# Role of Neoadjuvant Chemotherapy on Advanced Epithelial Ovarian Cancer

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## Abstract

**Introduction**: Ovarian cancer is the most lethal gynecological malignancy diagnosed at late stage in most of the cases. Management includes primary debulking surgery with a target of no gross residual disease or ≤ 1cm residual disease followed by paclitaxel and carboplatin-based chemotherapy. Neoadjuvant chemotherapy of at least 3 cycles followed by interval debulking surgery is an alternative option in selected cases of advanced disease. **Material and Method**: A prospective study was carried out at B.P. Koirala Memorial Cancer Hospital, Bharatpur, Chitwan from the period 1st November 2022 to 31st August 2023 (10 months). Patients diagnosed with advanced ovarian cancer based on clinical and CECT findings and confirmed with cytology or FNAC or biopsy undergoing Interval Debulking Surgery after 3 cycles of NACT (paclitaxel and carboplatin) were included. The role of NACT in terms of response according to RECIST criteria, regression of CA125 value, rate of complete or optimal cytoreduction, and postoperative complications were analyzed. **Results**: A total of 40 cases fulfilling the inclusion criteria were enrolled. Most patients 14(35%) were between 51-60 years with a mean age of 51.45 ± 11.46 SD years. Abdominal pain and/or distension were the most common presenting symptoms. The majority 32 (84.2%) of cases were given NACT based on CT scan findings of advanced disease. Confirmation of malignancy was done by positive USG-guided FNAC from ovarian mass in most cases 23 (57.5%), followed by positive ascitic fluid cytology in 8 (20%) patients. The median CA125 value before and after NACT were 844 U/ml and 27.89 U/ml respectively. After NACT, CA125 was normalized in 24 (60%) patients. Most patients 30 (75%) had complete cytoreduction during IDS; while 7 (17.5%) patients had optimal cytoreduction, and 3 (7.5%) had suboptimal cytoreduction. The median duration of surgery was 147.5 minutes, and the median blood loss was 287.5 ml. The postoperative period was uneventful in most cases. **Conclusions**:

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NACT followed by interval debulking surgery is an effective alternative in selected cases of advanced ovarian cancer as the complete and optimal cytoreduction rate is higher with fewer postoperative complications.

***Keywords***: Advanced Ovarian Cancer, Interval Debulking Surgery, Neoadjuvant Chemotherapy

## Introduction

Ovarian cancer is the third most common gynecological malignancy worldwide whereas in Nepal, it ranks second after cervical cancer[1]. Most cases of epithelial ovarian cancer present at an advanced stage. Primary debulking surgery (PDS) followed by platinum and taxane-based adjuvant chemotherapy is the standard treatment. Complete or optimal cytoreduction defined as no residual disease or ≤1cm residual disease at the end of surgery respectively is the most important prognostic factor associated with better survival outcomes. The availability of a gynecologic oncologist or a surgeon with specialized training in radical cytoreductive cancer surgery has been associated with a survival benefit in patients who have advanced EOC.[2]Several randomized controlled trials have shown the advantage of Neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) in selected cases of advanced ovarian cancer without compromising survival.[3] This protocol is followed at BPKMCH for advanced ovarian cancer patients with fewer chances of complete or optimal cytoreduction or a high chance of peri or postoperative morbidity and mortality. But the outcomes of such patients have not been studied previously so the present study was conducted to analyze the outcomes of such patients.

## Materials and Methods

A prospective study was carried out at B.P. Koirala Memorial Cancer Hospital, Bharatpur, Chitwan. Patients diagnosed with advanced ovarian cancer from the period 1st November 2022 to 31st August 2023 (10 months) with the listed below inclusion criteria were included.

- Advanced ovarian cancer involving the sub-diaphragmatic area, liver surface, mesenteric involvement, omental caking, and extensive peritoneal disease with or without ascites documented on CECT imaging or clinically fixed pelvic mass occupying POD with a high likelihood of bowel resection with increased perioperative morbidity, or suboptimal cytoreduction.
- Confirmation of ovarian cancer on USG-guided FNAC/ Biopsy/ cytology.
- Patient undergoing NACT (paclitaxel and carboplatin) 3 cycles based on the above inclusion criteria, followed by IDS.

Ethical approval was taken from the Institutional Review Committee of BPKMCH. Patients presenting in OPD or Emergency of BPKMCH suspected of ovarian/ fallopian tube/ primary peritoneal cancer were evaluated by a thorough history

and physical examination followed by baseline investigations including total protein, serum albumin, contrast-enhanced CT scan of abdomen and pelvis, tumor markers, upper Gastrointestinal endoscopy, stool for occult blood and if required sigmoidoscopy or colonoscopy in selected cases. If imaging were suggestive of advanced ovarian carcinoma i.e., omental mass, extensive upper abdominal disease like sub diaphragmatic deposits, deposits on mesentery, diffuse peritoneal thickening, lesions on the liver, malignant pleural effusion with or without ascites then the diagnosis was confirmed by ascitic/ pleural fluid cytology or USG guided FNAC or omental biopsy. The patient with a confirmed diagnosis of advanced ovarian cancer who have poor performance status or with fixed mass in POD with more chances of resection of the bowel, or one or more radiological features of advanced ovarian cancer were sent for NACT with paclitaxel (175mg/m2 and carboplatin AUC 5) once every 3 weekly for three cycles. After 3 cycles of NACT, the patients were reevaluated with clinical examination; CECT scans of abdomen and pelvis, and tumor markers CA125, CEA, and CA19.9. The response to NACT was assessed with RECIST criteria. If patients were fit for surgery and had stable or responsive disease, IDS was performed. The standard operative procedure includes total abdominal hysterectomy with bilateral salpingo-oophorectomy + supra-colic omentectomy ± pelvic lymph node dissection ± paraaortic lymph node dissection ± peritonectomy ± bowel resection. At the end of surgery if no residual disease was left then it was recorded as complete cytoreduction, if ≤ 1cm of residual disease then recorded as optimal cytoreduction, and when > 1cm of residual disease was left behind then recorded as suboptimal cytoreduction. The total duration of surgery and the amount of blood loss were recorded. Peri and post operative complications if any were recorded. Written informed consent was obtained from all patients. A set of fixed Performa-based questionnaires was filled from the above-collected data. Statistical analysis was performed using SPSS 25.

## Results

A total of 40 patients satisfied the inclusion criteria during the study period from 1st November 2022 to 31st August 2023 (10 months). Most patients 14 (35%) were between 51-60 years. The mean age of patients was 51.45 ± 11.46 SD years with an age range between 24 to 74 years. Most patients were postmenopausal 21 (52.5%). Abdominal pain was the most common presenting complaint seen in 15 (37.5%) patients, followed by abdominal pain and distension seen in 12 (30%) patients, and abdominal distension only seen in 11 (27.5%) patients. Loss of weight and appetite accompanying abdominal pain and distension was seen in one patient while another patient had decreased urine output along with abdominal distension. Out of 40 patients, 26 (65%) patients had no co morbidities while 5 (12.5%) had diabetes, 4 (10%) patients had hypertension, and two (5%) had both. Two patients (5%) had hypothyroidism and one (2.5%) patient had all three co morbidities. One patient had a history of breast cancer treated with MRM

and adjuvant chemotherapy one year back. She had BRCA 1 mutation positive. The majority of patients 20 (50%) had normal BMI; eleven (27.5%) patients were overweight, while five (12.5%) patients were underweighting and four (10%) were obese. Out of 40 patients, only four (10%) patients were nulligravida out of which one was unmarried, five patients (12.5%) had parity one while the rest had parity two or more.

Table 1: Baseline Characteristics of Study Participants:

| **Age group (years)** | **n (%)** |
|---|---|
| ≤30 | 1(2.5%) |
| 31-40 | 6(15%) |
| 41-50 | 11(27.5%) |
| 51-60 | 14(35%) |
| 61-70 | 6(15%) |
| 71-80 | 2(5%) |
| **Menopausal status** | |
| Premenopausal | 19(47.5%) |
| Postmenopausal | 21(52.5%) |
| **Body Mass Index** | |
| <18.5 | 5(12.5%) |
| 18.5-24.9 | 20(50%) |
| 25-29.9 | 11(27.5%) |
| 30 | 4(10%) |
| **Pretreatment CA125** | |
| 36-1000 | 22(55%) |
| 1001-2000 | 8(20%) |
| >2000 | 10(25%) |

Out of 40 patients, 34 (85%) cases were given NACT based on CT scan findings of advanced disease like gross ascites, multiple deposits in the mesentery and serosal surface of the bowel, sub-diaphragmatic, sub-hepatic space, diffuse and nodular thickening noted in the peritoneum, omentum, moderate pleural effusion ( in five cases), hypodense space-occupying lesion in the liver ( in two cases), enlarged retroperitoneal nodes >2cm ( in three cases), etc. while 5 (12.5%) cases were based on clinical judgments like hard fixed mass occupying POD and 1 (2.5%) based on both. Before giving NACT malignancy was confirmed by positive USG-guided FNAC from ovarian mass in the majority of cases 23 (57.5%), followed by positive ascitic fluid cytology in 8 (20%) patients, positive USG-guided FNAC from liver space-occupying lesion in 1 (2.5%) patient, while all of the above three tests were positive in the other patient. Omental biopsy was positive in two cases, pleural fluid cytology was positive in another case, and USG-guided Trucut biopsy from ovarian mass, and laparoscopic guided biopsy from POD deposit were positive in the other two patients respectively.

The median CA125 value before NACT was 844 U/ml (range between 37.91-5500 U/ml) and the majority 22 (55%) had a CA25 value between 36-1000 U/ml, followed by >2000 U/ml in 10 (25%) patients and 1001-2000 U/ml in 8 (20%) patients. After NACT, CA125 was normalized in 24 (60%) patients whereas it was above the normal limit in 16 (40%) patients. The median value of CA125 after NACT was 27.89 U/ml (7.72- 358.8). After NACT two patients (5%) had a complete response, partial response was seen in 24(60%) patients, and 14 (35%) patients had stable disease.

Table 2: Characteristics after NACT

| **RESPONSE AFTER NACT (RECIST CRITERIA)** | N (%) |
|---|---|
| Partial response | 24(60%) |
| Stable disease | 14(35%) |
| Complete response | 2(5%) |
| **CA125 after NACT** | |

| | |
|---|---|
| Normalized (< 35 IU/ml) | 24(60%) |
| Above normal | 16(40%) |

Most patients 29 (72.5%) underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy with total omentectomy and rest surgical procedures were shown in Table 3.

Most patients 30 (75%) had complete cytoreduction during IDS, while 7 (17.5%) patients had optimal cytoreduction. Residual diseases <1cm were mostly localized in the diaphragm, intestine, and peritoneum scattered as military nodules. Three patients (7.5%) had suboptimal cytoreduction and the reason behind it was omental cake with dense adhesion with the stomach in one case where only TAH with BSO was done, omental caking with frozen pelvis with a tumor on the left ovary densely adherent to sigmoid, multiple deposits on the lesser omentum, spleen, in the diaphragm, and mesentery in whom only biopsy was taken and closure done. The third case of suboptimal cytoreduction had a deposit in the mesentery and lesser omentum which could not be removed, intraperitoneal cisplatin 60mg was given via drain after the closure of the abdomen. The median duration of surgery was 147.5 minutes with a range of 40 minutes to 300 minutes. The median blood loss during IDS was 287.5 ml with a range of 30 to 1830 ml.

There was no need for blood transfusion in 21(52.5%) out of 40 patients, while 4 (10%) patients required blood transfusion preoperatively while 15 patients (37.5%) required it postoperatively. Bowel resection was done in 3 out of 40 cases of which one had a permanent colostomy and the other had loop ileostomy. Out of 40 patients, 33 (82.5%) had uneventful postoperative periods, postoperative complications in the form of surgical site infection requiring oral antibiotics and need of abdominal wall re-suturing were seen in 6 patients (15%), and one patient (2.5%) who had undergone splenectomy during IDS had. fever postoperatively due to chest infection requiring higher antibiotics.

Table 3: Characteristics of Interval Debulking Surgery

| **TYPE OF SURGERY** | **N (%)** |
|---|---|
| TAH+BSO+Omentectomy | 29 (72.5%) |
| TAH+BSO+Omentectomy + Appendectomy + bladder peritoneal resection+ intraperitoneal cisplatin | 1(2.5%) |
| TAH+BSO+Omentectomy+ Appendectomy+LAR with Ileostomy | 1(2.5%) |
| TAH+BSO+Omentectomy+ Appendectomy | 3(7.5%) |
| TAH+BSO+Omentectomy+ Appendectomy + BL PLND+PARAAORTIC LND | 1(2.5%) |
| TAH+BSO+Omentectomy+Appendectomy + LAR+Permanent Colostomy | 1(2.5) |
| TAH+BSO+Omentectomy+ BL PLND+PARAAORTIC LND + LAR+Appendectomy | 1(2.5) |
| TAH +BSO+ Omentectomy+ Splenectomy | 1(2.5) |
| Laparotomy+ Trial dissection + Peritoneal biopsy | 1(2.5%) |
| TAH+BSO | 1(2.6%) |
| **Surgical outcome** | |
| Complete cytoreduction | 30 (75%) |
| Optimal cytoreduction | 7 (17.5%) |
| Suboptimal cytoreduction | 3 (7.5%) |

Table 4: Complications of Surgery

| | |
|---|---|
| LAR | 1 (2.5%) |
| LAR with Loop ileostomy | 1 (2.5%) |
| LAR with Permanent colostomy | 1 (2.5%) |
| Blood transfusion | 15 (37.5%) |

| | |
|---|---|
| Surgical site infection | 6 (15%) |
| Postoperative pneumonia | 1(2.5%) |

**Discussion:**

Epithelial ovarian cancer is a disease mostly occurring in old age after menopause. In the present study, the mean age of patients was 51.45± 11.46 years which is like the study done by Batra et al where the mean age was 50.14 ± 8.2 years.[4]

Germline mutations in Breast cancer susceptibility genes, BRCA1 and BRCA2 are responsible for most hereditary ovarian epithelial cancer and hereditary breast cancers. Society of gynecologic oncology (SGO) and National Comprehensive Cancer Network (NCCN) guidelines recommend genetic counseling and genetic testing irrespective of age or family history in all patients with epithelial ovarian cancer at diagnosis.[5] But it is not a routinely practiced in our country due to economic burden. Only one patient with a past history of treatment for left breast cancer was offered genetic testing which showed a nonsense mutation in the BRCA1 gene. Available literature shows genetic testing offers clinical benefits not only to the patient in terms of the use of targeted therapies but also to their family members. After genetic testing, if family members are found to be carriers then they can be offered risk-reducing surgery and those who tested negative can be assured that they have a lifetime ovarian risk, similar to the general population.[6]

Different models based on clinical factors, radiological factors, and laparoscopic findings have been studied and are used to select patients for primary upfront surgery or NACT. Fagotti and colleagues developed a laparoscopic-based predictive model, where predictive index value (PIV) was calculated and PIV ≥ 8 was found to associate suboptimal cytoreduction with specificity and a positive predictive value of 100%. [7] In our setup clinical and radiological parameters were used to select patients for NACT. Most patients (85%) were given NACT based on CT scan findings of advanced disease, while 5 (12.5%) cases were based on clinical judgments, and one (2.5%) was based on both.

CA125 is the most common tumor marker used during the diagnosis of epithelial ovarian cancer and subsequent follow-up visits. Initial value of CA125 level if low or if its level subsequently decreases after NACT predictors the chance of optimal cytoreduction as shown by various studies.[8, 9] The median CA125 value before NACT in the present study was 844 U/ml which is comparatively lower than a study by Liang et al[9]where the median CA125 value was 1218.9U/ml and a study by Akhavan et al[10] where the median CA125 value was 980U/ml. After NACT, the CA125 level was normalized in 24 (60%) patients which is comparatively higher than in the study by Liang et al where 45.8% of patients had CA125 normalization.[9]

On analyzing the response to chemotherapy by RECIST criteria[11], two patients (5%) had a complete response, 24 (60%) patients had partial responses, and 14(35%) patients had stable disease. In a study by Raghavendrachar et al., 2% had a complete response, 78% had a partial response, 10% had stable disease and 10% had progressive disease.[12] Partial response is comparatively

less while stable disease is comparatively higher in the present study, patients with progressive disease were not in the inclusion criteria in the present study in contrast to the study by Raghavendrachar et al.

Complete cytoreduction was achieved in 30 (75%) while optimal cytoreduction was achieved in 7(17.5%) patients, with overall 92.5% patients with < 1cm tumor, and 3 (7.5%) patients had suboptimal cytoreduction. This is consistent with the study by Baruah et al. and Levy et al. where optimal cytoreduction was achieved in 92.3% and 94% respectively.[13, 14] In the present

study residual diseases <1cm were mostly localized in the diaphragm, intestine, and peritoneum scattered as military nodules; similar to the study by Yuan et al.[15]

Recently, the Lymphadenectomy in Ovarian Neoplasms (LION) trial showed that Systematic Lymphadenectomy after maximal cytoreduction did not improve survival and may cause additional harm. A similar concept applies to Interval debulking surgery. A study by HeM et al. showed no therapeutic benefit in patients undergoing IDS. [16] Only two patients underwent systematic lymphadenectomy in the present study.

The median duration of surgery was 147.5 minutes. The median blood loss during IDS was 287.5 ml. Surgical time and blood loss during surgery were less in the present study than in the study by Onda et al. where medial surgical time was 273 minutes and blood loss was 787ml in NACT- IDS group.[17]

One patient with suboptimal cytoreduction with 2cm deposit on the mesentery and lesser omentum was given intraperitoneal cisplatin mixed with normal saline intraoperatively through the drain clamped for six hours. The concept of Intraperitoneal Chemotherapy after complete or optimal cytoreductive surgery is to allow higher concentrations of the drug within the peritoneum where cancer tends to recur and therefore may improve survival.[18] Hyperthermic intraperitoneal chemotherapy (HIPEC) involves heated chemotherapy, administered intraperitoneally immediately after cytoreductive surgery. OVHIPEC-01 trial has shown the clinical benefit of HIPEC after interval cytoreductive surgery for stage III primary ovarian cancer in terms of decreased recurrence and mortality rates. Lim et al. also found the addition of HIPEC to the interval cytoreductive surgery provided an improvement in progression-free and overall survival.[19]Intra and postoperative complications were lower in the present study similar to the study by Baruah et al.[1] The study population is small. Progression-free survival and overall survival are not calculated, only short-term outcomes like optimal cytoreduction rate, surgical time, and postoperative complications are analyzed.

**Conclusion:**

Epithelial ovarian cancer usually presents at an advanced stage and the standard of care is the primary debulking surgery with a goal of no gross residual disease or <1cm residual disease. Neoadjuvant chemotherapy followed by interval debulking surgery is an alternative treatment in selected cases where the goal of complete or optimal cytoreduction is less likely or chances of

perioperative morbidity or mortality are high.

## References:


1. Globocon 2020. International Agency for Research on Cancer, World Health Organization, [ https://gco.iarc.fr/today/fact-sheets-cancers]
2. Hall TR, Dizon DS. Neoadjuvant chemotherapy for advanced epithelial ovarian cancer. Clin Adv Hematol Oncol. 2016 Apr 1;14(4):262-8.
3. Cho JH, Kim S, Song YS. Neoadjuvant chemotherapy in advanced ovarian cancer: optimal patient selection and response evaluation. Chinese clinical oncology. 2018 Dec;7(6):58-
4. Batra S, Nayak H, Dave KS. Role of neoadjuvant chemotherapy (NACT) followed by surgical cytoreduction in advanced epithelial ovarian cancer. The journal of obstetrics and Gynecology of India. 2012 Oct;62:541-5.
5. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. International Journal of Gynecology & Obstetrics. 2021 Oct;155:61-85.
6. Fostira F, Papadimitriou M, Papadimitriou C. Current practices on genetic testing in ovarian cancer. Annals of Translational Medicine. 2020 Dec;8(24).
7. Patel A, Iyer P, Matsuzaki S, Matsuo K, Sood AK, Fleming ND. Emerging trends in neoadjuvant chemotherapy for ovarian cancer. Cancers. 2021 Feb 5;13(4):626.
8. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, Dizon DS, Kash JJ, Meyer LA, Moore KN, Olawaiye AB. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology clinical practice guideline. Gynecologic oncology. 2016 Oct 1;143(1):3-15.
9. Liang WF, Wang LJ, Li H, Liu CH, Wu MF, Li J. The added value of CA125 normalization before interval debulking surgery to the chemotherapy response score for the prognostication of ovarian cancer patients receiving neoadjuvant chemotherapy for advanced disease. Journal of Cancer. 2021;12(3):946.
10. Akhavan S, Jefrideh Y, Mousavi A, Modares-Gilani M, Sheikh-Hasani S. Does a Decrease in CA-125 in Advanced Ovarian Cancer Following Neoadjuvant Chemotherapy Predict the Clinical Outcome of Patients? A Cross-sectional Study. International Journal of Women's Health & Reproduction Sciences. 2022 Jul 1;10(3).
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009 Jan 1;45(2):228-47.
12. Raghavendrachar RB, Bhat RA, Dhakaria V. Surgical and Survival Outcomes with Neoadjuvant Chemotherapy in Advanced Epithelial Ovarian Cancer: A Longitudinal Study in a Tertiary Cancer Center. Journal of South Asian Federation of Obstetrics and Gynaecology. 2020 Nov 2;12(1):27-30.
13. Baruah U, Barmon D, Kataki AC, Deka P, Hazarika M, Saikia BJ. Neoadjuvant chemotherapy in advanced epithelial ovarian cancer: A survival study. Indian Journal of Medical and Paediatric Oncology. 2015 Jan;36(01):38-42.
14. Levy M, Menczer J, Boaz M, Wandel A, Mizrachi Y. Response Prediction to Neoadjuvant Chemotherapy Prior to Interval Debulking Surgery and the Outcome of Responders Compared to Nonresponders. Int J Cancer Clin Res. 2018;5:098.
15. Gao Y, Li Y, Zhang C, Han J, Liang H, Zhang K, Guo H. Evaluating the benefits of neoadjuvant chemotherapy for advanced epithelial ovarian cancer: a retrospective study. Journal of ovarian research. 2019 Dec;12(1):1-8.
16. He M, Lai Y, Peng H, Tong C. Role of lymphadenectomy during interval debulking surgery performed after neoadjuvant chemotherapy in patients with advanced

ovarian cancer. Frontiers in Oncology. 2021 Mar 26;11:646135.

17. Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, Wakabayashi M, Takehara K, Saito M, Ushijima K, Kobayashi H. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. European journal of cancer. 2016 Sep 1;64:22-31.
18. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review—past, present and future. Journal of Gastrointestinal Oncology. 2016 Feb;7(1):143.
19. Lim MC, Chang SJ, Park B, Yoo HJ, Yoo CW, Nam BH, Park SY, Seo SS, Kang S, Yun JY, Cho DS. Survival after hyperthermic intraperitoneal chemotherapy and primary or interval cytoreductive surgery in ovarian cancer: a randomized clinical trial. JAMA surgery. 2022 May 1;157(5):374-83.