Retrospective Study Comparing Primary Debulking Surgery (PDS) with Adjuvant Chemotherapy vs. Neoadjuvant Chemotherapy (NACT) Followed by Interval Debulking Surgery (IDS) with Adjuvant Chemotherapy in Advanced Carcinoma Ovary

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ABSTRACT

Introduction: Ovarian carcinoma is the major cause of mortality among women with gynecological problems as its reported very late. We have evaluated and compared two modalities of treatment for advanced (stage III and selected stage IV) ovarian cancer, done at our hospital from January 2003 to June 2010 and also analyzed patient, tumour, and treatment related variables.

Materials and Methods: Records of 72 patients of advanced epithelial ovarian cancer were reviewed. Arm1 included 32 patients who underwent primary debulking surgery (PDS)->adjuvant chemotherapy (6cycles). Arm 2 included 40patients who were given neoadjuvant chemotherapy (NACT) (average2-4cycles)->response assessed->interval debulking surgery(IDS) in responders-> adjuvant chemotherapy(rest2-4cycles). Chemotherapy (both NACT and Adj.CT) given was Cisplatin (intravenous)–75mg/m^2+Paclitaxel(intravenous)-175mg/m^2 over 3hrs with adequate hydration and premedication. Repeated every 3 weeks.

Results: There were relatively elderly patients with higher stage and grade of disease in arm 2. In this arm, 75% patients responded and 25%didn't respond to NACT. Optimal cytoreduction was possible significantly more in Arm2 (83.3%) patients compared to Arm1 (53.1%) patients and also with comparatively less perioperative morbidity and mortality. With median follow-up of 39 months, median disease-free, progression-free and overall survival were same with more systemic recurrences in arm1.

Conclusion: In this study, we found that in ovarian cancer, NACT has good response rate. It significantly increases optimum cytoreductive surgery rate, that too with less aggressive approach, morbidity and mortality. Although, there was no significant gain in survival, but an alternative approach of NACT->Surgery->Adj.CT, which gives equivalent survival to conventional approach of primary debulking surgery, can be considered equal or, even better especially in poor prognostic patients.

Keywords: Carcinoma ovary, primary debulking surgery, neoadjuvant chemotherapy, interval debulking surgery, optimum cytoreduction.

INTRODUCTION

Ovarian cancer is the leading cause of gynaecological cancer related deaths. Unfortunately, 60-70% patients present in advance stage. In stage III and selected stage IV disease, optimal cytoreduction by primary debulking surgery (PDS) followed by platinum and taxol based adjuvant chemotherapy has been standard of care.[1,2] Due to advanced stage, optimum primary debulking surgery is possible in 30-60% patients only. Various trials have shown that even in advanced stage, ovarian tumour is sensitive to chemotherapy and gives overall response rate of about 70-80%, including complete response of 20-30%. Studies done in this setting of, neoadjuvant chemotherapy followed by secondary cytoreductive surgery, have shown mixed results.[3-10] We have evaluated and compared the outcome of two modalities of treatment for advance stage (stage III and selected stage IV) ovarian cancer, at our hospital from January 2003 to June 2010. In this study, we have analyzed in terms of response to neoadjuvant chemotherapy, optimal cytoreductive surgery rate, rate of non standard surgery, treatment related morbidities and mortalities, hospital and intensive care unit (ICU) stay, disease free survival and overall survival. We also analyzed certain patient and tumour related variables.

MATERIALS AND METHODS

The analysis includes total 72 patients of advanced stage (stage III and selected stage IV) epithelial ovarian cancers, treated in our hospital from January 2003 to June 2010.

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How to cite this article: Mohammad Shadab Alam, Roshan Perween, Shahid A Siddiqui. Retrospective study comparing primary debulking surgery (PDS) with adjuvant chemotherapy vs. neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) with Adjuvant chemotherapy in advanced carcinoma ovary. International Journal of Contemporary Medical Research 2016;3 (1):265-270.

On the basis of treatment modality used, patients were grouped in 2 arms -

Arm 1 included 32 patients in whom primary debulking surgery (PDS) followed by adjuvant chemotherapy (6 cycles) was done.

Arm 2 included 40 patients, treated with neoadjuvant chemotherapy (NACT) (average 2-4 cycles) followed by interval debulking surgery (IDS) done in chemo-responding patients and then adjuvant chemotherapy (rest 2-4 cycles).

The initial work-up of all patients included clinical examination, radiological studies, serum tumour marker (CA-125) level and histo/cytological evidence of malignancy by FNAC or, biopsy. In all patients, surgical exploration was done, to assess resectibility of tumour. Primary debulking surgery was performed when optimal cytoreduction seemed feasible and neoadjuvant chemotherapy was given for primary unresectable tumours. Surgical exploration was usually done laparoscopically (44 cases). Laparotomy was done (28 cases) when laparoscopy was contraindicated. Regarding treatment modality to be used, it was based on combined decision of operating surgeon and oncologist. Primary debulking surgery was performed when optimal cytoreduction could be achieved by the standard surgery (32 patients). However, in a few such cases non-standard surgery, meaning resection of one or more organ (e.g., small intestine, colon, spleen), was done to achieve an optimal cytoreduction. Neoadjuvant chemotherapy was given to those patients who were deemed unresectable due to disease related or, inoperable due to patient related factors. The criteria used for selection of patients for neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy included general condition of patient not fit for aggressive upfront debulking surgery, optimum cytoreduction not possible, optimum cytoreduction possible at cost of significant morbidity / mortality, extensive pelvic and metastatic tumour load, uncountable peritoneal metastasis, involvement of upper abdominal area especially diaphragmatic area, extensive bowel involvement, involvement of portal triad, stage IV disease especially liver/ lung metastasis and patient refusing for primary surgery.

Response assessment was done by clinical examination, serum CA 125 level, and radiological studies. WHO criteria was used to assess tumour response. Patients responding to NACT were referred for interval cytoreduction. Patients, who did not respond to NACT, were given second line chemotherapy.

Debulking surgery included total abdominal hysterectomy + bilateral salpingoophorectomy + total infragastric omentectomy + peritonectomy limited to the pelvis, paracolic gutters, anterolateral diaphragmatic area + pelvic and common illiac lymphadenectomy + paraaortic lymph node sampling + maximum possible metastatectomy + ascitic and peritoneal cytology.

Chemotherapy (in both neoadjuvant and adjuvant setting) used was Cisplatin (intravenous) – 75mg/m^2 + Paclitaxel (intravenous) 175mg/m^2, over 3hrs with adequate hydration and premedication. This regimen was repeated every 3 weeks.

Blood loss rates, the length of postoperative intensive care unit and/or, hospital stay were used to assess aggressiveness of surgical cytoreduction. Perioperative, postoperative and chemotherapy related complications were recorded in both groups. After completion of treatment, patients were kept on regular follow-up of every three months for first two years, every six months for next three years and then on yearly basis. On each follow-up, patients were assessed by clinical and if needed by radiological and pathological evaluation.

STATISTICAL ANALYSIS

Analysis was done using statistical tool SPSS 11.0. Two-tailed corrected chi-square test and unpaired student's *t*-test were used for P value calculation. For calculation of survival, patients were evaluated at the time of last follow-up. The results were studied on an intention-to-treat basis.

RESULTS

The median follow up in our study was 39 (range of 5 – 84) months. Between January 2003 and June 2010, 72 patients presented with locally advanced epithelial ovarian carcinoma. After surgical exploration, 32 patients seemed resectable and primary cytoreductive surgery was carried out in these patients. They were included in arm 1. Rest 40 patients were found to be unresectable and/or, inoperable. Neoadjuvant chemotherapy was given to them. They were kept in arm 2. The patient and tumour related features are given below in table 1.

In arm 1, all 32 patients tolerated and completed their treatment of primary surgery followed by adjuvant chemotherapy as per the schedule.

In arm 2, all 40 patients tolerated and completed scheduled neoadjuvant chemotherapy. Ten (25.0%) patients did not respond to neoadjuvant chemotherapy. Among them, four (10.0%) patients had stable disease and six (15.0%) patients had progressive disease. They were not operated and planned for second line chemotherapy. Rest 30 (75.0%) patients responded to neoadjuvant chemotherapy. Among them, 24 (60.0%) patients had partial response and 6 (15.0%) patients were complete responders. In those patients responding to chemotherapy, 2 (6.7%) had response after 2 cycles and rest 28 (93.3%) after 3-4 cycles of chemotherapy. All these 30 responding patients were subjected to interval debulking surgery followed by adjuvant chemotherapy (rest 2-4 cycles). All of them completed their assigned treatment. In this group, the mean interval between surgical staging and the start of chemotherapy was 15 (range 5–33) days after laparoscopy and 19 (range 7–41) days after laparotomy. Evaluation of surgical results is given below in table 2.

Non standard surgeries included small intestinal resection, colectomy, low anterior resection, partial gastric resection, partial cystectomy and splenectomy.

Findings during surgery and perioperative events are given below in table 3. Most important findings were significantly less perioperative blood loss; hospital / ICU stay in arm 2, with nonsignificant difference in perioperative morbidities. Chemotherapy related complications were comparable in both arms.

There was no significant difference in recurrence rates in the two arms. In both arms, most of the recurrences were in the first 2-3 years of follow-up. As per the sites of relapse, it was more peritoneal in arm 2 and more metastatic recurrence in arm 1 (table 4). Metastatic sites were lung, liver, spleen and brain. Statistics shows trend towards better survival in patients who received NACT (table 4). However, no definite conclusion could be made as the difference as well as the duration of follow up was insufficient. The recurrence pattern and the survival analysis are given below in table 4.

	Arm 1 (n = 32)	Arm 2 (n = 40)	P value
Age (years) Mean +/- SD	53.0 +/- 9.0	58.0 +/- 4.5	0.003
30-40 years	2 (6.2%)	2 (5.0%)	0.8
41-50 years	14 (43.8%)	13 (32.5%)	0.46
51-60 years	13 (40.6%)	19 (47.5%)	0.7
61-70 years	3 (9.4%)	6 (15.0%)	0.7
Disease stage			
III	19 (59.3%)	22 (55.0%)	0.89
IV	13 (40.7%)	18 (45.0%)	0.89
Tumour grade			
1	8 (25.0%)	5 (12.5%)	0.29
2	19 (59.4%)	26 (65.0%)	0.16
3	5 (15.6%)	09 (22.5%)	0.66
Tumour histology			
Serous	15 (46.8%)	20 (50.0%)	0.98
Mucinous	5 (15.6%)	4 (10.0%)	0.72
Undifferentiated	12 (37.5%)	16 (40.0%)	0.83
CA-125(>30KU/L)	27 (84.4%)	35 (87.5%)	0.97
Staging procedure			
Laparoscopy	21 (65.6%)	23 (57.5%)	0.65
Laparotomy	11 (34.4%)	17 (42.5%)	0.65

Table-1: Patient and tumour characteristics

Surgical results	Arm 1 (n = 32)	Arm2 (n = 30)	P value
Optimum Cytoreduction	17 (53.1%)	25 (83.3%)	0.02
Suboptimum Cytoreduction	15 (46.8%)	5 (16.7%)	0.02
Nonstandard Surgery	11 (34.4%)	8 (26.6%)	0.7
Organ Resected			
Small Bowel	5 (15.6%)	3 (10.0%)	0.78
Colon	4 (12.5%)	3 (10.0%)	0.76
Bladder	1 (3.1%)	1 (3.3%)	0.96
Spleen	1 (3.1%)	0 (0.0%)	0.33
Stomach	0 (0.0%)	1 (3.3%)	0.97

Table-2: Surgical results

DISCUSSION

Ovarian carcinoma is the leading cause of gynecologic cancer-related deaths in most advanced countries, as it leads to death of approximately half of patients.[11] In most patients, it is in the advanced stage at the time of presentation. Management of advanced ovarian cancer is a difficult and challenging task.[12] In management of both early and advanced carcinoma ovary, optimal cytoreduction by primary debulking surgery (PDS) followed by platinum and taxol based adjuvant chemotherapy, has been standard of care.[1,2] However, primary cytoreduction has not been established as the standard of care, by any prospective randomized trial

Operative Finding	Arm 1 (n = 32)	Arm 2 (n = 30)	P value
Advanced Disease	32 (100%)	30 (100%)	1.0
Ascites	28 (87.5%)	26 (86.6%)	0.92
Omental Disease	24 (75.0%)	18 (60.0%)	0.32
Peritoneal Disease	20 (62.5%)	12 (40.0%)	0.13
Paraaortic Lymphadenopathy	6 (18.8%)	6 (20.0%)	0.9
Subdiaphragmatic Nodules	16 (50.0%)	12 (40.0%)	0.59
Liver Deposits	5 (15.6%)	3 (10.0%)	0.78
Largest Metastatic Size			
2cm	31 (96.8%)	21 (70.0%)	0.01
5cm	17 (53.1%)	9 (30.0%)	0.11
Surgery Duration			
Mean (minutes)	186	164	0.28
Range (minutes)	70.0-350.0	90.0-270.0	
Blood Loss Rate			
Mean (cc)	2203	1148	0.001
Range (cc)	50.0-5000.0	50.0-3000.0	
ICU Stay			
Mean (days)	5.3	3.0	0.0001
Range (days)	1.0-9.0	1.0-5.0	
Hospital Stay			
Mean (days)	28.6	16.1	0.0001
Range (days)	6.0-50.0	4.0-30.0	
Perioperative Mortality	2 (6.3%)	1 (3.3%)	0.59
Perioperative Morbidity			
Wound Infection	4 (12.5%)	3 (10.0%)	0.76
Wound Dehiscence	1 (3.1%)	1 (3.3%)	0.96
Fever	5 (15.6%)	1 (3.3%)	0.23
Chest Infection	1 (3.1%)	1 (3.3%)	0.96
Intestinal Fistula	3 (9.4%)	2 (6.6%)	0.69
Intestinal Obstruct.	1 (3.1%)	1 (3.3%)	0.96
Urinary Fistula	1 (3.1%)	0 (0.0%)	0.33
DVT / Embolism	1 (3.1%)	2 (6.6%)	0.95

ICU: Intensive care unit, DVT: Deep venous thrombosis

Table-3: Surgical findings and Perioperative events

	Arm 1 (n = 32)	Arm 2 (n = 30)	P value
Recurrence Pattern			
Peritoneal Recurrence	5 (15.6%)	7 (23.3%)	0.65
Metastasis	4 (12.5%)	2 (6.7%)	0.73
First year recurrence rate			
0-3 month	1 (3.1%)	0 (0.0%)	0.33
4-6 month	1 (3.1%)	0 (0.0%)	0.33
7-9 month	2 (6.3%)	2 (6.7%)	0.95
10-12 month	5 (15.6%)	3 (10.0%)	0.78
5-year DFS Rate	9 (27.0%)	9 (29.0%)	0.87
5-year OS Rate	10 (31.0%)	9 (30.0%)	0.9
Median PFS (months)	7.59	9.87	0.05
Median DFS (months)	19.0	22.0	0.4
Median OS (months)	28.0	25.0	0.5
PFS: Progression-free survival, DFS: Disease-free survival, OS: Overall survival			

Table-4: Recurrence and survival analysis

till yet.[13] Various randomized trials and meta analysis have shown that "optimum cytoreduction and amount of residual disease after surgery" are the most important modifiable prognostic factors for survival in ovarian cancer.[14,15] The fact that, the amount of post operative residual disease, significantly affects survival, makes the optimum cytoreductive surgery, a very crucial component in management of ovarian cancer. According to Gynaecological Oncology Group, the definition of optimum debulking is "Nil visible or, palpable residual disease or, minimum goal of <1cm or, preferably 0.5cm of residual disease". Also, after optimum cytoreduction is achieved, survival is same irrespective of surgery, if it is radical or, non radical surgery. Unfortunately, in 60-70% patients, there will be only little benefit from primary debulking surgery, as optimum debulking is not possible, due to widespread extension of disease at presentation. Other than aggressive surgery, tumour biology is also a factor that determines the prognosis of surgery as is shown in several trials.[16-18] Advanced stage at presentation and biology of the tumour, co-determine the poor prognosis and dismal survival in these patients. On the other side, chemotherapy has shown good response rate even in advanced stages of ovarian cancer. It has lead to various studies and trials incorporating chemotherapy in the neoadjuvant setting. Other possible advantages of neoadjuvant chemotherapy are that, due to the advanced stage at diagnosis, patients are usually in poor general condition. NACT leads to improved patient's performance status prior to surgery, owing to the reduction in tumour volume. Nutritional improvement ensues due to control of disease and relief of distressing symptoms of abdominal distension and discomfort, resulting in improved surgical results. Tumour volume reduction also leads to enhancement of sensitivity to chemotherapy.[19] NACT also allows the in vivo assessment of tumour chemo sensitivity, which makes it easy to choose appropriate chemotherapy regimen. In the beginning, NACT was mainly used in patients who were medically unable to tolerate aggressive cytoreductive surgery. Later, this approach has been employed in women who, by diagnostic analysis, were unlikely to undergo successful optimal cytoreductive surgery.[20] Recently, interval debulking surgery has been introduced as a new concept, meaning a surgical procedure with debulking intent foreword and followed by cytoreductive chemotherapy.[21] In some studies, platinum based chemotherapy regimens, in addition to producing higher response rates, have also shown to give a statistically significant survival advantages compared with drug regimens without platinum.[3,22] Unfortunately, most of the studies done, in this setting of neoadjuvant chemotherapy followed by secondary cytoreductive surgery are retrospective in nature.[3-10] They have shown mixed results, mainly in favor of this modality of treatment with increase rate of optimum cytoreduction, less rate of aggressive mutilating surgery, less morbidity and mortality, and similar or, better quality of life (QoL), median survival, disease-free survival (DFS) and overall survival (OS). After review of various trials and meta-analysis, it has been recommended by Gynaecological Cancer Intergroup Ovarian Cancer in the Consensus Conference (2004) that, "In advanced ovarian cancer, upfront maximum cytoreduction by primary debulking surgery (PDS), with goal of no residual disease should be undertaken, and when this is not possible, interval cytoreductive surgery (IDS), after 3-5 cycles of neoadjuvant chemotherapy, should be considered in patients who don't have progressive disease".[23] An area of controversy are the criterias which will define the resectability of the tumour and consequently will lead to the selection of patients which might benefit from NACT approach. Different studies have used imaging based criteria for this purpose.[24,25] Nelson *et al.* showed, that the predictive value of a computed tomography scan demonstrating non resectability was only 67%.[24] A predictive index was developed by Bristow *et al.*, that was able to correctly predict surgical outcome.[26] The ability to identify patients undergoing optimal debulking was 80%. Ansquer *et al*.[3] and Vergote *et al*.[21] showed that, laparoscopy and in certain situations exploratory laparotomy can be used as a selection tool. Histological diagnosis, objective documentation of the extent of the disease and identification of patients who can be optimally debulked, are the possible benefits of such a procedure. Proper technique and immediate start of chemotherapy can overcome the issue of port site implantation, when such procedures are done.[26] In this retrospective analysis, we found that those patients, who were deemed unresectable or, inoperable because of disease or, patient related factors, they responded significantly well to neoadjuvant chemotherapy. Because of such response to neoadjuvant chemotherapy, there was significant increase in rate of optimum cytoreductive surgery in those patients. Our observations are similar to some of previous studies, which reported similar optimal debulking rate following NACT.[27] The most important aspect of this study was that, not only increased optimum surgery could be done in such poor prognostic pa-

tients, but also it was done with less aggressive approach depicted by significantly less blood loss rate, hospital / ICU stay and nonsignificant less rate of non standard surgeries to achieve optimum debulking along with less perioperative morbidities. These finding are consistent with the data of Schwartz *et al*.[20] who reported that neoadjuvant chemotherapy leads to decrease in the aggressiveness of debulking surgery. There was no significant gain in disease free survival (DFS) and overall survival (OS). Regarding overall survival, some previous studies have results similar to us,[7,21,28] but some have shown gain in survival with NACT.[5,29] The nonsignificant difference in disease free survival between the two arms is similar to the results of previous studies.[18] But it should be considered here that, in the neoadjuvant chemotherapy arm 2, patients were in poorer prognostic state than the conventional arm 1, according to disease and patient condition. The limitations of this study are that it is retrospective in nature, has small sample size, short follow-up, and the data regarding the quality of life or, disease free progression, are incomplete.

CONCLUSION

In this study, we found that ovarian cancer even in advanced stages shows good response rate to neoadjuvant chemotherapy. It leads to significantly increased optimum cytoreductive surgery rate, that too with less aggressive approach, perioperative morbidity and mortality. Although, there was no significant gain in survival, but an alternative approach of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy, which gives equivalent survival to conventional approach of primary debulking surgery followed by adjuvant chemotherapy, can be considered equal or, even better especially in poor prognostic patients. If ongoing randomized trials show that this approach does not adversely affect long term survival, "morbidity related to ovarian cancer management" may evolve as a crucial factor in deciding treatment options.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 05-12-2015; **Published online**: 20-12-2015