"EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA"

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA"** is a bonafide record of work done by **Dr. J.LINU GRACIA,** during the period of March 2017 to February 2018 under the guidance of **Dr.PREMA KUMARI M.D., D.G.O,** Professor, Institute of Social Obstetrics, Government Kasturba Gandhi Hospital, Chennai – 600 005, in partial fulfillment of the requirement of M.S. Obstetrics and Gynaecology Degree Examination of The Tamilnadu Dr. M.G.R. Medical University to be held in May 2019.

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DECLARATION

I, **Dr.J. LINU GRACIA,** Post Graduate, Department of Obstetrics and Gynaecology, Madras Medical College, solemnly declare that the dissertation titled **"EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA"** is the bonafide work done by me at Department of Obstetrics and Gynaecology, Madras Medical College under the expert guidance and supervision of **Dr.PREMA KUMARI M.D., D.G.O,** Professor, Institute of Social Obstetrics, Government Kasturba Gandhi Hospital, Chennai-600 005. The dissertation is submitted to the Tamil Nadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.S., Degree (Branch II) in Obstetrics and Gynaecology.

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CONTENTS

INTRODUCTION

Ovarian cancer is the second most common gynecological malignancy. Patients with ovarian tumors are often asymptomatic for a long time. Most cases are diagnosed late because effective screening methods are not available 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. Therefore it is the most common cause of gyneacological cancer mortality.

Surgical resection of tumor remains the cornerstone of current treatment for patients with advanced and early stage ovarian cancer. But 70% of the patients present with advanced disease and 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 allows a less aggressive surgery and better clearance to be performed.

Incidence:

Overall, Ovarian cancers account for 5% of all cancer diagnosis. The lifetime risk of developing ovarian cancer is approximately 1.4-1.9%. Epithelial ovarian cancer is a disease of the older women mean age at diagnosis being 60 but it can occur at any age.About 40% of EOCs occur at>70 years of age and 70% are at stage 3 or 4 at diagnosis.

The incidence in developing countries is 9.4/100,000.In India, ovarian cancer rank 6th most common cancer in women. Overall survival rate is about 20%.

RISK FACTORS:

1.Age

The risk of developing ovarian cancer increases as age increases. Ovarian cancer is rare in women younger than 40. Most ovarian cancers are postmenopausal. 50% of all ovarian cancers are found in women more than 60 years.

2.Obesity

Obesity increases the risk of developing many cancers. Obese women with a body mass index [BMI] of more than 30 may have a higher risk of developing

ovarian cancer. Obesity may also affect the overall prognosis of a woman with ovarian cancer.

3.Nulliparity

Women who have their first full-term pregnancy after age 35 or who never carried a pregnancy to term have a higher risk of ovarian cancer.

4.Infertility

Fertility treatment with in vitro fertilization (IVF) seems to increase the risk of the type of ovarian tumors known as "borderline" or "low malignant potential. Other studies, however, have not shown an increased risk of invasive ovarian cancer with fertility drugs.

5.Hormone therapy after menopause

Women using estrogens after menopause have an increased risk of developing ovarian cancer than with women who took both oestrogens and progesterone.

6.Having a family history of ovarian cancer, breast cancer, or colorectal cancer

Ovarian cancer can run in families. Risk of ovarian cancer is increased if your first degree relative has ovarian cancer.

A family history of colorectal and breast cancer also increases the risk of ovarian cancer. This is because these cancers can be caused by an inherited mutation in certain genes that cause a family cancer syndrome that increases the risk of ovarian cancer.

Hereditary breast and ovarian cancer syndrome

This syndrome is caused by inherited mutations in the genes BRCA1 and BRCA2, and also by some other genes that have not yet been found. This syndrome is linked to a high risk of breast cancer as well as ovarian, fallopian tube, and primary peritoneal cancers. The risk of some other cancers, such as pancreatic cancer and prostate cancer, are also increased.

Mutations in BRCA1 and BRCA2 are also responsible for most inherited ovarian cancer. The lifetime risk of developing ovarian cancer for women with a BRCA1 mutation is estimated to be between 35% -40%. For women with BRCA2 mutations the risk has been estimated to be between 13%-23%.In comparison, the lifetime risk of developing ovarian cancer for the women in the general population is less than 2%.BRCA 1 associated cancer occurs earlier.BRCA 2 have a better prognosis.

PTEN tumor hamartoma syndrome

In this syndrome, also known as Cowden disease, people are primarily affected with thyroid problems, thyroid cancer, and breast cancer. Women also

have an increased risk of endometrial and ovarian cancer. It is caused by inherited mutations in the PTEN gene.

Hereditary nonpolyposis colon cancer

Women with this syndrome have a very high risk of colon cancer and also have an increased risk of developing endometrial cancer and ovarian cancer. Many different genes can cause this syndrome. They include MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, and PMS2. The lifetime risk of ovarian cancer in women with hereditary nonpolyposis colon cancer (HNPCC) is about 10%. Up to 1% of all ovarian epithelial cancers occur in women with this syndrome. Another name for HNPCC is Lynch syndrome.

Peutz-Jeghers syndrome

People with this rare genetic syndrome develop polyps in the stomach and intestine while they are teenagers. They also have a high risk of cancer, particularly cancers of the digestive tract (esophagus, stomach, small intestine, colon). Women with this syndrome have an increased risk of ovarian cancer, including both epithelial ovarian cancer and a type of stromal tumor called sex cord tumor with annular tubules (SCTAT). This syndrome is caused by mutations in the gene STK11.

MUTYH-associated polyposis

People with this syndrome develop polyps in the colon and small intestine and have a high risk of colon cancer. They are also more likely to develop other cancers, including cancers of the ovary and bladder. This syndrome is caused by mutations in the gene MUTYH.

Having had breast cancer

Breast cancer also have an increased risk of developing ovarian cancer. There are several reasons for this. Some of the reproductive risk factors for ovarian cancer may also affect breast cancer risk. A strong family history of breast cancer may be caused by an inherited mutation in the BRCA1 or BRCA2 genes and hereditary breast and ovarian cancer syndrome, which is linked to an increased risk of ovarian cancer.

7. **Smoking and alcohol use**

Smoking doesn't increase the risk of ovarian cancer overall, but it is linked to an increased risk for the mucinous type.

Drinking alcohol is not linked to ovarian cancer risk.

Factors with unclear effects on ovarian cancer risk

Androgens

Androgens, such as testosterone, are male hormones. There appears to be a link between certain androgens and specific types of ovarian cancer, but further studies of the role of androgens in ovarian cancer are needed.

Talcum powder

It has been suggested that talcum powder might cause cancer in the ovaries if the powder particles (applied to the genital area or on sanitary napkins, diaphragms, or condoms) were to travel through the vagina, uterus, and fallopian tubes to the ovary..

Diet rich in animal fat

Some studies have shown a reduced rate of ovarian cancer in women who ate a diet high in vegetables or a low fat diet. The American Cancer Society recommends eating a variety of healthful foods, with an emphasis on plant sources. Eat at least 2½ cups of fruits and vegetables every day, as well as several servings of whole grain foods from plant sources such as breads, cereals, grain products, rice, pasta, or beans. Limit the amount of red meat and processed meats you eat. The effect of these dietary recommendations on ovarian cancer risk remains uncertain.

Factors that can lower risk of ovarian cancer

Pregnancy and breastfeeding

Women who have had full term pregnancy before 26 years have a lower risk of ovarian cancer than women who have not. The risk decreases each full-term pregnancy. Breastfeeding also reduces the risk even further.

Oral contraceptives

Women who have used oral contraceptives for a longer period have a lower risk of ovarian cancer. This lower risk continues for many years even after stopping the pill. Other forms of birth control such as tubal ligation (having fallopian tubes tied) and short use of IUDs (intrauterine devices) have also been associated with a lower risk of ovarian cancer.

A hysterectomy (removing the uterus without removing the ovaries) also seems to reduce the risk of getting ovarian cancer by about one-third.

PATHOGENESIS:

Ninety percent of ovarian tumors are epithelial in origin with the majority being serous cystadenocarcinomas. A small number are mucinous in origin, endometrioid or of clear cell morphology . Approximately 5% will be germ cells or gonadal- stromal cells with further 5% being secondary tumors. The epithelial tumours arise from surface epithelium or serosa of ovary. Serous carcinoma can

resemble the fallopian tube. Mucinous tumour arise from walthard inclusions and the cells resemble lining cells of endocervix. Endometroid tumors arise from endometrial cells and histological features are the same as endometrial cells.

PATTERN OF SPREAD:

The predominant method of spread is by exfoliation of malignant cells into peritoneal cavity that is deposited on the surface of various intraabdominal organs. The cells are carried by peritoneal fluid as it circulates.

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.

Lymphatic drainage is the other primary mode of spreadTumour. Malignant cells move through channels that follow the ovarian blood supply in the infundibulopelvic ligament to lymph node around the aorta and venacava to the level of renal vessel.Other lymphatics pass laterally through the broad ligament and parametrium and consequently to external ilac, obturator, hypogastric and internal iliac nodal chains. More rarely metastasis 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.

Direct extension of a progressively enlarging ovarian cancer can involve pelvic peritoneum and adjacent structures including the uterus, adjacent peritoneal surfaces of the bladder, rectosigmoid and fallopian tube.

Histological classification of ovarian tumour(WHO)

1.Common epithelial tumours:

Serous tumours

Mucinous tumour

Endometrioid tumours

Clear cell(mesonephroid tumours)

Brenner tumours

Mixed epithelial tumours

Undiffentiated tumours

Unclassified epithelial tumours

2. Sex cord (gonadal stromal) tumours:

Granulosa-stromal cell tumours,

Theca cell tumours.

Androblastomas:Stertoli-leydig cell tumours.

Gynandroblastomas

3.Lipoid cell tumors

4. Germ cell tumours

Dysgerminoma

Endodermal sinus tumours

Polyembryoma

Choriocarcinoma

Teratoma

Mixed forms

5.Gonadoblastoma

6.Soft tissue tumors not specific to ovary

7. Unclassified tumours

8. Secondary (metastatic) tumours

9.Tumor like conditions

A.SEROUS TUMOR:

Tumours composed of epithelium resembling that of the fallopian tube or the surface epithelium of the ovary; ciliated calls are found almost always in the

benign serous tumours, usually in those of borderline malignancy and rarely in the carcinomatous forms,.Psammoma bodies may be present, but do not in themselves indicate malignancy. The tumour cells may produce considerable mucin, which *is almost entirely extracellular. The* borderline and carcinomatous forms typically have a well developed papillary pattern but the carcinoma is often prcdominantly solid in its architexture.

B.MUCINOUS TUMOR:

Mucinous tumors are multiloculated cysts lined by epithelium resembling the endocervix and occasionally contain argentaffin cells and rarely paneth cells.The tumors can grow to a large size and often pedunculated..They are usually unilateral.If the tumor ruptures it may lead to formation of pseudomyxoma peritoni. When a mucocde of the appendix is present in addition to a mucinous ovarian mass it is difficult to determine the primary sites of involvement. The possibility of metastatic adenocarcinoma, particularly of large-intestinal origin should always be considered is cases of tumours having the appearance of mucinous adenoearcinoma.

CENDOMETRIOID TUMORS:

These tumors are lined by glandular epithelium resembling the endometrium. The tumors are of moderate size and are essentially solid with cystic areas and in between filled with hemorrhagic fluid. In 15% of cases ovarian endometriosis may coexist. They are associated with endometrial cancer in 20%.

The cells of endometrioid tumor may produce mucin which is extracelluiar. Squamous differentiation of the neoplastic cell is common and if present in an endometrioid carcinoma, justifies the diagnosis of adenoacanthoma.Endometrioid carcinomas may have a markedly papillary pattern, which is rare in carcinomas of the endometrium. Often an endometrioid carcinoma of the ovary is associated with a carcinoma of the endornetrium that appears similar on microscoptc examination. In such cases it may be impossible to determine whether either or both tumours are primary, and the presence and extent of each should be recorded in the diagnosis,

D. CLEAR CELL [MESONEPHROID] TUMOURS

Tumours composed of clear cells containing glycogen and resembling those of the renal cell carcinoma and/or hobnail, or peg-shaped, cells liniqg small cysts and tubules; "hobnail" cells are characterized by scant cytoplasm and large nuclei that project into the lumen.

Cells with abundant eosinophilic cytoplasm may also be seen. Mucin secretion is often present within the cysts and tubules, but is absent intracellulariy. The patterns encountered include solid, glandular, tubular, papillary, and microcystic$_4$ and their combination On very rare occasions, a renal cell carcinoma metastasizes to the ovary and may be confused with a primary clear cell carcinoma. This tumour must also be distinguished from the endodermal sinus tumour, the dysgerminoma and the lipid cell tumour.

E. BRENNER TUMOURS

Fibroepithelial tumours composed of stroma derived from the ovarian stroma and nests of polyhedral or rounded epithelial cells of transitional, or urothelial, type. These cells often contain grooved, coffee-bean nuclei.

The nests may form glands or cysts lined by flat, cuboidal or columnar cells; these cells often contain mucin and are occasionally ciliated. Cells of transitional cell type –walthard cell rests. The tumor is generally unilateral,small to moderate in size. It usually occurs in women around menopause.It may also be associated with ascitis and hydrothorax –pseudo Meigs syndrome.

F. MIXED EPITHELIAL TUMORS:

Tumours composed of a mixture of two or more of the five *types* described above.

G. UNDIFFERENTIATED CARCINOMA:

A malignant epithelial tumour which is too poorly differentiated to be placed in any of the other groups.

H.UNCLASSIFIED EPITHELIAL TUMORS:

Tumours of common epithelial type *with* features intermediate between two or more of the specific categor

II. SEX CORD STROMAL TUMOURS

Tumours containing granulosa cells, theca cells, collagen-producing stromal cells, Sertoli cells, Leydig cells, and cells resembling their embryonic precursers, singly or in various combinations,

These tumours have also been designated gonadal stromal tumours; sex cord- mesenchyme tumors and mesenchymomas.

A. GRANULOSA-STHOMAL CELL TUMOUR

Tumours containing granulosa cells, theca cells, and stromal cells resembling fibroblaststs singly or in various combinations.

1. Granulosa cell tumour :

A tumour of female cell types containing more than a small component of granulose cells The cells may be arranged in a variety of patterns, including *foilicular*, trabecular ,insular and diffuse. The microfollicular pattern is characterised by the presence of the distinctive Call-exner bodies Granulosa cell tumours are usually oestrogenic, but may be inactive or rarely androgenic. They are clinically malignant in a minority of cases; the course of malignancy is usually low-grade, being characterized by a slow evolution or a late recurrence.

2. Thecoma-fibroma group

Tumours forming a continuous spectrum from those composed entirely of cells resembling fibroblasts and producing collagen to those containing a predominance of cells resembling lipid-rich theca cells.

(a) Thecoma [theca cell tumour]:

A stromal tumour, many cells of which contain abundant lipid-rich cytoplasm and resemble theca cells. The fibrous component varies in quantity. Thecomas should be differentiated from diffuse granulosa cell tumours; reticulin staining, which reveals an abundance of fibrils investing individual theca cells and relatively little within aggregates of granulosa cells, is often helpful in the differential diagnosis. The thecoma is typically oestrogenic and causes post menopausal bleeding.

(b) *Fibroma* :

A stroma tumour composed of spindle cells producing abundant col-lagen.Some tumours are markedly oedematous and associated with ascites and hydrothorax (Demons-Meigs syndrome). It is possible that an occasional fibroma is derived from nonspecific fibrous tissue within the ovary rather than from the ovarian stroma. The fibroma is non-functioning.

B. ANDROBLASTOMAS; SERTOLI-LEYDIG CELL TUMOURS

Tumours containing Sertoli and Leydig cells of varying degrees of maturity; indifferent gonadal cells of embryonal appearance are present in certain cases. Although most of these tumours are virilizing, some are endocrinologically inactive and others are oestrogenic.

Sertoli-Leydig cell tumour

A tumour containing more than a small component of Leydig cells as well as Sertoli cells arranged in a tubular pattern,

It may be androgenic or oestrogenic.

Leydig cell tumour;

A tumour composed entirely of Leydig cells.

Hilus cell tumor:

The presence of reinke cells is the distinguishing feature of hilus cell tumor.

C. GYNADROBLASTOMA:

It is a very rare tumour in which collections of granules a cells with typical Call-Exner bodies coexist with hollow tubules lined by Sertoli cells.

III. LIPOID CELL TUMOURS:

These tumors are composedd of cells that resemble Leydig* lutein, and adrenal cortical cells, but cannot be identified specifically as any one of the three types. These tumours are also known as adrenal like tumours. They are usually virilising but may be non-functioning. A few have been associated with *some* of the manifestations of Cushmg's syndrome. These tumours are generally thought to be of lutein cell or Leydig cell origin.

IV. GERM CELL TUMOUR

These account for 15 to 20% of all ovarian tumors .Below the age of 20 years 60% of the tumors are of germ cell origin and below 10 years almost 85% are invariably malignant.

A. Dysgerminoma:

A tumour of uniform appearance composed of large, rounded, clear cells that resemble primordial germ cells both morphologically and histo-chemically .It is usually unilateral .The tumor consists of large cells arranged in bunches or alveoli. Lymphocytes and giant cells are always found among the tumor cells. This appearance of large dark stained nuclei with clear almost transclucent cytoplasm and lymphocytic infiltration of fibrous septa is diagnostic

B.ENDODERMAL SINUS TUMOR:

A tumour characterized by the presence of a loose vacuolated network ot embryonal cells, distinctive perivascular structures resembling the endodermal sinuses of the rat placenta, and both intracellular and extracellular hyaiine globules giving a positive periodic acid Schiff reaction This tumour has also been called yolk sac tumour and may contain cysts resembling yolk sac vesicles. It is important to distinguish the endodermal sinus tumour from the clear cell [mesonephroid] carcinoma, which has different patterns, lacks endodermal sinuses and hyaline bodies typically occurs in older women, and has a much better prognosis.

C.EMBRYONAL CARCINOMA

A tumour composed of anaplastic embroyanal cells of epithelial appearance growing in a variety of patterns - acinar, tubular, papillary and solid, This tumour, which is commonly seen in the testis, is very rare in the ovary.

D POLYEMBRYOMA:

A very rare tumour composed predominantly of embryonic bodies. It *is* also known as polyernbryonic embryoma.

E. CHORIOCARCINOMA

A rare tumour composed of both cytotrophoblast and synctiotrophoblast

F. TERATOMA:

Tumours that are generally composed of several types of tissue representing two or three embryonic layers. The structures present may be immature, mature or both.

1. *Immature teratima* [embroyonal teratoma]

A teratoma that contains immature (embryonal) structures, Mature tissue may be present as well Although most immature teratoma are predominantly solid, but can be cystic.

2. *Mature teratotma* [adult teratoma]

A teratoma composed exclusively of mature (adult) structures it is important to differentiate immature and mature solid teratornas bacause of a striking difference in prognosis; while the former are often clinically malignant the latter are almost invariably benign.

Dermoidcyst with malignant transformation squamous cell carcinoma is the usual form of malignant change; adeno-carcinoma and sarcoma are much less common, and melanoma is very rare.

3. *Monodermal and highly specialized teratomas*

(a) Struma ovarii

A teratonia in which thyroid tissue is exclusively present or constitutes a grossly recognizable component of a more complex teratoma.

The tumour often has the appearance of a follicular adenoma rather than normal thyroid parenchyma, A small number of strumas are malignant on microscopical examination, but only a minority of these have been shown to be clinically malignant.

(b) Carcinoid

A tumour of argentaffin cells.

Besides being associated with a struma, a primary carcinoid may be pure, or relatively pure, or may be part of a complex teratoma* Primary carcinoid tumours must be distinguished from rmetastases of intestinal origin, which are bilateral in a high proportion of cases, and from granulosa cell tumours.

(c) *Struma ovarii and carcinoid*

V. GONADOBLASTOMA

A tumour composed of two principal cell types: large germ cells similar to those of toe dysgerminoma and seminoma, and small cells resembling immature granulosa and Sertoli cells; in addition, the stroma may contain cells resembling lutein and Leydig cells.Hyaline bodies that simulate Call-Exner bodies are typically present, and foci of calcification are common. In some tumours the nests

composed of the two major cell types are circumscribed, but in others the germ cells transgress the margins of the nests and grow as a dysgerminoma or seminoma. Certain tumours appear in *the* form of a dysgerminoma or a more highly malignant type of germ cell tumour with only small foci of gonadoblastoma within them or at their margins.

Gonadoblastomas arise almost exclusively in patients with dysgenetic ovaries or testes, most of whom are phenotypic females and almost all of whom are chromatin-negative and have a Y-chromosome

These tumours have also been called dysgenetic gonadornas and gono-cytomas II and III- A gonadoblastoma composed entirely of germ cells and sex cord elements corresponds to the gonocytoma II; if the tumour contains additional cells resembling lutein and Leydig cells, it corresponds to the gonocytoma III.

VI. SOFT TISSUE TUMOURS NOT SPECIFIC TO THE OVARY

These should be classified according to *Histological Typing of Soft Tissue Tumours* .

VII.UNCLASSIFIED TUMORS:

These are primary ovarian tumors that cannot be placed in any of the categories above.

VIII.SECONDARY(METASTATIC) TUMORS:

The krukenberg tumor is characterized by the prescence of mucus filled signet ring cells accompanied by a sarcoma like proliferation of ovarian stroma. Carcinomas of the breast, genital tract, and gastrointestinal tract are most commonly seen.

SYMPTOMS:

Epithelial cancers of ovary has been described as silent killers because overwhelming majority of patients are asymptomsatic until disease has spread outside the ovary and indeed outside pelvis. However many studies 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.

The symptom index includes the following if they are new symptoms and occur >12 times/month:

-abdominal discomfort/pain.

-abdomial swelling/bloating.

-difficulty in eating

When ascitis or pleural effusion develops women present with massive abdominal distension and dyspnoea. Compression of the bladder or rectum by the ovarian mass results in urinary frequency or bowel symptoms. Occasionally women present with irregular menses or postmenopausal bleeding.

The most common physical signs are ascites and pelvic mass

DIAGNOSIS:

In 90% of women presenting with malignant ovarian tumor CA125 levels are elevated.

CA125 levels are also elevated in variety of benign conditions and in other non-gynaecological malignancies.In postmenopausal women CA125 measurement may predict a higher likelihood of malignancy

Half of stage 1 ovarian tumors will have a normal CA125 measurement. Other markers such as CA-19-9 and carcinoembryonic antigen are less frequently used.

It is also useful for early diagnosis of recurrence and response to therapy.

Trans vaginal sonography is typically the most useful imaging test to differentiate benign tumors and early stage ovarian cancer .It is also useful in the evaluation of pelvic mass because of their ability to accurately discern the ovarian morphology and pelvic pathology. Malignant tumors are multiloculated irregular

ovarian border, solid elements within the cyst, papillary projection, thick septa, bilateral ovarian enlargement and presence of ascites.

Colour Doppler imaging evaluates blood flow to an ovarian mass. Increased vascularity with low resistance index indicates malignancy.

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

Positron emission tomography is useful in detecting metastatic disease. Its role 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

Laprotomy is mandatory for appropriate staging of the disease. 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 limited 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.

11C 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, ascitis fluid if 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 ascitis is present, 50 -100 ml of saline should be instilled into the pelvis abdomen subdiapragmatic space and paracolic gutters using a rubber catheter and the fluid should be aspirated.. 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 for assessing the prognosis and for appropriate postoperative therapy.

Clinicopathological prognostic parameters:

FIGO Staging

Histological sub-type

Histologocal grade

Factors associated with dissemination

Malignant ascites or malignant peritoneal washings

Tumor excrescences on ovarian surface or ruptured capsule

Volume of residual tumour after cytoreductive surgery

5 YEARS SURVIVAL RATE

1.	Stage 1	–	80 to 90%
2.	Stage 11	–	60 to 70%
3.	Stage 111A	–	41%
	111 B	–	25%
	111 C	–	23%
4.	Stage 1V	–	15-20%

TREATMENT OF ADVANCED OVARIAN CANCER:

Approximately two thirds of patients will have stage 3-4 disease. Ideally surgical cytoreduction is initially performed to remove all gross disease and is followed by six courses of platinum-based chemotherapy. But some patients are not appropriate candidates for primary surgery due to their medical condition and some will have unresectable tumor. Aggressive debulking surgery may not be well tolerated in such patients. They are potential high post operative morbidity and mortality. Post operative complications can also delay in starting adjuvant chemotherapy. Some studies have concluded that initial treatment with

chemotherapy before 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.

The goal of primary cytoreductive surgery is to remove all the primary tumor and metastatic disease if possible so as to reduce the residual tumor to optimal status. Debulking of the tumor us done for various reasons namely:

-The large tumor and deposits are poorly vascularised and the chemotherapeutic agents donot reach the tissues in adequate concentrations.

-Large tumors contain more cells in resting phase which donot respond to chemotherapy.

-Cells in small residual mass are rapidly growing and respond better to chemotherapeutic agents

Debulking surgery includes Total Abdominal Hysterectomy with Bilateral and Salpingo-Oopherectomy and Omentectomy with or without lymphadenectomy.

If the residual tumor masses are <1cm it is optimal cytoreduction. Patients whose tumor is completely removed or cytoreduced have the best overall survival.

If the residual tumor masses are >1cm it is suboptimal cytoreduction and the prognosis is poor in these patient.

Patients who underwent optimal cytoreduction had poor prognosis if they had extensive metastatic disease before cytoreduction and clinically evident ascites .

Complications of Primary cytoreductive surgery

Wound infection / Dehiscence

Cardiac failure

Deep vein thrombosis

Pulmonary embolism

Genitourinary fistula

Relaparotomy for bleeding

Small bowel obstruction

Cerebrovascular disease

Operative mortality

INTERVAL DEBULKING SURGERY

Interval debulking surgery is a cytoreductive surgery after three cycles of combination chemotherapy 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 :

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

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

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 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 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 31 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 ovarian carcinoma. 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 was performed for overall and progression free survival 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 showed benefit only in the patients whose primary surgery was not performed by gynaec oncologists or the tumor was 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 Obstetrics and Gyneacology, IOG,Egmore, Chennai-5 from February 2017 to Dec 2017 were included in the study.

Sample Size

25

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.
- 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.

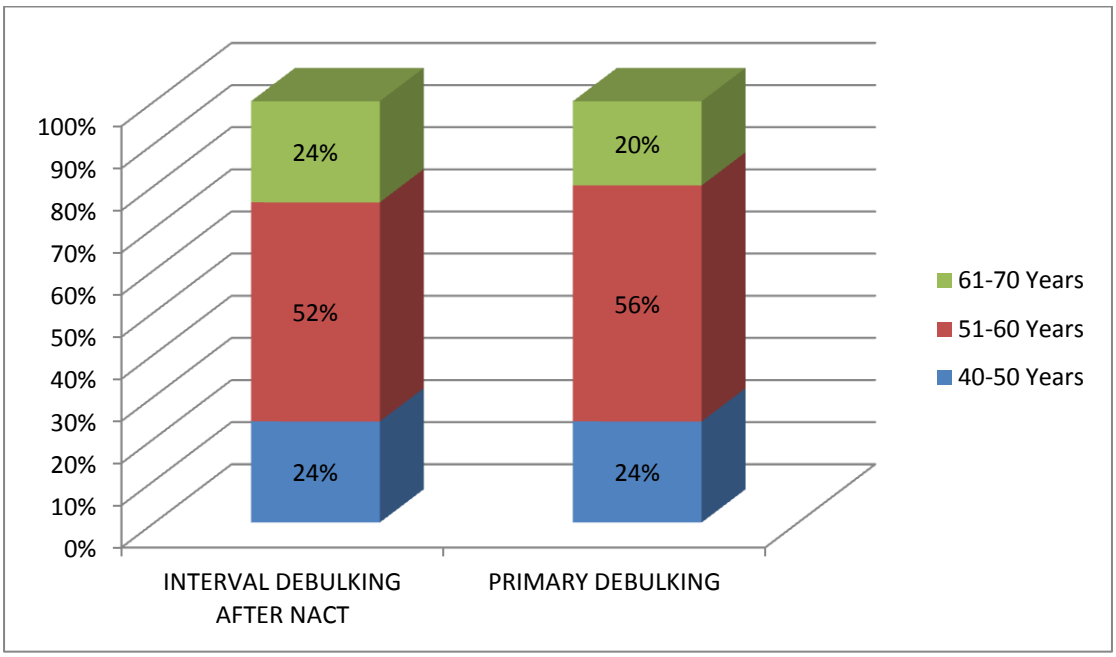
RESULTS

AGE

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
AGE_GROUP	40-50 Years	Count	6	6	12
		% within GROUP	24.0%	24.0%	24.0%
	51-60 Years	Count	13	14	27
		% within GROUP	52.0%	56.0%	54.0%
	61-70 Years	Count	6	5	11
		% within GROUP	24.0%	20.0%	22.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

AGE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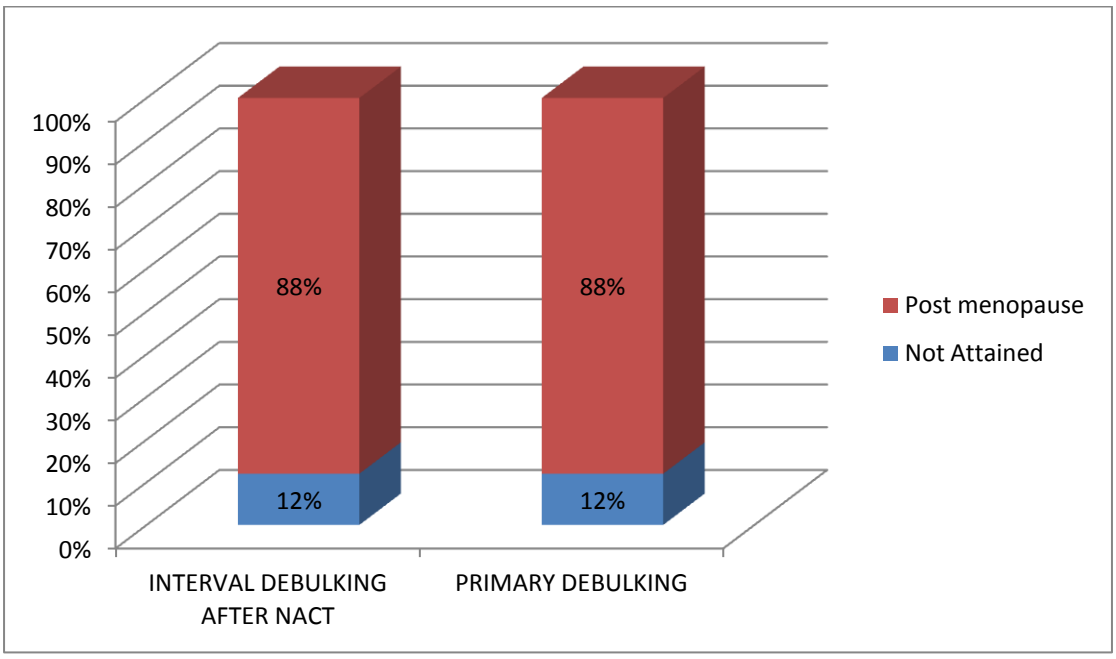
10%
0%
24%
52%
24%
20%
56%
24%
INTERVAL DEBULKING AFTER NACT
PRIMARY DEBULKING
61-70 Years
51-60 Years
40-50 Years

MENOPAUSAL STATUS

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Menopausal_Status	Not Attained	Count	3	3	6
		% within GROUP	12.0%	12.0%	12.0%
	Postmenopause	Count	22	22	44
		% within GROUP	88.0%	88.0%	88.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

MENOPAUSAL STATUS

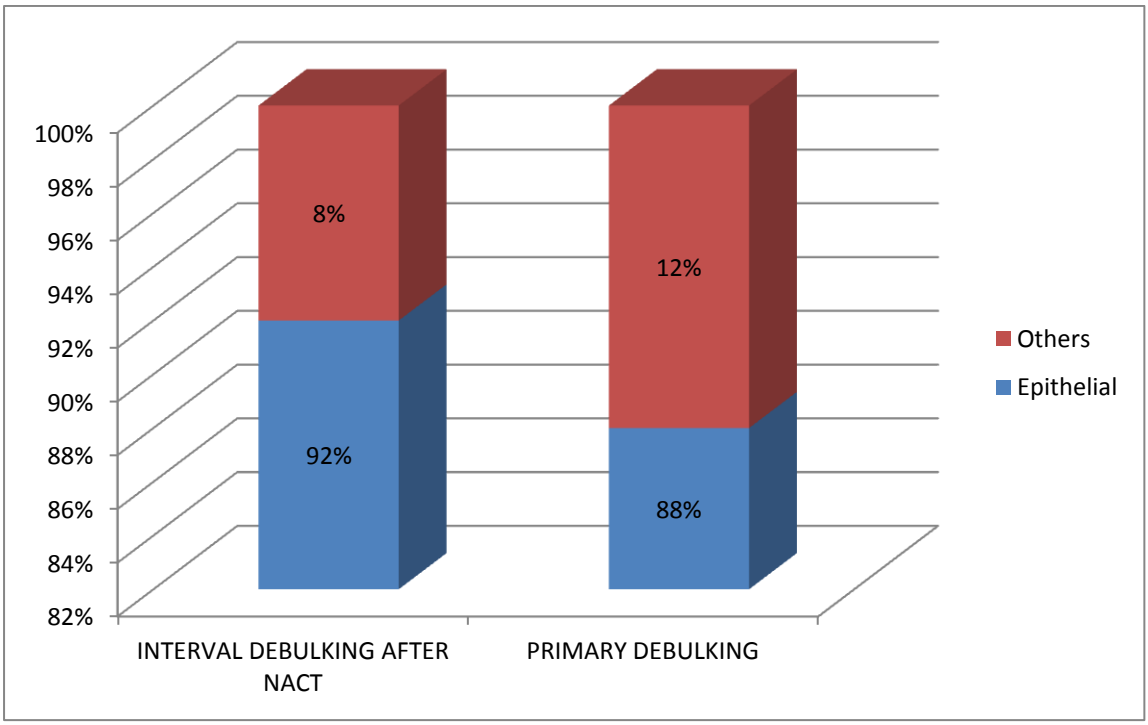


HISTOLOGICAL DIAGNOSIS

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Type_of_Ovarian_Ca	Epithelial	Count	23	22	45
		% within GROUP	92.0%	88.0%	90.0%
	Others	Count	2	3	5
		% within GROUP	8.0%	12.0%	10.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

HISTOLOGICAL DIAGNOSIS



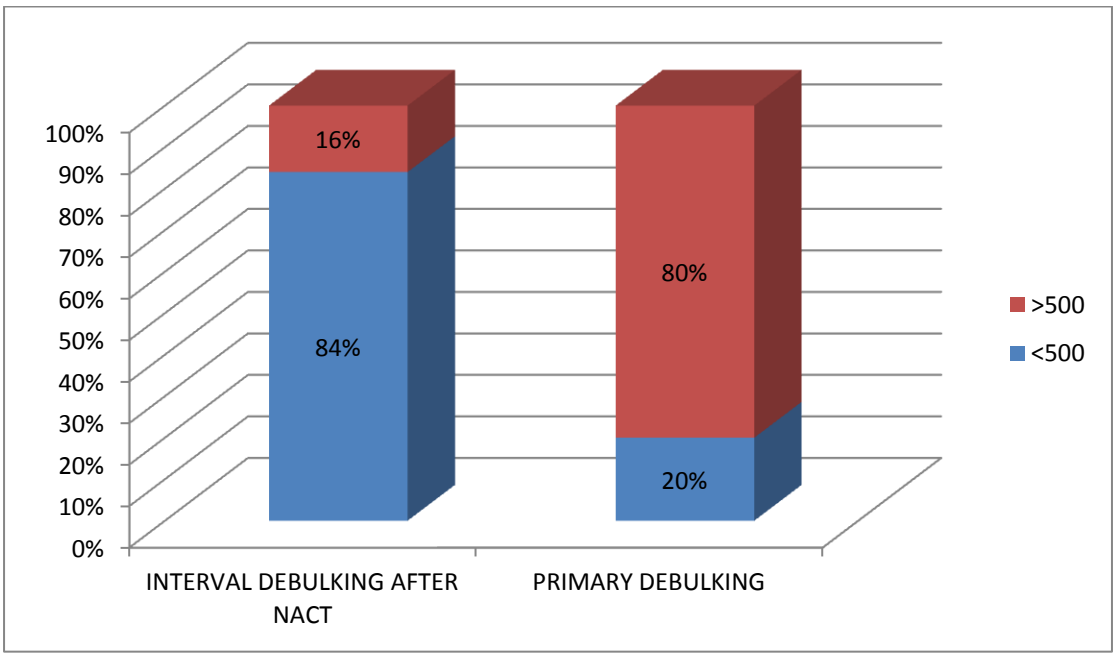
ACITIS

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Ascitis_ml	<500	Count	21	5	26
		% within GROUP	84.0%	20.0%	52.0%
	>500	Count	4	20	24
		% within GROUP	16.0%	80.0%	48.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=20.513** p<0.001

ACITIS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30%
20%
10%
0%
16%
84%
80%
20%
INTERVAL DEBULKING AFTER NACT
PRIMARY DEBULKING
>500
<500

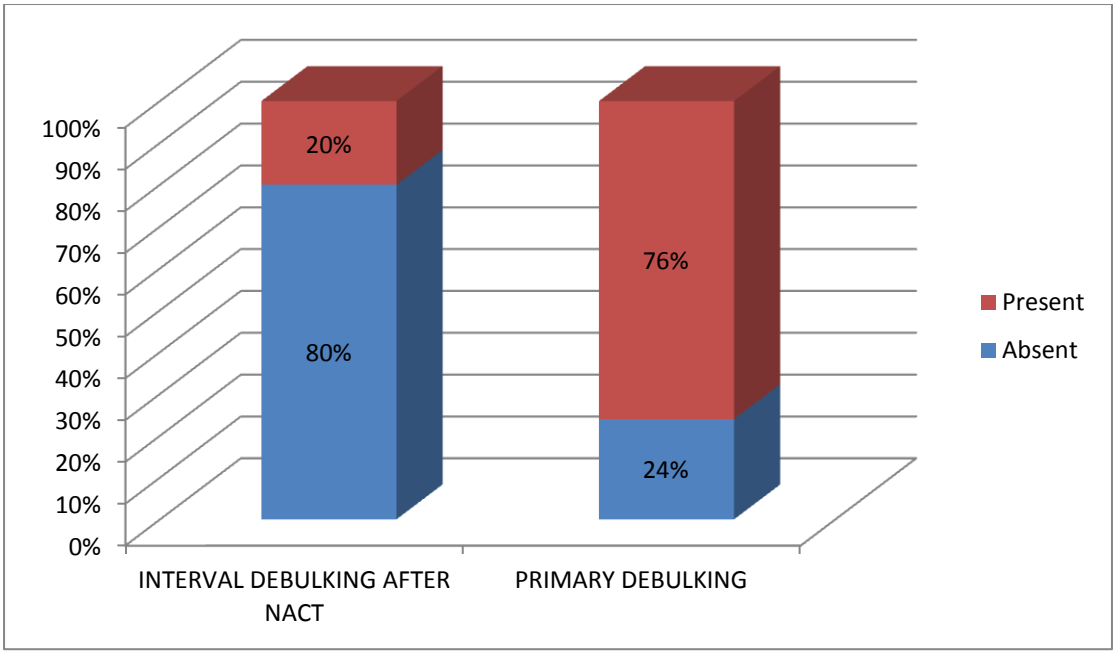
ADHESIONS

CROSSTAB

				GROUP		TOTAL
				INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Adhesions	Absent	Count		20	6	26
		%	within GROUP	80.0%	24.0%	52.0%
	Present	Count		5	19	24
		%	within GROUP	20.0%	76.0%	48.0%
Total		Count		25	25	50
		%	within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=15.705** p<0.001

ADHESIONS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10%
0%
20%
80%
76%
24%
INTERVAL DEBULKING AFTER NACT
PRIMARY DEBULKING
Present
Absent

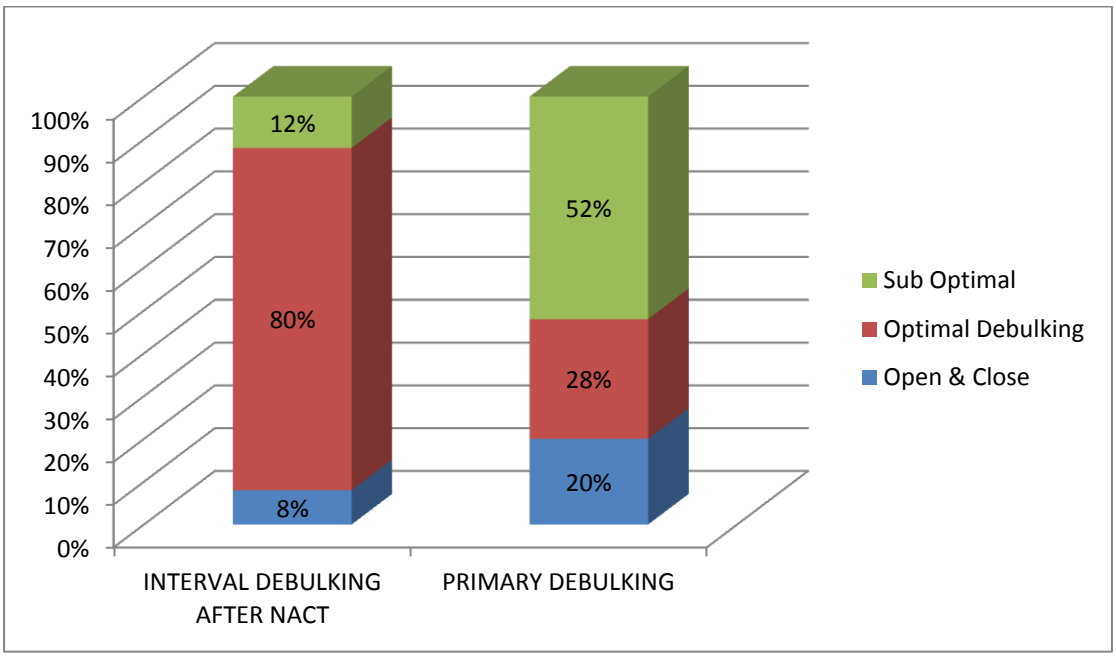
RESIDUAL TUMOR VOLUME

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Tumor_Clearance	Open & Close	Count	2	5	7
		% within GROUP	8.0%	20.0%	14.0%
	Optimal Debulking	Count	20	7	27
		% within GROUP	80.0%	28.0%	54.0%
	Sub Optimal	Count	3	13	16
		% within GROUP	12.0%	52.0%	32.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=13.795** p<0.001

RESIDUAL TUMOR VOLUME



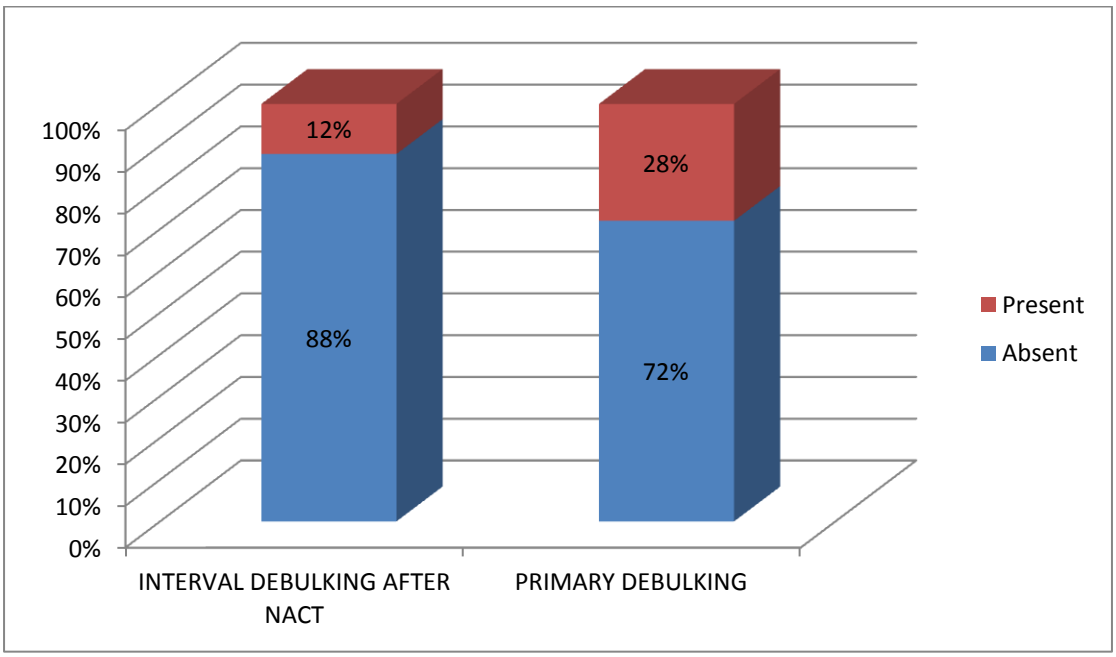
INJURY TO ADJACENT STUCTURES

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Injury_to_Adjacent_structures	Absent	Count	22	18	40
		% within GROUP	88.0%	72.0%	80.0%
	Present	Count	3	7	10
		% within GROUP	12.0%	28.0%	20.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=2.000 p=0.157

INJURY TO ADJACENT STUCTURES



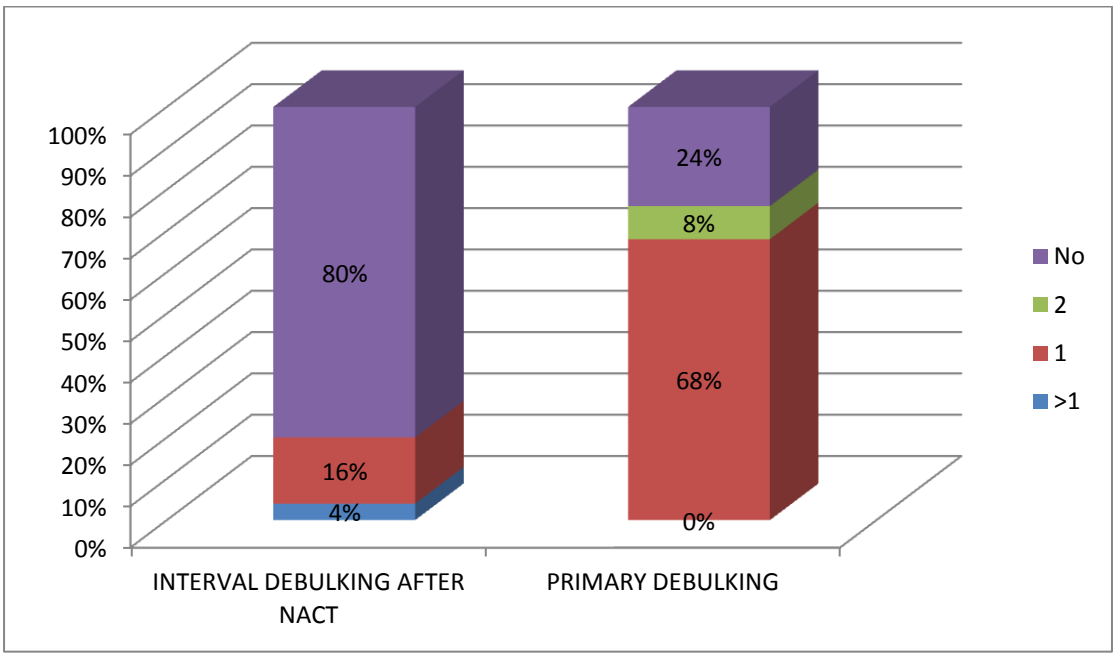
BLOOD TRANSFUSION

Crosstab

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Blood_Transfusion	>1	Count	1	0	1
		% within GROUP	4.0%	0.0%	2.0%
	1	Count	4	17	21
		% within GROUP	16.0%	68.0%	42.0%
	2	Count	0	2	2
		% within GROUP	0.0%	8.0%	4.0%
	No	Count	20	6	26
		% within GROUP	80.0%	24.0%	52.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=18.586** p<0.001

BLOOD TRANSFUSION



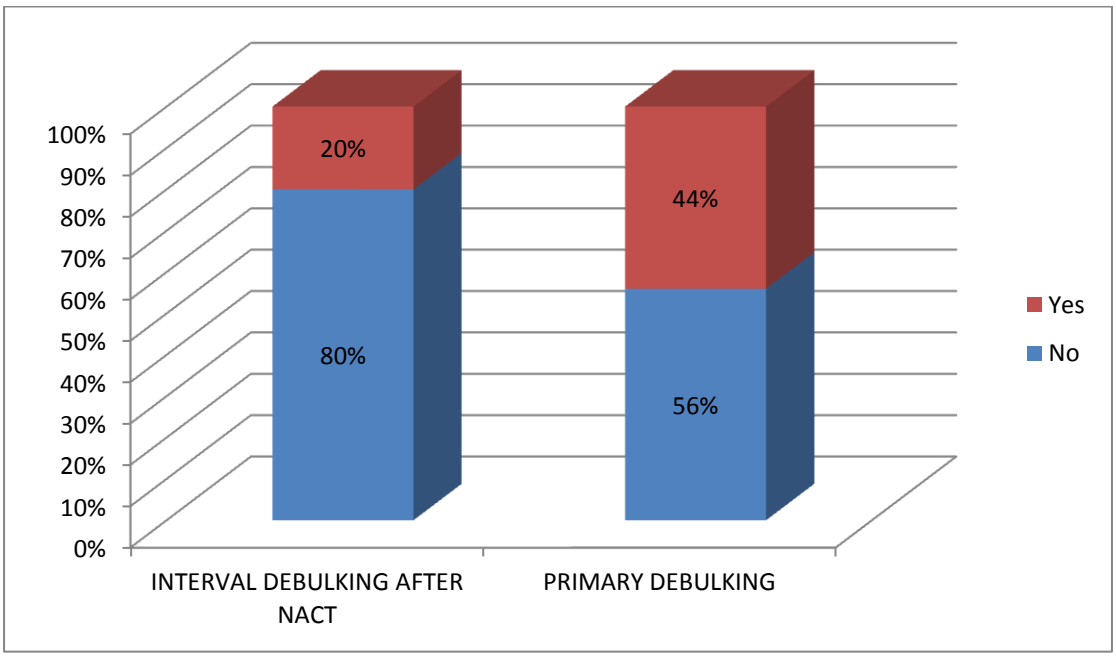
HDU STAY

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
HDU_Stay	No	Count	20	14	34
		% within GROUP	80.0%	56.0%	68.0%
	Yes	Count	5	11	16
		% within GROUP	20.0%	44.0%	32.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=3.309 p=0.069

HDU STAY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20%
10%
0%
20%
80%
44%
56%
INTERVAL DEBULKING AFTER NACT
PRIMARY DEBULKING
Yes
No

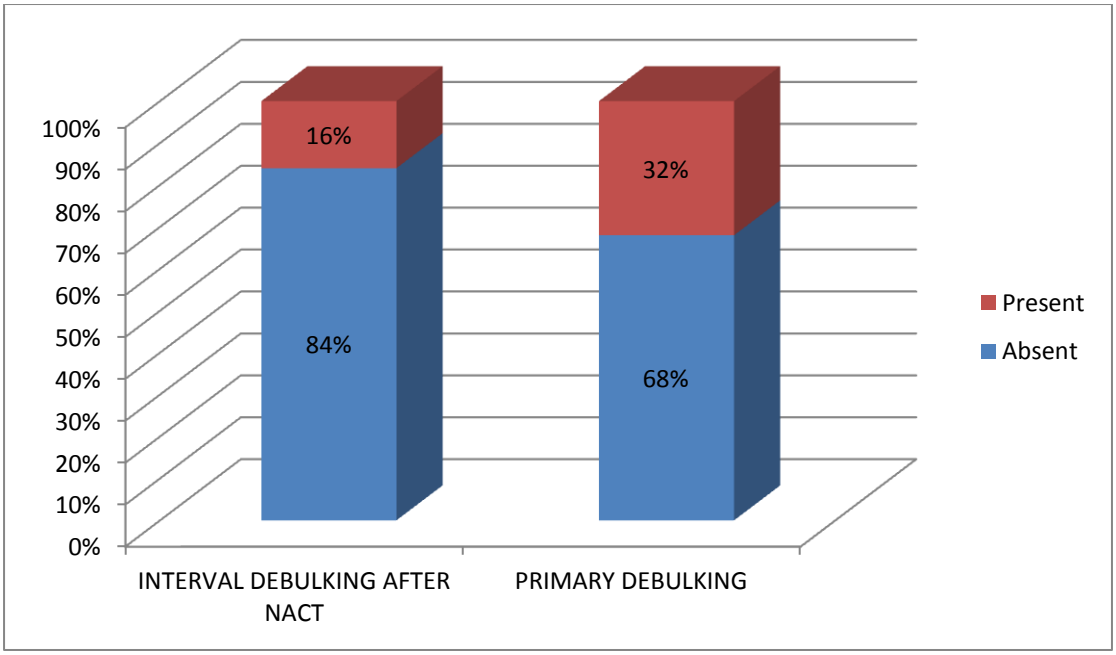
POST OPERATIVE COMPLICATIONS

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Post_Operative_ Complications	Absent	Count	21	17	38
		% within GROUP	84.0%	68.0%	76.0%
	Present	Count	4	8	12
		% within GROUP	16.0%	32.0%	24.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.754 p=0.185

POST OPERATIVE COMPLICATIONS



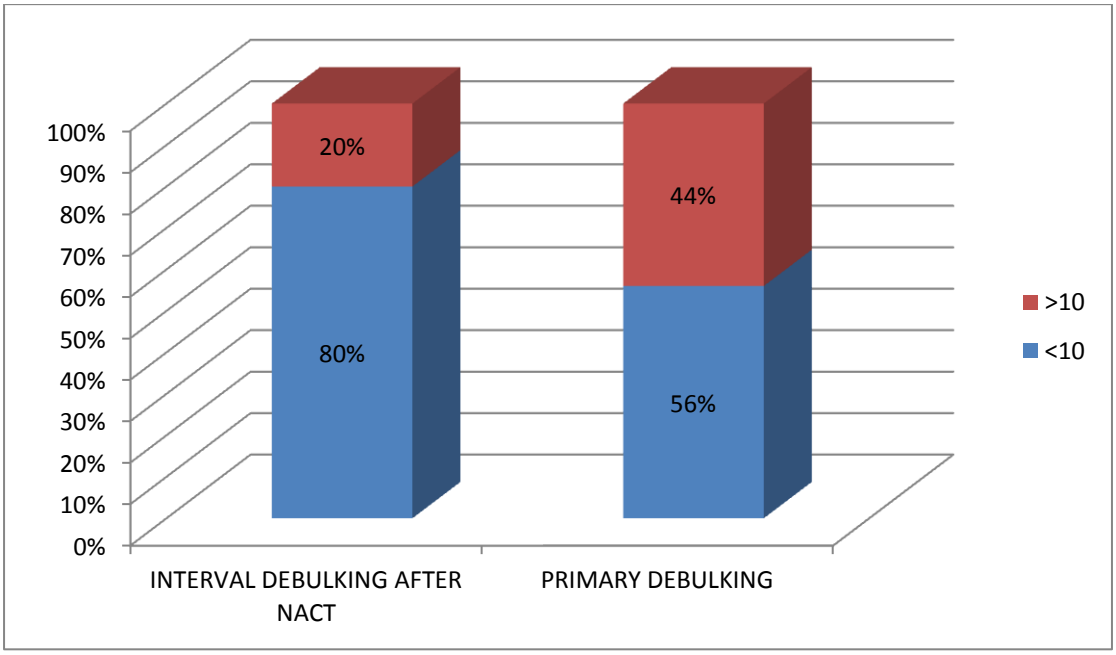
DURATION OF HOSPITAL STAY

CROSSTAB

			GROUP		TOTAL
			INTERVAL DEBULKING AFTER NACT	PRIMARY DEBULKING	
Duration_of_stay_days	<10	Count	20	14	34
		% within GROUP	80.0%	56.0%	68.0%
	>10	Count	5	11	16
		% within GROUP	20.0%	44.0%	32.0%
Total		Count	25	25	50
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=3.309 p=0.069

DURATION OF HOSPITAL STAY



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 our 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 20 cases in PDS

group (80%), and it was present only in 4 cases (25%) 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 5 cases (20%) in NACT /IDS group at the time of surgery in our study.

In our study, injury to adjacent structures was present in 7 cases of PDS group (28%) whereas 3 cases in NACT had injury. Out of the total 10 cases, 2 had bladder injury, 2 had injury to the small bowel, 3 had ureteric injury, 2 had sigmoid colon and the other had rectal injury.

11(44%) cases of PDS group were admitted in High Dependency Unit whereas only 5(20%) cases of NACT/IDS group were admitted in HDU in our study.

Post –op complications were present in 8 cases of PDS group (32%), 4 cases (16%) of NACT/IDS group in our study.

Post-op complications noted are:

1.Wound infection – 4

Cardiopulmonary Complication -3

Paralytic ileus -2

Wound dehiscence -2

Deep vein thrombosis-1

In PDS group, 11 cases (44%) stayed more than 10 days in hospital but in NACT/IDS group 5 cases (20%) 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, 20 cases (80%) 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 13 cases (52%) of PDS group and 3 cases (12%) of NACT/IDS group.

Laparotomy and closure due to frozen pelvis done in 5 cases (20%) 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.

BIBILIOGRAPHY

- 11. Ansquer Y, Leblanc E, dough K, Morice P, Dauplat J, Mathevet P, et al. Neoadjuvant chemotherapy for unresectable ovarian carcinoma: A French multicenter study. Cancer.2001;91:2329-34. [PubMedl
- Chan YM, Ng TY , Ngan HY, Wong LC. Quality of life in women treated with neoadjuvant chemotherapy for advanced ovarian cancer: a prospective longitudinal study. Gynecol Oncol. 2003 Jan;88(1):9-16.
- Chi DS, Zivanovic O, Levinson KL, Kolev V, Huh J, Dottino J, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecol Oncol. 2010;19:38-42. [PubMed]
- Deo et al. Neoadjuvant chemotherapy followed by surgical cytoreduction in advanced epithelial cancer. Indian Journal of Cancer 2006 volume 43 .pg 117 to 121.
- Devita, et al. Cancer 8 th edition. Volume 2 sec 5 pg 1568-86
- Donato D, Angelides A, Irani H, Penalver M, Averette H. Infectious complications after gastrointestinal surgery in patients with ovarian carcinoma and malignant ascites. Gynecol Oncol. 1992;44:40-7. [PubMed]

- Giannopoulos T, Butler –Manuel S, Tayllor A, Ngeh N, Thomas H. Clinical outcomes of neoadjuvant chemotherapy and primary debulking surgery in advanced ovarian carcinoma. Eur JGynecol Oncol.2006;27(1):25-8.
- Goto T, Takano M, Hirata J, Konno T, Ontsuka S, Fujiwara K, Tsuda H.P16INK4a expression in cytology of ascites and response to chemotherapy in advanced ovarian cancer. Int J Cancer .2009 Jul 15;125(2): 339-44.
- Hacker, Berek JS, Lagasse LD; Primary cytoreductive surgery for epithelial ovarian cancer. Obst and Gynec. 1983;6 :413-420
- Heinz AP, Van Otecom AT. Trimbos JB et al. The treatment of advanced ovarian carcinoma clinical variables associated with prognosis. Gynec Oncology 1988:30:347-358.
- Hou JY, Kelly MG, Yu H, Mc Alpine JN, Azodi M, Rutherford TJ, Schwartz PE. Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease. Gynecol Oncol .2007 Apr;105(1):211-7.
- Kang S, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer?
- Kayikcoglo F, Kose MF, Boran N et al. Neoadjuvant chemotherapy or primary surgery in advanced epithelial cancer. Int J Gynec Cancer 2001;11:466-70.
- Kayikioglu F, Kose MF, Boran N, Caliskan E, Tulunay G. Neoadjuvant chemotherapy or primary surgery in advanced epithelial ovarian carcinoma. Int J Gynecol Cancer.2001;l 1:466-70. [PubMed]

- Kuhn , Rutke S et al. Cancer 2001 Nov 15;92(10):2585-91.
- Kuhn W, Rutke S, Spathe K, Schmalfeldt B, Florack G, von Hundelshausen B, et al. Neoadjuvant chemotherapy followed by tumor debulking prolongs survival for patients with poor prognosis in International Federation of Gynecology and Obstetrics Stage IIIC ovarian carcinoma. Cancer. 2001;92:2585-91. [PubMed]
- Le T Faught w, Hopkins L, Fung kee fung M.primary chemotherapy and adjuvant tumour debulking in the management of advanced stage epithelial cancer.Int J Gynaec cancer 2005 sep –oct ;15(5):770-5
- Maurice P, Dubernard G ,Reg A, Atllah D , Pautrier P, Pomel C et al. Results of interval debulking compared with primary debulking surgery in advanced ovarian cancer. J Am Coll Surgery 2003;197:955-63.
- Meta-analysis of 21 studies . Ann Surg Oncol.2009 Aug ; 16(8):2315-20.
- Novaks et al. Textbook of Gynecology 13 th Edition. Chap 32. Ovarian Cancer pg 1245-54.
- P.Hicher, M. Mahner S., Ortmann O, Hilfrich J et al., Neoadjuvant chemotherapy with carboplatin and docetaxel in advanced overian cancer a prospective multicentre phase II trial Oncol Rep. 2009 Sep: 212(3) : 605-13.

- Recchia F, De Fillippis S, Rosselli M, Saggio G, Carta G. Primary chemotherapy in stage IV ovarian cancer; Eur Journal Gynecol Oncol:2001;22(4);287-91.
- Safra t, Menczer J, Bernstein RM, Shpigel S , Matcejevsky D, Inbar MJ, Golan A, Grisaru D, Levy t. Combined weekly carboplatin and paclitaxel as primary treatment of advanced epithelial ovarian carcinoma. Gynecol Oncol. 2009 Aug;114(2):215-8.
- Shimada M, Kigawa J, Minagawa Y, Irie T, Takahashi M, Terakawa N. Significance of cytoreductive surgery including bowel resection for patients with advanced ovarian cancer. Am J Clin Oncol. *l999;22;481-4.* [PubMed]
- Shimizu Y, Hasumi K. et al. Nippon Sanka Fujinka Gakkai Zasshi. 1993 Sep;45(9):1007-14.
- Shwartz PE, Rutherford TJ, Chamber JT et al. Neoadjuvant chemotherapy for advanced ovarian cancer and long term survival. Gynec Oncol 1999; 72:93-9.
- Supra sert P Tiyanon J ,Kiet peare kool C.Outcome of interval debulking in advanced ovarian cancer patients.Asian pac J Cancer prev.2008.july-sep;9(3):519-24
- Surwit E , Childers J, Atlas I et al.Neoadjuvant Chemotherapy for advanced ovarian cancer. Int J Gynec Cancer 1996;6;356-61.

- Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. Interval debulking surgery for advanced ovarian cancer. Cochrane Database Syst Rev. 2009 Apr 15 ; (2): CD0006014.
- Tate S, Hirai Y, Takeshima N, Hasumi K et al. CA 125 regression during neoadjuvant chemotherapy as an independent prognostic factor for survival in patients with advanced ovarian serous adenocarcinoma. Gynecol Oncology. 2005 Jan;96(1):143-9.
- Tien Le, Ghadeer Alshaikh, Laura Hopkins, Wylam Faught, Michael Fung Kee Fung. Prognostic significance of post operative morbidities in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy and delayed primary surgical debulking; Annls of Surgical Oncology 13(12):1711-1716.
- Ushijima K, Ota S, Komai K , Matsuo G, Motoshima S, Honda S, Tomonari R, Sujiyama T, Kamura T. Clinical assessment of neoadjuvant chemotherapy and interval cytoreductive surgery for unresectable advanced ovarian cancer. Int Surg. 2002 Jul –Sep;87(3):185-90.
- Vergote I, De Wever I , Tjalma W, Van Gramberen M, Decloedt J, Van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma. Gynecol Oncol.1998 Dec;71(3);431-6.
- Vergote IV, De Wever, Decloedt J , Tjalma W, Van Gramberam M et al. Neoadjuvant chemotherapy Vs. Primary debulking Surgery in advanced ovarian cancer. Jun;27 (3 Suppln 7):31-6.

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

KEYWORDS

- Menopause
- Histology
- Ascities
- Residual Tumer volume
- Sub Optimal debulking
- Blood Transfusion
- Adhesions
- HDU Stay
- Post op complications
- Duration of Hospital Stay
- PDS - Primary Debulking Surgery
- NACT – Neoadjuvant Chemotherapy

INFORMATION SHEET

We are conducting a study on **"EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA"** among patients delivered in Department of Obstetrics and Gynecology, Madras Medical College, Chennai and for that your clinical details may be valuable to us.

We are selecting certain patients and if you are found eligible, we may be using your clinical details in such a way so as to not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date: ……..

CONSENT FORM

STUDY TITLE : "EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA"

STUDY CENTRE : DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, MADRAS MEDICAL COLLEGE, CHENNAI

PARTICIPANT NAME : AGE: SEX: MRD.NO:

I confirm that I have understood the purpose of procedure for the above study, I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during the procedure. I understand that my participation in the study in voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any or results that arise from the study.

I hereby consent to participate in this study of ""**EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA".**

Signature of Investigator : Place : Chennai

Date :

Study Investigators Name
Institution

Signature / Thumb Impression of patient

Tamil

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.J.Linu Gracia
Post Graduate in M.S. O & G
Madras Medical College
Chennai 600 003

Dear Dr.J.Linu Gracia ,

The Institutional Ethics Committee has considered your request and approved your study titled **"EFFECT OF NEOADJUVANT CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA " - NO.14012017 (IV).**

The following members of Ethics Committee were present in the meeting hold on **31.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.S.Suresh,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document:	Introduction - Conclusion.docx (D42373936)
Submitted:	10/10/2018 2:42:00 PM
Submitted By:	linugraciadr@gmail.com
Significance:	13 %

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