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Dr. Bidhan Roy
Associate Professor & Gynae Oncosurgeon, Dept of Obstetrics & Gynaecology, Armed Forces Medical College, Pune, Maharashtra, India

Dr. D Barmon
Professor, Dept. of Gynaecology, Dr. B. Borooah Cancer Institute, Regional Cancer Center, Guwahati, Assam, India

Dr. AC Kataki
Director & Professor, Dr B. Borooah Cancer Institute, Regional Cancer Center, Guwahati, Assam, India

Corresponding Author:
Dr. Bidhan Roy
Associate Professor & Gynae Oncosurgeon, Dept. of Obstetrics & Gynaecology, Armed Forces Medical College, Pune, Maharashtra, India

Evaluation of the neo-adjuvant chemotherapy by intra-operative mapping of ovarian tumour during interval cytoreductive surgery in epithelial ovarian cancer

Dr. Bidhan Roy, Dr. D Barmon and Dr. AC Kataki

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Abstract
Background: Epithelial ovarian cancer usually presents at an advanced stage and neoadjuvant chemotherapy followed by interval cytoreduction is a standard treatment procedure. Visual intraoperative impression of the extent of the disease, total disease burden and resection status at the end of the cytoreductive surgery are important prognostic factors. Systematic documentation of the operative findings forms the cornerstone of an oncology center.
Methods: A prospective observational study was carried out to carry out intra-operative mapping of ovarian cancer at the time of interval cytoreduction after a course of 3-4 cycles of neo-adjuvant chemotherapy.
Results: 110 patients were included in the study. Profile of the patient were documented in the study along with the operative findings. It has evolved as a clinical and surgical audit of our center. Maximum tumour burden was evident in omentum (37.2%), followed by ovaries (11.8%) and deposits in pouch of douglas (7.2%). Notably, in 64.5% cases there was complete resection followed by R1 (residual disease status up to 1 cm) in 22.7% cases and R2 (residual disease status more than 1 cm) in 12.7% cases. In 43.6% there was complete remission of the disease with no evidence of the disease on histopathological examination.

Keywords: Epithelial ovarian cancer, neo-adjuvant chemotherapy, primary cytoreduction, interval cytoreduction

Introduction

Globally, 70 % of epithelial ovarian cancer is diagnosed in advanced stage and hence has got the highest fatality to case ratio of all the gynecologic malignancies [1]. This advanced stage of presentation is mainly due to inadequate screening tools and a lack of early clinical symptoms [2]. Presently, there are two modalities of treatment namely; primary debulking surgery (PDS) aiming to remove all visible tumor tissue, followed by first line adjuvant chemotherapy (ACT) with paclitaxel and carboplatin and the other modality being neoadjuvant chemotherapy (NACT) and then followed by interval debulking surgery (IDS) [3]. However, practically the choice between the two modalities depends upon the general condition of the patient and clinical and imaging extent of the disease, level of bio-markers like albumin, CA 125 and whether how best the complete cytoreduction is achieved by either of these two modalities. As the prognosis depends upon resection of all the visible metastatic deposits and hence the extent of surgery widens. Many a times, the patients are not fit enough to withstand such an extensive cytoreductive surgery. Thus, the current scenario offers NACT to those patients who are not fit for surgery and in very advanced staged of the disease [4, 5]. Staging is surgical and based on laparotomy findings with histological confirmation. Visual estimation by the surgeon is critical for the evaluation of intra-abdominal tumor spread.

Intra-operative mapping of ovarian tumour is a visual real time intra-operative observation of the malignant extent or disease burden. It is known that the uncertainty of perioperative visual assessment of tumor dissemination after NACT is due to tumour induced inflammation and infiltration, fibrosis, adhesions and necrosis in the peritoneal cavity after NACT and this may lead to incomplete resection of tumor in potentially resectable areas [6, 7]. In addition, development of chemo-resistance may develop due to the presence of cancer stem cells in these scarred tissues [8, 9]. Our study gives an outlook of the intra-operative mapping of the ovarian tumour in interval cytoreductive surgeries after neoadjuvant chemotherapy.

Material & Methods

Ethical Committee: Approval of the study taken.
Study Type: Prospective Observational Study
Study Period: 24 months

Inclusion Criteria

Patients were given three or four cycles of NACT at three weekly intervals before they were being considered for interval cytoreduction surgery. Both single agent (Carboplatin AUC 5) and double agent chemotherapy (Carboplatin AUC 5 and Paclitaxel 175 mg/m^2) patients of NACT were included in the study protocol. Interval between the last dose of chemotherapy and interval cytoreduction surgery was usually between 14 to 21 days (maximum limit of within 42 days).

The following points were considered for the institution of NACT:

1. Clinical Conditions for consideration of NACT.
2. Advanced cases of ovarian cancer proved by cytology of ascitic fluid / pleural effusion or core biopsy of abdomino-pelvic mass in co-relation with the tumour markers namely Cancer Antigen 125 (CA 125), Carcino-embryonic Antigen (CEA), Cancer Antigen 19.9 (CA 19.9). In addition, upper gastro-intestinal endoscopy, colonoscopy and mammogram were done where deemed necessary to rule out other primary disease.
3. Advanced cases of ovarian cancer with low performance status as per WHO criteria.
4. Advanced cases of ovarian cancer with pleural effusion, gross ascites, fixed abdomino-pelvic mass, fixed deposits in pouch of Douglas, poor nutritional status.
5. Advanced cases of ovarian cancer deemed unfit for surgery in view of advanced age, co-morbid factors and poor general conditions. Length of the surgery and anticipated morbidity were taken into account.
6. Extent of the disease predicts non-feasibility of optimal cytoreduction.
7. Radiological Assessment (Contrast Enhanced CT scan) considered for NACT
8. Gross pleural effusion or evidence of extra-abdominal disease like supra-clavicular nodes/ inguinal nodes.
9. Deposits in the liver parenchyma, porta hepatis, extensive peritoneal carcinomatosis, extensive bowel and mesenteric involvement, supra-renal regions, fixed pelvic mass below the levator ani involving the urinary bladder and rectum.

Exclusion Criteria

10. NACT or Interval cytoreduction done outside our institution.
11. Gap between the last dose of chemotherapy and interval cytoreduction surgery exceeds 42 days.
12. All primary debulking surgery for ovarian cancers done in our hospital.

Aim of the study

Standard documentation and objective evaluation of tumour burden after NACT as assessed during the interval cytoreduction surgery in advanced epithelial ovarian cancer.

Results

Table 1: Intra-operative Mapping of Ovarian Cancer

Intra-operative Mapping	Intra-operative Mapping	Number of cases
Ascitis	Nil	52 (47.2%)
	< 500 mL	44 (40%)
	>500 mL	14 (12.7%)
Tumour Involvement (upper abdominal) 9 sites	Diaphragm	22 (20%)
	Liver deposists (superficial & parenchymal & Both)	06 (5.4%), 08(7.2%) 08 (7.2%)
	Porta hepatis	05 (4.5%)
	Splenic deposits	03 (2.7%)
	Omental deposits	47 (42.7%)
	Stomach wall	02 (1.8%)
	Peritoneal wall	19 (17.2%)
	Mesenteric	09 (8.1%)
	Enlarged Para-aortic LN	07 (6.3%)
Tumour Involvement (lower abdominal) 6 sites	Ileal/Jejunal	14 (12.7%)
	Appendix	14 (12.7%)
	Colonic	17 (15.4%)
	Peritoneal wall	19 (17.2%)
	Mesenteric	09 (8.1%)
	Enlarged Para-aortic LN	07 (6.3%)
Tumour Involvement (pelvis) 5 sites	Ovaries	43 (39 %)
	Bladder deposits	16 (14.5%)
	POD deposits	43 (39 %)
	Recto-sigmoid	16 (14.5%)
	Enlarged Pelvic LN	09 (8.1%)
Maximum Tumour Burden (Dimension) seen before the surgery in Interval Cytoreduction	Omental caking	31 (28.1%)
	Ovaries	13 (11.8%)
	POD deposits	08 (7.2%)
	Peritoneal deposits	03 (2.7%)
	Intestinal deposits	05 (4.5%)
	Others (Bladder deposits, Splenic, Liver SOL, pelvic or para-aortic LN,etc.)	03 (2.7%)
Resection status at the end of surgery	R0	71 (64.5%)
	R1	25 (22.7%)
	R2	14 (12.7%)

Table 2: Post-operative Histopathological Examination after IDS

Structures affected on Final HPE Report	Serous Adenocarcinoma			Mucinous Adenocarcinoma 3(2.7%)	Endometroid Adenocarcinoma 4(3.6%)	Clear Cell Carcinoma 2(1.8%)	Nil on HPE 48(43.6%)
	Low Grade 2(1.8%)	High Grade 36 (32.7%)	Poorly Differentiated 15(13.6%)				
Ovaries	02	36	15	3	4	2	
Tubes	-	36	15	3	4	2	
Omentum	-	36	15	3	4	2	
Deposits on Uterus	-	35	15	-	-	2	
Deposits on Bladder	-	09	07	--	-	-	
Deposits on POD	-	26	15	1	-	-	
Deposits on Rectum	-	05	11	-	-	-	
Deposits on Colon	-	05	11	-	-	--	
Deposits on Small Intestine	-	05	09	-	-	--	
Deposits on Peritoneal Surface	-	08	11	-	-	-	48(43.6%)
Deposits on Liver Surface	-	06	08	-	-	-	
Mesenteric Deposits	-	05	04	-	-	-	
Deposits on Diaphragm	-	10	11	-	-	-	
Appendix	-	04	07	03	--	-	
Pelvic Lymph Nodes	-	02	02	-	-	-	
Para-aortic Lymph Nodes	-	--	-	-	-	-	
Splenic deposits	-	02	01	-	-	-	
Skin deposits	-	01	-	-	-	-	
Others (Adhesion/Bands)	-	---	-	-	-	-	

Discussion

With this background at hand we could carry out our findings in ovarian cancers in 110 cases meeting our inclusion criteria. There were highest number of 59 (53.59%) cases between 41 to 60 years and 25 (14.4%) cases were above 60 years of age. Clinical assessment, imaging and CA 125 level of all the 110 cases revealed advanced signs and symptoms of the disease at the time of first examination at our hospital. On admission the performance score status as per WHO performance scoring system were WHO (2) – 25.4% and WHO (3) - 47.2% and formed one of the important deciding factors for preferring NACT options for these patients. However, before the Interval cytoreduction surgical (ICS) procedure; performance status improved and tallied up to 78 (70.9%) cases in WHO (2) level.

A Wilcoxon Signed Rank test showed that NACT did elicit a statistically significant change in clinical signs and symptoms (Z= -8.598, p=0.000) as noted above by the change in WHO performance status.

All cases were diagnosed by cytology of the ascitic fluid confirming epithelial ovarian cancer origin. About 27% (30 cases) showed CA 125 level below 500 IU/mL and rest showed a higher level thus confirming the advanced disease status of the study population. But following the NACT; in 68 (61.8%) cases the CA 125 level were below 100 IU/mL. Statistically, the Wilcoxon Signed Rank test showed z= -9.377 and proved that the CA 125 level on admission and after NACT is significant prognostic wise.

The tumour burden as depicted by imaging study before NACT and post NACT as per the study protocol is noted. RECIST criteria were used to assess the effect of NACT. It showed 70.9% complete responders, 25.4% partial responders and in 3.6% there were progressive disease.

Intra-operative mapping of ovarian tumour was carried out as per the protocol of the study. Primary and objective assessment of ascites, tumour presence, maximum tumour burden and residual malignant disease status at the end of interval cytoreduction surgery were done meticulously by the study team as done in other studies [10, 11, 12]. Ascites of more than 500 ml were seen in 14(12.7%) patients and ascites of less than 500 ml were seen in 44(40%) patients respectively. No ascites was noticed in 52(47.2%) patients during ICS.

To know the patterns of failure and its distribution; we considered 9 upper abdominal sites, 6 lower abdominal sites and 5 pelvic sites for presence of tumour during intra-operative assessment.

Most common site of involvement in the upper abdomen is omental caking which was seen in 47 (42.7%) individuals. This was followed by the involvement of the diaphragm in 22 (20%) patients. Peritoneal wall and mesenteric involvement were still evident in 19 and 9 cases respectively. The pre-operative CT scan could not show small diaphragmatic, peritoneal and mesenteric seedlings as found during intra-operative findings. We also found enlarged para-aortic nodes in 7 (6.3%) and went ahead with para-aortic lymph node dissection.

Small intestine and large intestine were found to be involved in 14(12.7%) and 17(15.4%) cases respectively. Suspicious involvement of the appendix was noticed in 14(12.7%) cases.

In the pelvis, post NACT residual disease was seen in ovaries in 39% (43 cases), 14.5% in urinary bladder surface (16 cases) and 39% in pouch of douglas (43 cases). Also, during intra-operative assessment 9 suspicious pelvic lymph nodes were given for histo-pathological examination.

Maximum tumour burden was mapped during the operation. It was evident maximum in omentum (37.2%), followed by ovaries (11.8%) and deposits in pouch of douglas (7.2%) respectively.

Documentation of the resection status was carried out at the end of the operation. Notably, in 71 (64.5%) cases there was complete resection followed by R1 (residual disease status up to 1 cm) in 25(22.7%) cases and R2 (residual disease status more than 1 cm) in 14 (12.7%) cases.

Total abdominal hysterectomy, bilateral salpingo-ophorectomy, infra-gastric omentectomy, resection of tumour deposits from peritoneal wall, hepatic surface, bladder surface, abdominal wall was done as a part of the interval cytoreductive procedure. In addition; splenectomy, non-anatomic hepatic resection, diaphragmatic stripping, pelvic and para-aortic lymph node dissection, peritoneal stripping was done where deemed

necessary. Post-operative surgical morbidity was noted and managed as per institutional protocol. There was no mortality in the study population during the study period. Antibiotics (3rd generation cephalosporins and fluoroquinolones) were used for 5 days post operatively in all the cases.

Validation of NACT was further achieved during the final histopathological result after the interval cytoreduction surgery. Notably, in 71 (64.5%) cases there was complete resection followed by R1 (residual disease status up to 1 cm) in 25(22.7%) cases and R2 (residual disease status more than 1 cm) in 14 (12.7%) cases. In 43.6% (48cases) there was complete remission of the disease with no evidence of the disease on histopathological examination. High grade serous adenocarcinoma was noticed in 36 (32.7%) cases. There were 15 (13.6%) cases with poorly differentiated adenocarcinoma. Meticulous documentation of the series of surgical specimen was carried out and thus evaluated the response of NACT. Methodical surgical staging reveals the correct introspection of the residual malignant disease status post NACT.

Further post-operative follow-up was conducted and adjuvant chemotherapy (total 6 to 8 cycles of chemotherapy) was given to all the patients. The study has its limitation as the duration of the study was only 18 months. However, during this short period there was no relapse seen and all patients completed the adjuvant chemotherapy within the stipulated time period.

Conclusion

Intra-operative assessment of chemotherapy effect was reflected by the presence of ascites, tumour presence, maximum tumour burden and residual malignant disease. The study provided the frame work for institutional clinical audit and gave a composite index for the success of optimal cytoreduction. Objective evaluation of the location of the disease burden and residual disease guides us to understand the patterns of failure in combating advanced ovarian cancer. The study also provided an idea about the morbidity and mortality associated with NACT and IDS. This research project provided a basis for initiation of an institutional randomized controlled trial for the NACT in advanced epithelial ovarian cancer.

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