

Comparing the Effectiveness of the Treatment with Neoadjuvant Chemotherapy Followed By Interval Debulking and Primary Debulking Followed By Adjuvant Chemotherapy in Advanced Stage Malignant Ovarian Tumors –Rural Based Study

Abstract:

Background: Advanced epithelial ovarian cancer is also a poorly prognosed condition with elevated death rate. The management of advanced ovarian carcinoma is surgical debulking which is followed by adjuvant chemotherapy. Prognosis reflects primarily on the level of cytoreduction obtained in primary surgery. In order to enhance survival, attempts are therefore being made to increase the optimal rates of surgical cytoreduction. NACT has emerged as an important treatment modality. The reasoning behind the NACT protocol is to make advanced untreatable disease operable, increase resection rates of optimal cyto reduction (R0) and promote organ preservation. The application of neoadjuvant chemotherapy will structurally reduce the load of the tumour because of the chemo sensitive nature of the ovarian tissue and enable a greater optimal cytoreduction rate for surgery and an increase in overall survival.

Methods: This observational and retrospective study was conducted from 2018-2020, including 71 patients who visited the oncology clinic of OBGY department at AVBRH. Only those who have already diagnosed as stage III and IV ovarian neoplasms and who received primary debulking surgery followed by adjuvant chemotherapy along with neoadjuvant chemotherapy followed by interval debulking surgery were included to study the better treatment outcome in terms of intra-operative and post-operative complications and overall survival without progression in these patients with a follow-up of 2 years.

Results: The statistical difference in overall survival and progression free survival between primary debulking and NAC / IDS groups was >0.005 . But intra operative findings like blood loss, residual disease, Bowel bladder injury, surgery time & post-operative morbidity were less in NAC/IDS group with P value <0.005 .

Conclusion: In patients having cytoreducible disease which is non optimal or low performance status, NAC / IDS is also a reasonably secure and may be an alternative method for achieving optimal cytoreduction. Investigations aimed at appropriately selecting patients to be treated with NAC and to search for the proper opportunity to conduct IDS can have much better benefits for patients having advanced EOC. It should be underscored that the study is limited to patients with stage 3c or 4 disease.

Keywords: PDS, NAC or IDS, Ovarian carcinoma stage 3C,4.

Background:

The ovarian tumour has a broader spectrum of structural, human variation and a more complex embryonic development and histogenetic background than any other organ and has avoided

adequate assessment for this reason (James Ewing 1940).

Every year worldwide 239,000 new cases and 152,000 deaths are noted due to ovarian carcinoma(1).The estimated occurrence of female OC growth is 1 in 75 and the possibility of death is 1 in 100.(2)

Ovarian cancer is the 5th most common cause of death in all women with gynae malignancies [American Cancer Society, 2003]. It is the third most common gynecological malignancy among women in the western world, hence is the most lethal. Almost 2/3 of the patients present in advanced stage(3). The 8th most frequent cancer in females is epithelial ovarian cancer, and the 4th is uterine (corpus and endometrial). The ovaries are the 9th most common cancer site in women, accounting for around 3 percent of all new cases, but 5 percent of cancer deaths are caused by ovarian cancer, more than any other female reproductive system cancer. The incidence of ovarian cancer, however, decreased at a pace of 2.4 percent annually during 2001-2005, and the mortality rate from ovarian cancer has been steady since 1998 (3) .

The prevalence of ovarian cancer raises with age due to its gradual onset lack of successful screening. The preferred management for advanced stage eepithelial oovarian carcinoma is primary debulking surgery(PDS) with optimal cyto reduction. After that adjuvant chemotherapy comprising of platinum compounds except patients who are not appropriate for surgical extreme comorbidities or severe tumor spread should be given. Since the use of platinum-based therapy for OC management started more than 30 years ago, survival in these patients has improved to a limited degree methods without early clinical symptoms. According to FIGO classification, two third of patients will present with advanced ovarian cancer staging of grade IIIC or IV.

In advanced EOC, NAC/IDS method has shown a higher rate of optimal cytoreduction surgery. Taxan and platinum chemotherapy has a high sensitivity response of up to 80 percent. Unoperable tumours with massive ascites and diffuse spreading have a dramatic disappearance following them in patients with stage IV,NAC-IDS was shown to be a valid strategy. For this reason, NACIDS is expected to become the gold-standard treatment in the coming years. The purpose of this study was to observe the effective treatment in terms of intra operative blood loss resectability of macroscopic disease and peri operative morbidity mortality and survival outcomes in advanced stage malignant ovarian tumours.

Materials and Methods:

This was a retrospective observational study, it was conducted in Department of OBGY, at AVBRH, Sawangi (Meghe), Wardha, a tertiary care centre, over a period of two years from august 2016 to august 2018.According to the retrospective data there were only 76 Epithelial ovarian carcinoma patients. Of which 71 patients were in stage 3C & 4 of FIGO confirmed by Cytological and histopathological examination .

A total of 71 patients were chosen, of whom 42 had primary debulking followed by adjuvant chemotherapy and 29 had NACT followed by interval debulking. Prior to PDS or NACT all 71 patients were diagnosed by cytology samples obtained by abdominal paracentesis.

IDS group patients were received 3 cycles of platinum based chemotherapy then IDS has performed during IDS for all patients Histopathological confirmation done,. Then again minimum 3 more cycles were given. PDS group patients were received 6 platinum based chemo cycles was given.

Clinical Statistics And Follow Up:

Demographic data including name, age, education, socio economic status, BMI, area of residency, History including age of menarche, parity, TL history, previous surgeries, Co-morbidities (Diabetes, Hyper tension, Thyroid disorders, Heart diseases, previous surgical history, familial disorders, h/o breast surgery) h/o Oral contraceptive use, age of menopause and Clinical data regarding pre-operative characteristics like Stage, type of histopathology , pleural effusion, malignant ascites, serum CA 125, findings of (CT) Computerized tomography were taken from patients records. Findings of surgery were documented using a consistent form that initial residual tumor sites and volume, and type of surgical procedure.

No residual tumour described as R0. Residual tumour <1cm described as R1 and R2 was showed as residual tumour >1cm. Optimal cytoreduction was defined as residual tumor less than or equal to 1 cm. omental caking, multiple nodules at more than 2 different cites like peritoneum, mesentrium ad intestine, diaphragm, defined as a diffuse tumour pattern.

After completion of primary treatment, patients were followed up 3 monthly for 12 months; then after 6 monthly . At each follow-up visit, a complete physical examination and serum CA125 level was performed by using an Eletro-chemi luminescent immunoassay (ECLIA).

Imaging was advised in case patient presented with symptoms, or a rise in serum CA-125 levels(serological relapse). Chemo-resistance has been described as recurrence after full recovery after <6 months of initial treatment or worsening of the disease throughout chemotherapy. Chemo sensitive patients have been described as having recurrence following having complete recovery after 6 months of primary treatment. From the date of intervention (chemotherapy or surgery) to the date of death or the date of last follow-up (end of follow-up, 28 August 2020) calculated as Overall survival (OS).The period from management (chemotherapy or surgery) to physical , biological or radiological evidence of progression of the disease or mortality from any reason described as Progression-free survival (PFS). Four patients were absent during the follow-up time. The median time for follow-up was 20.8 months.

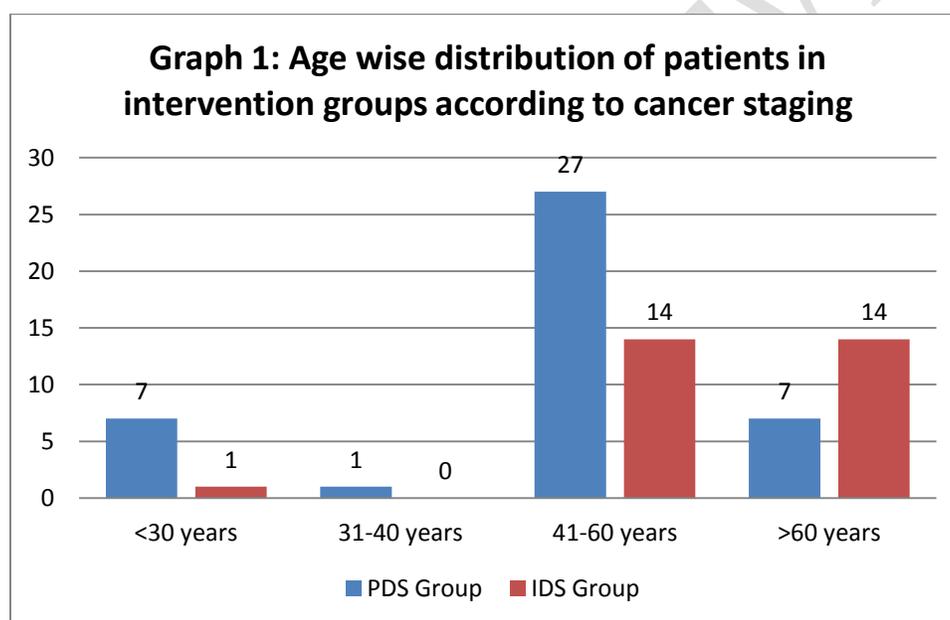
Statistical Analysis:

The characteristics were compared using Chi-square test. Clinical factors were assessed for their correlation with chemosensitivity. Kaplan–Meier method was used for analysis of overall survival (OS) and progression-free survival (PFS).

Statistical analysis were performed using SPSS software version 20.0 (SPSS). *P* values<0.05 were considered statistically significant.

Table 1: Distribution of patients according to age in intervention groups

Age Group (years)	PDS	IDS	Total
<30 years	7	1	8
31-40 years	1	0	1
41-60 years	27	14	41
>60 years	7	14	21
Total	42	29	71
Mean±SD age in years	46.66±13.49	60.06±12.57	52.14±14.63



In our study we have divided the patients in to 5 classes according to the age distribution. Maximum women i.e.41 out of 71 were in the age group between 40-60years. Minimum number of women were <30 years group had 7 and 1 patients, in PDS group and IDS group respectively. The mean age of patients in PDS group was 46.66±13.49 years and in IDS group it was 60.06±12.57years.

Table 2: Distribution of patients according to intra op findings in intervention groups:

Findings	PDS	IDS	Total	χ^2 -value, p-value
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Enlarged lymph nodes	Present	23	21	44	$\chi^2=6.254$ $p=0.012^*$
	Absent	21	6	27	
Malignant pleural effusion	Present	14	21	35	$\chi^2=10.482$ $p=0.001^*$
	Absent	28	8	36	
Omental cake	Present	23	20	43	$\chi^2=10.112$ $p=0.001^*$
	Absent	19	9	28	
Malignant ascitis	Present	19	16	35	$\chi^2=0.677$ $p=0.411$
	Absent	2	13	36	
Blood loss	<500ml	14	15	29	$\chi^2=4.506$ $p=0.0486$
	500-1000ml	25	12	37	
	>1000ml	3	2	5	
Bowel/bladder injury	Present	6	0	17	$\chi^2=4.978$ $p=0.026^*$
	Absent	36	29	54	
Surgery time	<4 hrs	18	16	34	$\chi^2=1.043$ $p=0.307$
	≥ 4 hrs	24	13	37	
Total		42	29	71 (100%)	

Table shows distribution of patients according to findings in intervention groups. Enlarged lymph nodes were present in 21 patients of PDS group as opposed to 23 patients in IDS group and the difference was statistically significant ($p < 0.05$). Malignant pleural effusion was present in 14 patients of PDS group as opposed to 21 patients in IDS group and the difference was statistically significant ($p < 0.05$). Omental cake was observed in 19 (26.8%) patients of PDS group as opposed to 24 patients in IDS group and the difference was statistically significant ($p < 0.05$). Malignant ascites was observed in 19 patients of PDS group as opposed to 16 patients in IDS group and Blood transfusion of <500 ml was required by 14 and 15 patients, 500-1000ml was required by 25 and 12 and >1000ml was required by 3 and 2 patients in PDS Group and IDS Group respectively and the difference between the groups was not significant statistically ($p > 0.05$). Bowel/bladder injury was present in 14 patients in PDS group as opposed to only 3

patients in IDS group with statistically significant difference between two groups ($p < 0.05$). Based on surgery time in the group of < 4 hours, there were 18 and 16 patients and in ≥ 4 hours there were 24 and 13 patients in PDS group and IDS group respectively with no significant difference between two groups. the difference was insignificant statistically ($p > 0.05$).

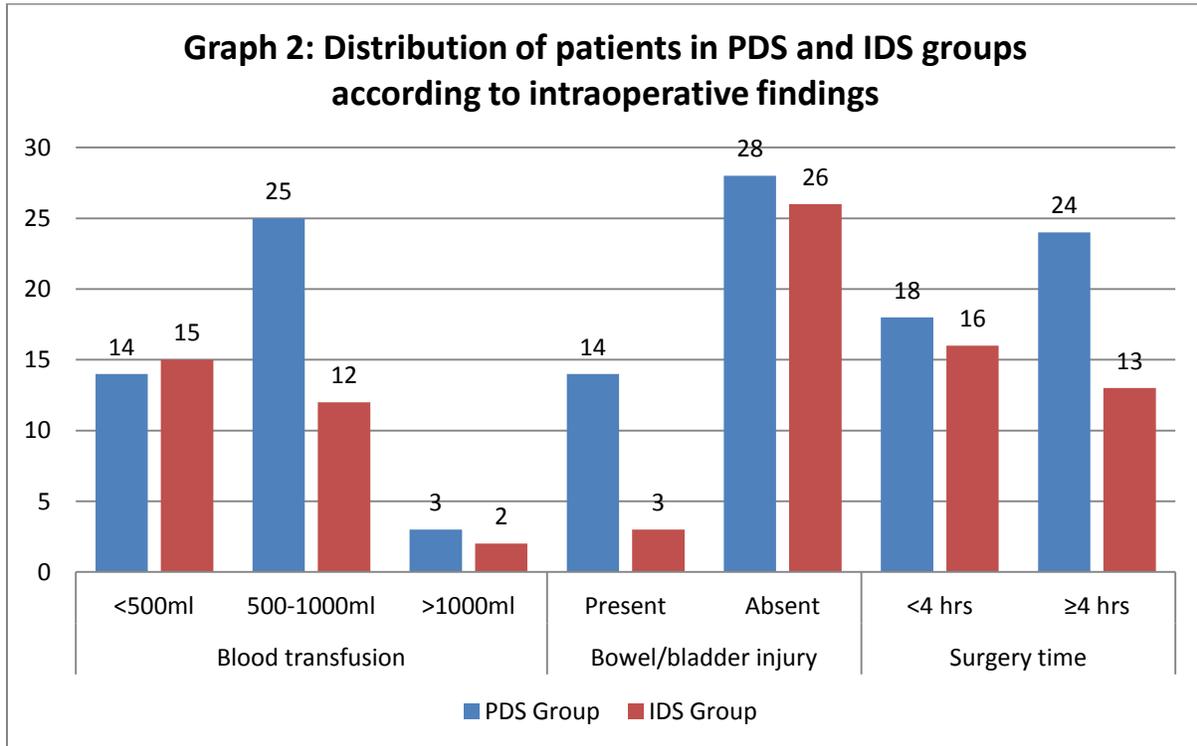


Table 3: Distribution of patients according to residual disease in intervention groups:

Residual disease	PDS Group	IDS Group	Total n (%)	χ^2 -value, p-value
Optimal residual	15	20	35	$\chi^2=9.201$ $p=0.010^*$
Suboptimal residual	27	9	36	
Total	42	29	71 (100%)	

* $p < 0.05$ - Statistically significant

Table shows distribution of patients according to residual disease in intervention groups. In PDS group Optimal residual disease was seen in 15 patient,. Sub optimal residual disease was seen in 27 patients out of 42. In IDS group optimal residual disease was seen in 20 patients and sub optimal disease was seen in 9 patients out of 29 patients. The difference is statistically significant $p < 0.005$.

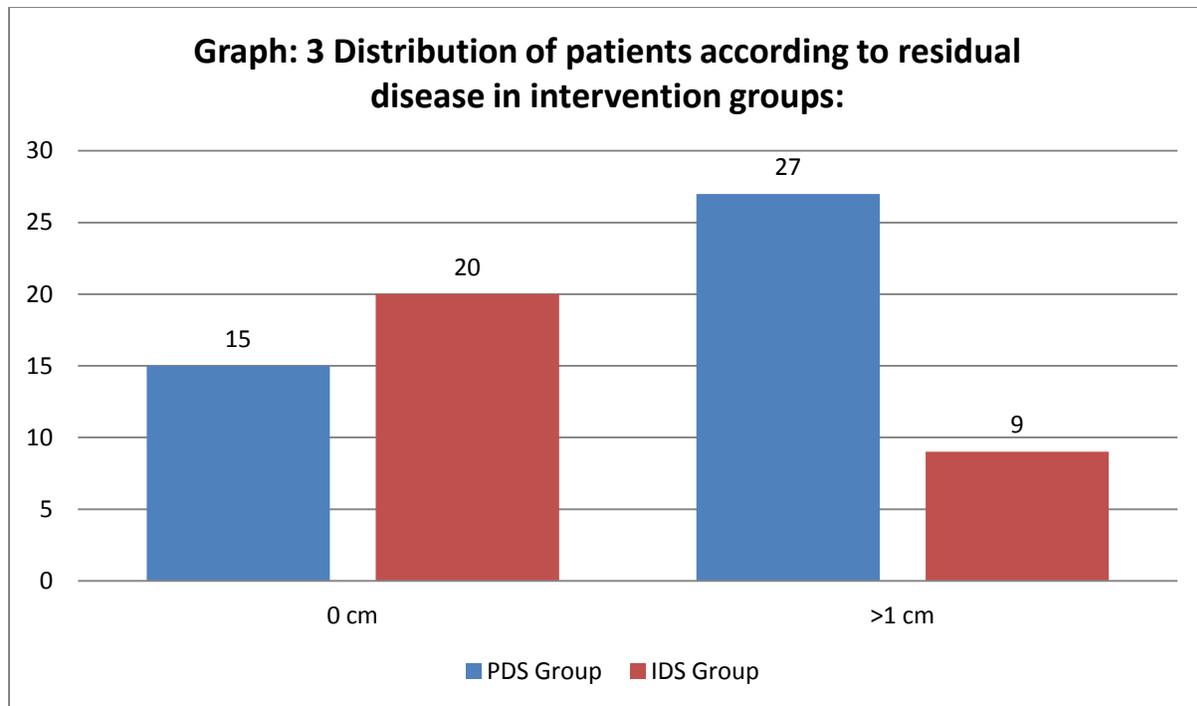


Table 4: Distribution of patients according to post-op complications in intervention groups:

Post-op complications		PDS Group	IDS Group	Total	χ^2 -value, p-value
Hospital stay	< 7 days	4	8	12	$\chi^2=3.985$ p=0.046*
	> 7 days	38	21	59	
Wound infection	Present	9	1	20	$\chi^2=7.697$ p=0.006*
	Absent	33	28	51	
Total		42	29	71 (100%)	

Table shows distribution of patients according to post-op complications in intervention groups. Hospital stay of < 7 days was required for 4 patients in PDS group and 8 patients in IDS group whereas >7 days was required for 38 patients in PDS group and 21 patients in IDS group and the difference was statistically significant (p<0.05). ICU stay of < 7 days was required for 25 patients in PDS group and 27 patients in IDS group whereas >7 days was required for 17 patients in PDS group as opposed to only 2 patients in IDS group and the difference was statistically significant (p<0.05). Wound infection was present in 17 patients in PDS group as opposed to only 3 patients in IDS group with statistically significant difference (p<0.05).

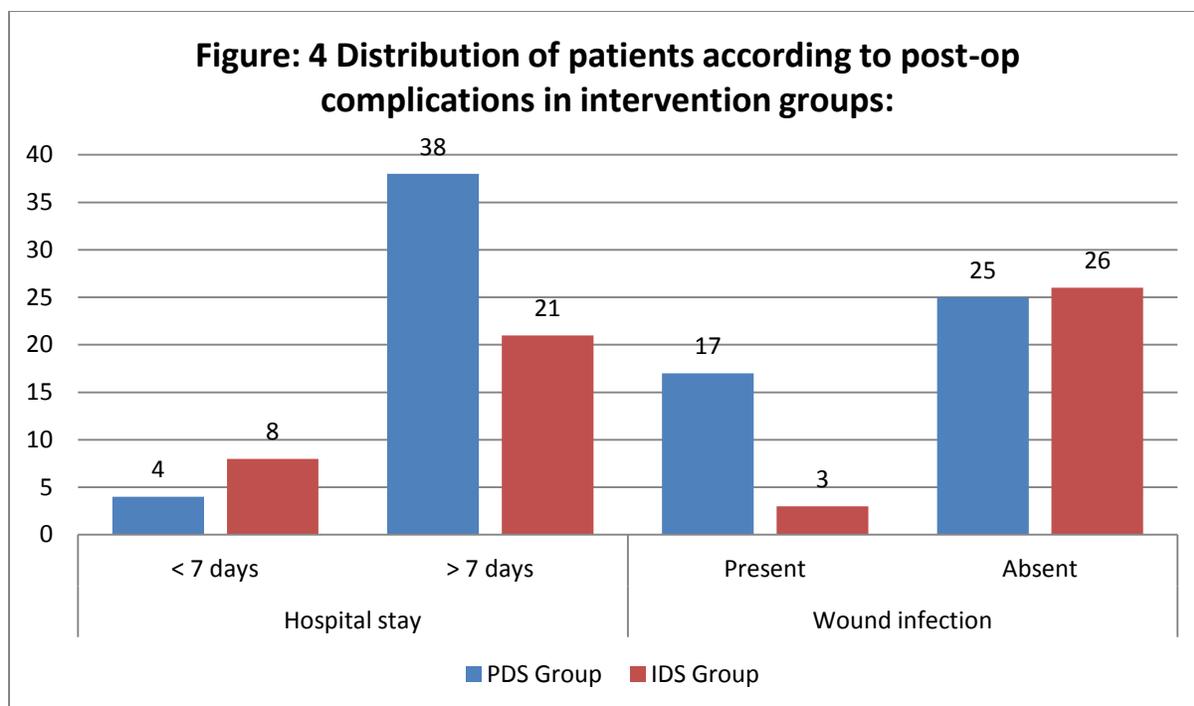


Table 5: Distribution of patients in according to on mortality in intervention groups

Mortality	PDS Group	IDS Group	Total	χ^2 -value, p-value
Alive	41	28	69	$\chi^2=0.071$ $p=0.789NS$
Death	1	1	2	
Total	42	29	71 (100%)	

Table shows distribution of patients in according to on mortality in intervention groups. There was mortality of 1 patient in each IDS and PDS group and remaining 41 and 28 patients were alive in PDS group and IDS group respectively with no statistically significant difference ($p>0.05$). In PDS group on day 6 post-operative day patient developed breathlessness and cardio pulmonary arrest followed by death. In IDS group the patient had severe anemia and hypertension and hyper thyroid comorbidities, after 1nd cycle of neoadjuvant chemotherapy patient developed breathlessness because of malignant ascites and malignant pleural effusion followed by death.

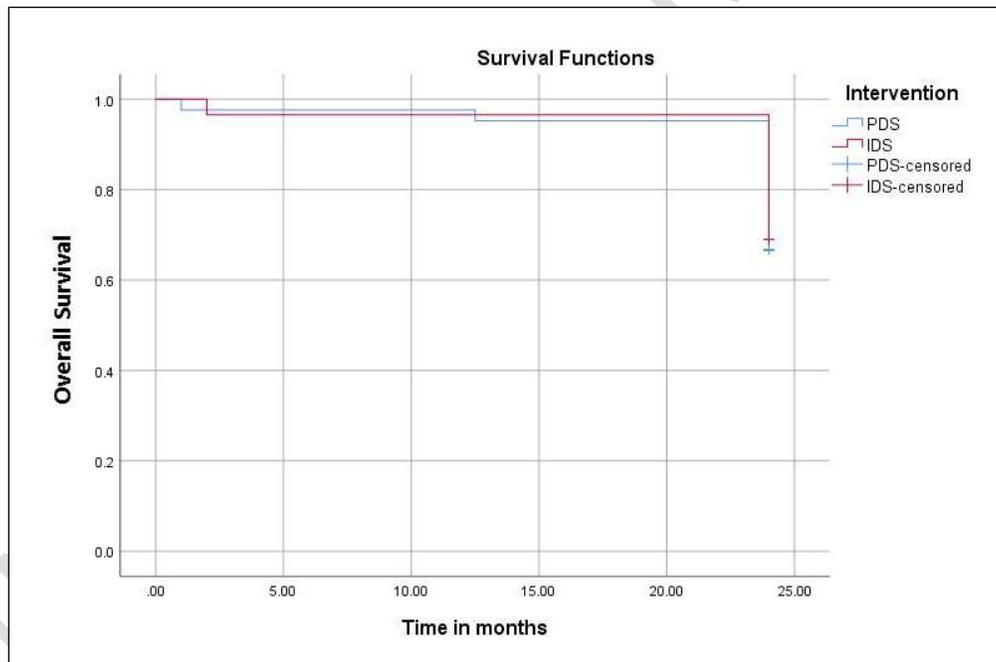
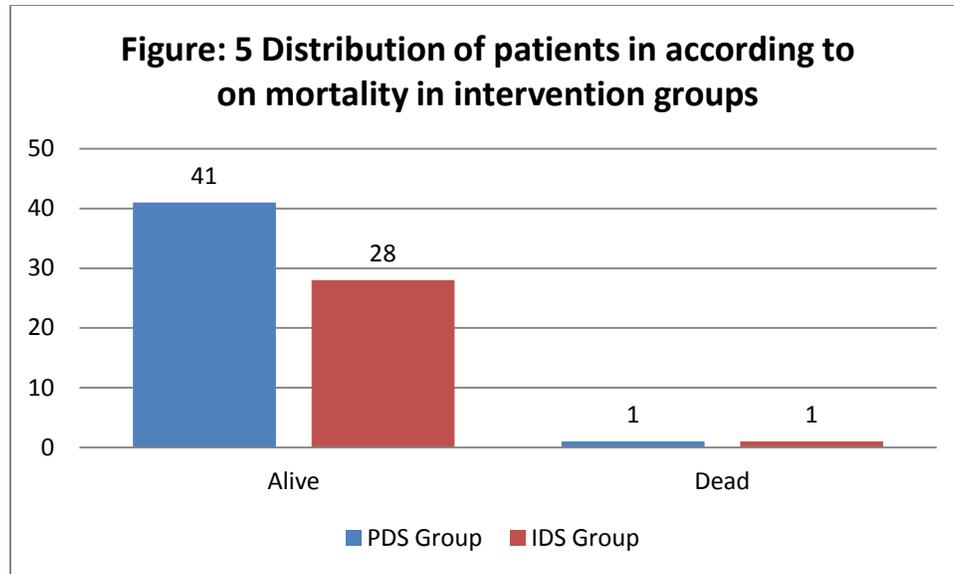


Figure 1: Overall survival corresponding to management received and status with respect to disease which is residual. This shows total survival according to management received and its status with respect to disease which is residual. The mean age of overall survival in PDS group is 23.179 months whereas in IDS group it was 23.241 in IDS group and the difference was statistically insignificant ($\chi^2=0.051$, $p=0.821$).

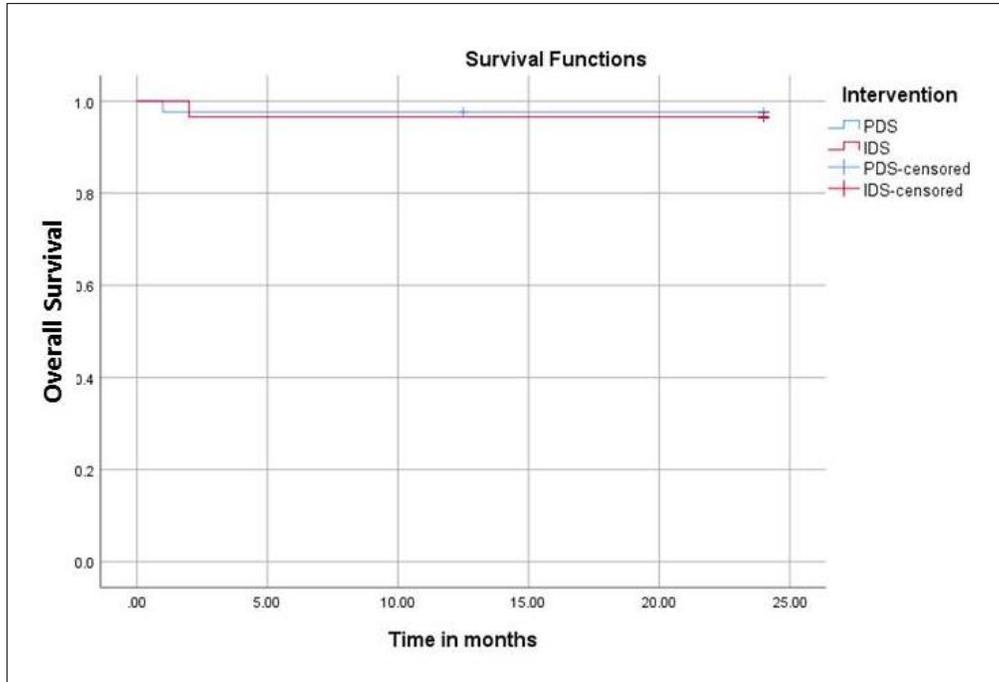


Figure 2: Total survival appropriate for management received and status with respect to mortality. This shows total survival according to management received and status with respect to mortality. The mean age of overall survival in PDS group is 23.452 month whereas in IDS group it was 23.241 in IDS group and the difference was statistically insignificant ($\chi^2=0.065$, $p=0.799$).

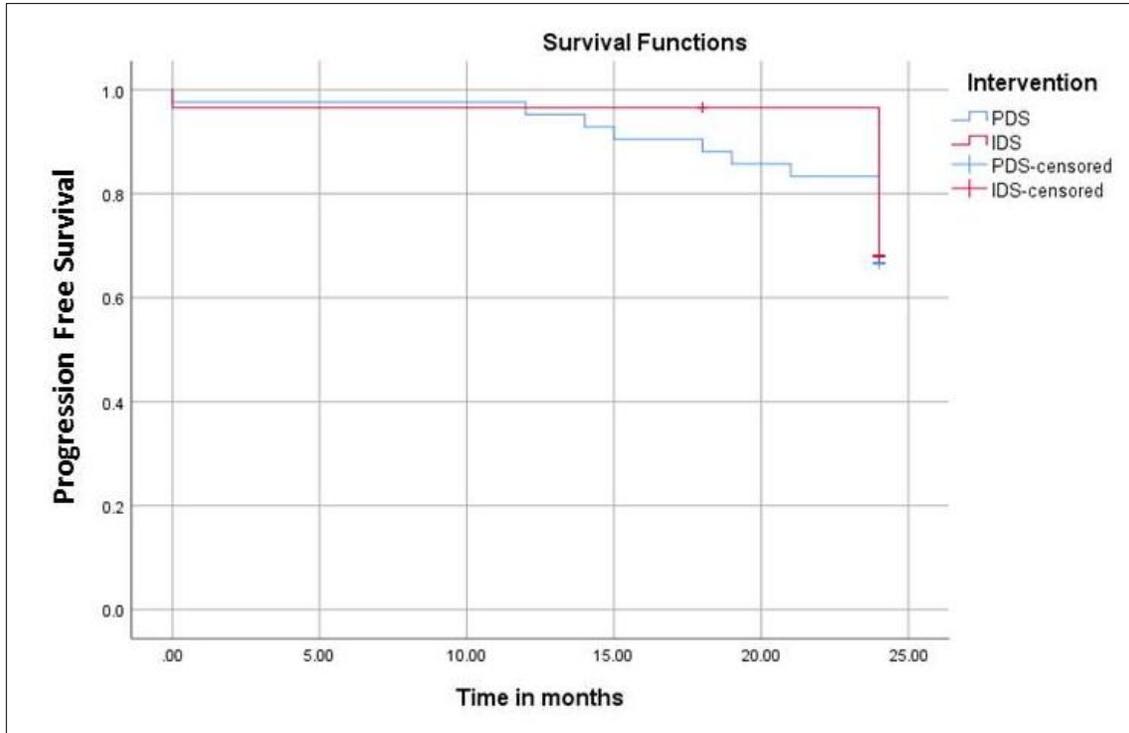


Figure 3: Progression free survival appropriate to management received and status with respect to disease which is residual.

Figure shows progression free survival appropriate to management received and status with respect to residual disease. The mean age of overall survival in PDS group is 22.357 months whereas in IDS group it was 23.172 in IDS group and the difference was statistically insignificant ($\chi^2=0.155$, $p=0.694$).

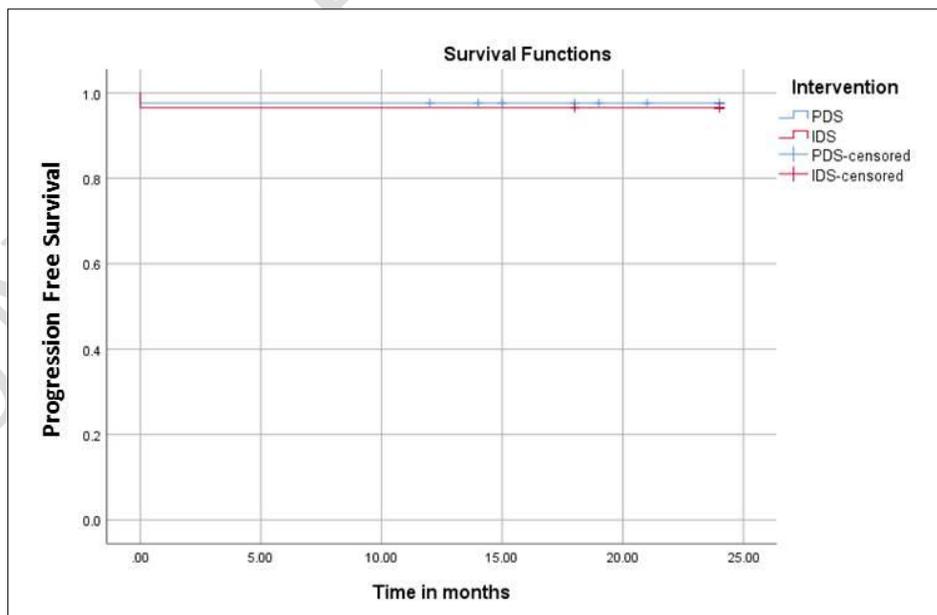


Figure 4: Survival which was not progressive according to management received and status with respect to mortality.

Figure shows survival not progressive according to treatment received and status with respect to mortality. The mean age of overall survival in PDS group is 23.429 months whereas in IDS group it was 23.172 in IDS group and the difference was statistically insignificant ($\chi^2=0.070$, $p=0.791$).

Discussion:

According to table 1 in our study the mean age of PDS group is 46.66 ± 13.49 years and mean age of IDS group is 60.06 ± 12.57 years. This conclusion coincides with study of **Gao et al** in 2019 who has revealed mean Age (years), in PDS as 55.99 ± 11.10 and in IDS as 57.08 ± 10.38 respectively (4). which was more compared to our study. **Gabriele Siesto, and Raffaele Cavina**, came to the conclusion in pds group the median Age (y) as 60.8 ± 10.7 and in IDS group as 63.2 ± 10.1 . According to above studies compared with our study we can conclude that the median age for PDS and IDS groups are 50 and 60 yrs respectively. Although the incidence of malignancy is higher after 40 years of age group, even in lower age group malignancy must be ruled out.

Even though NAC / IDS offers no survival advantage, this therapeutic approach provides favorable peri-operative morbidity. In our study, we observed that patients treated with NAC / IDS had less expected blood loss during surgery and faster recovery in terms of intestinal function and ambulation.

According to Table No.2.

In this observational study intra operative findings like blood transfusion, bowel and bladder injury, operating time are less in IDS group compare to PDS group with p value < 0.05 (bowel and bladder injury) Which coincides with the study conducted by **Hong zheng et al** in 2012, in which the following findings were less in NAC/IDS group than PDS group

1. minimal blood loss & transfusions intra-operative blood loss and blood transfusion,
2. less intubation rate,
3. early ambulation
4. early intestinal function improvement than the PDS group with statistical significance.
5. operating time (5).

Refky and Basel conducted a cohort study in 2018 in which intra operative findings like blood loss and urinary bladder injury and ureteric injury were compared to less in IDS group with p value 0.22 (blood loss) coincides with our study in which the p value of blood loss in PDS and IDS is 0.28. (6)

In our present observational study according to table no.3 post-operative complications like wound infection and prolonged hospital stay are less in IDS group compared to PDS group with statistically significant difference ($p=0.002$) & The patients who received with NAC/IDS had early ambulation and improved function of intestines. It coincides with a study conducted by **Ahmed et al in 2019**, post-operative complications was higher in PDS group than in NACT + IDS group. (7). Post-operative complications were low in IDS group that is 3.3% compared to PDS group in which post-operative complications were 16% Also hospital stay also prolonged in PDS

group than NACT/IDS with significant p value 0.003; complications like cardiac trauma, intestinal or urinary injury, wound gaping, post-operative ileus.

J.Y. Hou et al and others suggested in their study the IDS group had minimal percentage of wound infections, ICU stay, bladder injury (10%) and in PDS group it was (14.4%).

17 patients (27.8%) in the NAC had post-op complications other than SICU admissions, versus 37 patients (33.9%) in the PDS group (6).

In our study as per table no.4: out of 42 patients in PDS arm 15 patients are debulked optimally (residual disease=0 and <1cm) and 27 patients are debulked sub optimally (residual disease>1cm) and in IDS group 20 patients out of 29 patients are debulked optimally, and 9 patient is debulked sub optimally. Which is almost similar to study conducted by **Kobal et al** and others (7). who analysed in their study, and confirmed NACT + IDS had better result in term of median OS and PFS when compared to PDS..

In 2006 **Lee et al.**, conducted the efficiency of NAC. Total 40 patients were included in this study, 22 were treated with PDS and 18 with NAC-IDS. In 77.8% of the patients Optimal debulking surgery (R=0; R< 1cm) was possible in the NAC group which was 45.5% in the PDS group; The elevated rate of optimal cytoreduction is equivalent to the current study with minimal invasive surgery and decreased morbidity. (8). **Vergote et al** recruited 670 stage IIIC and IV FIGO patients randomly to these methods. They observed that 80.6 percent of patients had optimum cytoreduction with the largest residual tumour <1 cm after NAC-IDS, compared to PDS with 41.6 percent with the largest residual tumour < 1 cm. (9) similar to our study. The rate of complete residual disease was 45.5% in PDS vs 57.7% in NAC-IDS in The **SCORPION** (Surgical complications related to Primary or Interval debulking in Ovarian Neoplasm) trial published in 2016 (10).

In the present study, although residual tumor burden did not show a major result on 2- year survival, Progression free survival according to treatment received and condition with respect to residual disease shows The mean period of overall survival in PDS group is 22.357 months whereas in IDS group it was 23.172 and the difference was statistically insignificant ($\chi^2=0.155$, p=0.694). overall survival according to treatment received & presence of residual disease. The mean period of overall survival in PDS group is 23.179 months whereas in

IDS group it was 23.241 and the difference was statistically insignificant ($\chi^2=0.051$, p=0.821). Mortality in both groups PDS and IDS also similar (1 death in each group). In our study the overall survival in PDS group is 23.452 months whereas in IDS group it was 23.241 in IDS group and the difference was statistically insignificant ($\chi^2=0.065$, p=0.799). The mean age of overall survival in PDS group is 23.429 months whereas in IDS group it was 23.172 in IDS group and the difference was statistically insignificant ($\chi^2=0.070$, p=0.791).

Our study coincides with the study conducted by **Kobal et al** and others analysed in their study and stated that no significance was observed statistically in both PDS and NACT/IDS in terms of survival (7). **Shimoji et al** in which PFS and OS were similar in both PDS and IDS groups (11-14). Articles on recent advanced additive therapies have been reported (15-18).

Conclusion:

We conclude that the present study has explained that Neo adjuvant chemotherapy followed by interval debulking surgery in stage IIIc–IV ovarian, had similar overall and progression-free survival as primary debulking surgery followed by chemotherapy, with minimal peri-operative complications and less postoperative morbidity. In patients with non-optimally cytoreducible disease or low performance status, NAC / IDS is also a reasonably secure and may be an alternative method for achieving optimal cytoreduction.

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