SHORT TERM OUTCOMES OF LAPAROSCOPIC INTERVAL DEBULKING SURGERY POST NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA

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Abstract

OBJECTIVE: The objective of this study is to establish the feasibility of the Laparoscopic debulking surgery in post neoadjuvant chemotherapy advanced ovarian cancer. METHODS / MATERIALS: We performed a retrospective review of laparoscopic approach in patients with histologically confirmed epithelial ovarian cancer (International Federation of Gynaecology Obstetrics stages IIIC-IV) who received 3 courses of neoadjuvant chemotherapy, from January 2015 to December 2017, at the Gynecologic Oncologic Unit, Galaxy care hospital and research centre, Pune, Maharashtra, India. Results: A total of 30 patients were included. The median age was 48.3 years (range, 26-63 years), median body mass index was 24.5 kg/m2 (range, 19-39 kg/m2). All patients had a good clinical response to 3 cycles of neoadjuvant chemotherapy. All women underwent a complete debulking surgery with no residual disease. The median operating time was 152 minutes (range, 70-335 minutes), the median blood loss was 70 mL (range, 50-130 mL). The median number of removed pelvic lymph nodes was 17 (range, 13-25). The median length of hospital stay was 4.6 days (range, 2-15 days). The median follow-up was 15 months (range, 2-54 months). Twenty patients are free from recurrence at the time of this report. The most common site of recurrence was the local (five out of 30). All patients received chemotherapy postoperatively on median post-op day 9 (range, 7-14) Conclusions: Laparoscopic cytoreduction in patients with advanced ovarian cancer after neoadjuvant chemotherapy, when performed by skilled surgeons, seems feasible and may decrease the impact of aggressive surgery on high-morbidity patients after chemotherapy.

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OBJECTIVE: The objective of this study is to establish the feasibility of the Laparoscopic debulking surgery in post neoadjuvant chemotherapy advanced ovarian cancer.

Design – retrospective study

Sample – 30 patients

METHODS: We performed review of laparoscopic approach in patients with histologically confirmed epithelial ovarian cancer (International Federation of Gynaecology Obstetrics stages IIIC-IV) who received 3 courses of neoadjuvant chemotherapy, from January 2015 to December 2017, at the Gynecologic Oncologic Unit, Galaxy care hospital and research centre, Pune, Maharashtra, India.

Results: The median age was 48.3 years (range, 26-63 years), median body mass index was 24.5 kg/m2 (range, 19-39 kg/m2). All patients had a good clinical response to 3 cycles of neoadjuvant chemotherapy. All women underwent a complete debulking surgery with no residual disease. The median operating time was 152 minutes (range, 70-335 minutes). The median number of removed pelvic lymph nodes was 17 (range, 13-25). There was 1 (3.3%) intraoperative complication and 2 (6.6%) postoperative short-term complications. The median length of hospital stay was 4.6 days (range, 2-15 days). The median follow-up was 15 months (range, 2-54 months). Twenty patients are free from recurrence at the time of this report. The most common site of recurrence was the local (five out of 30). All patients received chemotherapy postoperatively on median post-op day 9 (range, 7-14)

Conclusions: Laparoscopic cytoreduction in patients with advanced ovarian cancer after neoadjuvant chemotherapy, when performed by skilled surgeons, seems feasible and may decrease the impact of aggressive surgery on high-morbidity patients, such as on women after chemotherapy.

Introduction -

Epithelial ovarian cancer (EOC) is the most common cause of death for gynaecologic malignancy among women in industrialized countries, typically reflecting advanced-stage disease at the clinical diagnosis.[1] Although the conventional treatment of advanced ovarian cancer is based on associating surgery and chemotherapy, the residual of disease after surgery seems to be the most important factor affecting survival.[2] Over the last few decades, the use of surgery (interval surgery) after a few cycles of neoadjuvant chemotherapy (NACT) in patients with unresectable disease (International Federation of Gynaecology and Obstetrics [FIGO] stage IIIC/ IV) or in patients with poor general conditions have been proposed to increase the rate of the optimal debulking and reduce the number of complications.[3] Interval surgery after NACT and primary surgery showed similar results in terms of overall survival (OS) and disease-free survival (DFS), although the selection criteria for NACT and the optimal timing of surgery have not yet been defined.[4] Complete surgery, whether performed as primary surgery or after NACT, without macroscopic residual tumor, was the aim of the surgical management of advanced EOC. Traditionally, extended vertical midline abdominal incision was the recommended approach, but with the advent of minimally invasive surgical techniques, surgeons can perform all procedures for comprehensive surgical staging using laparoscopic and robotic surgery.[5] Laparoscopic and, more recently, robotic surgery have been performed in apparent early ovarian cancer with no adverse effect on patient's overall prognosis, demonstrating a survival rate of around 90% similar to the range observed in patients staged by laparotomy. These data have also been confirmed by our recent experience.[6] The feasibility of laparoscopic debulking surgery in advanced ovarian cancer in patients treated with NACT has not yet been thoroughly investigated. The purpose of the present study was to evaluate the feasibility of total laparoscopic debulking (TLD) surgery in the treatment of advanced ovarian cancer following NACT.

MATERIALS AND METHODS: -

INCLUSION CRITERIA: -

1. Study Design and Data Collection Patients with histologically confirmed EOC (FIGO stages IIIC-IV)[7] were eligible for the study.

2. From January 2013 to December 2016, patients received 3 courses of NACT and were then evaluated with CA-125 serum levels and CT scan and/or PET-CT before and after chemotherapy.

3. At our unit, we administer NACT, when it is not possible to achieve the optimal tumor clearance at the time of primary diagnosis. This is based on preoperative CT scan and /or PET-CT scan and exploratory laparoscopic evaluation.[8]

4. Compare with pre and post NACT CT / PET-CT scan suggestive of a reduction in tumor size complete resolution / partial resolution > 50%

5. Eastern Cooperative Oncology Group performance status of 2 or less.

6. Adequate bone marrow reserve (absolute granulocyte count Q2000/mL, platelet count Q100,000/mL).

7. Adequate renal, hepatic, and cardiac function.

8. For those women who showed an optimal clinical response to NACT were considered eligible for TLD surgery.

EXCLUSION CRITERIA: -

1.Documented clinically important cardiopulmonary disease defined as a history of cardiac failure, myocardial infarction, unstable angina.

2. Stable disease or progressive disease post NACT three cycles.

2.Pulmonary obstructive disease.

3. Prior pelvic or abdominal radiotherapy.

4. Severe hip disease precluding the use of the dorsal lithotomy position.

5. Metastatic disease.

6. Contraindications for general anesthesia.

7. Systemic infections.

8. A positive plasma pregnancy test result.

TABLE 1: Surgical Approach: -

Informed consent, including to NACT, clinical evaluation, and laparoscopic surgery, was obtained from all patients in accordance with local and international legislation (Declaration of Helsinki).[9] All patients who underwent TLD were informed about conversion to AD would be carried out if optimal debulking was not possible laparoscopically.

Intraoperative parameters included operative time, blood loss, and complications.

Blood transfusions were administered if the pre-operative hemoglobin value was decreased by 1.5 gm/dl in intra op or post-op period.

Postoperative parameters included short-term (within 30 days of the procedure) and long-term complications (930 days after the procedure).

Complications were defined according to Clavien-Dindo classification[10] and Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.17[11]. Moreover, status and number of removed pelvic lymph nodes, pathological response, length of hospitalization, median follow-up duration, recurrence, DFI, and OS were obtained. NACT and Evaluation of Clinical Response Platinum-based chemotherapy (area under the curve = 6) in combination with paclitaxel regimen (175 mg/m2) for 3 cycles every 21 days was chosen as NACT for EOC. Evaluation of clinical response was based on CA-125 serum levels (Gynaecological Cancer Intergroup criteria,) and abdomen and pelvis computed tomographic scan within 30 days before surgery (RECIST criteria [12,])[13]. For each patient, preoperative American Society of Anaesthesiologists risk evaluation and Performance Status-Eastern Cooperative Oncology Group were assessed, and informed consent was obtained.

A diagnostic laparoscopy was done before proceeding for TLD. The timing of the surgery was 2 weeks following the last chemotherapy. ALL Women after TLD underwent further chemotherapy and follow-up.

Criteria to defer to surgery following NACT were: -

1. Less than 50% decrease or less than 25% increase in the product of the 2 largest perpendicular diameters of the measurable lesion,
2. Patients progressive after NACT, defined as greater than 25% increase in the product of the 2 largest perpendicular diameters of one measurable lesion or,
3. The appearance of new ones was offered second-line chemotherapy.

Follow-up - All patients were regularly evaluated at the end of the treatment for evidence of disease recurrence. Clinical examinations, tumor marker assays (CA-125), and ultrasound scans were performed every 3 months and computed tomographic scans every 6 months and PET scan at the completion.

RESULTS: - All patients were treated by the same surgical team with extensive training in gynecology oncology and minimally invasive surgery, between January 2013 and December 2016, at the Oncologic Unit, Galaxy care hospital, Pune Maharashtra, INDIA.

None of the patients refused to undergo a laparoscopy. Patient Characteristics from January 2013 to December 2016, 30 patients were included in the study. Twenty-five patients with FIGO stage IIIC or IV advanced EOC underwent primary laparoscopic surgical exploration at our institute. Five (16.6%) of 30 women underwent initial surgery in different hospitals and then were referred to our institution to complete treatment during the indicated period. The median age was 50 years (range, 26-73 years), and median BMI was 24.5 kg/m2 (range, 19-39 kg/m2). 5 patients (16.6%) had undergone previous abdominal surgery.

All patients were evaluated for toxicity and response to chemotherapy (Table 2). The surgical procedures are detailed in (Table 1). The median operating time was 152 minutes (range, 70-335 minutes), the median blood loss was 70 mL (range, 50-200 mL); one of the patients required intraoperative blood transfusion. The median number of removed pelvic lymph nodes was 15 (range, 13-25). The superior border of the dissection in the para-aortic lymphadenectomy was the left renal vein, and the median number of removed para-aortic lymph nodes was 15(range, 4-30)[15]. There was 1 (3.3%) intraoperative complication: 1 patient had injury of the left hypogastric artery. Posterior exenteration was done in 8 patients with primary rectal anastomosis and diversion ileostomy was done in all patients.

TABLE 2. Patients' characteristics:

There were 2 (6.6%) postoperative short-term complications: postoperative bleeding from the rectus abdominis (grade 3 according to CTCAE v4.03) that was successfully recovered by drainage and sutured. one patient had chylous ascites (grade 3 according to CTCAE 4.03) and was treated conservatively with total parenteral nutrition and a low-fat diet.

The median length of hospital stay was 4 days (range, 3-13).

TABLE 3. Surgical outcome Characteristics

Further Management and Follow-Up : All patient's adjuvant chemotherapy. This was started 10 days after surgery. An optimal debunking was achieved in all the patients.

The median follow-up was 15 months (range, 2-54 months).

Twenty-six patients are free from recurrence at the time of this report.

One patient had a pelvic lymph node recurrence with a DFI of 8 months she was offered second-line chemotherapy and is disease-free at present.

Three patients had a peritoneal recurrence with a disease-free interval of 6, 12, and 14 months and underwent second-line chemotherapy. They all succumbed to the disease. the optimal survival was 23,31 and 24 months.

DISCUSSION :

The aim of the present study indicates that cytoreduction by laparoscopy is technically feasible and in advanced ovarian cancer after NACT, with less blood loss and fewer intraoperative and postoperative short-term complications. Complete resection of all macroscopic diseases at the primary debulking surgery or after NACT remains the most important prognostic factor in the treatment of advanced ovarian cancer. The inclusion criteria for surgery following NACT remains the same whether we chose laparoscopy or open.

To standardize this selection process, some authors have described the criteria for the selection for primary surgery or NACT in patients with stage FIGO IIIC/IV disease.[14] Despite the preoperative imaging study and the exploratory laparoscopic evaluation, the identification of patients requiring NACT remains a challenge.

Abdominal debulking surgery is considered as the gold standard surgical approach for patients with advanced ovarian cancer, minimally invasive approach has revolutionized the management of gynecologic cancer, the main advantage in reducing comorbidities and faster postoperative time of recovery. Although laparoscopy is a well-accepted treatment of endometrial and cervical cancer, such success is yet to be achieved in the treatment of ovarian cancer, particularly for advanced disease.[16,17] In a recent study, we published one of the largest series on laparoscopic management of early ovarian cancer demonstrating laparoscopy technique as a safe, feasible, and comprehensive treatment.6 Moreover, recent advances in laparoscopic instruments and techniques have allowed the use of laparoscopy in cytoreduction in advanced ovarian cancer.[18,19] Amara et al 20 described the first report of 5 patients who underwent successful total laparoscopic primary staging or secondary cytoreduction by laparoscopy in advanced ovarian cancer. Laparoscopic debulking has been demonstrated to be a feasible technique also for upper abdominal diseases, including resection of bulky omental diseases and diaphragmatic implants.[21] In our series, all patients underwent an omentectomy, and 25/ 30 patients underwent a subdiaphragmatic peritonectomy without any complications.

Traditional concerns about laparoscopy in advanced ovarian cancer include inadequate resection and port-site metastases. A surgeon must have skills for intestinal, ureteral, or retroperitoneal disease.[16] In our series, 8 patients (table 3)presented with rectal involvement and were treated with posterior exenteration. No port-site metastases were noted in our patients. This may be due to irrigation of the port site with normal saline before removal of the ports. Our median recurrence-free interval is 20 months. This is better than the results reported in other studies.[22,23] This may be explained by the combination of optimal surgery and optimal cytoreduction. A careful selection of a subset of patients following NACT is needed. There was non-major morbidity and no mortality. The nodal retrieval (pelvic and para-aortic) was the same as in open surgery.

The perioperative outcomes, including the median blood loss, the median hospital stay, and the intraoperative complications, are in accordance with that reported in other studies better than results from studies on laparotomic series.[24]

Laparoscopic cytoreduction in patients with advanced ovarian cancer after NACT should be performed by skilled surgeons. Advances in laparoscopic instrumentation and technique have made a laparoscopic approach to surgical cytoreduction possible in the selected subset of patients. In our experience, the decision to proceed with laparoscopy was limited by the reduced ability to tolerate lengthy pneumoperitoneum, extensive bowel adhesions, a significant metastatic disease involving the hepatic hilum and great omental, or ovarian masses.

The management of advanced ovarian cancer disease requires radical pelvic and upper abdomen surgical dissection. The question is whether the outcome matches those of open surgeries should be in a randomized trial. The short-term outcomes of laparoscopic debulking surgery after NACT in advance ovarian cancer should remain under evaluation until randomized trials on long-term follow-ups are available.

REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9Y29.

2. Carney ME, Lancaster JM, Ford C, et al. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? Gynecol Oncol. 2002; 84:36Y42.

3. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy, or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010; 363:943Y953.

4. Vergote I, De Wever I, Tjalma W, et al. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol. 1998; 71:431Y436.

5. Liu CS, Nagarsheth NP, Nezhat FR. Laparoscopy and ovarian cancer: a paradigm change in the management of ovarian cancer? J Minim Invasive Gynecol. 2009; 16:250Y262.

6. Ghezzi F, Malzoni M, Vizza E, et al. Laparoscopic staging of early ovarian cancer: results of a multi-institutional cohort study. Ann Surg Oncol. 2012; 19:1589Y1594.

7. Benedet JL, Bender H, Jones H 3rd, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynecol Obstet. 2000; 70:209Y262.

8. Fagotti A, Ferrandina G, Fanfani F, et al. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. Ann Surg Oncol. 2006; 13:1156Y1161.

9. World Medical Association Inc. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc. 2009; 107:403Y405.

10. The Clavien-Dindo Classification of Surgical Complications Five-Year Experience Pierre A. Clavien, MD, PhD,* Jeffrey Barkun, MD, Michelle L. de Oliveira, MD, PhD,* Jean Nicolas Vauthey, MD, Daniel Dindo, MD,* Richard D. Schulick, MD, Eduardo de Santiban es, MD, PhD, Juan Pekolj, MD, PhD, Ksenija Slankamenac, MD,* Claudio Bassi, MD, Rolf Graf, PhD,* Rene´ Vonlanthen, MD,* Robert Padbury, MD, PhD,** John L. Cameron, MD,§ and Masatoshi Makuuchi, MD, PhD

11. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published May 28, 2009; revised version 4.03 June 14, 2010. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/ CTCAE_4.03_2010-06-14_-QuickReference_5x7.pdf.

12. Rustin GJ, Quinn M, Thigpen T, et al. RE: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Nat Cancer Inst. 2004; 96:487Y488.

13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205Y216.

14. Barletta F, Corrado G, Vizza E. Use of new instruments in the management of total laparoscopic radical hysterectomy (TLRH). J Minim Invasive Gynecol. 2014;21: S89.

15. Vergote I, Leunen K, Amant F. Primary surgery, or neoadjuvant chemotherapy in ovarian cancer: what is the value of comparing apples with oranges? Gynecol Oncol. 2012; 124:1Y2.

16. Farache C, Alonso S, Ferrer Marsollier C, et al. Robotic surgery in gynecologic oncology: retrospective and comparative study with laparotomy and laparoscopy. J Gynecol Obstet Biol Reprod. 2012; 41:353Y362.

17. Nezhat FR, DeNoble SM, Liu CS, et al. The safety and efficacy of laparoscopic surgical staging and debulking of apparent advanced stage ovarian, fallopian tube, and primary peritoneal cancers. JSLS. 2010; 14:155Y168.

18. Krivak TC, Elkas JC, Rose GS, et al. The utility of hand-assisted laparoscopy in ovarian cancer. Gynecol Oncol. 2005; 96:72Y76.

19. Nezhat FR, Denoble SM, Cho JE, et al. Safety and efficacy of video laparoscopic surgical debulking of the recurrent ovarian, fallopian tube, and primary peritoneal cancers. JSLS. 2012; 16:511Y518.

20. Amara DP, Nezhat C, Teng NN, et al. Operative laparoscopy in the management of ovarian cancer. Surg Laparosc Endosc. 1996; 6:38Y45.

21. Chi DS, Franklin CC, Levine DA, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol. 2004; 94:650Y654.

22. da Costa Miranda V, de Souza Fe$^{d}eA^{B,DosAnjosCH,etal.Neoadjuvantchemotherapywithsixcyclesofcarboplatinandpaclitaxelinadvancedo}$

23. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med. 2004; 351:2489Y2497.

24. Nezhat FR, Finger TN, Vetere P, et al. Comparison of perioperative outcomes and complication rates between conventional versus robotic-assisted laparoscopy in the evaluation and management of early, advanced, and recurrent stage ovarian, fallopian tube, and primary peritoneal cancer. Int J Gynecol Cancer. 2014; 24:600Y607.

Table 1

S.NO.	TOTAL LAPAROSCOPIC DEBULKING (TLD) APPROACH	NUMBER OF PATIENTS
1.	BILATERAL SALPINGO-OOPHORECTOMY WITH HYSTERECTOMY	22
2.	OMENTECTOMY	30
3.	PELVIC LYMPH NODE DISSECTION	30
4.	PARAAORTIC LYMPH NODE DISSECTION	30
5.	DIAPHRAGMATIC STRIPPING	25
6.	POSTERIOR EXENTRATION	08

Table 2

S.No.	Particulars	Data
1.	Patients	30
2.	BMI	24.2 (19-39) kg/m2
3.	Prior abdominal surgery	5
4.	Histology Serous	23,
	Clear cell	6,
	Endometroid	1
5.	Grading G 2 G 3	
		8
		22

Table 3

s.no	Surgical complications	Median	Range
1.	Operative time,	152 min	70-335 minutes
2.	Blood Loss	70 ml	50- 200 ml
3.	Pelvic lymph nodes	15	13-25
4.	Paraaortic lymph nodes	14	4-30
5.	Major intraoperative complications	1	3.33%
6.	Major early postoperative complications	0	0
7.	Blood transfusion	1	3.33 %
8.	Hospital stays	4	2-13

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Consent – all patients consents are taken for publication

ethics committee **approval taken for study**

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Dr Renu Sharma wrote the manuscript and reviewed the final version.

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The authors have no conflicts of interest to declare.

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