TUMOR CLEARANCE IN ADVANCED OVARIAN CANCER WITH AND WITHOUT NEOADJUVANT CHEMOTHERAPY

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"TUMOR CLEARANCE IN ADVANCED OVARIAN CANCER WITH AND WITHOUT NEOADJUVANT CHEMOTHERAPY"** is the original work done by **Dr. V. CHITRA DEVI,** postgraduate in the Department of Obstetrics and Gynaecology, Institute of Social Obstetrics and Government Kasturiba Gandhi Hospital, Madras Medical College, Chennai to be submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai-600032, towards the partial fulfillment of the requirement for the award of M.D. Degree in Obstetrics and Gynaecology, March 2010. The period of study is from July 2008 to October 2009.

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Age	1. < 55 years 2. ≥ 55 years
Menopause	1. attained 2. not attained
Histology	1. Serous Papillary 2. Others
Ascities	1. ≥ 500 ml 2. < 500 ml
Residual Tumer volume	1. Optimal debulking 2. Sub Optimal debulking 3.Open and Close
Blood Transfusion	1. No transfusion 2. One Unit given 3. Two units given
Adhesions	1. Present 2. Absent
Injury to adjacent Structure	1. Present 2. Absent
HDU Stay	1. Present 2.Absent
Post op complications	1.Present 2. Absent
Duration of Hospital Stay	1. < 10 days 2. ≥ 10 days
PDS	Primary Debulking Surgery
NACT	Neoadjuvant Chemotherapy
IDS	Interval Debulking Surgery

CONTENTS

INTRODUCTION

Ovarian tumors are one of the most common gynecological malignancy in India. It is the leading cause of death from malignancies arising in female genital tract. Patients with ovarian tumors are often symptom free for a long time. By the time ovarian malignancy is diagnosed, about 2/3rd of these have already become far advanced and the prognosis in such cases is unfavourable.

Patients with advanced ovarian cancer should be treated by radical debulking surgery aiming at complete tumor resection. But 70% of the patients present with advanced disease optimal debulking cannot be obtained due to multifactorial reasons like biological aggressiveness of tumors, coexisting medical problem and experience of surgeon. Many trials proved that giving neoadjuvant chemotherapy and post chemotherapy debulking had significant improvement in progression free interval and overall survival. It also permits a less aggressive surgery to be performed.

Incidence:

Overall, Ovarian cancers account for 5% of all cancer diagnosis. The lifetime risk of ovarian cancer is approximately 1.7%. Vast majority of epithelial ovarian carcinoma diagnosed in postmenopausal women with median age of 63 years.

Incidence of ovarian cancer in India is 7/100,000.In India, ovarian cancer rank 6th most common cancer in women. The ovary after uterus is the second common site for development of gynaecological malignancy.

Pathogenesis:

Common epithelial tumours accounts for 80% of all ovarian neoplasm. The remaining tumours arise from ovarian germ cells or stromal cells. The epithelial tumours arise from surface epithelium or serosa of ovary. Serous carcinoma can resemble the fallopian tube, mucinous tumour the endocervix and endometroid carcinoma the endometrium. In majority of causes malignant epithelial ovarian tumours disseminate through out the peritoneal cavity after exfoliation of malignant cells from the surface of the ovary.

The typical circulation of peritoneal fluid along the under surface of the right hemidiaphragm facilitates the frequently observed pattern of wide spread dissemination of malignant cells within the peritoneal cavity. In addition omentum frequently attracts these malignant cells and is thus a common site of metastasis.

Tumour spread also occur via lymphatics from the ovary. A primary source of drainage follows the ovarian blood supply in the infundibulopelvic ligament to lymph node around the aorta and venacava to the level of renal vessel. There is also lymphatic drainage through the broad ligament and parametrial channels. Consequently pelvic side wall lymphatics including external ilac, obturator, hypogastric chains are also frequently involved. More rarely spread occur along the course of round ligament resulting in involvement of inguinal lymph node. Approximately 10% of patient with ovarian cancers that appears to be localised to the ovaries have metastasis to paraaortic lymph nodes.

There can also be direct extension from the ovary to involve adjacent peritoneal surfaces of the bladder, rectosigmoid and pelvic peritoneum.

Histological classification of ovarian tumour

1. Common epithelial tumours:

   · Serous tumours

   · Mucinous tumours

   · Endometrioid tumours

   · Clear cell(mesonephroid tumours)

   · Brenner tumours

   · Mixed epithelial tumours

   · Undiffentiated tumours

   · Unclassified epithelial tumours

11. Sex cord (gonadal stromal) tumours:

   · Granulosa-stromal cell tumours, theca cell tumours.

   · Androblastomas:Stertoli-leydig cell tumours.

   · Gynandroblastomas

   · Unclassified.

III. Lipoid cell tumours

1V. Germ cell tumours

- Dysgerminoma
- Endodermal sinus tumours
- Polyembryoma
- Choriocarcinoma
- Teratoma
- Mixed forms

V. Gonadoblastoma

- Pure
- Mixed with dysgerminoma or other germ cell tumour

VI. Soft tissue tumours not specific to ovary

VII. Unclassified tumours

VIII. Secondary (metastatic) tumours

IX. Tumour-like conditions.

Diagnosis and management:

Epithelial cancers of ovary has been described as silent killers because overwhelming majority of patients do not present with symptoms until disease has spread outside the ovary and indeed outside pelvis .However many studies surveying ovarian cancer patient have demonstrated that 95% of these women have non specific abdominal symptoms many months before diagnosis.

Approximately 70% of patients with epithelial ovarian cancers present with stage III or stage IV disease.

Abdominal discomfort and bloating are the most common symptoms experienced by women with epithelial ovarian cancers followed by vaginal bleeding, gastrointestinal symptoms, genitourinary symptoms.

Patients presenting with nonspecific lower abdominal discomfort and bloating require atleast prompt and careful evaluation of pelvic and recto vaginal examination.

The most common physical signs are ascites and pelvic mass

Level of cancer antigen (CA-125) tumour biomarker is elevated in more than 80% of serous epithelial tumours, but it can

also be elevated in variety of benign conditions and in other non-gynaecological malignancies.

Furthermore in early stage ovarian cancer, CA-125 levels are elevated in less than half of cases. Other markers such as CA-19-9 and carcinoembryonic antigen are less frequently used.

Pre operatively tumour marker levels are useful n predicting the possibility of malignancy. During treatment for ovarian carcinoma, CA-125 level is very useful parameter of disease activity and can also be used to follow response to treatment and to detect an early recurrence. Chest radiographs are routinely performed to look for malignant effusion.

Trans vaginal sonography and abdominal ultrasonography are the most useful diagnostic examination in the evaluation of pelvic mass because of their ability to accurately discern the ovarian morphology and pelvic pathology. Some sonographic characters associated with ovarian cancers include irregular ovarian border, solid elements within the cyst, papillary projection, bilateral ovarian enlargement and presence of ascites.

Colour Doppler imaging evaluates blood flow to an ovarian mass and identify a malignant process in the presence of abnormal vascularisation.

Cross sectional imaging such as computed tomography and magnetic resonance imaging may be helpful in characterising the liver, identifying lymph node involvement, peritoneal studding, omental caking and involvement of mesentery of the bowel.

The role of positron emission tomography in preoperative evaluation for suspected recurrent ovarian carcinoma is being studied in many centres.

Diagnostic laparoscopy may be extremely useful to evaluate unexplained pelvic pain or adnexal mass of uncertain pathology.

STAGING

Ovarian cancer staging is done surgically. Thus it is important for physician to be thoroughly familiar with the International Federation of Gynaecology and Obstetrics staging system for primary carcinoma of ovary.

Stage 1 Tumour restricted to one or both ovaries

1A Tumour restricted to one ovary.No tumour on external surface. Capsule intact. No malignant ascites.

1B Tumour limited to both ovaries. No tumour on external surface. Capsule intact. No malignant ascites.

1C Tumour 1A or 1B, positive for surface malignant growth, capsule ruptured, malignant ascites or positive washings.

Stage 11 Tumour involves one / both ovaries with pelvic extension

11A Extension / metastasis to uterus,or and tubes

11B Extension to other pelvic organs. No malignant cells in ascites or washings.

11 C Tumour 11A or 11B with surface growth, capsule ruptured at / or prior to surgery, malignant ascites or positive washings

Stage 111 Tumour involving one/ both ovaries with microscopic implants outside the pelvis and / or positive nodes (inguinal, retroperitoneal). Tumour limited to true pelvis but with histological evidence of spread to bowel, omentum, presence of superficial metastasis on the liver

111A Tumour grossly limited to the pelvis, nodes negative, but microscopic seeding of peritoneum of the abdominal wall

111B	Tumour with abdominal peritoneal implants of less than 2 cm size and nodes negative
111C	Abdominal implants of more than 2 cm size and / or positive nodes

Stage 1V Growth involving one or both ovaries with distant metastasis in liver, lungs and pleura

Complete surgical staging is a necessity to properly evaluate the patient and to determine whether additional therapy should be recommended.

Proper surgical staging requires thorough and complete inspection of the peritoneal cavity and its content as well as evaluation of the retroperitoneal space and lymph nodes. When the peritoneal cavity is entered, any fluid present should be aspirated and sent for cytological studies. Peritoneal fluid even if limited to the pelvis is more likely to yield malignant cells.

If no fluid is present, however one should routinely irrigate the pelvis and paracolic gutter and sent for cytologic examination. Adhesions should be lysed to restore normal anatomy and samples of adhesions should be sent for pathological examination.

If peritoneal carcinomatosis is not present, it may be most appropriate first to resect ovarian tumour and then to proceed with surgical staging to help avoid rupturing of the mass.

For women who desire future fertility when the tumour is limited to one ovary, staging may be completed without hysterectomy and complete castraction. The grossly normal opposite ovary may undergo biopsy, any visible benign appearing cyst may be excised. Preservation of fertility should be considered in any women of reproductive age with either borderline malignant tumour of the ovary or invasive epithelial cancer grossly confined to one ovary.

To fully assess and resect disease in the upper abdomen, it is frequently necessary to extend the vertical incision above the umbilicus.If gross disease is not present in the omentum, an infracolic omentectomy is sufficient for diagnostic purpose.

When omentum is caked with tumour, omentum should be excised from the greater curvature of the stomach. Right hemidiaphragm, liver, serosa and parenchyma, spleen, left hemidiaphragm are carefully inspected.

The paracolic gutter space, large bowel, small bowel and mesentery are evaluated any implants present are removed. If tumour is involving small or large bowel transluminally, resection and reanastomosis should be performed.

In postmenopausal women, one should perform Bilateral Salpingo-oopherectomy and Total Abdominal Hysterectomy at the time of staging. Hysterectomy is performed because the serosal surface of the uterus is large peritoneal surface for implantation of malignant cells.

PROGNOSTIC FACTORS

At the conclusion of comprehensive laparotomy, the following clinical and pathological findings are used to assess prognosis and to select appropriate postoperative therapy.

Clinicopathological prognostic parameters

1. FIGO Staging
2. Histological sub-type
3. Histologocal grade
4. Factors associated with dissemination
5. Malignant ascites or malignant peritoneal washings
6. Tumor excrescences on ovarian surface or ruptured capsule

7. Volume of residual tumour after cytoreductive surgery

5 YEARS SURVIVAL RATE

1. Stage 1 – 76 to 93%
2. Stage 11 – 60 to 74%
3. Stage 111A – 41%

   111 B – 25%

   111 C – 23%
4. Stage 1V – 11%

TREATMENT OF ADVANCED OVARIAN CANCER:

The recommended treatment for patients with advanced stage ovarian cancer (111, 1V) is optimal cytoreductive surgery to remove all visible tumour followed by Platinum and Taxane based chemotherapy. Patients with advanced stage disease present in a malnourished performance status. Aggressive debulking surgery may not be well tolerated. They are potential high post operative morbidity and mortality. Post operative complications can delay in starting adjuvant chemotherapy. Giving neo adjuvant chemotherapy

in these patients prior to surgery produces reduction in tumour volume, allow a less extensive surgery, hence decreasing perioperative morbidity, finally improving better prognosis and survival.

PRIMARY CYTOREDUCTIVE SURGERY (DEBULKING)

Standard treatment of advanced ovarian carcinoma includes primary cytoreductive surgery followed by chemotherapy.

Primary cytoreductive surgery represents the cornerstone in the treatment of ovarian cancer. It aims at removing as much primary and metastatic disease as possible, in order to facilitate response to subsequent chemotherapy and to improve survival.

Debulking surgery includes Total Abdominal Hysterectomy with Bilateral and Salpingo-Oopherectomy and Omentectomy with or without lymphadenectomy. The definition of optimal cytoreduction has been changed many times in the last 20 years from a residual mass of 2 cm to complete absence of residual tumour.

Despite the controversies in the definition of optimal cytoreduction all investigators do agree that who fails to undergo optimal debulking have poorer prognosis.

Patients with extensive metastatic disease before cytoreduction or with clinically evident ascites had poor prognosis even if the patient was cytoreduced to an optimal status.

Complications of Primary cytoreductive surgery

1. Wound infection / Dehiscence
2. Cardiac failure
3. Deep vein thrombosis
4. Pulmonary embolism
5. Genitourinary fistula
6. Relaparotomy for bleeding
7. Small bowel obstruction
8. Cerebrovascular disease
9. Operative mortality

INTERVAL DEBULKING SURGERY

Interval debulking surgery is a cytoreductive surgery following induction chemotherapy (neoadjuvant chemotherapy). Procedure done here is same as primary cytoreductive surgery.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy represents any cytototoxic drug given prior to surgery. Drug is admistered soon after histological confirmation of ovarian cancer.

Treating the patients prior to surgery has three theoretical advantages :

1. Patients performance status is improved prior to surgery owing to reduction in tumour volume, ascites and pleural effusion and improvement in oral intake.

2. Reduction in tumour volume may allow a less extensive surgery, hence decreasing perioperative morbitity

3. Finally surgical reduction may be improved which inturn leads to better prognosis and survival.

CHEMOTHERAPEUTIC DRUGS:

Advanced stage ovarian epithelial cancers is a chemoresoponsive tumour. Platinum compounds remain the single most active drug in the management of this disease.

PLATINUM COMPOUNDS:

Cisplatin is hydrolysed intracellularly to produce a highly active moiety which causes cross linking of DNA. It is highly emetic. It causes damage to kidneys,vestibulo cochlear apparatus and peripheral nerve. Antiemetic drugs are routinely administered before infusing it. Renal toxicity can be reduced by maintaining good hydration.

Carboplatin is a second generation platinum compound with less toxic effects. Nephrotoxicity. ototoxicity, neurotoxicity are low. Thrombocytopenia is the dose limiting toxicity

ALKYLATING AGENTS

These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. Alkylation results in cross linking of abnormal base paring of DNA strand.

Cyclophosphamide is transformed into active metamobolites in liver (aldophosphamide, phosphoramine mustard). Alopecia and haemorrhagic cystitis are the prominent side effects

Ifophamide, thiotepa are the other alkylating agent used in ovarian cancer.

TAXANES:

Paclitaxel is a complex diterpin taxane. It enhances polymerization of tubulin , abnormal microtubules are produced throughout the cell cycle.

Myelosuppression, glove and stocking neuropathy are the commonest side effects. Toxicity is reversible. It is dose dependent.

Docetaxel is another Taxane group of drug. Major toxicity is Neutropenia.

ANTITUMOR ANTIMETABOLITES:

It intercalates between DNA strands interfering with its template function. Drugs used in this group are Doxorubicin and Mitoxantrane. The side effects are cardiomyopathy, bone marrow depression.

STANDARD CHEMOTHERAPY REGIMENS:

1.	CISPLATIN	75 mg / m 2
	CYCLOPHOSPHAMIDE	750 mg / m2
2.	CISPLATIN	75 mg / m2
	PACLITAXEL	135 mg /m2
3.	CARBOPLATIN - AUC	5-6
	PACLITAXEL	175 mg / m 2

REVIEW OF LITERATURE

Neoadjuvant Chemotherapy was originally introduced in the year 1969 for patients with advanced stage ovarian cancer and were medically disabled. Over the ensuing decade reasonable experience was obtained suggesting that patients who were medically unable to tolerate aggressive cytoreductive surgery at the time of their initial presentation, but who received chemotherapy and then were able to undergo cytoreductive surgery, had a survival that was quite similar to those patients who initially had large volume disease present in the upper abdomen or Stage IV disease. A decade later, neoadjuvant chemotherapy followed by aggressive surgery was introduced for patients who are not medically compromised but who, by CT scan criteria, appeared to have disease that was not surgically cytoreducible.Basically, patients with disease >2 cm in diameter in the upper abdomen that involved coating the diaphragm and was confluence with implants in the liver serosa, Omentum replaced by tumor with the tumor in the omentum reaching the hilum of spleen, porta hepatis metastasis, enlarged (<2 cm) supra-renal para aortic lymph nodes and disease in the thorax were indications to recommend neoadjuvant chemotherapy as these preoperative CT findings were usually

associated with extensive upper abdominal metastasis that could not be optimally cytoreduced.

SVS. Duo et al (India) conducted a retrospective analysis of 82 patients with advanced Ovarian cancers (Stage III & IV) who were treated with NACT followed by surgical cytoreduction between 1995 and 2004.There were 59 patients (72%) with Stage III C and 23 patients (28%) with Stage IV disease with a mean age of 49.9 years. 27 (32.9%) were premenopausal while the rest were postmenopausal.

The median duration of symptoms was 3 months. Optimal cytoreduction achieved in 59 out of 82 patients (72%). In 15 patients (18.2%) had sub-optimal cytoreduction and in 8 patients (9.8%) exploratory laparotomy and closure was performed in view of frozen pelvis. Gut resection was required only in 6 patients (7.3%) (small bowel -3,large bowel-3). Mean hospital stay was 4 days (Range 2-30 days).Post-operative complications occurred in 4 patients (4.9%) in the form of wound infection in 3 and pancreatic fistula in one patient, 5 year survival rate was 32%.

He concluded that a significant number of patients respond to NACT leading to higher optimal cytoreduction which may result in improved survival.[1]

Schim uzu et al conducted a comparative study in the year 1993 with 138 patients with stage III and 21 with Satge IV malignant Ovarian tumor registered during 1969 -1991. 77 patients deemed resectable received primary debulking followed by post-operative chemotherapy. 74 patients received NACT and the remaining 8 did not receive planned NACT, because of their poor performance status.Among the 74 patients receiving NACT 34 (46%) had optimal debulking. 35 patients among the post –op chemotherapy group out of 165 achieved optimal debulking (21%). He concluded that optimal debulking is significantly more in NACT. [2]

P Hicher et al, M Mahnar et al studied early response criteria and surgical outcome in patients with advanced epithelial cancer treated with NACT. Response was monitored by measuring target lesions, ascitic fluidvolume, CA 125 levels. The primary outcome measure was the preoperative reduction of ascitic fluid volume, CA 125 level. Secondary outcome measures were the evaluation of residual tumor and perioperative morbidity and mortality. Any amout of residual disease after cytoreductive surgery, persistant ascities, less pronounced decrease of CA 125 were associated with poor progression free survival rate. In conclusion he found ascitic

fluid volume reduction and CA 125 decline appeared to be appropriate response criteria.[27]

Tate et al in the year 2005 studied associations of CA 125 regression rate with initial responses to chemotherapy and prognosis. He found out that based on CA 125 regression rate it is possible to stratify TIII C or M1 Ovarian serous adenocarcinoma cases into those with a good prognosis of survival and those with poor prognosis. Regression coefficient of CA125 level greater than -0.039 predicts good 3 year survival after subsequent radical surgeries.[3]

Goto et al, Takeno M et al investigated P16INK4a expression by immunocytochemistry for ascites in advanced ovarian cancer. The possibility to predict chemotherapeutic response and prognosis. The immunocytochemical study was performed on cytology of ascites obtained from 37 Stage III or stage IV ovarian cancer with measurable disease before Platinum/Taxane based first line chemotherapy following primary cytoreductive surgery or NACT. 21 of 21 responder (100%) and 6 of 16 (44%) non responder showed P16INK4a immunopositivity. Their data suggest that P16INK4a expression of cytology in ascites is a candidate marker in prediction of primary response to chemotherapy and prognosis.[4]

Safra et al, Menezer et al evaluated safety and outcome of weekly Carboplatin and Paclitaxel as initial post-op chemotherapy for epithelial ovarian cancer. Intravenous Carboplatin AUC=2 and Paclitaxel 80 mg/m2 were administered on days 1,8 and 15th of a 28 day cycle for 6-8 cycles. Study results are: 64 women were enrolled with an median age of 65 years. 56 of them (87.6%) were diagnosed with stage III & IV. Neutropenia was the most common hematological toxicity. 25% of subjects had grade III to IV neutropenia. 89 % of the patients had Grade I alopecia and 7.1% had Grade II alopecia,7.8% had grade III fatigue ,3.1%had Grade III neuropathy. Median progression free survival was 25.74 months. They concluded that weekly Carboplatin and Paclitaxel is a initial Chemotherapy for epithelial Ovarian cancer is a feasible and well tolerated regimen and should be evaluated in a larger phase III study.[5]

Vergote et al, De wever et al conducted a study in the year 1998 found out that if total metastatic load was more than 1000gms prior to debulking surgery had poor survival despite cytoreduction to no or less than 1 gm of total residual tumor load.[7]

Giannopoulos et al conducted a non randomized prospective cohort study of 35 patients who underwent IDS and 29 patients

treated with PDS were included. All patients had Stage III C or IV based on pre-operative computed tomography findings or laparascopy. All patients were operated by the same lead surgeons and received same regimen of chemotherapy. Median intraoperative blood loss, the incidence of pelvic lymphadenectomies, median hospital stay and the possibility of admission to intensive care unit were significantly less in IDS group . He concluded that IDS for advanced ovarian cancer may be associated with less morbidity compared to PDS and appears to require less hospital resources.[8]

Houjy et al compared the survival and perioperative morbidities of patients with advanced ovarian cancer treated by NACT followed IDS or primary cytoreductive surgery followed by adjuvant chemotherapy. He found NACT patients had significantly less intraoperative blood loss,operative time,unit of blood transfusion and shorter hospital stay.Optimal cytoreduction was achieved in 95% of NACT patients.[9]

Kang et al,Nam BH et al analysed (meta analysis) 21 studies regarding neoadjuvant chemotherapy in advanced ovarian epithelial cancer to determine whether NACT can improve the rate of optimal cytoreduction. Metaanalysis showed that NACT helped gynaec oncologists achieve an increased rate of optimal cytoreduction.[10]

Chan YM et al studied quality of life with advanced ovarian cancer treated with NACT. Patients QOL studied over time using European organization for research and treatment of cancer ,QOL quiessionaire c30 and compared with that of patients treated with conventional treatment. Conclusion in the study was QOL and functional status improved after NACT.[12]

Tangjitgamol et al assessed the effectiveness and complication of IDS in patients with advanced stage ovarian cancer. They searched the Cochrane central register of controlled trials (central), (The Cochrane Library, issue 2,2008), MEDLINE (jan 1966 to june 2008), EMBASE (jan 1966 to june 2008) and reference lists of included studies. Two review authors independently assessed trial and extracted data. Searches for additional information from study were attempted. Metaanalysis of overall and progression free survival was performed using fixed effects models. No conclusive evidence was found to determine whether IDS between cycles of chemotherapy would improve or decrease survival rates of woman with advanced ovarian cancer compared with conventional treatment. IDS appeared to yield benefit only in the patients whose primary surgery was not performed by gynaec oncologists or less extensive.[11]

Le T et al 61 patients who have undergone IDS following NACT.All surgeries performed after 3 cycles of Platinum / Taxol combination chemotherapy.80% had a residual disease status of 2cm or less after surgery. Suboptimal debulking was statistically associated with tumour involvement of upper abdominal organs and non –normalisation CA -125 before surgery. The cox regression modelling identified the microscopic tumour residual status as the only significant predictor of progression free interval. The estimated mean survival for the group was 41.7 months. NACT with IDS appeared safe and feasible in patients with metastatic disease.[15]

Suprasert et al reviewed 29 patients retrospectively who have undergone IDS following NACT. Most had stage 3c serous cystadenoma carcinoma. Progression free overall survival was 25%. Multivariate analysis showed that a suboptimal residual tumour volume was statistically significant adverse prognostic factor for overall survival. In conclusion, IDS and NACT before cytoreductive surgery lead to a more favorable outcome with advanced epithelial cancer.[26]

AIM OF THE STUDY

The Aim is to study the tumor clearance effect of neoadjuvant chemotherapy in advanced ovarian tumor in terms of optimal debulking, ascitic fluid volume reduction,blood transfusion requirements and to compare it with those who have not received neoadjuvant chemotherapy

STUDY

Prospective study

SETTING

Patients with advanced ovarian tumor admitted in Institute of Social Obstetrics, Triplicane, Chennai-5 from July 2008 to Dec 2009 were included in the study.

MATERIALS

INCLUSION CRITERIA

- Patients with advanced epithelial ovarian tumor (stage 3 & 4).
- No previous Chemotherapy.
- No Previous Surgery for the same complaint.
- Willing to take neoadjuvant Chemotherapy and then follow it up with surgery.

EXCLUSION CRITERIA

- Early stage epithelial ovarian tumor (Stage 1 & 2).
- Borderline tumor.
- Non-epithelial ovarian tumor.
- Those who were treated with some form of Oncotherapy.
- Not willing to wait for surgery following CT.

METHODOLOGY

All patients enrolled in the study will undergo detailed physical examination, routine hematological, biochemical investigations, Ultrasound and CT Scan.

For those patients with ascites, ascitic fluid sent for cytology.

If Cytology report cofirms that it is Epithelial ovarian tumor. Patient receives Neoadjuvant chemotherapy of Cisplatin 75mg/sq. m, Cyclophosphamide 750mg/sq. m for 3 cycles – 6 weeks

After 6 weeks, undergo interval debulking surgery

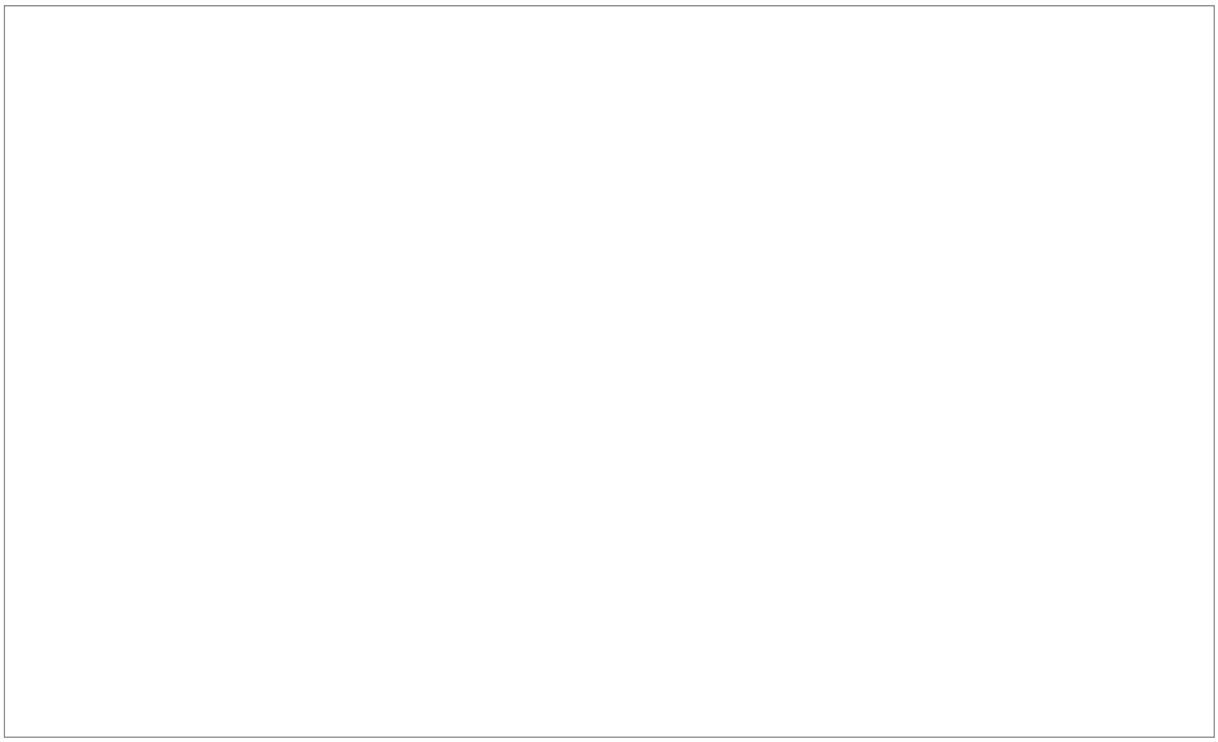
Optimal Debulking,Ascitic fluid volume,Blood transfusion rate are compared with the control group.

Control group in this study will be those patients with advanced epithelial tumor who have not received neoadjuvant chemotherapy and undergone primary cytoreductive surgery in the past in Institute of Social Obstetrics, Triplicane, Chennai – 5

The results were analysed using Chi-Square tests.

AGE

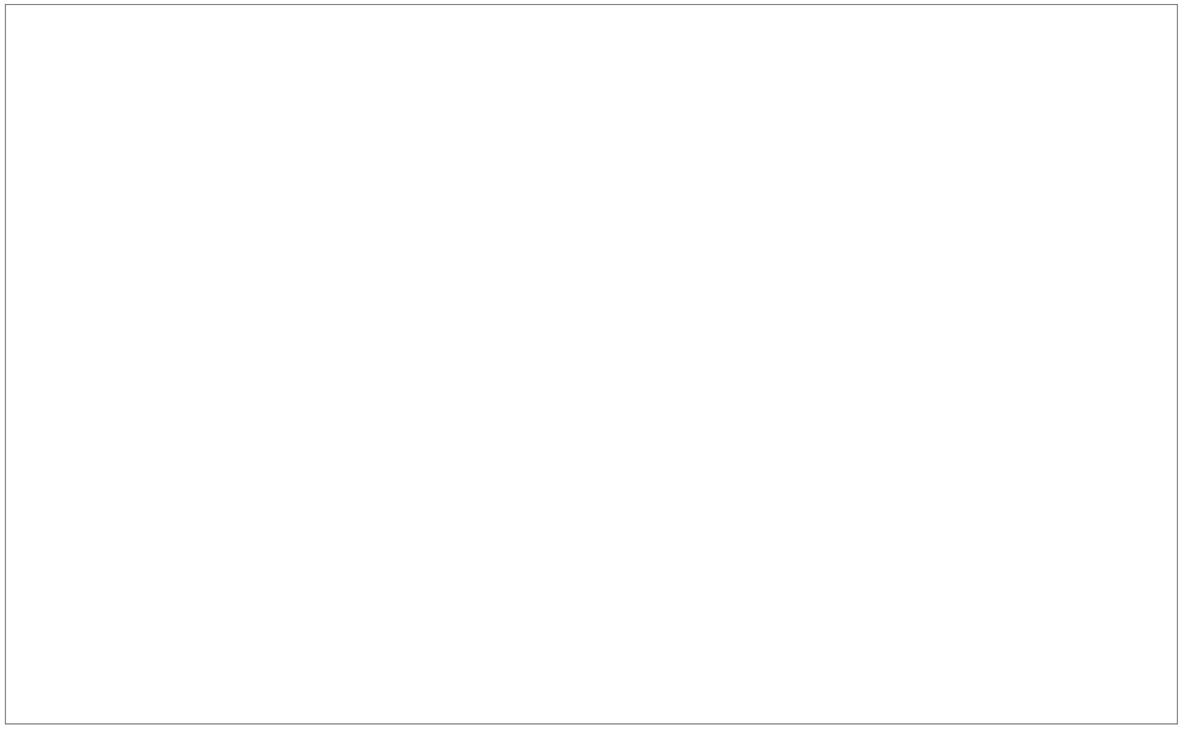
Age	PDS	NACT / IDS	Percentage
<55 yrs	8	12	40%
> 55 yrs	17	13	60%



MENOPAUSAL STATUS

Menopause	PDS	NACT / IDS	Percentage
Attained	21	23	88%
Not attained	4	2	12%

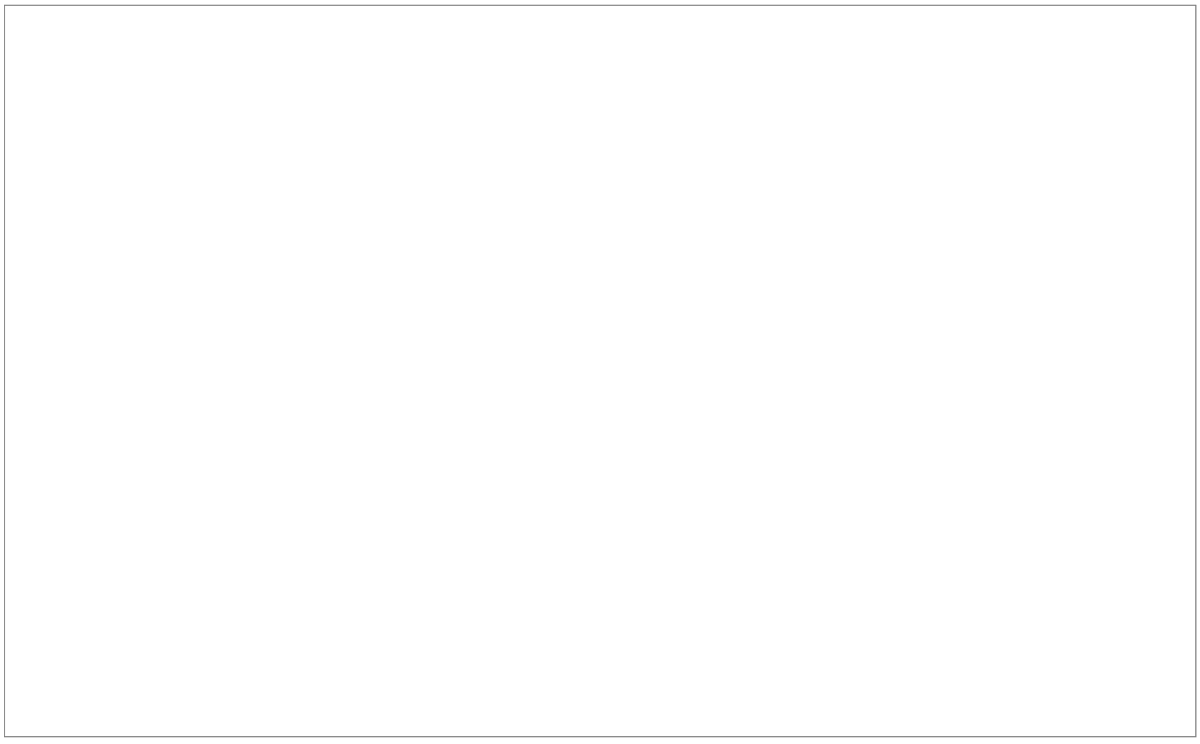
MENOPAUSAL STATUS



HISTOLOGICAL DIAGNOSIS

Histological Diagnosis	PDS	NACT / IDS	Percentage
Serous Papillary	21	24	90%
Others	4	1	10%

HISTOLOGICAL DIAGNOSIS

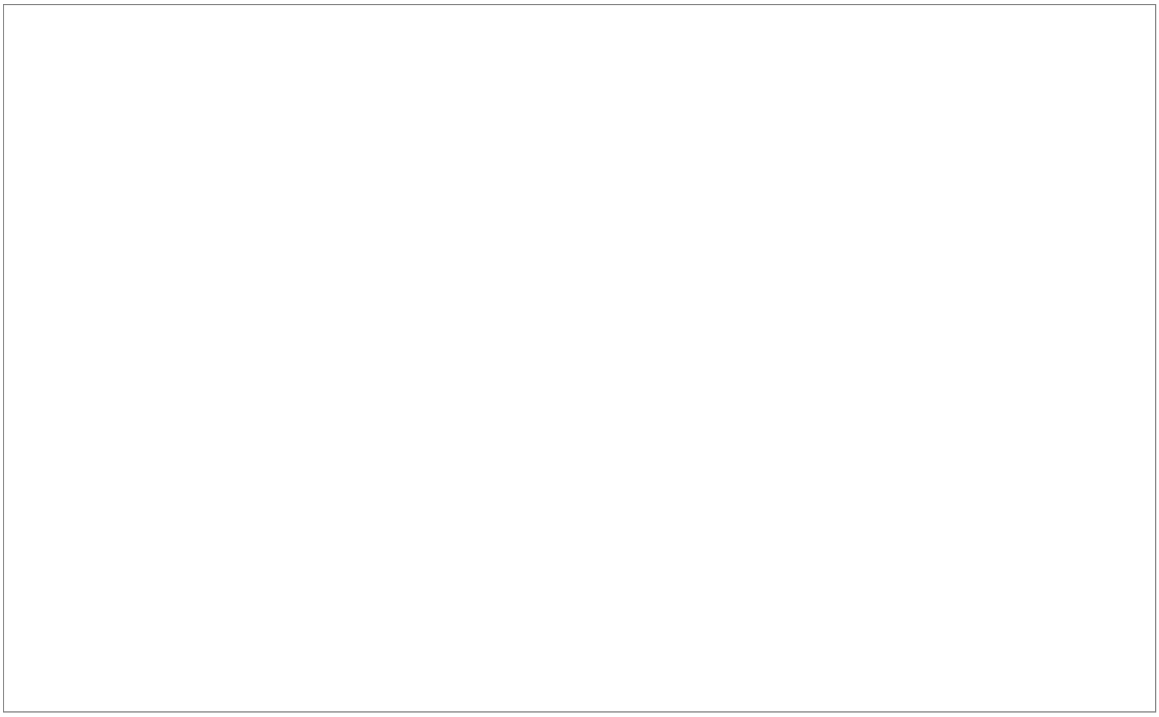


ASCITES

Ascites	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
>500 ml	21	84%	5	20%
< 500 ml	4	16%	20	80%

P Value: 0.000

ASCITES

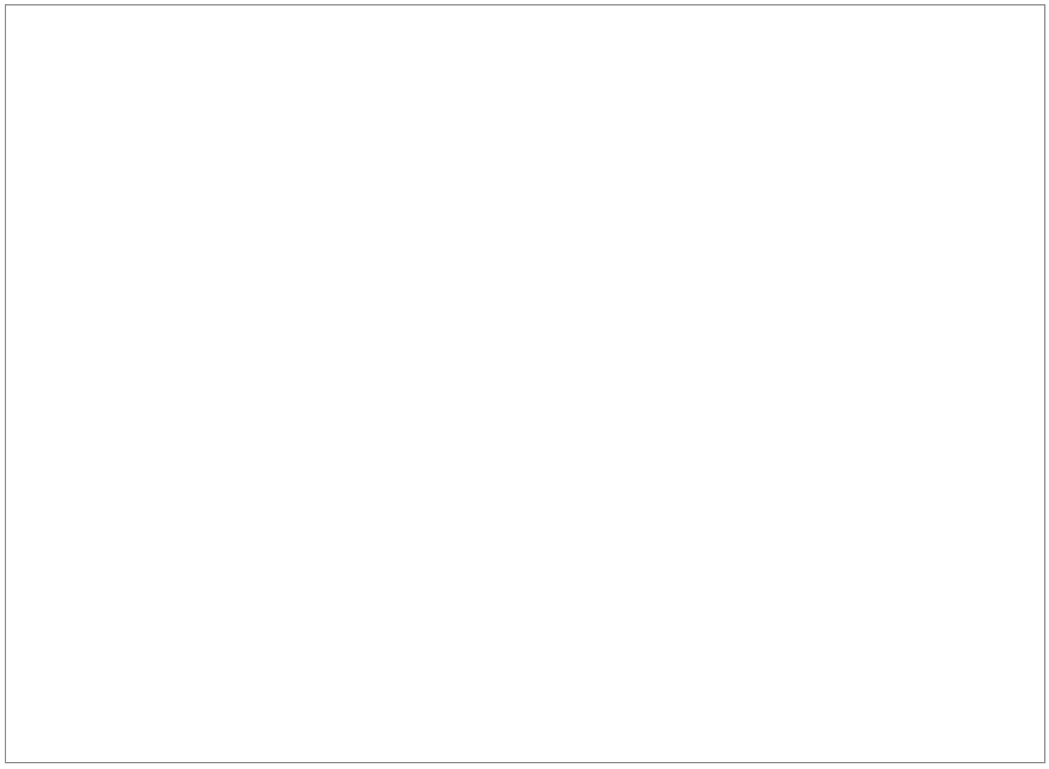


RESIDUAL TUMOUR VOLUME

Residual Tumour Volume	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
Optimal debulking	7	28%	19	76%
Sub optimal debulking	12	48%	4	16%
Open and close	6	24%	2	8%

P Value: 0.002

RESIDUAL TUMOUR VOLUME

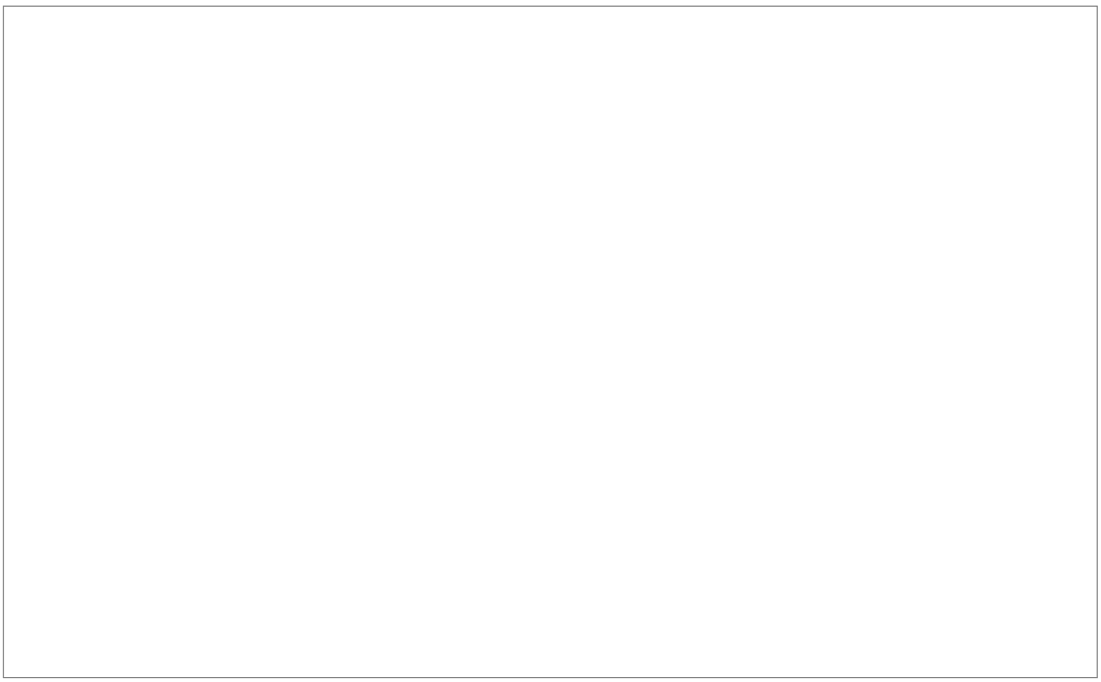


BLOOD TRANSFUSION

Blood Transfusion	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
No Transfusion	6	24%	19	76%
≥ 1 unit transfusion	19	76%	6	24%

P Value: 0.000

BLOOD TRANSFUSION

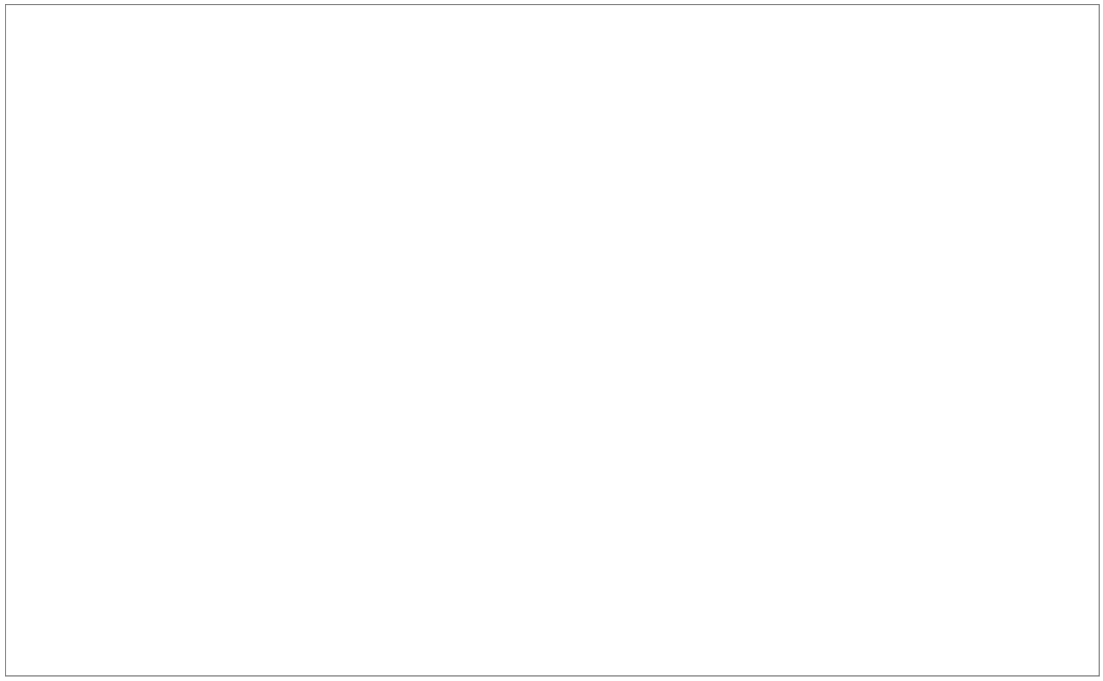


ADHESIONS

Adhesions	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
Present	19	76%	6	24%
Absent	6	24%	19	76%

P Value: 0.000

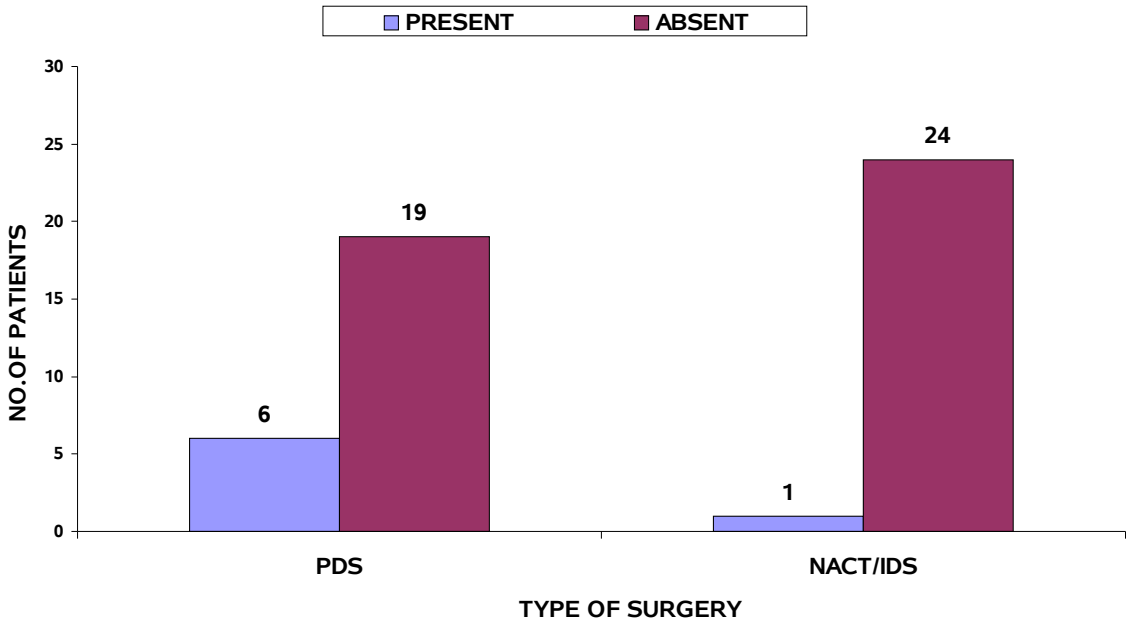
ADHESIONS



INJURY TO ADJACENT STRUCTURES

Injury to Adjacent Structures	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
Present	6	24%	1	4%
Absent	19	76%	24	96%

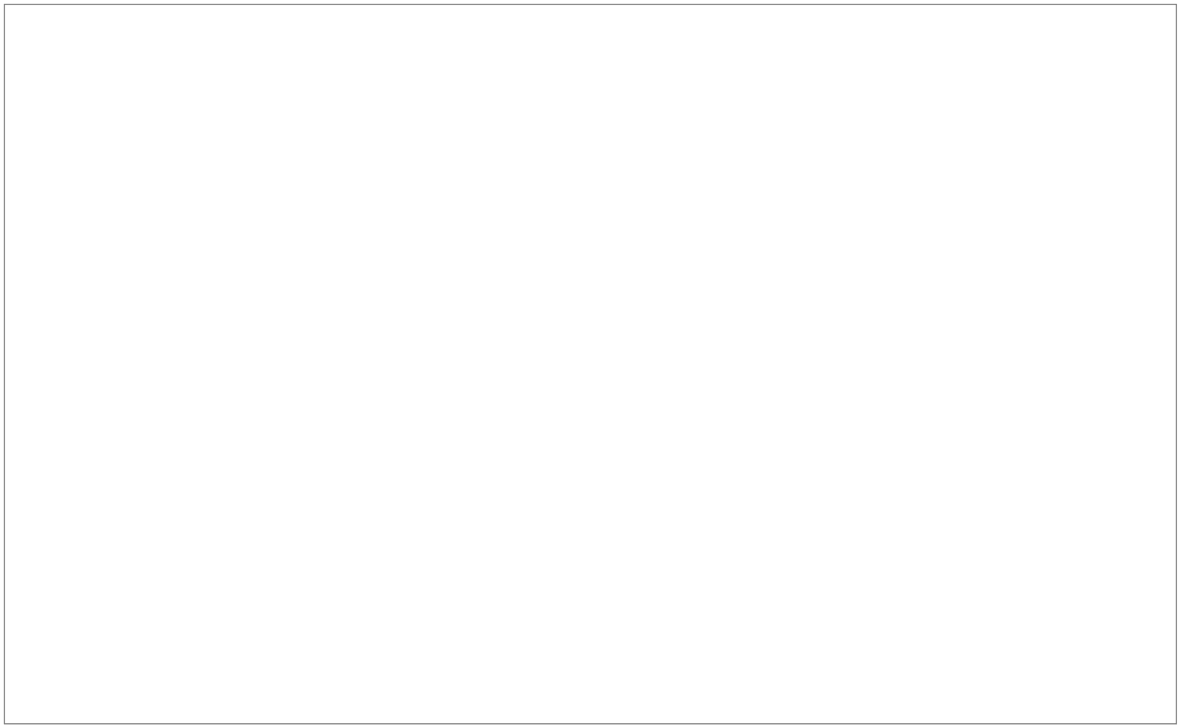
INJURY TO ADJACENT STRUCTURES



HDU STAY

HDU Stay	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
Present	12	48%	6	24%
Absent	13	52%	19	76%

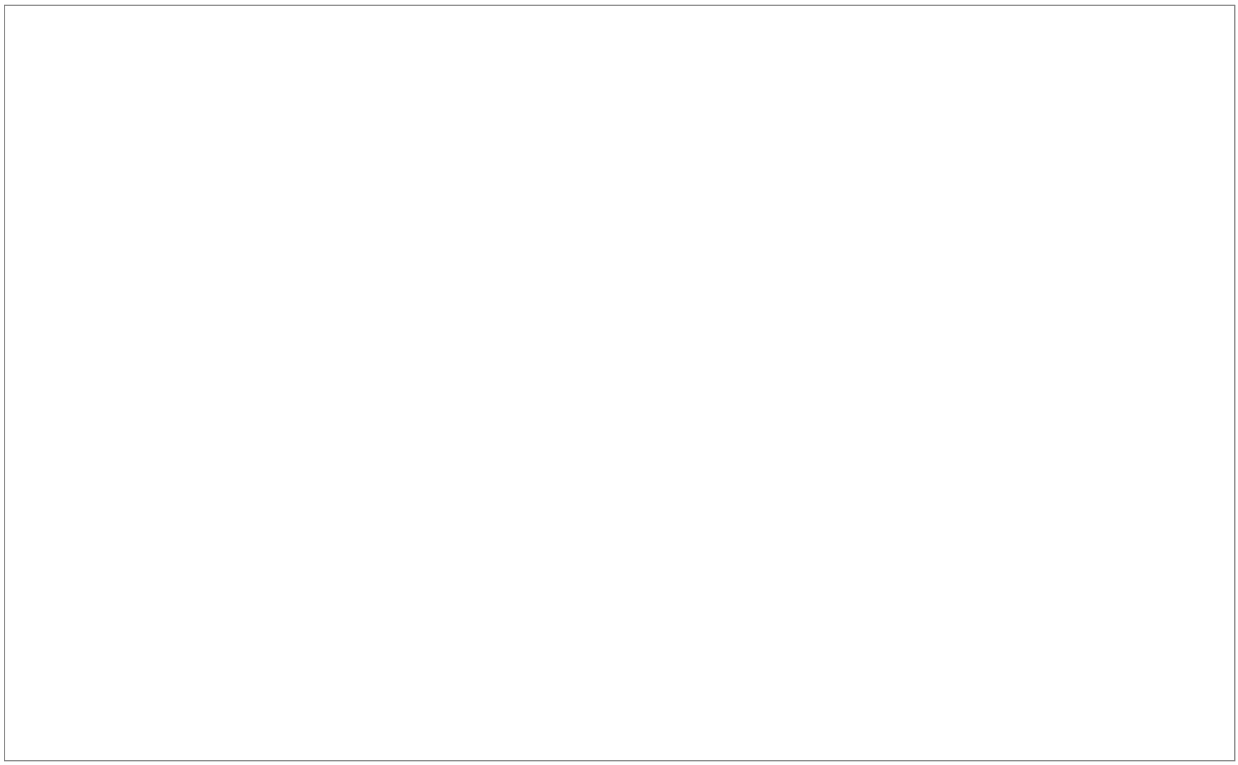
HDU STAY



POST OPERATIVE COMPLICATIONS

Post Operative Complications	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
Present	8	32%	3	12%
Absent	17	68%	22	88%

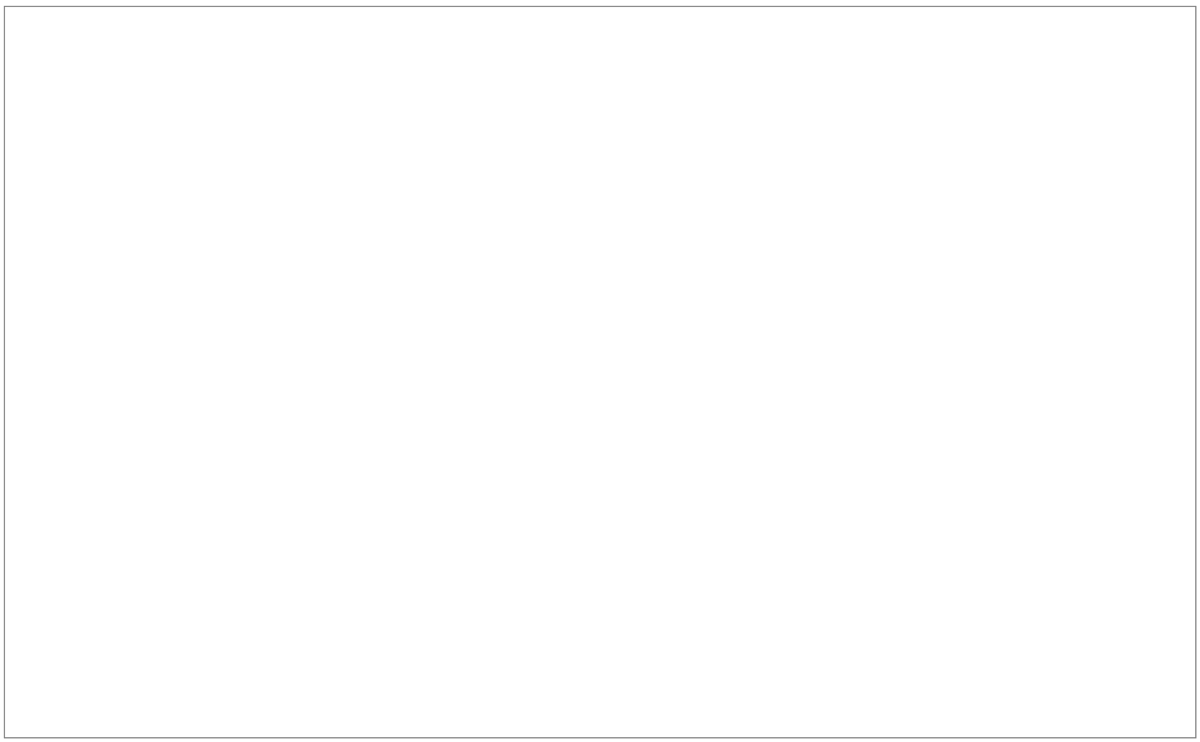
POST OPERATIVE COMPLICATIONS



DURATION OF HOSPITAL STAY

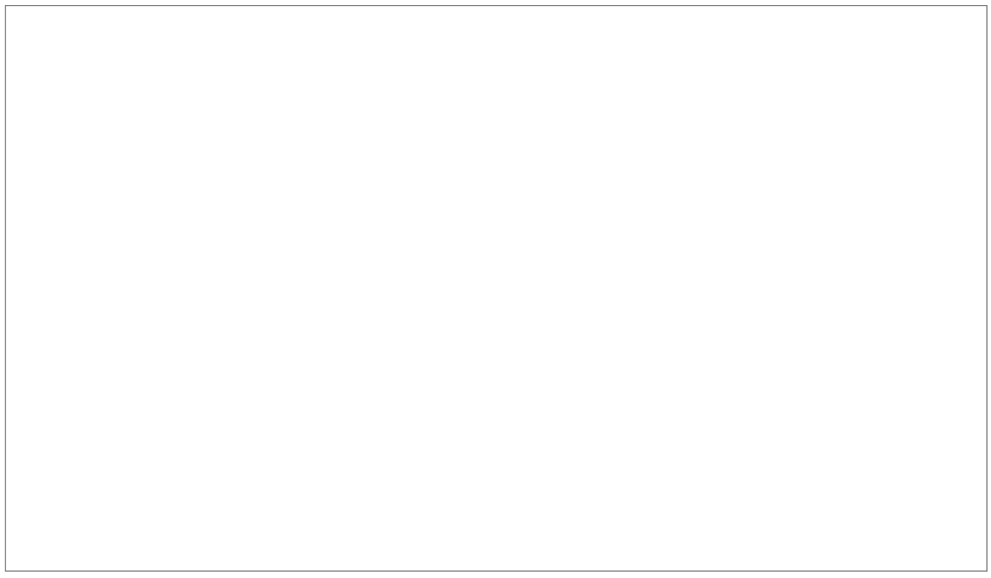
Duration of Hospital Stay	PDS		NACT / IDS	
	No.	Percentage	No.	Percentage
<10 days	15	60%	21	84%
> 10 days	10	40%	4	16%

DURATION OF HOSPITAL STAY



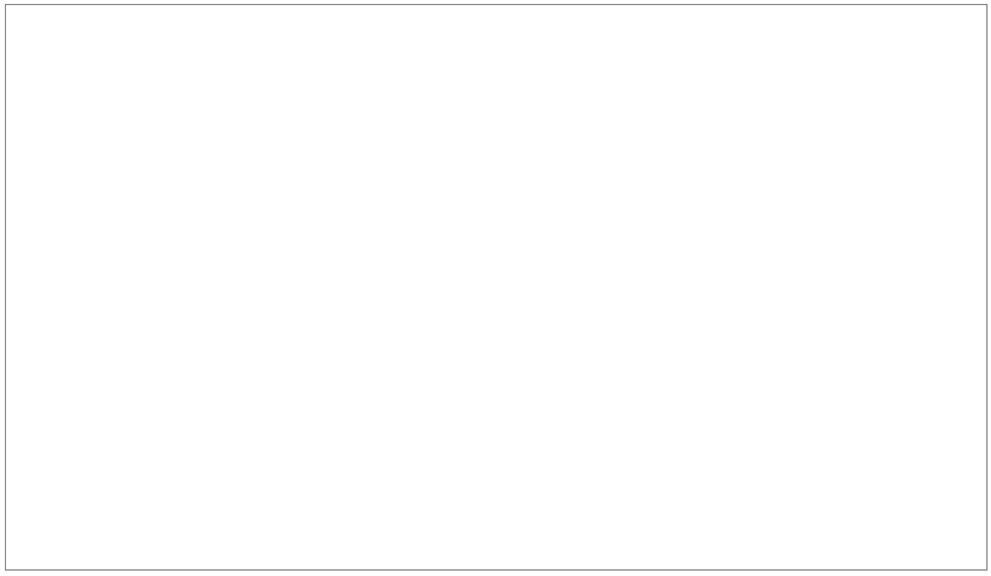
POST OPERATIVE COMPLICATIONS

Wound Infection	4
Cardiopulmonary Complication	3
Paralytic Ileus	2
Would Dehiscence	1
Deep Vein Thrombosis	1



INJURY TO ADJACENT STRUCTURES

Bladder Injuries	2
Small Bowel Injuries	2
Ureteric Injury	1
Sigmoid colon injury	1
Rectal injury	1



DISCUSSION

In our study the range of age is from 40 to 70 years with a median age of 55 years. Devita et al reported that increased incidence occurs between 60-70 years.[13] Reechia et al in his study found that median age for ovarian cancer was 61 years.[14] The range was 52-73 years.

Most of the women were postmenopausal (44 cases-88%)in ou study. Tien Le et al in his study reported that 81 % were postmenopausal[15] at the time of diagnosis.

Novak's et al reported that 75 % of epithelial cancers are serous papillary carcinomas,[16] but in our study serous papillary carcinomas was the most common type carcinomas in 45 cases (90%).

Hacker et al reported that patients with extensive metastasis or massive ascitis before cytoreduction had a poor prognosis even if the patient was cytoreduced to an optimal status. [17] In addition Heinz et al noted that a diameter of largest metastasis and presence of ascitis before cytoreduction influenced survival. [18] In our study ascitic fluid was present in 21 cases in PDS group (84%), and it

was present only in 5 cases (20%) of NACT / IDS group at the time of surgery.

Adhesions was present in 19 cases (76%) in PDS group but it was seen only in 6 cases (24%) in NACT /IDS group at the time of surgery in our study.

In our study, injury to adjacent structures was present in 6 cases of PDS group (24%) whereas only 1 case in NACT had injury. Out of the total 7 cases, 2 had bladder injury, 2 had injury to the small bowel, one had ureteric injury, one had sigmoid colon and the other had rectal injury.

12 cases of PDS group were admitted in High Dependency Unit whereas only 6 cases of NACT/IDS group were admitted in HDU in our study.

Post –op complications were present in 8 cases of PDS group (32%), 3 cases (12%) of NACT/IDS group in our study.

Post-op complications noted are:

1.Wound infection – 4

2. Cardiopulmonary Complication -3

3. Paralytic ileus -2

4. Wound dehiscence -1

5. Deep vein thrombosis-1

In PDS group, 10 cases (40%) stayed more than 10 days in hospital but in NACT/IDS group only 4 cases (16%) admitted in hospital for more than 10 days.

Schwartz et al., Surwit E., et al., in their study reported that NACT can decrease tumour volume and increase resectability. Patients may have less intraoperative blood loss, shorter operative time, less ICU admission and shorter hospital stay. [19&21]

Maurice et al., have shown the rate of bowel resection, large peritoneal resection and post operative morbidity and mortality were significantly reduced in NACT group as compared to primary surgery. [22]

Kayikclogluf., et al., in his study 2001 quoted that optimal cyto reduction is significantly higher in NACT group. ($p<0.001$) [20]

Kuhn et al., in his study reported the resection rate in the group receiving NACT was significantly higher ($p=0.04$) than that of conventional group.

In our study, optimal cytoreductive debulking that is , no gross residual

disease to less than 2 cms residual disease was achieved in 7 cases (28%) out of 25 cases in PDS group, 19 cases (76%) out of 25 cases in NACT/IDS group.

Suboptimal cytoreduction that is, gross residual disease to residual

disease more than 2 cms was present in 12 cases (48%) of PDS group and 4 cases (16%) of NACT/IDS group.

Laparotomy and closure due to frozen pelvis done in 6 cases (24%) of

PDS group and 2 cases (8%) of NACT/IDS group.

Schimizu et al in his study reported that 35 cases (21%) out of 165

acheived optimal cytoreduction in PDS group, 34 cases (46%) out of 74

cases had optimal cytoreduction in NACT/IDS group [2].

Deo et al in his study reported that 59 cases (72%) out of 82 cases

achieved optimal cytoreduction, 15 cases (18.2%) out of 82 cases achieved

suboptimal cytoreduction and 8 cases (9.8) out of 82 cases exploratory laprotomy and closure was performed.[1]

CONCLUSION

Neo adjuvant chemotherapy is significantly more effective in achieving optimal cytoreduction and reducing ascitic fluid volume in advanced ovarian cancer.

Blood transfusion requirement is significantly less in neo adjuvant chemotherapy group.

Adhesions are found to be significantly less in NACT group.

PROFORMA

Name Age Sex I.P. No. S.E.Class

Address

Complaints

Mass abdomen

Abdominal distension

Loss of weight

Loss of appetite

Abdominal pain

Altered bowel habits

Menstrual history

Cycles

Flow

LMP

Attained menopause Yes No

Marital history Married Unmarried

Obstetric history Para Live Abortion

Drug history

H/O oral pills intake

H/O clomiphene intake

Personal history

Smoking Yes No

Alcohol Yes No

Family history

H/0 breast cancer in the family Yes No

H/O ovarian cancer in the family Yes No

GENERAL EXAMINATION

Yes No

Anemia

Jaundice

Pedal edema

Enlarged cervical glands

Enlarged Inguinal glands

Per abdomen

Ascites

Mass

size

consistency

tenderness

mobility

Per Vaginal examination

Mass felt or not

Pouch of Douglas deposits Yes No

Per Rectal examination

INVESTIGATIONS

Haemogram

Renal function tests

Liver function tests

Ultrasound pelvis and abdomen

CT Scan pelvis and abdomen

X ray Chest – PA view

Examination under anaesthesia

Aspiration of ascitic fluid / FNAC / Biopsy

TREATMENT

Neoadjuvant chemotherapy

Drug Dose

Interval Debulking surgery Yes No

Primary Cytoreductive surgery Yes No

Per operative findings

Adhesions

Ascitic fluid amount

Ovary

Right Mass size

Consistency

Left Mass size

Consistency

Uterus

Fallopian tubes

Pouch of douglas

Omentum

Peritoneum

Liver

Retroperitoneal nodes

Volume of tumour left behind

Blood Transfusion

HDU admission

Post op complication

Duration of hospital stay

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