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Case Series

Oncology Section

Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery in Ovarian Cancer Patients: A Series of Five Cases

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ABSTRACT

Ovarian cancer is a leading cause of gynaecological cancer related-death in Indian women. Majority of ovarian cancer patients present in advanced stage with peritoneal disease, which poses a significant major challenge in the clinical management. The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cytoreductive Surgery (CRS) in ovarian cancer with peritoneal disease has evolved over the last decade as a promising modality with potential advantages. HIPEC after CRS is relatively new treatment modality for these patients with advanced or recurrent disease in ovarian cancer. Authors are sharing their experience of five ovarian cancer patients managed with HIPEC and CRS in a single institute. Five patients diagnosed with ovarian cancer underwent HIPEC following CRS in standardised manner from April 2021 to May 2022 after proper evaluation and consent. Interval cytoreduction in three and secondary cytoreduction in two patients with Platinum sensitive recurrence were performed. All the patients were followed in immediate postoperative period and for 12 months after surgery. Complete cytoreduction was achieved in all patients. A 30-day morbidity was grade I and II. One patient who underwent splenectomy as a part of cytoreduction succumbed to death in postoperative period due to septic shock. One patient developed locoregional recurrence during the follow-up period after six months. Rest of the three patients were disease free during 12 months of follow-up. HIPEC is a promising method along with CRS in advanced ovarian cancer with peritoneal disease and selected patients with recurrent disease.

Keywords: Advanced ovarian cancer, Gynaecological cancer, Peritoneal Disease

INTRODUCTION

Ovarian cancer is the second most common gynaecological cancer in India after cervix uteri and is the ninth most common cause of cancer-related mortality in women. In 2020, there were 47,333 new cases of ovarian cancer with 32,978 deaths from this disease Global Cancer Observatory (GLOBOCAN) [1]. Majority of patients presented with an advanced stage (International Federation of Gynecology and Obstetrics (FIGO) III, IV) disease due to a lack of effective screening modality and non specific symptoms at presentation with a dismal ten-year overall survival rate of 10-15% [2]. Surgery with curative intent is the standard of care for early-stage disease. The goal of treatment in advanced-stage disease is to minimise the tumour burden through surgery followed by six cycles of intravenous platinum-based chemotherapy. Alternatively, interval CRS is performed after Neoadjuvant Chemotherapy (NACT) [3-5].

John Spratt pioneered the use of HIPEC to treat patients with pseudomyxoma peritonei in 1980. Surgical pioneers such as Gilly, Elias, Yonemura and Sugarbaker refined the techniques and management strategies of HIPEC and CRS. Several HIPEC techniques have been described but no single technique has yet demonstrated superiority over the others [6,7]. HIPEC's role in improving survival outcomes in patients with the peritoneal disease has been established with interval debulking surgery and is currently being evaluated in the setting of Primary Cytoreductive Surgery (PCS) (OVHIPEC 2) [8]. PCS is the initial operation for advanced ovarian cancers to remove as much tumour as possible, aiming for microscopic disease, while Secondary Cytoreductive Surgery (SCS) happens later for recurrent disease, removing tumours that have grown back after initial treatment, often in harder-to-reach areas, improving survival in carefully selected patients, especially those with platinum-sensitive recurrence. PCS is the established first-line approach, while SCS offers benefits in specific relapse scenarios, improving quality of life and survival, but typically with higher risks and less success at complete removal than PCS.

Intraperitoneal (IP) chemotherapy was developed keeping in mind that ovarian cancer spreads locally to the peritoneum and remains confined to the peritoneal cavity for much of its natural history. The IP chemotherapy increases drug concentration at the peritoneal surface due to the peritoneal-plasma barrier resulting in more efficient addressal of residual microscopic peritoneal disease than intravenous chemotherapy. In a retrospective analysis of the data from GOG 0114 and GOG 0172 trials, Tewari D et al., showed that a combination of intravenous and IP chemotherapy following CRS is associated with an improvement in overall survival in patients with stage III ovarian cancer. There was also a 12% reduction in mortality risk with each cycle of IP therapy administered [9].

The synergistic effect of hyperthermia with IP chemotherapy enhances the cytotoxicity of chemotherapeutic agents [10]. Over the last decade, HIPEC with CRS has emerged as a promising modality for the treatment of FIGO Stage III ovarian cancer as evidenced by the OVHIPEC in view of significantly improved median OS (45.7 vs 33.9 months) [11]. Currently, randomised controlled trials are underway to evaluate the role of HIPEC in the setting of PCS as well as SCS.

Authors report a series of five cases of ovarian cancer treated with interval CRS with HIPEC with postoperative morbidity and six months and 12 months follow-up.

CASE SERIES

According to standard institutional protocol, five patients underwent CRS with HIPEC at Department of Surgical Oncology, AIIMS Rishikesh, over a period of one year (April 2021-May 2022). They were pauci-symptomatic at the diagnosis, with abdominal swelling and progressive asthenia being the most frequent presenting symptoms. The mean age of the patients was 46.8 years (range 40-56). The clinical characteristics of the patients are summarised in [Table/Fig-1]. The Eastern Cooperative Oncology Group (ECOG) performance status was one for all patients. All patients had

Case No.	1	2	3	4	5
Age at diagnosis (years)	40	50	48	56	40
1st CT cycle	04.11.2020	05.04.2021	18.08.2021	06.10.2021	07.03.2022
NACT cycles	6	6	8	6	4
Last NACT cycle	12.02.2021	05.08.2021	23.02.2022	04.02.2022	20.04.2022
Date of surgery	30.03.2021	15.09.2021	24.03.2022	16.03.2022	13.05.2022
Surgery type	Interval	Secondary	Interval	Secondary	Interval
CA 125 at diagnosis (U/mL)	1913	135	261	278	345
CA 125 at time of surgery (U/mL)	51.3	2.1	4.5	7.9	27.2
Histology	Serous	Serous	Mucinous + Sertoli-Leydig	Serous	Serous
Grade	High	High	High	High	High
FIGO stage	IVB	IIIC	IIIA1	IIIC	IIIC
ECOG PS	1	1	1	1	1
Peritoneal Cancer Index (PCI)	5	9	12	4	11
HIPEC drug	Cisplatin	Cisplatin	Cisplatin	Cisplatin	Cisplatin
Temp during HIPEC (°C)	42	42	42	42	42
Duration of HIPEC (mins)	90	90	90	90	90
30-day post op morbidity score (Clavien-Dindo)	I	V	I	I	II

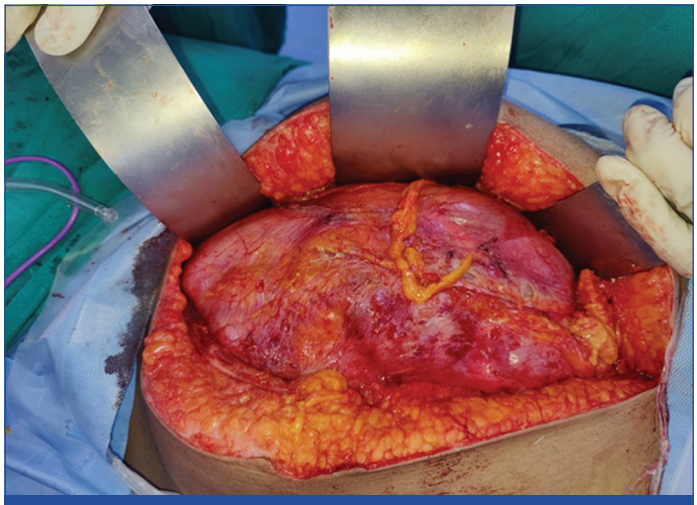
[Table/Fig-1]: Patient details.

received at least four cycles (mean 6 cycles) of NACT (carboplatin + paclitaxel). The mean duration between the last cycle of NACT and surgery was 4.6 weeks (range: 3-6 weeks). Three patients underwent interval cytoreduction while two patients underwent secondary cytoreduction. The most common histology was of epithelial serous type (4 out of 5 patients). The mean CA 125 levels before the initiation of NACT was 586.4 (Range: 135-1913), and it underwent significant reduction at the time of surgery with a mean of 18.6 (range 2.1-51.3).

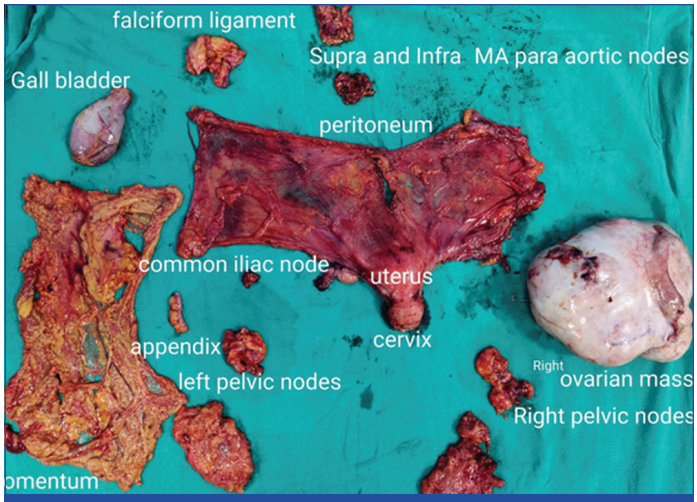
Reassessment radiological scans were done and the decision for surgery was taken after a detailed case-based discussion in the multidisciplinary tumour board. A complete Cytoreduction (CC-0) was achieved in all of the patients. Complete peritonectomy was accomplished by an extra-serosal approach along with total omentectomy in all the patients [Table/Fig-1-3]. HIPEC was administered intraoperatively using the closed technique. IP Cisplatin was administered at 100 mg/m^2 while maintaining a temperature of 42°C for a duration of 90 minutes. A 30-day postoperative morbidity was graded as per the Clavien-Dindo score. All the patients received adjuvant chemotherapy (carboplatin + paclitaxel).

Follow-up and Outcome

One patient succumbed to postoperative septic shock, while the remaining patients had grade I/II 30- day morbidity (three patients had grade I and one patient had grade II). After a median follow-up of 12 months, one patient (Patient 2) died in the postoperative period from sepsis and shock, and of the remaining four, one patient (Patient no-5) had disease recurrence after six months. The remaining three patients continued to be disease-free in the 12 month follow-up period.



[Table/Fig-2]: Extraserosal approach for peritonectomy during CRS.



[Table/Fig-3]: Comprehensive staging in ovarian cancer.

DISCUSSION

Authors operated on five different cases of carcinoma ovary with CRS and HIPEC over the period of one year. All of the patients received NACT, which lead to a significant reduction in serum CA-125 levels. They had a low disease burden with a mean Peritoneal Cancer Index (PCI) score of 8.2 (range: 4-12). Interval cytoreduction was carried out in three patients, while secondary cytoreduction was carried out in the rest. Two patients undergoing secondary cytoreduction had a platinum-sensitive relapse and were considered for secondary cytoreduction based on Memorial Sloan Kettering Cancer Centre (MSKCC) criteria [12].

Complete cytoreduction (CC-0) was achieved in all cases. Splenectomy was done in one case in view of disease involvement. Low anterior resection with diversion transverse loop colostomy was performed in one case in view of the tumour deposits in the upper rectum. Complete parietal with pelvic peritonectomy was accomplished in all patients through the extraserosal approach.

HIPEC was administered using the closed technique with cisplatin -100 mg/m^2 for 90 minutes at 42°C in all cases. Inflow and outflow drain along with the temperature probes were placed in the four quadrants of the abdomen. After the termination of the procedure, these drains were kept in situ for postoperative drainage. All of the patients required intensive postoperative haemodynamic monitoring in the critical care unit. Aggressive fluid resuscitation was needed in all patients in view of significant third-space fluid loss. Postoperative abdominal drain output on an average of 1.5-2 litres per day was observed for a period of 4-5 days following which drains were removed sequentially based on individual drain output. All of the patients received albumin and octreotide in the postoperative period, which was seen to result in a gradual decrease in drain output. Patients were encouraged for breathing exercises along with incentive spirometry in the perioperative period. One patient developed severe septicaemia in the postoperative period leading to septic shock and death. The rest of the patients had 30-day postoperative morbidity of grade I/II and were started on adjuvant chemotherapy after recovery. All of the patients were followed-up for one year during which period one patient developed recurrence.

The results of the phase III Randomised Controlled Trial (RCT), Ovarian Cancer and Hyperthermic Intraperitoneal Chemotherapy (OVHIPEC) Trial demonstrated the role of combined HIPEC with interval cytoreduction in patients with ovarian cancer. Although there is a lack of randomised control trials evaluating the role of HIPEC in recurrent ovarian cancer patients, meta-analysis by Huo YR et al., and Cianci S et al., demonstrated a significant survival benefit of HIPEC in patients of recurrent ovarian cancer as well [13,14]. The currently ongoing Italian randomised HORSE trial (NCT01539785) is expected to provide some robust statistical data in this patient subset [15]. The platinum-free interval and the extent of disease involvement form the main points for patient selection for SCS, which is quintessential to justify the significant postoperative morbidity this procedure entails.

In this case series, carefully selected patients who had undergone SCS with HIPEC one patient died in postoperative period. Since our three primary patients presented with locally advanced disease, platinum-based NACT was given in all, and they underwent interval cytoreduction with HIPEC. In this group, one patient had recurrent disease while the other two survived in the 12 months of follow-up period. Long-term follow-up is required for analysing survival outcomes.

CONCLUSION(S)

The HIPEC is promising adjunct to interval CRS in advanced ovarian cancer. Complete cytoreduction with IP local chemotherapy in highly selected patients have shown improved oncological outcomes compared to cytoreduction alone. Although safe, HIPEC requires specialised centres and expertise limiting its use in resource constraint settings. Ongoing studies are investigating its role in upfront (primary) surgery with evidence continuing to build for its effectiveness in recurrent cases.

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