Original Article-II

Primary Versus Interval Cytoreductive Surgery in Treatment of Advanced Ovarian Cancer

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ABSTRACT

Background: Prognosis of patients with advanced epithelial ovarian cancer (EOC) is poor. We studied case records of 43 such patients to evaluate the impact of primary and interval debulking surgery.

Patients and Methods: Between January 2001 and June 2003, 43 patients underwent either primary surgery followed by chemotherapy (group A, n=23) or primary chemotherapy followed by interval debulking surgery then chemotherapy (group B, n=20). A combination of paclitaxel and cisplatin or carboplatin was used for all patients.

Results: Patients median age in group A and B was 46 and 50 years, respectively. In group A 56.5% of patients underwent optimal cyto reduction (≤ 1.5cm residual tumour) compared to 30% in group B. Median overall survival was 24 and 14 months in group A & B, respectively, p=ns and two year probability of over survival was 61% and 50%, respectively, p = ns. Grade3-4 GI toxicity and grade 1-2 neuropathy were main treatment related complications and were similar in both groups.

CONCLUSIONS:

Neoadjuvant chemotherapy results in survival rates comparable to those associated with primary cytoreductive surgery.

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INTRODUCTION

Primary debulking surgery followed by platinum based chemotherapy is currently the standard of care for patients with advanced EOC. Amount of residual tumour following cytoreductive surgery is inversely proportional to survival.

The study suggesting role of cytoreductive surgery in primary treatment of ovarian cancer was published in 1975.[1] Since then, a number of retrospective and prospective studies have demonstrated superior survival in patients who undergo optimal cyto-reduction with a median survival of 36.7 months vs. 16.6 months with sub-optimal cytoreduction. However, the optimum debulking rate in various studies has varied from 20% to 80%.[2-3]

Many investigators have also used upfront chemotherapy (neoadjuvant chemotherapy) for patients with significant medical problems or those with large, fixed mass, peritoneal carcinomatosis, subacute intestinal obstruction and have reported comparable results to approach of primary surgery followed by chemotherapy.

MATERIAL AND METHODS

Between January 2001 to June 2003, 43 patients with advanced epithelial ovarian cancer (Stage IC to Stage IV (FIGO), WHO performance score ≤ 2, were included in the present study after the informed written consent. The study was approved by the Institute Ethics committee.

Baseline investigations included: hemogram, liver and kidney function tests, chest X-Ray, CA-125, ultrasound and CT scan of abdomen and pelvis. Patients with co morbidity and deranged renal functions were excluded. Patients were divided into two groups :Group 'A' comprised of 23 patients who underwent initial surgery followed by adjuvant chemotherapy. Group 'B' comprised of 21 patients who received neo-adjuvant chemotherapy (NACT) followed by cytoreductive surgery and further chemotherapy.

In group 'A', after preoperative evaluation, surgery was performed as per standard guidelines which was either optimal or sub-optimal depending on the operative findings. Careful inspection of the abdominal cavity was performed, an attempt was made to completely resect the tumour and typical sites including omentum, serosa and mesentery of entire GI tract, paracolic gutters, pouch of douglas, pelvic side walls, superior surface of liver and under surface of diaphragm were examined and multiple biopsies were taken from these sites. An infracolic omentectomy, bilateral salpingo-oophorectomy and total abdominal hysterectomy were performed. Patients were staged based on these findings and post operatively patients received chemotherapy using Inj. Paclitaxel 175 mg/m^2 day^1 over 3 hour infusion after proper premedication followed by Inj. Cisplatin 75 mg/m^2 on day 1, every 21 days or Inj. Paclitaxel 175 mg/m^2 day 1 followed by Inj. Carboplatin (AUC 6). At the end of 3 cycles patients were assessed clinically for response, radiologically and with CA-125 estimation, followed by three more cycles and after documenting complete remission, patients were put on regular follow up. In group 'B' after proper evaluation patients were given primary chemotherapy. After three cycles, patients were subjected to interval cytoreductive surgery, which was either optimal or suboptimal depending on the operative findings. Post surgery, patients again received three more cycles of same chemotherapy. Once the patients were in clinical and biochemical remission, they were put on follow up.

Data was analysed using SPSS 11.5 stastical software. Survival analysis was done by Kaplan Meir method.

RESULTS

A total of 44 patients were enrolled 23 were assigned to group 'A' (primary cytoreductive surgery) and 21 to group 'B' (interval cytoreductive surgery) by systematic random sampling. One patient in group 'B' died after first cycle of chemotherapy due to arrhythmia unrelated to disease or chemotherapy and was excluded from the final analysis. Median age of patients in group A was 46 years and in group B was 50 years. Distribution of cases in two groups as per pretreatment evaluation is shown in table 1.

Patients received a median of 5.5 cycles of chemotherapy in group A and in group B, 3 cycles were given pre-operatively and 3 cycles postoperatively. The age at presentation, pre-operative CA-125 level, stage of disease and type of surgery had impact on survival. However, number of patients is small in each subgroup.

61% patients were alive in group A and 50% in group B at 2 years follow up ($p>0.05$) (Table 2). In group A, patients with age < 50 years had a median survival of 24 months and patients with age > 50 years, 12 months ($p<0.05$). In group B, patients with age < 50 years, had median survival of 14 months and of 12 months in patients with age > 50 years, ($p>0.05$).

In the primary cytoreductive surgery group, optimal cytoreduction (residual tumour <1.5 cm diameter) was achieved in 26%. The median survival in these patients was 24 months and 2 year overall survival was 56.5%. In 17 patients (73.9%),

Table 1: Patient Characteristics

Patient data	Group A (n=23)	Group B (n=20)
Age (Year)		
Median	46	50
Range	15 - 60 yrs	17 - 65 yrs
Premenopausal	7 (30.4%)	9 (45.0%)
Postmenopausal	16 (69.6%)	11 (55.5%)
Nulli gravid	3 (13.0%)	2(10.0%)
Parous	20(87.0%)	18(90%)
Family history of cancer		
Present	1 (4.34%)	1(5.0%)
Absent	22 (95.7%)	19(95%)
Presenting Symptoms		
Abdominal distension	16 (69.6%)	14 (70%)
Abdominal pain	12 (52.2%)	5 (25.0%)
Abdominal lump	1 (4.37%)	1 (5.0%)
Ascites	12 (52.1%)	10(50%)
Adjacent organ involvement	1(4.3%)	5(25%)
FIGO Stage		
IC	1 (4.3%)	1(5%)
IIB	3 (13%)	2(10%)
IIC	-	3 (15%)
IIIA	3 (13%)	-
IIIB	1 (4.3%)	-
IIIC	15(65.2%)	14(70%)
Histopathology		
Serous adenocarcinoma	13 (56.5%)	15 (75%)
Mucinous adenocarcinoma	7 (30.9%)	5 (25%)
Endometroid	2 (8.7%)-	
Brenner	1 (4.3%)	-
CA 125 level (U/ml)		
< 35	3 (13%)	3 (15%)
35 - 100	6 (26%)	1 (5%)
101-500	4 (17.4%)	4 (2%)
> 500	10 (43.5%)	12 (10%)

Table 2: Survival with respect to stage and type of surgery

Group		Parameter	Median survival (Months)	2 year overall survival (%)
Group A	(Stage)	IC(n=1)	30	-
		II (n=3)	24	66.67(n=2)
		III(n=19)	15	63.16(n=12)
Group B	(Stage)	IC(n=1)	30	100(n=1)
		II(n=5)	13	60(n=3)
		III(n=14)	12	42.86(n=6)
Primary cytoreductive Surgery		Optimal	24	56.5
		Suboptimal	18	4.5
		Overall	**24**	**61**
Interval cytoreductive Surgery		Optimal	16	30
		Suboptimal	12	20
		Overall	**14**	**50**

Table 3: Treatment related complications

Complications	Group A n (%)	Group B n(%)
Nausea/Vomiting	9(39.1)	6(30.0
Wound infection	-	1(5.0)
Hematological (Grade III-IV)		
- Anemia	2(8.7)	2(10.0)
- Neutropenia	-	1(5.0)
Renal	1(4.3)	1(5.0)
Hepatic	-	1(5.0)

suboptimal cytoreduction was achieved, their median and 2 year overall survival was 18 months and 4.5%, respectively, which was significant demonstrating advantage in patients who had undergone primary cytoreduction optimally. In the interval cytoreductive surgery group, optimal cytoreduction was achieved in 10(50%) patients and their median survival was 16 months and 2 years overall survival of 30%, as compared to median survival of 12 months and 2 year overall survival of 20% in patients in whom sub-optimal cytoreduction was done, (p=ns) the (Fig. 1 and 2).

Fig. 1. Survival time with resepct to type of cytoreductive surgery (optimal)

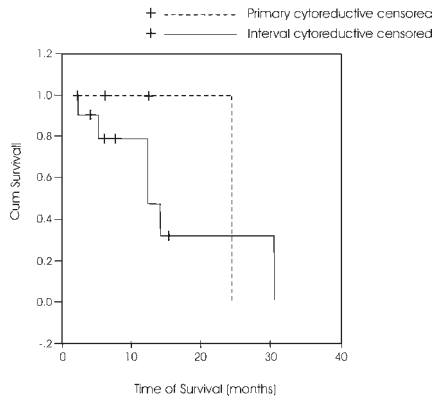
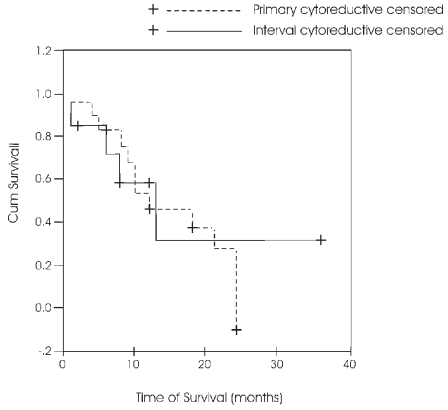


Fig. 2. Survival time with resepct to type of cytoreductive surgery (sub - optimal)



In group A, 5 patients (21.7%) relapsed, median time to relapse was 12 months. Two patients had biochemical relapse after one month and another after 12 months whereas 2 patients (8.6%) had progression of disease and their median survival was 8 months. In group B, 6 patients (30%) relapsed, median time to relapse was 12 months, their median survival being 30 months, two patients had biochemical relapse at 10 and 12 months whereas one patient (5%) had progression of disease with a median survival of 12 months($p<0.05$). Complications in both the groups were mainly GIT and neuropathy (Table 3).

The overall survival in primary cytoreductive surgery group is 24 months and in interval cytoreductive surgery group 14 month, (p=ns) Table 2. The overall relapse related mortality in group A was 39% and in group B 50% (p=ns).

DISCUSSION

Primary treatment for advanced ovarian cancer consists of appropriate surgical staging and cytoreduction, followed by systemic chemotherapy. This synergy has been ascribed to the ability of chemotherapeutic molecules to interact with smaller tumours.

The present trial was undertaken to study and compare the impact of the primary and interval cytoreductive surgery in terms of survival in advanced ovarian carcinoma.

In the present study, patients below 50 years of age had a median survival of 24 months compared to 12 months in patients ≥ 50 years of age ($p<0.05$). In interval cytoreductive surgery group, patients whose age was below 50 years median survival was 14 months compared to 12 months in patients with more than 50 years age($p>0.05$). The 2 year overall survival in our study in group A was 39% in age group of less than 50 years and 22% in age group of more than 50 years ($p<0.05$). In group B, the overall survival rate in both groups was same (25%) (p=NS).

Stage as a prognostic variable is well established. In our study in group 'A' patients with stage IC had median survival of 30 months, stage II, 24 months and stage III, 15 months, the overall survival rate was 66.67% in stage II and 63.2% in stage III($p<0.05$). In group B, stage IC had median survival of 30 months, stage II, 13 months and stage III, 12 months. The overall survival rate was 100% for stage I, 60% for stage II and 42.86% for stage III. The likelihood of death was seven times more in patients with stage III as compared to stage I and II (Table 2).

In the group A-optimal cytoreduction was achieved in 6(26%) patients. The median survival in these patients was 24 months and 2 year overall survival was 56%. In 17 (73.9%) patients sub-optimal surgery was achieved, there median survival was 18 months and 2 year overall survival was 4.5% (p=<.05). In group B optimal cytoreduction was achieved in 10(50%) patients and their median survival was 16 months and 2 year overall survival of 30% compared to median survival of 12 months and 2 year overall survival of 20% (p=<.05) in patients where sub-optimal surgery was done (Table 2). The histopathological sub-type and type of chemotherapy did not have any significant effect on overall survival in both groups.

These data suggest that patients with advanced epithelial ovarian cancer benefit from optimal cytoreductive surgery performed either as a primary step or after receiving neoadjuvant chemotherapy.[4] Thus, in patients where optimal debulking is not possible at presentation, neo-adjuvant chemotherapy can be considered.

REFERENCES:

1. *Griffiths CT. Surgical resection of tumour bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975; 42: 101-104.*

2. *Cannistra S. Cancer of the ovary. N Engl J Med 1993; 329:1550-1559.*

3. *Dauplat J, Le Bouedec G, Pomel C, Scherer. Cytoreductive surgery for advanced stages of ovarian cancer. Semin Surg Oncol 2000; 19(1):42-8.*

4. *Van der Burg ME, Van Lent J, Buyse M et al. The effect of debulking surgery after induction chemotherapy or the prognosis in advanced epithelial ovarian cancer. New Eng J. Med. 1995; 332(10):629-634*