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TUMOUR CLEARANCE IN ADVANCED OVARIAN CANCER WITH AND WITHOUT NEO ADJUVANT CHEMOTHERAPY

KEYWORDS

NEO ADJUVANT CHEMOTHERAPY (NACT), INTERVAL DEBULKING SURGERY (IDS), PRIMARY CUTIE EDUCATIVE SURGERY(PDS), PRIMARY CYTOREDUCTIVE SURGERY (PDS)

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ABSTRACT *Ovarian malignancies are one of the most common gynecological malignancies in India next to uterine malignancies presenting very late in advanced stages accounting for 7% of all cancer diagnosis.Life time risk of ovarian carcinoma is 1.9%.Most common of these ovarian tumors are the epithelial cancers described as silent killers because overwhelming majority of these don't present with any of these symptoms except vague abdominal discomfort and bloating sensation.Tumor markers like ca125 elevated only in advanced stages and more it is like a prognostic indicator only.Neoadjuvant chemotherapy was introduced in the year 1969 for patients with advanced ovarian cancer who were medically unfit .Later neoadjuvant chemotherapy was extended to all severe stages of ovarian malignancy to achieve better survival rate after surgery.Aim of this study is to identify tumour clearance effect of neoadjuvant chemotherapy in advanced ovarian tumour and to compare it with those who have not received neoadjuvant chemotherapy(NACT).*

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. Incidence of ovarian malignancy ,the age-standardized incidence rates for ovarian cancer varied from 0.9 to 8.4/100,000 person years among various registries. The age-specific incidence rate for ovarian cancer revealed that the disease increases from 35 years of age and reaches a peak between the ages 55 and 64. Devita et al reported that increased incidence occurs between 60-70 years.It ranks as the sixth most common cancer next only to cancer uteri

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 various reasons .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.

Common epithelial tumours accounts for 80% of all ovarian neoplasm. The remaining tumours arise from ovarian germ cells or stromal cell. In majority of cases malignant epithelial ovarian tumours disseminate throughout the peritoneal cavity after exfoliation of malignant cells from the surface of the ovary. They also spread via lymphatic to pelvic,paraaortic and inguinal nodes

Table 1. HISTOLOGICAL CLASSIFICATION OF OVARIAN TUMOURS:

COMMON EPITHELIAL TUMOURS:	SEX CORD (GONADAL STR-OMAL)TUMOURS:	GERM CELL TUMOURS
• Serous tumour • Mucinous tumours • Endometrioid tumours • Clearcell(mesonephroid tumours) • Brenner tumours • Mixed epithelial tumours • Undiffentiated tumours • Unclassified epithelial tumours	• Granulosa-stromal cell tumours, theca cell tumours. • Androblastomas: Stertoli-leydig cell tumours. • Gynandroblastomas • Unclassified. • Lipoid cell tumours	• Dysgerminoma • Endodermal sinus tumour • Polyembryoma • Choriocarcinoma • Teratoma • Mixed forms
LIPOID CELL TUMORS	**GONADOBLASTOMAS**	**SOFT TISSUE - NONSPECIFIC TUMORS**

Table 2:

FIGO Ovarian Cancer Staging
Effective Jan. 1, 2014

(Changes are in italics.)

STAGE I: Tumor confined to ovaries			
OLD		NEW	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites.	IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.	IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites.	*IC Tumor limited to 1 or both ovaries*	
		IC1	*Surgical spill*
		IC2	*Capsule rupture before surgery or tumor on ovarian surface.*
		IC3	*Malignant cells in the ascites or peritoneal washings.*

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer			
OLD		NEW	
IIA	Extension and/or implant on uterus and/or Fallopian tubes	IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues	IIB	Extension to other pelvic intraperitoneal tissues
IIC	IIA or IIB with positive washings/ascites.		

Old stage IIC has been eliminated

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STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes			
OLD		NEW	
IIIA	Microscopic metastasis beyond the pelvis.	*IIIA (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)*	
		IIIA1	*Positive retroperitoneal lymph nodes only*
		IIIA1(i)	*Metastasis ≤ 10 mm*
		IIIA1(ii)	*Metastasis > 10 mm*
		IIIA2	*Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes*
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in greatest dimension.	IIIB	*Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis.	IIIC	*Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*

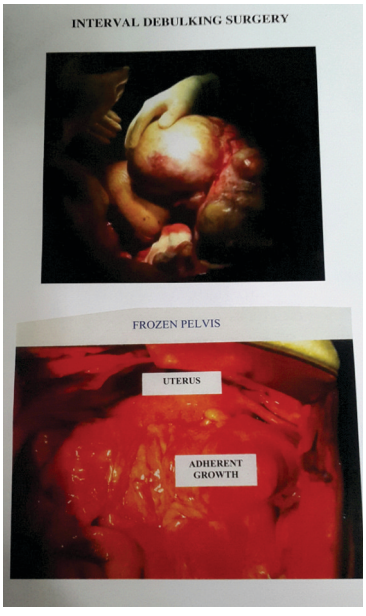
STAGE IV: Distant metastasis excluding peritoneal metastasis			
OLD		NEW	
IV	Distant metastasis excluding peritoneal metastasis. Includes hepatic parenchymal metastasis.	*IVA*	*Pleural effusion with positive cytology*
		IVB	Hepatic and/or *splenic parenchymal* metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

5 YEARS SURVIVAL RATE:

1.STAGE 1 - 76 TO 93%
2.STAGE 2 - 60 TO 74%
3.STAGE 3A - 41%
3B - 25%
3C -23%
4.STAGE 4 - 11%



NEO ADJUVANT CHEMOTHERAPY:

Neo adjuvant chemotherapy represents any cytotoxic drug prior to surgery after histological confirmation of ovarian cancer. Treating the patient prior to surgery has three theoretical advantages.

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

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

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

MATERIALS AND METHODS:

This is a prospective study conducted at Institute Of Social Obstetrics And Govt Kasturba Gandhi Hospital And Madras Medical College for 18 months for 50 cases. The study was approved by the Hospital Ethical committee.

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 underwent detailed physical examination, routine hematological, biochemical investigations ,ultrasound and CT Scan.

For those patients with ascites, ascitic fluid sent for cytology.If Cytology report confirmed that it was epithelial ovarian tumor patient received Neoadjuvant chemotherapy of Cisplatin 75mg/sqm

Cyclophosphamide 750mg/sq. m for 3 cycles for 6 weeks and underwent interval debulking surgery .

Optimal Debulking,Ascitic fluid volume,Blood transfusion rate are compared with the control group. (Control group in this study were those patients with advanced epithelial tumor who did not receive neoadjuvant chemotherapy and undergone primary cytoreductive surgery)

RESULTS:

In our study done on 50 patients at Institute Of Social Obstetrics And Govt Kasturba Gandhi Hospital And Madras Medical College,The Tamilnadu Dr.M.G.R.Medical University ,Chennai-600005 .the range of age was from 40 to 70 years with a median age of 55 years.optimal cytoreduction done in 76% of NACT/IDS group.only 6 cases of NACT/IDS group were admitted in HDU.Hospital stay was more than 10 days only in 4 cases.

POST OPERATIVE COMPLICATIONS

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

BLOOD TRANSFUSION

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

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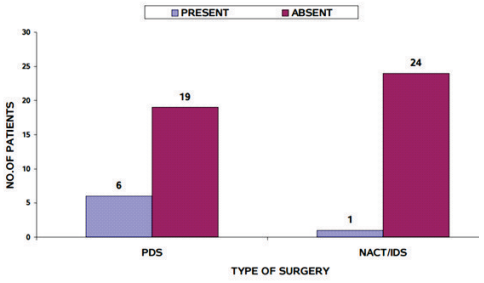

HDU STAY

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

HDU STAY

DISCUSSION

In our study the range of age is from 40 to 70 years with a median age of 55 years. Reechia et al in his study found that median age for ovarian cancer was 61 years. Most of the women were postmenopausal (44 cases-88%)in our study.

Tien Le et al in his study reported that 81 % were Postmenopausal at the time of diagnosis. Novak's et al reported that 75 % of epithelial cancers are serous papillary carcinomas, but in our study serous papillarycarcinomas was the most common type carcinomas in 45 cases (90%).

Ascitic fluid was present in 21 cases in PDS group(84%)and it as present only in 5 cases(20%) of NACT/IDS group at the time of surgery.

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.

In addition Heinz et al noted that a diameter of largest metastasis and presence of ascitis before cytoreduction influenced survivalascitic fluid was present in 21 cases in PDS group (84%) and it as present only in 5 cases(20%) of NACT/ IDS group at the time of surgery.

In our study,optimal cytoreductive debulking that is,no gross residual disease to less than 2 cm Residual disease as achieved in 7 cases(28%) out of 25 cases in NACT/IDS groups.

Suboptimal cytoreduction that is,gross residual disease more than 2 cm 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 stud reported that 35 cases(21%) out of 165 achieved optimal cyoreduction in PDS group,34 cases(46%) out of 74 cases had optimal cytoreduction in NACT/IDS group.

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 cytoredution and 8 cases(9.8%) out of 82 cases, exploratory laparotomy and closure was performed.

12 cases of PDF were admitted in High dependency unit where as only 6 cases of NACT/IDS group were admitted in HDU in our study

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 intra operative blood loss, shorter operative time, less ICU admission and shorter hospital stay.

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

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