42 days). No 30 days mortality. Bowel fistula happened in 7.6% cases requiring re-exploration, temporary stomas, and wound related complications in 26%. At median follow-up of eighteen months, 11.5% recurrences (both platinum resistant cases recurred in peritoneal cavity and one patient also in liver parenchyma) and one platinum sensitive patient recurred isolated in peritoneal cavity. One patient died at 5th month of follow up due to pulmonary embolism.

Conclusion: In our Indian study, secondary CRS+HIPEC are shown to be very promising in recurrent epithelial ovarian cancers patients with no extra-abdominal disease and good performance status. And can be done with acceptable morbidity, using dedicated HIPEC machine resulting in good peritoneal control of disease and disease free survival.

Keywords: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Epithelial ovarian cancer; Carcinoma; Chemotherapeutic agent

Introduction

Advanced epithelial ovarian carcinoma (EOC) is known for recurrences despite optimal treatment (complete cytoreduction and adjuvant platinum chemotherapy), which portends 5 year survival of approximately 30% [1]. The treatment for recurrent ovarian carcinoma still remains a field of discussion mainly owing to lack of randomised trials and to the broad variety of definition of surgical procedures. Unfortunately, the only prospective randomized trial addressing the role of secondary surgery in recurrent ovarian cancer, the LOROCSON trial, sponsored by European Organization for Research and Treatment of Cancer (EORTC) was aborted prematurely due to low recruitment. Still we lack strong evidence for the role of HIPEC in recurrent EOC. A systematic review by Chua et al. [2] showed severe morbidity and mortality associated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The high level of perioperative morbidity and mortality might be considered acceptable when no other alternate therapy has been shown to be effective in curing or controlling the disease but this is not the case of ovarian cancer recurrence in which surgery and platinum-based chemotherapy represent accepted, evidence-based, valuable options. With this background we conducted this prospective study to analyse perioperative outcomes and short term oncological outcomes in Indian patients with recurrent EOC.

Materials and Methods

In our prospective nonrandomised study, we included consecutive twenty six patients from February 2013 - Jan 2015 with recurrent ovarian carcinoma. The recurrent ovarian carcinoma refers to the peritoneal recurrence in previously operated ovarian peritoneal carcinomatosis. Our inclusion criteria patients with peritoneal only recurrent advanced EOC, treated with secondary CRS+HIPEC and good performance status (ECOG < 2). We excluded the patients with a known allergy to the intraperitoneally administrable chemotherapeutic agent and with poor respiratory, hepatic, cardiac, kidney and bone marrow function (absolute neutrophil count < 1500/mm^3, platelets < 150,000/µl, creatinine clearance < 60 ml/min according to Cockfort formula). All patients were treated in tertiary care hospital in southern India by an experienced team on peritoneal surface malignancies. This center performs on an average 60 to 80 cytoreductive surgeries per year for ovarian carcinoma. Written informed consent was obtained. The institutional ethics committee had given approval for our study.

All the patients were staged and evaluated with baseline renal function test, complete blood count, liver function test, cardiac evaluation, pulmonary function test. We used standard technique of CRS and HIPEC [3,4]. Platinum sensitive cases are defined as recurrence after 6 months from the completion of treatment. Platinum resistant cases are defined as recurrence within 6 months after completion of treatment. In our study Secondary CRS+HIPEC refers to the surgery done in recurrent ovarian peritoneal carcinomatosis. CRS for ovarian carcinoma includes pan hysterectomy, salpingo-opherectomy, omentectomy, appendectomy, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy. Involved field peritonectomy (i.e. total parietal peritonectomy, diaphragmatic peritonectomy, pelvic and bladder peritonectomy) and organs removed were mentioned separately (e.g. CRS with large bowel resection or CRS with gastrectomy). Multi visceral resections defined as ≥ 2 organs or parts resected (e.g. anterior resection with small bowel resection and splenectomy classified under multi visceral resection). The peritoneal carcinomatosis index was assessed intraoperatively by Sugarbaker method [5]. The Completeness of cytoreduction (CC Score) score defined as CC0 - no visible tumour tissue, CC1 < 2.5 mm tumor nodules, CC2-2.5 mm to 2.5 mm tumor nodules and CC3 - bulky disease > 2.5 mm. Only the patients with CC score of 0/1 submitted to HIPEC.

FDA approved *Belmont® Hyperthermia pump* (Belmont instrument company, USA) was used for HIPEC. HIPEC was done in semiopen (Figure 1) or closed methods. Dose of intraperitoneal chemotherapeutic agent calculated according to body surface area. For platinum sensitive cases we used cisplatin 100 mg/m^2 in a low calcium peritoneal dialysis solution PD4 (Dianeal 13.6 mg/ml, Baxter, Deerfield, IL, USA) and for platinum refractory cases cisplatin 75 mg/m^2 with doxorubicin 15 mg/m^2. Before starting the perfusion, the body temperature was lowered to 35°C with the help of Hemotherm machine (Cincinnati Sub-Zero products, Inc. Ohio, USA). Then the body temperature variations (Figure 2) monitored and managed around the basal body temperature.

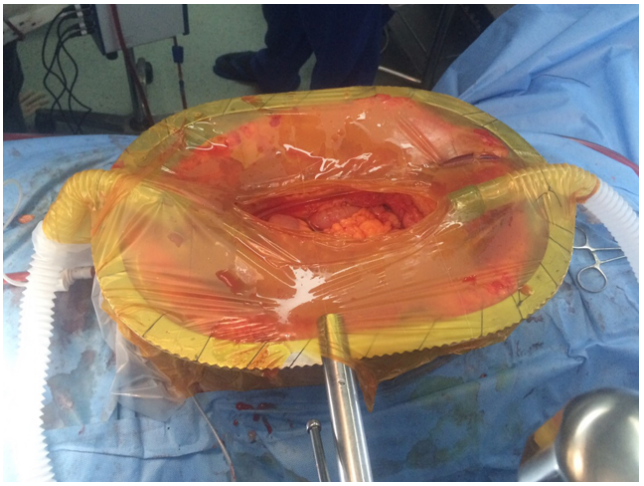

Figure 1: Semiopen method (wound is covered with a sterile plastic sheet and a vapor suction kept underneath).

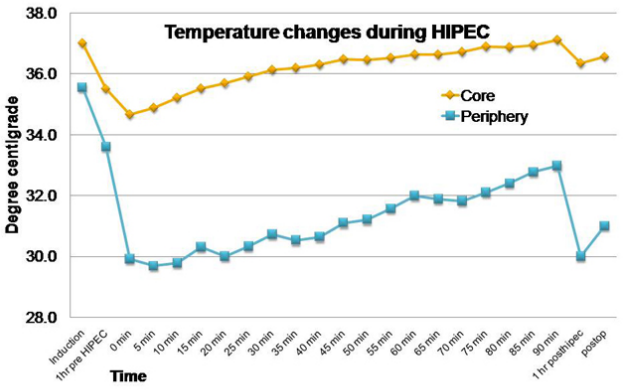

Figure 2: Core body temperature and peripheral body temperature changes during HIPEC.

In both semiopen and closed methods, perfusion was maintained for 90 minutes at 41.5°C to 43°C temperature. All patients were observed in intensive care unit (ICU) for the first 24-48 hours. Patient demographics, disease factors, surgical procedure related data, post-operative complications and adverse events were collected prospectively. Adverse events graded according to the NCI Common Terminology Criteria for Adverse events V 4.03 (2010). Based on existing guidelines, patients received adjuvant therapy and they were followed up with serum CA 125 levels and imaging.

Statistical Analysis

Descriptive statistics including means and standard deviations for continuous data and frequencies and percentages for categorical data were calculated. The correlation of the variables with the outcome parameter was calculated by Chi square test for non-continuous

variables and Student t test for continuous variables. Statistical significance was defined as a p value < 0.05 with 95% confidence interval. We used SPSS v16 software for the statistical analysis.

Results

Patient factors, disease factors, surgical parameters, HIPEC procedure related parameters and adverse events were depicted in Tables 1- 4. Most common (34.2%) age group was fifty to 60 years in our study. Twenty one (80.8%) patients had Eastern cooperative oncology group (ECOG) performance status 0 and five (19.2%) had ECOG performance status of 1. The average preoperative serum albumin level was 3.7 ± 0.27 mgs% (Range 2.9-4.2). Eighteen (69.2%) patients received pre operative chemotherapy after the diagnosis of peritoneal recurrence.

Mean peritoneal carcinomatosis index in our patients was 9.5 ± 4.73 (range 3-19). The median CA-125 level was 35.9 IU/L (range 4.1-6448). CC 0 achieved in twenty four (92.3%) patients and CC 1 in 2 (7.7%) patients. Bowel resection required in 34.6%. Diaphragm stripping (Figure 3) was required in 30.7% and with diaphragmatic resection in 7.6%.

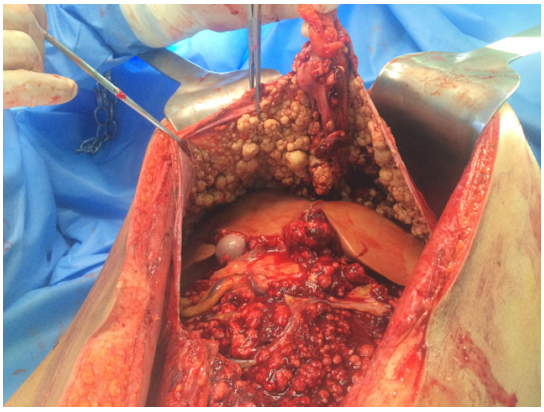

Figure 3: Extensive sub diaphragmatic disease requiring diaphragmatic peritoneal stripping.

The average blood loss was 1250 ml ± 250 ml. We used cisplatin 100 mg/m^2 in 23 (88.5%) patients and doxorubicin 15 mg/m^2 + cisplatin 75 mg/m^2 in 3 (11.5%) patients (for platin resistant ovarian carcinomas). The average duration of the surgery was 9 ± 3 (range 5.5-19) hours. Almost all patients had tachycardia in the first 24 hours after HIPEC. Multivisceral resections (Figure 4) associated with longer hospital stay (p < 0.001), delayed gastrointestinal recovery (p=0.039), more infections (p=0.036) and ARDS (p=0.041).

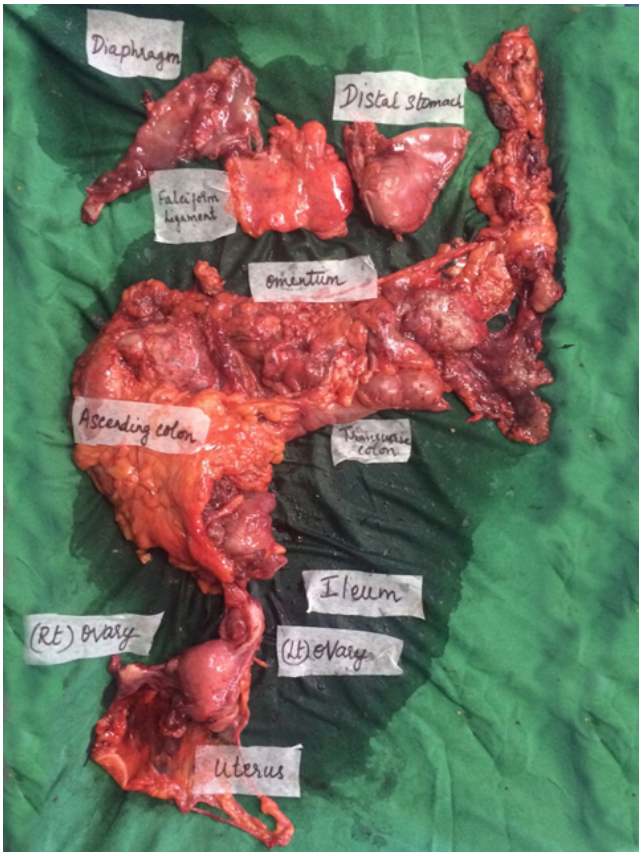

Figure 4: Extensive cytoreduction with multivisceral resections.

Bowel fistula happened in 7.6% cases requiring re-exploration and temporary stomas. One patient in addition to bowel fistula had delayed bladder perforation on post operative day 6. Wound related complications in 26% (n=7). With median follow-up of eighteen months, 11.5% (n=3) recurrences (both platinum resistant cases recurred in peritoneal cavity and one patient also recurred in liver parenchyma) and one platinum sensitive patient had isolated peritoneal recurrence. Upfront chemotherapy reduces recurrences in our study (p=0.011). One death at 5th month of follow up due to pulmonary embolism was observed.

S. no	Patient factor		Data
1	Age	20-40 Years	11.5% (n=3)
		41-50	30.8% (n=8)
		51-60 Years	34.2% (n=9)
		61-70 Years	15.2% (n=4)
		> 70 years	7.7% (n=2)
2	Performance status	ECOG 0	80.8% (n=21)

		ECOG 1	19.2% (n=5)
3	Diagnosis	Serous adenocarcinoma ovary	69.2% (n=18)
		Mucinous adenocarcinoma ovary	11.5% (n=3)
		Serous adenocarcinoma of fallopian tube	3.8% (n=1)
		Endometriod adnocarcinoma ovary	3.8% (n=1)
		Carcinosarcoma ovary	3.8% (n=1)
		Primary peritoneal carcinoma	7.7% (n=2)
4	Pre operative chemotherapy	Received	76.9% (n=20)
		Not received	23.1% (n=6)
5	Peritoneal carcinomatosis Index (Sugarbaker Index)		9.5 ± 4.73 (Range 3-19)
6	CA 125 levels (n=26)		Median 35.9 IU/L (Range 4.1- 6448)
ECOG: Eastern Cooperative Oncology Group, CA 125: Carbohydrate Antigen 125.			

Table 1: Patient characteristics.

S. no	Parameter		Data
1	Technique used	Open	92.3% (n=24)
		Closed	7.7% (n=2)
2	Temperature achieved during HIPEC (42 ± 0.49°C)	41.5°C	46.2% (n=12)
		42°C	38.5% (n=10)
		42.5°C	7.7% (n=2)
		43°C	7.7% (n=2)
3	Cytoreduction type	Cytoreduction alone	53.8% (n=14)
		Cytoreduction with small bowel resection	11.5% (n=3)
		Cytoreduction with large bowel resection	23.1% (n=6)
		Cytoreduction with Multivisceral resection	11.5% (n=3)
4	Surgery Duration in Hours		9 ± 3 (Range 5.5 – 19)

Table 2: HIPEC procedure characteristics.

S. no	Parameter		Data
1	Hospital stay (Days)		12 ± 7.078 (Range 8-42)
2	Gastrointestinal recovery (Days)		5 ± 1.5 (Range 4-10)
3	Ventilator support needed		7.7% (n=2)
4	Wound related Complications	Wound gapping	11.5% (n=3)
		Wound seroma	3.8% (n=1)

		Wound infection	11.5% (n=3)
5	Infectious complications	Fungal septicemia	3.8% (n=1)
		UTI	19.2% (n=5)
6	Adverse events (Grading done according to NCI Common Terminology Criteria for Adverse events V 4.03)	Hypoalbuminemia	46.2% (n=12)
		Hypokalemia (Grade 3 & 4)	46.2% (n=12)
		Hypocalcemia (Grade 3 & 4)	23.1% (n=6)
		Fall in Hemoglobin (Grade 3 & 4)	23.1% (n=6)
		Lymphocoele	23.1% (n=6)
		ARDS (Grade 3 & 4)	3.8% (n=1)
		Thrombocytopenia (Grade 3 & 4)	3.8% (n=1)
		Transaminase elevation (Grade 4)	3.8% (n=1)
		Sub-acute intestinal obstruction	11.5% (n=3)
		Ileal perforation/Bowel fistula	7.7% (n=2)
		Delayed bladder perforation	3.8% (n=1)
		Pneumonitis	3.8% (n=1)
		Acute kidney failure	3.8% (n=1)
		Acute cardiac failure	3.8% (n=1)
7	30 days Mortality		NIL
8	Recurrence		11.5% (n=3)
9	Death in the follow up		3.8% (n=1)
(Median follow-up period: 18 months. UTI: Urinary Tract Infection, ARDS: Acute Respiratory Distress Syndrome)			

Table 3: Surgical outcome and adverse events.

S. No	Procedure	Number
1	Omentectomy	53.8% (n=14)
2	Diaphragmatic peritonectomy	57.7% (n=15)
3	Hysterectomy	69.2% (n=18)
4	Pelvic peritonectomy	42.3% (n=11)
5	Large bowel resection	26.9% (n=7)
6	Total Parietal peritonectomy	30.8% (n=8)
7	Paracolic peritonectomy	42.3% (n=11)
8	Pouch of Douglasectomy	34.6% (n=9)
9	Mesenteric peritonectomy	11.5% (n=3)
10	Small bowel resection	15.4% (n=4)
11	Omental bursectomy	3.8% (n=1)
13	Splenectomy	3.8% (n=1)

14	Cholecystectomy	7.7% (n=2)

Table 4: Cytoreduction procedures.

Discussion

The extent of cytoreduction has a direct impact on survival and maximal cytoreduction was found to be one of the most powerful determinants of survival among patients with stage III or IV EOC in a meta-analysis of almost 7000 patients [6] and in other studies [7,8]. There is no doubt regarding the major impact of CRS against ovarian carcinoma; median survival is 86 months after CRS, 46 months when residual tumour deposits are less than 1 cm and 37 months when they are greater than 1 cm [9]. Given the high rate of recurrence after surgery (65%), HIPEC makes theoretical sense for the treatment of non-visible residual disease. The feasibility of HIPEC is established but neither the technique, nor the timing (upfront, as consolidation, or at recurrence), nor the survival benefit is yet established [10,11].

Three (11.5%) of our patients had recurrence in the peritoneum during follow up, in which two were platinum resistant ovarian carcinomatosis and 1 primary peritoneal carcinoma. Our study has the limitation of short median follow up of 18 months (range: 2-26 months). A long term follow up is required to substantiate the oncologic outcome of CRS+HIPEC in recurrent ovarian carcinomatosis. With unknown reasons patients who received upfront systemic chemotherapy had fewer recurrences in our study. This might suggest a new hypothesis for future studies. The unanswered question currently is whether HIPEC can improve survival for women with EOC and positively affect quality of life at any of the natural history time-points. We have seen a reasonable disease free survival after CRS +HIPEC in recurrent advanced ovarian carcinomatosis in our series. This may make a paradigm shift in the management of recurrent ovarian carcinomatosis. Among the published series and trials of CRS +HIPEC in recurrent ovarian carcinomatosis till date, only few showed improved overall survival and disease free survival. A series by Bakrin et al. [12], reported the overall median survival duration was 49 months, which is a good result considering that 25% of patients were platinum resistant among 246 patients treated for persistent or recurrent ovarian carcinoma. And a randomized trial of CRS+HIPEC with cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for recurrent International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and IV EOC reported a significantly improved mean survival in the HIPEC arm, 26.7 versus 13.4 months [13]. The main drawback of this study is the randomization was performed before the CRS.

Much of any additional morbidity was caused by the addition of chemotherapy after CRS. Our study showed acceptable morbidity and mortality in the initial experience. Notably there was no 30 days or in hospital mortality in our series. About 7.7% patients had major surgical complications requiring intervention. The most common medical complications were hypoalbuminemia and hypokalemia. The figures stand up well in comparison [14] to those from patients undergoing extensive CRS without HIPEC, especially with regard to perioperative mortality. The possible reasons for our good results could be mandatory pre operative oral protein supplementation with respiratory exercises, achieving good cytoreduction (CC0 or CC1 i.e. residual tumor < 2.5 mm) and a dedicated team of cytoreductive surgeon, anaesthetist, medical oncologist and intensivist.

Improved long-term results can be achieved in highly selected patients using CRS, including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy [15-23]. CRS+HIPEC have mainly been used to treat recurrent carcinoma in many studies, but there is heterogeneity in selection criteria and in techniques [12,19,24-27]. A well-constructed randomized study is the need of the hour to determine the role of secondary CRS+HIPEC in recurrent EOC. Worldwide many trials are ongoing to clarify the place of CRS+HIPEC in ovarian carcinoma. For recurrent ovarian carcinoma CHIPOR (NCT 01376752) [28], HORSE (NCT 01539785) [29], MSKCC trial (NCT 01767675) [30] and for the frontline ovarian carcinomas OVIHIPEC-1 (NCT 004262257) [31], CHORINE (NCT01091636) [32] and a French trial [33] are underway. These trials may give us a right path to manage recurrent advanced EOC.

Conclusion

In our Indian study, secondary cytoreduction and HIPEC was shown to be a promising therapy in recurrent epithelial ovarian carcinomatosis patients with no extra-abdominal disease and good performance status. The benefit of HIPEC in our study was limited only to platinum sensitive recurrent cases. With CRS+HIPEC we can achieve a good peritoneal control and a better disease free survival in recurrent ovarian carcinomatosis. A dedicated HIPEC machine and a dedicated team are pre requisite for an acceptable morbidity and mortality.

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