**DISSERTATION**

*on*

# EXPRESSION OF ER, PR, KI 67 AND CA125 IN OVARIAN SURFACE EPITHELIAL TUMORS WITH REFERENCE TO TNM STAGING OF THE DISEASE

*submitted in partial fulfillment of the requirements for the degree of*

**Doctor of Medicine (BRANCH-III)**

**M.D. PATHOLOGY**

**Register No.: 201713306**

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**
**CHENNAI**

**TIRUNELVELI MEDICAL COLLEGE**
**TIRUNELVELI**
**MAY 2020**

# CERTIFICATE

This is to certify that the dissertation titled **"EXPRESSION OF ER, PR, CA125 AND Ki67 IN OVARIAN SURFACE EPITHELIAL TUMORS WITH REFERENCE TO TNM STAGING OF THE DISEASE",** is a bonafide work done by **Dr.R.SRUTHI**, Post Graduate Student, Department of Pathology, Tirunelveli Medical College, Tirunelveli – 627011, in partial fulfilment of the university rules and regulations for the award of MD DEGREE in PATHOLOGY BRANCH-III, under my guidance and supervision, during the academic period from 2017 to 2020.

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## CERTIFICATE

I hereby certify that this dissertation entitled "**EXPRESSION OF ER, PR, CA125 AND Ki67 IN OVARIAN SURFACE EPITHELIAL TUMORS WITH REFERENCE TO TNM STAGING OF THE DISEASE"** is a record of work done by **Dr. R. SRUTHI** , in the Department of Pathology, Tirunelveli Medical College, Tirunelveli, during her postgraduate degree course period from 2017- 2020. This work has not formed the basis for previous award of any degree.

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## DECLARATION

I solemnly declare that the dissertation titled **"EXPRESSION OF ER, PR, CA125 AND Ki67 IN OVARIAN SURFACE EPITHELIAL TUMORS WITH REFERENCE TO TNM STAGING OF THE DISEASE"** was done by me at Tirunelveli Medical College, Tirunelveli– 627011, during the period august 2017 to march 2019 under the guidance and supervision of **Prof.DR.K.BHAGIYALAKSHMI, MD**,**AND Prof. DR.J.JHONSY MERLA, MD**, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of MD DEGREE in PATHOLOGY BRANCH-III.

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PRINCIPAL INVESTIGATOR: Dr.R.SRUTHI, MBBS.,
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**THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED**

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| 1. | TIREC Application Form | ☐ |
| 2. | Study Protocol | ☐ |
| 3. | Department Research Committee Approval | ☐ |
| 4. | Patient Information Document and Consent Form in English and Vernacular Language | ☐ |
| 5. | Investigator's Brochure | ☐ |
| 6. | Proposed Methods for Patient Accrual Proposed | ☐ |
| 7. | Curriculum Vitae of The Principal Investigator | ☐ |
| 8. | Insurance /Compensation Policy | ☐ |
| 9. | Investigator's Agreement with Sponsor | ☐ |
| 10. | Investigator's Undertaking | ☐ |
| 11. | DCGI/DGFT approval | ☐ |
| 12. | Clinical Trial Agreement (CTA) | ☐ |
| 13. | Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) | ☐ |
| 14. | Clinical Trials Registry-India (CTRI) Registration | ☐ |

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1. The approval is valid for a period of 2 year/s or duration of project whichever is later
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**STANDS APPROVED UNDER SEAL**

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## CERTIFICATE – II

This is certify that this dissertation work title **"EXPRESSION OF ER, PR, CA125 AND Ki67 IN OVARIAN SURFACE EPITHELIAL TUMORS WITH REFERENCE TO TNM STAGING OF THE DISEASE"** of the candidate **Dr.R.SRUTHI** with registration Number **201713306** for the award of **M.D.** Degree in the branch of **PATHOLOGY (III).** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **16 percentage** of plagiarism in the dissertation.

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| LIST OF ABBREVATIONS USED | |
|---|---|
| AAR | Age adjusted incidence rate |
| BMI | Body mass index |
| CA 125 | Carcinoma antigen 125 |
| CO | Cumulus oophorus |
| CCNE1 | Cyclin E1 |
| DPX | Dextrene Phthalate Xylene |
| DAB | Diaminobenzidine tetrachloride |
| EDTA | Ethylene diaminetetraacetic acid |
| EMA | Epithelial membrane antigen |
| ER | Estrogen receptor |
| EGFR | EGFR – epidermal growth factor |
| FOXL2 | Forkhead transcription factor 2 |
| FSH | Follicle stimulating hormone |
| FIGO | Federation of gynecology and obstetrics |
| GCIG | Gyencologic Cancer Intergroup |

| | |
|---|---|
| HNPCC | Hereditary nonpolyposis colon cancer |
| HRP | Horse Radhish peroxidase |
| IHC | Immunohistochemistry |
| IS | Immunohistochemical Score |
| IUDs | IUDs - intrauterine devices |
| IVF | In vitro fertilization |
| LGSC | Low grade serous carcinoma |
| MMR | Mismatch repair |
| NF1 | Nuclear Factor |
| PI3K | Phosphatidylinositol kinase |
| PR | Progesterone receptor |
| SBT | Serous borderline tumor |
| SCTAT | Sex cord tumor with annular tubule |
| SEER | Surveillance epidemiology and end results |
| STIC | Serous tubal intraepithelial carcinoma |
| TE | Theca externa |

| | |
|---|---|
| TI | Theca interna |
| WHO | World health organization |
| ZP | Zona pellucida |
| ZG | Zona granulosa |

## INTRODUCTION

Ovarian cancer is the sixth most common cancer in women and seventh most common cause of death, worldwide [1]. There are about 2,04,000 new cases and 1,25,000 death annually. Ovarian tumor ranks third among the female genital tract malignancy in India with age standardized ratio 6.7/1,00,000. Indian cancer registry data in 2011 projects AAR (age adjusted incidence rate) from 10.7-11.2 per 1,00,000 women in different parts of country[2].The most recent, surveillance epidemiology and end results (SEER) calculation of life time risk for ovarian cancers are that 1 in 55 women will develop ovarian cancer over their lifetime [3] .

World health organization (WHO) classifies ovarian tumor according to their most probable cell of origin and histomorphological features[4]. Most of the tumors are epithelial in origin. Surface epithelial tumors accounts for about 2/3$^{rd}$ of all ovarian neoplasm[5]. About 80% tumors are benign and occur in younger women and 10% among them are hereditary in nature[6]. Malignant epithelial ovarian tumor occurs most commonly in older women and accounts for approximately 3% of all cancers [7] ovarian surface epithelial tumor cells are characterized by increased expression of steroid hormone receptors (ER&PR), CA125 and shows high proliferative activity[8].

Greater than 80%of patients with epithelial ovarian cancer have elevated serum CA125 levels at diagnosis and serial serum CA125 levels correlate with changes in disease status in most cases[9]. Serum CA125 is routinely monitored in ovarian cancers and many

studies have proven their value in guiding treatment, but the immunohistochemical expressions are not clearly made out[10].

In this study we analyze the immunohistochemical expression of ER, PR, CA125 and Ki67 in surface epithelial ovarian tumor with corresponding to its TNM staging along with its level of serum CA125 expression.

## AIM

To analyze the immunohistochemical profile of estrogen receptor (ER), progesterone receptor (PR), cancer antigen 125 (CA125), proliferative marker (Ki 67) and serum CA125 in surface epithelial ovarian tumors according to their corresponding TNM staging.

## OBJECTIVES

1. To study the epithelial ovarian tumors using the immunohistochemistry markers ER, PR, Ki-67 and CA125.
2. To assess the correlation of hormone and other receptors expression with tumors of each grade in its TNM staging of the disease.
3. To estimate serum values of CA 125.
4. To correlate the serum value and tissue expression of CA 125 in surface epithelial tumors according to TNM staging of the disease.

# REVIEW OF LIERATURE

## HISTORY

The first documented case of ovarian tumor removal dates back to 1809, Jane Todd Crawford had an astonishing 22 pound tumor extracted from abdomen. This event holds a significant place in the medical history and there is no doubt that in the 200 year since ovarian cancer research has made significant leaps[11].

In the past 30 years, there is progression in the advancement of screening, diagnosis and treatment of ovarian cancer. One of the most common and heavily researched screening tools today is elevation of the blood protein CA 125. Robert bast MD first discovered this biomarker in 1981[12]. Study researchers recently demonstrated that routine use of Ca 125 or vaginal ultrasound resulted in 48 % of ovarian cancer being diagnosed at Stage I or II[12].

## EMBRYOLOGY

Most of the structures of female genital tract arise from mullerian duct system, the ovaries arise from the genital ridge, a thickening in the mesothelium high on the posterior wall of the peritoneal cavity[13]. Primordial germ cells migrate from the yolk sac to the urogenital ridges via the hindgut approximately 3 weeks post fertilization. In the absence of sex-determining region Y, the germ cells are incorporated into a proliferating mass of surface epithelial cells. From the 2$^{nd}$ to the early 3$^{rd}$ trimester, this thickened cortical mass of proliferating epithelial and germ

cells divides into small groups demarcated by strands of stromal tissue extending from the medulla to the cortex. They are further subdivided into primordial follicles composed of single germ cells surrounded by a layer of epithelial cells, the primitive granulosa cells. Interstitial (Leydig) cells develop within the stroma of the 2nd trimester female gonad, but most of the cells degenerate by term. The few found in the hilum of the adult ovary are called hilus cells[13]. Early epithelial proliferations, which in males contribute to the connection between the sex cords and the mesonephric tubules, undergo degeneration in gonads destined to become ovary, leaving a few tubular remnants in the ovarian hilum, the rete ovarii. The ovaries which are primarily an abdominal organ in early embryonic period later descends to its adult pelvic position. As a result the blood supply and the lymphatics are mainly derived from the upper Abdomen rather than pelvis. Hence the tumor spreads typically to para aortic nodes rather than to local lymph nodes in pelvic or inguinal area[13].

**ANATOMY**

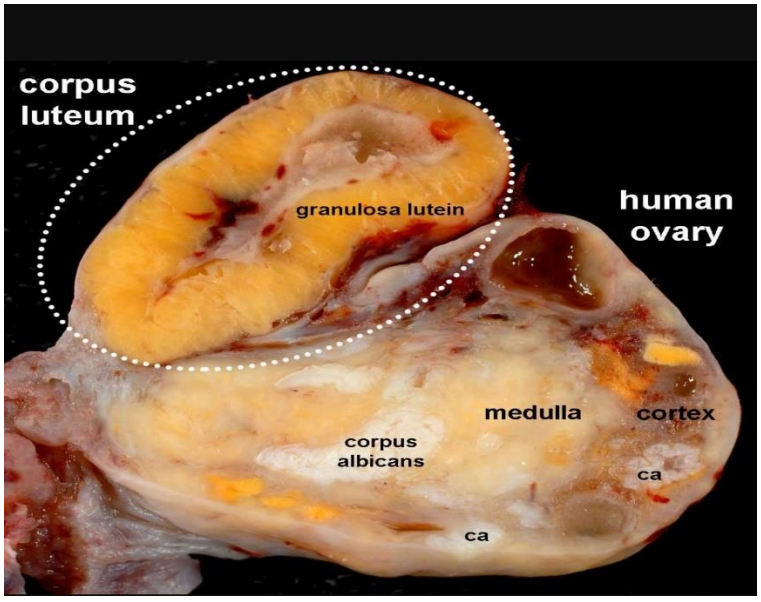
The ovaries, which are the site of oogenesis are paired pelvic organs located on the sides of the uterus. It lies close to the lateral pelvic wall, behind the broad ligament and anterior to the rectum[14]. They are connected to the broad ligament by the mesovarium (a double fold of peritoneum), to the uterine cornu by the ovarian (or utero- ovarian) ligament, and to the lateral pelvic wall by the infundibulopelvic (or suspensory) ligament. During reproductive period, their average size is 4×2×1 cm and their average weight is 5–8 g[15]. Their size and weight, vary considerably depending on their content of follicular

derivatives. Thin-walled, fluid-filled cystic follicles & bright yellow corpora lutea may be partially visible from the external aspect.

Three zones are poorly defined on the sectioned surface:

- An outer cortex,
- An inner medulla, and
- The hilus.

Follicular structures (cystic follicles and corpora lutea )are usually visible in the cortex. Small white scars (corpora albicantia) are seen within the medulla[16].After the menopause, the ovaries shrink to one half their size, have a shrunken, gyriform, external appearance[17].




**BLOOD SUPPLY**

The blood supply of the ovary is derived from the anastamoses formed by the ovarian artery, a branch of the aorta, and from the ovarian branch of the uterine artery[18] .

Approximately ten arterial branches from this arcade penetrate the ovarian hilus and course through medulla and at the corticomedullary junction, form a plexus. From which smaller, straight cortical arterioles arise and penetrate the cortex in a

radial fashion. These cortical arterioles branch and anastomose, forming sets of interconnecting vascular arcades that give rise to dense capillary networks within the theca layers of the ovarian follicles [13]. The veins within the ovary accompany the arteries and become large and tortuous in the medulla and join together in the hilus, forming a plexus, which drains into the ovarian veins the left and right and inturn into the left renal vein and the inferior vena cava, respectively[13].

**NERVE SUPPLY**

Ovarian plexus derived from renal, aortic and hypogastric plexus. It contains both sympathetic nerves (T10, T11) and parasympathetic nerves (S2,S3,S4)[18].

**LYMPHATIC DRAINAGE OF OVARY**

The ovarian lymph vessels form a plexus at the hilus from which they travel to the mesovarium to drain into the para aortic nodes. Others drain into the internal iliac, external iliac, common iliac and inguinal nodes[16]. Since the ovaries are primarily an abdominal organ in the embryonic period the blood supply and the lymphatics are mainly derived from the upper abdomen rather than pelvis. Hence the tumor spreads typically to para aortic nodes rather than to local lymph nodes in pelvic or inguinal area[17].

## HISTOLOGY

The ovary is covered by a single layer of modified mesothelium known as ovarian surface epithelium. This epithelium is immunoreactive for keratin, epithelial membrane antigen (EMA), Ber-EP4, CA 125, vimentin, estrogen (ER) and progesterone receptors (PR), and follicle-stimulating hormone [16, 17]. The ovarian stroma is divided into a cortical and a medullary region, but the boundaries between them are indistinct. It is composed mainly of spindle-shaped stromal cells resembling fibroblasts, typically arranged in whorls or storiform pattern. They are immunoreactive for FOXL2, ER, and PR [16].Some of these cells have myoid ("myofibroblastic") features and exhibit immunoreactivity for smooth muscle actin and desmin[19, 20]. Foci of smooth muscles may be present [19]. Other cells that may be found in the ovarian stroma are luteinized stromal cells, decidual cells, nests of cells resembling endometrial stromal cells, mature fat cells, and neuroendocrine cells [21].

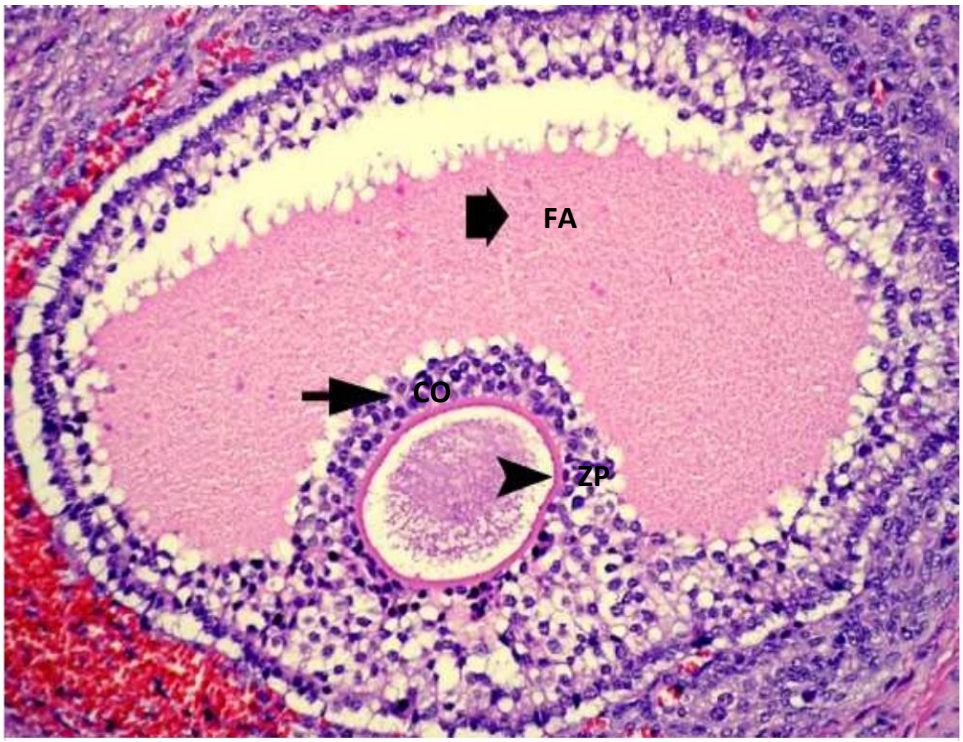
The life cycle of the ovarian follicle includes primordial, maturing (primary, secondary, tertiary, and graafian), and atretic forms, together with corpora lutea and corpora albicantia[14]. During early fetal development, primordial germ cells called oogonia migrate into the ovarian cortex where they multiply by mitosis. By the $4^{th}$ and $5^{th}$ months of fetal development, some oogonia enlarge and assume the potential for development into mature gametes. At this stage they are called primary oocytes and commence the first stage of meiotic division [13].

By the $7^{th}$ month of fetal development, a single layer of flattened follicular cells surrounds the primary oocytes to form primordial follicles. This encapsulation arrests the first meiotic division and no further development occurs until the female reaches sexual

maturity [13]. The process of meiotic division is only completed during follicular maturation leading up to ovulation and fertilization. Follicular maturation is stimulated by FSH secreted by the anterior pituitary gland [13]. During each ovarian cycle, up to 20 primordial follicles is activated for the maturation process, among that only one follicle reaches full maturity and ovulation while the remainder regress. The primary purpose of the other follicles may be to act as an endocrine gland which may be far beyond the capacity of a single follicle [13].

In the mature ovary, undeveloped follicles exist as primordial follicles PF, which are composed of a primary oocyte surrounded by a single layer of flattened follicular cells. When primordial follicles gets stimulated, it increases in size to form a primary follicle; the oocyte has enlarged greatly with multiplication of follicular cells by mitosis and assumes cuboidal shape; they are now known as granulosa cells [13].

A thick homogeneous layer of glycoprotein and acid proteoglycans, the zona pellucida, develops between the oocyte and the follicular cells. Granulosa cells continues to proliferate, forming a layer several cells thick called the zona granulosa ZG. Thus Primary follicles continue to develop to form secondary follicles. Small fluid filled spaces appear within proliferating zona granulosa, these fuse to form follicular antrum FA. At this stage, the oocyte has reached its full size and becomes situated eccentrically in a thickened area of the granulosa called the cumulus oophorus CO[13]. The theca folliculi develop two layers, the ***theca interna*** composed of rounded cells , and ***theca externa*** **TE** consisting of spindle-shaped cells that merges with the surrounding stroma. Theca interna cells are typical steroid-secreting cells.




Produce oestrogen precursors (e.g. androstenedione), oestrogen, and in the preovulatory stage produces progesterone. The granulosa cells also produce hormones like estrogen from its precursor secreted by theca interna, intrafollicular FSH at ovulation, FSH inhibitor[13] .

***Inhibin F*** and progesterone which promotes the changes in the endometrium and make it ready for implantation of the embryo after fertilisation. The theca externa has no endocrine function. Approaching maturity, further growth of the oocyte ceases and the first meiotic division is completed just before ovulation. At this stage, the oocyte becomes the ***secondary oocyte*** and commences the second meiotic division, which is not completed until ovum is pierced by spermatozoon[13]. At ovulation, the mature follicle ruptures, the ovum is expelled into the peritoneal cavity near the entrance to the Fallopian tube. Following ovulation, the ruptured follicle collapses which is filled with blood clot to form

the corpus luteum of menstruation**.** Without the continuing stimulus of LH, the corpus luteum cannot be maintained and12-14 days after ovulation it regresses, ultimately forming a functionless corpus Albicans which is then replaced by atretic follicles. In the postmenopausal woman, primordial follicles are absent and the cortex consists of stroma and corpora albicantes only, with no developing follicles[13].

## CARCINOMA OVARY

Worldwide, ovarian cancer is the sixth most common cancer in women and seventh most common cause of death [22]. Ovarian cancer is often known "the silent killer". Its early detection is difficult because the ovaries are deep within the pelvis and initial symptoms often are ambiguous. The cancer goes undiagnosed until after the disease is far advanced and has spread throughout the abdomen or to the distant organs [23, 24].

## CLINICAL PRESENTATION

Epithelial tumors occur mainly in adults. Uncommon in children and teenagers [25,26]. Benign and borderline tumors occur at all ages, but are often detected in premenopausal women. Carcinomas occur chiefly in perimenopausal and postmenopausal women. More than 70% of women with ovarian cancer have extensive extraovarian tumor spread at the time of diagnosis, Partly because the symptoms caused by epithelial tumors are vague and nonspecific and do not prompt early diagnosis[27].

The most common symptoms are pelvic discomfort or pain, a sensation of abdominal fullness or pressure, gastrointestinal disturbances, urinary frequency and occasionally menstrual abnormalities[28,29] .

The CA 125 monoclonal antibody blood test detects antigenic site on MUC16, a high molecular weight glycoprotein of uncertain function. The test is most useful in women with serous carcinoma, although positive results are obtained in other histologic types as well. It is usually positive in women with advanced borderline and malignant epithelial tumors and in some women with localized disease[32,33].

**EPIDEMIOLOGY**

Ovarian cancer is one of the most prevalent diseases affecting women. Ovarian tumor ranks third among the female genital tract malignancy in India with age standardized ratio 6.7/1,00,000 [34]. It is the most common malignancy after carcinoma breast in women over 40 years of age in developed countries. It is a neoplasm that responds well to systemic chemotherapy more than 80% of the cases, when it is accompanied by optimal cytoreductive surgery. Despite complete response with first line chemotherapy, ovarian epithelial cancer type presents recurrence in more than 50% of women [35]. So, determination of various histologic patterns of ovarian tumors is very important in diagnosis, prognosis as well as treatment of ovarian tumors [35]. Epithelial ovarian cancer, the most frequent of them, occupies the 3rd place of gynecological malignancies worldwide[35] . most of them are diagnose in 50 to 70 years of age, in locally advanced stage[36]. 80% of the cases respond to primary treatment although they have a higher percentage of relapse due to lack of appropriate research methods, favoured by low

symptoms and the lack of early stage screening techniques that hinder the only curable timely diagnosis [37]. Ovarian carcinoma etiology and pathogenesis are poorly understood [38, 39]. Researchers have discovered several risk factors that might increase a woman's chance of developing epithelial ovarian cancer [40].

## RISK FACTORS

These risk factors don't apply to other less common types of ovarian cancer like germ cell tumors and stromal tumors

**AGE**: Risk of developing ovarian tumors gets higher with age. Rare in women younger than 40 years . Most ovarian cancers develop after menopause. Mean age of ovarian cancers are found in women 63 years of age or older [41].

**OVERWEIGHT OR OBESE :** Obesity is a higher risk of developing many cancers. The connection between ovarian cancer risk and obesity is not clear. Obese women with a body mass index [BMI] of atleast 30 may have a higher risk of developing ovarian cancer [42].

**INCREASED MATERNAL AGE AT PREGNANCY AND 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 [43].

**FERTILITY TREATMENT :** 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[41].

**HOMONE THERAPY AFTER MENOPAUSE :** Women using estrogens after menopause have an increased risk of developing ovarian cancer. Risk seems to be higher

in women taking estrogen alone without progesterone for atleast 5 or 10 years. Risk is less for those taking estrogen and progesterone[42].

**FAMILY HISTORY OF OVARIAN, BREAST OR COLORECTAL CANCER**

Ovarian cancer can run in families. An individual has risk of ovarian cancer when more of her family members present with ovarian cancers. A family history of some other types of cancer such as colorectal and breast cancer is linked to an increased risk of ovarian cancer. Because these cancers can be caused by an inherited mutation (change) in certain genes that cause a family cancer syndrome that increases the risk of ovarian cancer [43].

**FAMILY CANCER SYNDROME :** About 5 to 10% of ovarian cancers are a part of family cancer syndromes resulting from inherited changes(mutations)in certain genes [42].

**HEREDITARY BREAST AND OVARIAN CANCER SYNDROME**

This syndrome is caused by inherited mutations in the genes BRCA1 and BRCA2. This syndrome is linked to a high risk of breast cancer as well as ovarian, fallopian tube, and primary peritoneal cancers [44]. Mutations in BRCA1 and BRCA2 are also responsible for most inherited ovarian cancers. The lifetime ovarian cancer risk for women with a BRCA1 mutation is estimated to be between 35% and 70%. For women with BRCA2 mutations the risk estimated to be between 10% and 30% by age 70 [45].

**PTEN TUMOR HAMARTOMA SYNDROME:** Also known as Cowden disease, caused by inherited mutations in the PTEN gene. People are primarily affected with problems, thyroid cancer, and breast cancer. Women also have an increased risk of endometrial and ovarian cancer [46].

**HEREDITARY NONPOLYPOSIS COLON CANCER** (HNPCC)

Women with this syndrome have a very high risk of colon cancer and also have an increased risk of developing endometrial and ovarian cancer. Mutated genes include MLH1, MLH3,MSH2, MSH6, TGFBR2, PMS1, and PMS2. Risk of ovarian cancer in women with HNPCC is about 10%. 1% of all ovarian epithelial cancers occur in women with this syndrome[46].

**PEUTZ-JEGHERS SYNDROME:** They have a high risk of cancer and develops polyps, 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 tubule (SCTAT).This syndrome is caused by mutations in the gene STK11[47].

**MUTYH-ASSOCIATED POLYPOSIS:** patients develops polyps in the colon and small intestine and have high risk of colon cancer and other cancers, including cancers of the ovary and bladder. This syndrome is caused by mutations in the gene MUTYH[47].

**SMOKING AND ALCOHOL USE:** Smoking is directly linked to an increased risk for the mucinous type of epithelial ovarian tumorsv[47].

## FACTORS WITH UNCLEAR EFFECTS ON OVARIAN CANCER RISK

**ANDROGENS:** Androgens, such as testosterone, are male hormones. There is a link between androgens and specific types of ovarian cancer, but further studies are needed [48].

**TALCUM POWDER:**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. The findings of

possible link between talcum powder and cancer of the ovary have been mixed. Some studies reports a slightly increased risk and some studies says no significant increase in risk. Many case-control studies have found a small increase in risk[49].

**DIET :** Some studies have shown a reduced rate of ovarian cancer in women who having a diet high in vegetables or a low fat diet[50].

## FACTORS THAT CAN LOWER RISK OF OVARIAN CANCER

**PREGNANCY AND BREASTFEEDING:** Women whose pregnancy has been carried to term before age 26 have a lower risk. The risk goes down with each full- term pregnancy. Breastfeeding may lower the risk even further [51].

**BIRTH CONTROL**

**ORAL CONRTRACEPTIVES:** Women who have used oral contraceptives (also known as birth control pills) have a lower risk of ovarian cancer. Longer usage of the pills reduces the risk of ovarian tumors[52].

**TUBAL LIGATION AND INTRA UTERINE DEVICE** : Other forms of birth control such as tubal ligation (having fallopian tubes tied) and short use of IUDs (intrauterine devices) also been associated with a lower risk of ovarian cancer[53].

**HYSTRECTOMY:** Hysterectomy (removing the uterus without removing the ovaries) also seems to reduce the risk of getting ovarian cancer by about one-third[54]

**WHO CLASSIFICATION OF OVARY (2014)**

**SURFACE EPITHELIAL TUMORS**

1. SEROUS TUMORS

**Benign**

- Serous cystadenoma
- Serous adenofibroma
- Serous surface papilloma

**Borderline**

- Serous borderline tumour
- Atypical proliferative serous tumour
- Serous borderline tumour – micropapillary variant / Non-invasive low-grade serous carcinoma

**Malignant**

- Low-grade serous carcinoma
- High-grade serous carcinoma

2. MUCINOUS TUMOURS

**Benign**

- Mucinous cystadenoma
- Mucinous adenofibroma
- **Borderline**
- Mucinous borderline tumour / Atypical proliferative mucinous tumour

**Malignant**

- Mucinous carcinoma

3.ENDOMETRIOID TUMOURS

**Benign**

- Endometriotic cyst
- Endometrioid cystadenoma
- Endometrioid adenofibroma

**Borderline**

- Endometrioid borderline tumour / Atypical proliferative endometrioid tumour

**Malignant**

- Endometrioid carcinoma

4. CLEAR CELL TUMOURS

**Benign**

- Clear cell cystadenoma
- Clear cell adenofi broma

**Borderline**

- Clear cell borderline tumour / Atypical proliferative clear cell tumour

**Malignant**

- Clear cell carcinoma

5.BRENNER TUMOURS

**Benign**

- Brenner tumour

**Borderline**

- Borderline Brenner tumour / Atypical proliferative Brenner tumour

**Malignant**

- Malignant Brenner tumour

6. SEROMUCINOUS TUMOURS

**Benign**

- Seromucinous cystadenoma
- Seromucinous adenofibroma

**Borderline**

- Seromucinous borderline tumour / Atypical proliferative seromucinous tumour

**Malignant**

- Seromucinous carcinoma

7.UNDIFFERENTIATED CARCINOMA[55]

**GENE CHANGES RELATED TO OVARIAN TUMORS INHERITED GENETIC MUTATIONS**

A small proportion of ovarian tumors occur in women with inherited mutations linked to an increased risk of ovarian tumor. These include mutations in the BRCA1 and BRCA2 genes, as well as the genes related to other family cancer syndromes linked to an increased risk of ovarian tumors, such as PTEN (PTEN tumor hamartoma syndrome), STK11 (Peutz-

Jeghers syndrome), MUTYH (MUTYH-associated polyposis, and many genes involved in hereditary Non-polyposis colon cancer (MLH1, MLH3,MSH2, MSH6, TGFBR2, PMS1, PMS2)[56].

High grade serous tumors are associated with 10-15% inherited germline BRAC1 or BRAC 2 mutation, hence genetic counselling and test should be considered in such patients[57] .Low grade serous carcinoma, mucinous tumors, endometrioid and clear cell tumors are associated with lynch syndrome.

## ACQUIRED GENETIC MUTATIONS

Most mutations related to ovarian tumors are not inherited but instead are acquired mutations. Most ovarian tumors have several acquired mutations. Research has suggested that tests to identify acquired mutations in ovarian cancers, like the *TP53* tumor suppressor gene or HER2 oncogene, can help predict a woman's prognosis. The role of these tests is still not certain, and more research is needed[58].

**SEROUS TUMORS:** The most common mutations are *KRAS* and *BRAF* in Serous borderline tumors and low-grade serous carcinoma and have relatively few mutations which are typically diploid[59,60]. High grade serous carcinoma is associated with genomic instability ,TP53 tumor suppressor gene mutation, homologous recombination DNA damage repair resulting in aneuploidy or copy number abnormalities, defects amplification of cyclin E1 (CCNE1) a molecular abnormality that is mutually exclusive of BRCA mutation and is associated with a worse prognosis/platinum resistance. CCNE amplification often coexists with AKT amplification; NOTCH3 activation; mutation in retinoblastoma (Rb) tumor suppressor gene, NF1 inactivation [61-62].

**MUCINOUS TUMORS:** Borderline and malignant mucinous tumors are associated with mutation in KRAS/ ERBB2/ BRAF and activation of MEK pathway[63].

**ENDOMETRIOID TUMORS CLEAR CELL TUMORS**

Both tumors are associated with Mutation in Wnt-catenin activation; ARID1A chromatin remodeling complex inactivation; Phosphatidylinositol (PI3K) activation; PTEN inactivation and mismatch repair (MMR) abnormalities[63].

**BRENNER TUMORS :** Rarely Benign Brenner tumor are associated with KRAS mutation and amplification of 12q14–21[64] . Malignant Brenner tumours are low-grade carcinomas with activation of the PI3K/ AKT pathway through EGFR [65].

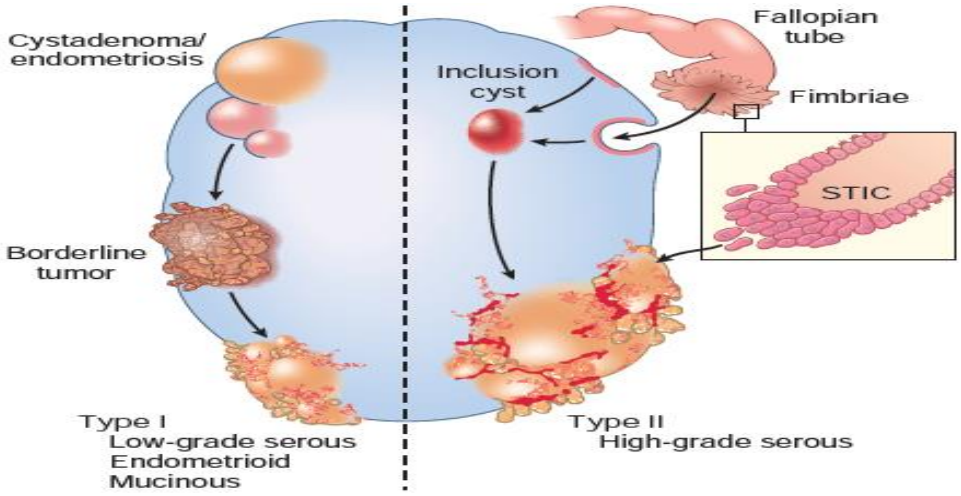
**SEROMUCINOUS CARCINOMA:** ARID1A mutations and loss of expression in a proportion of these tumors similar to endometrioid and clear cell carcinomas [66].

## CARCINOGENESIS OF SEROUS TUMORS

Low grade Serous carcinomas may arise in association with serous borderline tumors, while high-grade carcinomas arise from in situ lesions in the fallopian tube fimbriae or from serous inclusion cysts within the ovary[67]. The lesions, called serous tubal intraepithelial carcinoma (STIC), have since been described in association with sporadic high-grade serous ovarian cancers. Historically it was thought that the vast majority of serous ovarian carcinomas arose from cortical inclusion cysts.

These cysts were thought to arise through invagination of the surface epithelium, followed by serous metaplasia[68].A recent alternative hypothesis is that the cysts

arise from implantation of detached fallopian tube epithelium at sites where ovulation has disrupted the surface of the ovary. The percentage of sporadic high- grade serous carcinomas that arise in the fallopian tube or from ovarian inclusion cysts is currently unknown, as is the origin of the cortical inclusion cysts [69].




## INICEDENCE OF OVARIAN TUMOUS

**SEROUS TUMORS :** Together with benign, borderline and malignant types accounts for about 30% of all ovarian tumors and just over 50% of ovarian epithelial tumors. About 70% are benign or borderline and 30% malignant [70].

**MUCINOUS TUMORS:** Accounts for about 20% to 25% of all ovarian tumors. Approximately 3% of primary ovarian carcinoma accounts for all ovarian cancers[70].

**ENDOMETRIOID TUMORS:** Endometrioid carcinoma accounts for approximately 10% to 15% of all ovarian cancers[70].

**CLEAR CELL TUMORS:** Incidence of cysatadenomas are very rare. Borderline tumors comprise less than 1%. And 50%-70% of clear cell carcinoma arises from endometriosis[55].

**BRENNER TUMORS:** Brenner tumours account for approximately 10% of benign ovarian epithelial tumours. Within that Malignant Brenner tumours account for less than 5% of brenner tumours[55].

**SEROMUCINOUS TUMORS:** Benign tumours account for approximately 1% of benign epithelial neoplasms. Seromucinous carcinoma occurrence is very rare[55].

## AGE INCIDENCE IN SURFACE EPITHELIAL TUMORS

### SEROUS TUMORS

Benign serous tumors are more common in the age of 40-60 years . mean age of incidence of borderline tumors are 42 years. High grade serous carcinomas are common in older women[55].

**MUCINOUS TUMORS**: They occur principally in middle adult life and are rare before puberty and after menopause[70].

**ENDOMETRIOID TUMORS:** Endometriotic cysts are common in the fourth and fifth decades . Benign and borderline entity are rare. Carcinoma incidence are more during fifth to sixth decade[71].

**CLEAR CELL TUMORS:** Benign tumors are very rare. Borderline tumors are more common in post menopausal women. Clear cell carcinoma mean age of presentation is 55 years[72,73].

**BRENNER TUMOR:** Benign tumors are more common in fourth decade and often found incidentally. Mean age of presentation is 59 years for borderline tumors. Malignant tumors occur in women over 50 years of age[74,75].

**SEROMUCINOUS TUMORS:** Benign and borderlin seromucinous tumors are typically

seen in adults with a peak in the late reproductive age group. Seromucinous carcinoma ,the mean age in one reported series was 45 years[76].

## MACROSCOPIC FEATURES OF SURFACE EPITHELIAL TUMORS

### SEROUS TUMORS

Cystic tumours range from 1 to > 30 cm in greatest dimension, have smooth outer surfaces and contain one or more thin-walled cysts filled with clear, watery fluid. Cystadenofibromas are composed of cysts surrounded by a variable amount of fibrotic tissue. Adenofibromas are typically solid[55].

Serous borderline tumors are typically cystic (> 5 cm). Velvety, papillary tumour typically involves at least part of the cyst lining or represents the surface component. Bilateral in about 1/3$^{rd}$ of patients[55].

Low grade serous carcinoma is often bilateral and exhibits fine papillary growth. Necrosis is rare. Calcification is frequently present and extensive[55].

High grade serous carcinoma often bilateral, exophytic and demonstrate solid and papillary growth and fluid-filled cysts. The solid regions are tan-white and contains extensive necrosis and haemorrhage[55].

**MUCINOUS TUMORS:** Benign mucinous cystadenomas are unilateral (90%) most commonly multilocular. Borderline mucinous tumors are always unilateral; size ranges from several centimetres to 50 cm in greatest dimension, multilocular containing mucinous material but solid areas may be seen[77]. Mucinous carcinomas form large, unilateral, complex, solid and cystic masses.

**ENDOMETRIOID TUMOR :** The cysts range in size up to 15 cm. The cyst contents are typically dark brown due to old haemorrhage (chocolate cyst). Adenofibromas are solid, Cystadenomas resemble other cystadenomas. Both are associated with endometriosis[55]. Borderline tumors are solid but may be cystic. The cyst fluid is usually brown with the appearance of altered blood due to haemorrhage. Carcinomas have a mean size of 15 cm and have a smooth outer surface. The cut surfaces show friable soft masses or papillae partly filling cystic spaces that may contain blood-stained fluid [55].

**CLEAR CELL TUMORS**

Benign adenofibromas form a solid mass ranging from 3–16 cm, with a smooth, lobulated external surface and on sectioning, small cysts seen within a solid background [55]. Borderline tumors variable in size. On sectioning, they are solid but may contain tiny cysts [78]. Clear cell carcinoma are typically unilateral range from solid, to solid and cystic, to mainly cystic with fleshy and pale yellow nodules lining an endometriotic cyst[79].

**BRENNER TUMOR**

Benign Brenner tumor are < 2 cm. They are solid with firm rubbery consistency and circumscribed [80]. Borderline tumors are typically large, cystic tumors, papillary masses project into the cyst lumens. Malignant Brenner tumors are usually large, may be solid or cystic with mural nodules. Both benign and malignant tumors show benign Brenner component [81].

**SEROMUCINOUS TUMORS**

Benign tumors are typically present as a unilocular cyst with a smooth surface. They may contain serous or mucinous fluid. Borderline tumors are typically unilocular, smooth-

surfaced and contain viscid fluid. Friable papillary excrescences occupy variable proportions of the cyst lining [76]. Malignant tumors are unilocular or multilocular and contain solid areas. Papillary excrescences are present both on inner lining and on the surface of the cysts. Over half of the tumours are bilateral[82].

**UNDIFFRENTIATED CARCINOMA**

Composed of solid masses with extensive necrosis [55].

## HISTOPATHOLOGICAL FEATURES

### 1. SEROUS TUMORS

BENIGN TUMORS

Serous cystadenomas are composed of cysts and papillae lined by non-stratified or stratified cuboidal to columnar cells resembling fallopian tube epithelium. When there is a prominent fibrous stroma the tumour is designated an adenofibroma. Small papillary growths with bland, serous-type epithelium on the surface of the ovary are designated serous surface papillomas[83].

BORDERLINE TUMORS

**Criteria:** Serous Borderline Tumors lack the nuclear atypia of non-invasive Low grade serous carcinoma and measure < 5 mm in confluent growth. Hierarchical branching pattern characterized by irregular papillae that branch from large to progressively smaller papillae terminating in detached tufts of epithelial cells, is typical of borderline tumors. The papillae are lined by non-stratified or stratified cuboidal to columnar cells that are typically ciliated[84]. **Microinvasion** is defined as clusters of cells in the stroma with abundant

eosinophilic cytoplasm, similar to the eosinophilic cells on the surface of papillae, that measure < 5 mm in greatest dimension[85].

**Implants:** Peritoneal lesions associated with SBT were classified as“non-invasive” or “ invasive" implants based on whether the lesions were confined to the surface of organs (noninvasive) or infiltrated the underlying tissue (invasive)[86].

**Serous borderline tumour -micropapillary variant / Non-invasive low-grade serous carcinoma** is characterized by non-hierarchical branching architecture composed of fine, micropapillae, usually five times taller than they are wide, emanate directly from large, often fibrotic papillae. A diagnosis of non-invasive LGSC requires at least one confluent area of micropapillarity measuring 5 mm in one dimension and nuclear atypia greater than that allowed in a SBT [84].

SEROUS CARCINOMA

Low grade serous carcinoma characterized by a variety of architectural patterns including single cells and irregularly shaped small nests of cells haphazardly infiltrating stroma, micropapillae or less commonly, macropapillae. different patterns of invasion is present. Rarely necrosis or psammoma bodies are present and lower mitotic activity[87].

High grade serous carcinoma composed of epithelial cells displaying papillary, glandular (often slitlike) and solid patterns with high-grade nuclear atypia. Necrosis and psammoma bodies are frequent. Mitoses are numerous and often atypical. A papillary pattern or one of thick undulating bands of epithelial cells closely resembling urothelial carcinoma(transitional cell carcinoma)is present[88] .

## 2. MUCINOUS TUMORS

BENIGN TUMOR

Composed of multiple cysts and glands lined by simple, non- stratified mucinous epithelium resembling gastric foveolar-type or intestinal epithelium containing goblet cells. Around 10% Mucinous cystadenomas may be associatedwith a dermoid cyst or Brenner tumour [55].

BORDERLINE TUMOR

Composed of mild to moderately atypical gastrointestinal-type, Mucin containing epithelial cells with proliferation greater than benign mucinous tumours. Stromal invasion is absent[89]. **Microinvasion** is defined as small foci of stromal invasion measuring less than 5 mm in greatest linear extent. **Mural nodules** are associated with Borderline Tumor or carcinomas. Three varieties of mural nodules present namely reactive sarcoma-like mural nodules, foci of anaplastic carcinoma and sarcomatous nodules[89].

CARCINOMA

Invasive carcinoma is characterized by two different patterns of invasion, which may co-exist in a single tumour. The confluent glandular or expansile invasive pattern characterized by marked glandular crowding with little intervening stroma and cribriform pattern may be present [90].

## 3. ENDOMETRIOID TUMORS

BENIGN TUMORS

Endometriotic cyst is lined by endometrial epithelium overlying endometrial stroma

and associated with haemorrhage. Stroma contains many small blood vessels. Haemosiderin-laden macrophages and fibrosis are other hallmarks. When endometrial stroma is not clearly evident the tumour may be classified as an endometrioid cystadenoma. When associated with a dense fibromatous component the tumour is an endometrioid adenofibroma[91].

BORDERLINE TUMOR

Characterized by solid or cystic tumour composed of crowded glands lined by atypical endometrioid-type cells and lacking stromal invasion and/or confluent glandular growth[92].**Criteria:** Confluent glandular growth (expansile) measuring > 5 mm or unequivocal invasion warrants a diagnosis of carcinoma. **Microinvasion** is defined as either confluent glandular growth < 5 mm or haphazardly infiltrating single cells, glands or nests of cells with cytological atypia[92].

CARCINOMA

A malignant, epithelial tumour resembling endometrioid carcinoma of the uterine corpus. Most tumours show a back-to-back arrangement of the glands with confluent or cribriform proliferations of round, oval or tubular glands; villoglandular patterns also occur[93].

**GRADING:** endometrioid ovarian carcinoma are graded similar to endometrioid carcinoma of uterus.

Grade 1 - 5% or less of solid growth considered

Grade 2 - those with between 6 and 50% solid growth considered

Grade 3 - more than 50% solid growth of neoplasm considered

The presence of grade 3 nuclei (atypical or bizzare nuclei with prominent eosinophilic large macronucleoli or multinucleation) involving greater than 50% of the tumour is associated with more aggressive behaviour and therefore justifies upgrading the tumour by one grade[93].

**4.CLEAR CELL TMUOR**

BENIGN TUMOR

A tumour composed of glands or cysts lined by bland cuboidal to flattened cells with clear or eosinophilic cytoplasm embedded in a fibromatous stroma. In adeno-fibromas, widely spaced simple glands, often cystically dilated, are embedded in a fibromatous stroma[94].

BORDERLINE TUMOR

These are clear cell adenofibromatous tumours with atypia of the glandular epithelium but without stromal invasion. The cysts and glands are lined by cuboidal, hobnail, or flattened cells with clear or eosinophilic cytoplasm. Both tumors are associated endometriosis[94].

CLEAR CELL CARCINOMA

A malignant tumour composed of clear, eosinophilic and hobnail cells, displaying a combination of tubulocystic, papillary and solid patterns. The clear cells have glycogen-rich cytoplasm that is PAS positive and diastase sensitive. Psammoma bodies and eosinophilic hyaline bodies can be seen[95].

**5. BRENNER TUMOR**

BENIGN TUMOR

Composed of nests of bland, transitional-type cells (resembling urothelial cells) within a fibromatous stroma.[96]

BORDERLINE TUMOR

A neoplasm of transitional cell type (resembling non-invasive, low-grade urothelial neoplasms) displaying epithelial proliferation more than benign Brenner tumours and lacking stromal invasion[97].

CARCINOMA

Composed of malignant transitional cell type, resembling an invasive urothelial carcinoma. Tumours are associated with a benign or borderline Brenner tumour [98].

**7.SEROMUCINOUS TUMORS**

BENIGN TUMOR

A benign cystic neoplasm with two or more Müllerian cell types, all accounting for at least 10% of the epithelium. The cysts are lined by a variable admixture of serous and mucinous cells (endocervical- type) but endometrioid and less often transitional or squamous cells may be seen [99].

BORDERLINE TUMOR

A non-invasive, proliferative, epithelial tumour composed of more than one pithelial cell type, most often serous and endocervical-type mucinous, endometrioid, and less often, clear cell, transitional or squamous may be seen [99].

CARCINOMA

A carcinoma composed predominantly of serous and endocervical-type mucinous epithelium. Foci containing clear cells and areas of endometrioid and squamous differentiation also seen. The most common pattern of invasion is cribriform and confluent

(expansile), although destructive infiltrative growth also occurs. The tumors are classified by the predominant type but the smaller components can be included in the diagnosis[100].

**UNDIFFERENTIATED CARCINOMA**

A malignant, epithelial tumour showing no differentiation of any specific müllerian cell type. They display sheet like growth, frequently associated with geographic necrosis. Malignant cells arranged in Nests, cords, clusters and single cells may be seen[101].

**IMMUNOHISTOCHEMICAL STAINS OF OVARIAN CARCINOMA [102,103]**

| Carcinoma Type | PAX8 Positive | WT1, positive | TP53 aberrant | CDKN2A, diffuse | ER positive. | PR positive. |
|---|---|---|---|---|---|---|
| LOW GRADE SEROUS CARCINOMA | 100% | 100% | 0 | 0 | 96% | 50% |
| HIGH GRADE SEROUS CARCINOMA | 98% | 92% | 93% | 60% | 80% | 30% |
| MUCINOUS CARCINOMA | 50-60% | 0% | 50% | 14% | 6% | 0 |
| ENDOMETRIOID CARCINOMA | 84% | 4% | 11% | 6% | 86% | 72% |
| CLEAR CELL CARCINOMA | 99% | 0% | 12% | 12% | 13% | 6% |

**STAGING OF OVARIAN TUMOR**

Staging system describe the severity of the cancer. Staging was developed to optimize treatment planning, a lower stage at diagnosis generally have a superior clinical outcome

[104]. The international federation of gynecology and obstetrics (FIGO) developed the ovarian cancer staging system. This system has been extensively studied and its prognostic significance is well established. It correlates well with the TNM classification system [104].

**TNM AND FIGO STAGING OF OVARIAN TUMORS**

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 **I** Tumour limited to the ovaries

T1a **IA** Tumour limited to one ovary (capsule intact) or fallopian tube surface; no malignant cells in ascites or peritoneal washings.

T1b **IB** Tumour limited to one or both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings.

T1c **IC** Tumour limited to one or both ovaries or fallopian tubes with any of the following:

T1c1 **IC1** Surgical spill

T1c2 **IC2** Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface

T1c3 **IC3** Malignant cells in ascites or peritoneal washings

T2 **II** Tumour involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer

T2a **IIA** Extension and/or implants on uterus and/or fallopian tubes and/or ovaries

T2b **IIB** Extension to other pelvic intraperitoneal

T3 **III** Tumour involves one or both ovaries or fallopian tubes,and/or primary peritoneal carcinoma, with cytologically or

N1 histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

N1 **IIIA1** Retroperitoneal lymph node metastasis only

N1a **IIIA1i** Lymph node metastasis up to 10 mm in greatest dimension

N1b **IIIA1ii** Lymph node metastasis more than 10 mm in greatest dimension

T3a **IIIA2** Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without retroperitoneal lymph node

T3b **IIIB** Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension with or without retroperitoneal lymph node metastasis.

T3c **IIIC** Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without retroperitoneal lymph node metastasis (excludes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)

M1 **IV** Distant metastasis excluding peritoneal metastasis

M1a **IVA** Pleural effusion with positive cytology

M1b **IVB** Parenchymal metastasis and metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

**N — Regional Lymph Nodes**

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

N1a Lymph node metastasis up to 10 mm in greatest dimension

N1b Lymph node metastasis more than 10 mm in greatest dimension

**M — Distant Metastasis**

M0 No distant metastasis

M1 Distant metastasis

M1a Pleural effusion with positive cytology

M1b Parenchymal metastasis and metastasis to extra abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

**pTNM Pathological Classification**

The pT and pN categories correspond to the T and N categories.

pM1 Distant metastasis microscopically confirmed

pM0 and pMX are not valid categories.

**pN0** Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0 [105].

**STAGE GROUPING**

| | | | |
|---|---|---|---|
| Stage IA | T1a | N0 | M0 |
| Stage IB | T1b | N0 | M0 |
| Stage IC1 | T1c1 | N0 | M0 |
| Stage IC2 | T1c2 | N0 | M0 |
| Stage IC3 | T1c3 | N0 | M0 |
| Stage IIA | T2a | N0 | M0 |
| Stage IIB | T2b | N0 | M0 |
| Stage IIIA1 | T1/T2 | N1 | M0 |
| Stage IIIA2 | T3a | N0/N1 | M0 |
| Stage IIIB | T3b | N0/N1 | M0 |
| Stage IIIC | T3c | N0/N1 | M0 |
| Stage IV | Any T | Any N | M1 |

**IMMUNOHISTOCHEMISTRY**

Nowadays, Immunohistochemistry plays a significant role not only for diagnosis but Also for other parameters including prognosis, microscopic tumor staging, Prediction of response to therapy, and for the selection of therapeutic agents[106]. Immuno histochemical markers used in this study are ER, PR, Ki-67 and Ca125.

ROLE OF STEROID HORMONES AND RECEPTORS IN OVARIAN TUMORS

Steroid hormones such as estrogen and progesterone play an important role in the process carcinogenesis of ovarian tumors[107]. Cytosol estrogen and progesterone receptors are

present in many organs including the breasts, endometrium, myometrium, cervix, fallopian tubes and ovaries[108] .Ovaries produce sex steroid hormones and they are the target of their action simultaneously because of the presence of adequate quantity of receptors [109].

Receptors phenotype of neoplasm is one of the basic criteria of ovarian tumors sensitivity. Ovarian tumors are characterized by change in the receptor status and consequently tumor can be either primary receptor negative or as a result of their progression, they may lose the receptors[107].

In number of studies it is Shown that both missense and nonsense mutation resulting in complete Loss of expression in ER genes are common in ovarian tumors. Steroid

Hormone receptors are a significant link in hormonal transduction. They Modulate important events such as cell differentiation, proliferation and death through interaction with the respective ligands[109]. ER and PR level depends on the tumor histological types, patients age that determines their Responsiveness to hormonal therapy with synthetic progestogen and antiestrogen.

The receptors status and proliferative activity determines the Tumorgenesis and disease course. Together with efficacy of hormonal therapy it predetermines the prognosis of the disease [109]. Estrogen is considered as a primary culprit in the development of ovarian cancers as 70% of ovarian tumors particularly carcinomas express positivity for estrogen receptors (ER), whereas progesterone and its receptor (PR) protective against ovarian cancer. High serum levels of estrogen have been implicated as a risk factor for ovarian carcinoma. The most commonly considered hypothesis of ovarian carcinogenesis proposes that incessant ovulatory cycles lead to long term exposure of the epithelium to an estrogen

rich environment, which may promote cellular proliferation, inclusion cyst formation, and possibly malignant transformation [110]. Some studies shows a significant association between Progesterone receptor and other favourable prognostic parameters such as young age, benign tumors and early FIGO stage [110] .

ROLE OF PROLIFERATIVE MARKER [Ki-67] IN OVARIAN TUMORS

Uncontrolled cellular proliferation is one of the definitive characteristics of malignancies. Mitotic count is a traditional and practical method to determine the proliferative activity, but is hampered by several conflicting factors. Alternatively, Immunohistochemical detection of proliferating cells may help to determine the proliferative potential of a tumor. Ki-67 is a nuclear locate protein that is closely linked to cell proliferation [111]. It is expressed during all active phase of the Cell cycle, and the monoclonal Ki-67 antibody MIB-1 binds to the nuclear Ki-67 Antigen. Growing evidence underlines that high expression of Ki-67 indicates poor Prognosis in several types of cancers.

In several studies it is shown that patients with high Ki-67 were found to have a less favourable 5- year survival. These patients were also likely to have other poor prognostic factors, including advanced tumor stage, higher Tumor grade and postoperative residual tumor burden.

However, other studies have indicated that high grade serous carcinoma patients With higher Ki-67 expression tended to experience longer progression free survival because highly proliferative tumors seemed to respond better to first line chemotherapy [112].In epithelial ovarian cancers however Ki-67 Has not yet been fully established as a reliable prognostic factor thus showing the Need for further investigation[113].

ROLE OF MEMBRANE ASSOCIATED MUCIN ANTIGEN CA 125 –IHC

Carcinoma antigen or carbohydrate antigen CA125 also known as mucin 16 or MUC 16 discovered initially by Bast and Colleagues in 1983. It is a high molecular weight glycoprotein that ranges from 2,00,000 to Greater than 10,00,000.

It is encoded by MUC16 gene located in chromosome 19[114]. Immunohistochemical studies have revealed that CA 125 is detectable on the apical surface of normal epithelial cells of the pleura, pericardium, peritoneum, fallopian tube, endometrium and endocervix. In contrast normal ovarian epithelium although. Also derived from colemic epithelium does not express immunohistochemically detectable CA 125[114]. But CA 125 is expressed by 80 % of the epithelial ovarian Cancers. OC 125 is a murine monoclonal IgG1 antibody that was raised against a Human ovarian serous cystadenocarcinoma cell line. CA 125 is the antigenic Determinant for OC 125 as it is expressed by most of the serous ovarian carcinomas [114].

**SERUM LEVEL OF CA 125 IN OVARIAN TUMOR PATEINTS**

CA 125 is a transmembrane glycoprotein derived from epithelium of coelemic and mullerian origin. The extracellular domains of CA 125 binds to the antibodies to render easy quantification of levels for clinical use. In 93% of the cases foe women with ovarian cancer, CA 125 levels were found to correlate with tumor burden. So screening of serum value of CA 125 is used in many women with suspected ovarian tumors[115].

The cut off value is set to 35 IU/ml for the upper limit of normal in the first generation CA 125 assays. Apart from screening and diagnostic purposes, the CA 125 is used for monitoring response to active treatment (chemotherapy) by assessing serial serum values

in patients with having elevated values. Using the criteria set forth by the Gyencologic Cancer Intergroup (GCIG), a response is defined as a 50% reduction in CA 125 maintained for at least 28 days. It is applied for women with recurrent disease and for those undergoing first line chemotherapy. In some studies it is shown the utility of CA125 for monitoring the response to chemotherapy and predict progression free survival in patients with recurrent ovarian cancer[115].

## MATERIALS AND METHODS

**STUDY DESIGN:** Prospective study

**STUDY AREA:** Department of Pathology, Tirunelveli Medical college and hospital.

**STUDY POPULATION:** 61 cases reported as ovarian tumors clinically, radiologically and histopathologically during the study period of 2017 to 2019.

**STUDY SAMPLE**

1. Includes the tissue materials from 61 cases, reported as epithelial ovarian tumors in the histopathological laboratory.
2. Blood samples in patients diagnosed as ovarian tumors clinically and radiologically.

**INCLUSION CRITERIA**

All the cases reported as epithelial ovarian tumors.

**EXCLUSION CRITERIA**

1. Cases reported as ovarian tumors other than epithelial origin
2. Patients underwent chemo and radiotheraphy preoperatively
3. Patients with recurrence of ovarian cancers.

**DURATION OF STUDY**

18 months (2017 to 2019)

## METHODOLOGY

A total of 61 female patients within the age group of 20 to 80 years reported as epithelial ovarian cancers were selected for this study within the study period of august 2017 to 2019. These patients were diagnosed both clinically and radiologically as having ovarian tumors.

Blood samples were collected preoperatively as per the standard procedures from the patients and for serum CA 125 was estimated using a Chemi-Luminiscence Immuno assay analyser (Beckmann & coulter inc) and by using Access II kits and calibrators. Paraffin blocks containing tissues of ovarian tumors reported as epithelial ovarian tumors from these 61 patients were Collected and subjected to histopathological study.

## STEPS IN H&E STAINING

1. Tissue sections of 4-5 µm thickness were cut.
2. Obtained on albumin coated slides followed by dewaxing by incubation of slides at 60-70$^{o}$ C for one hour.
3. Sections were then rehydrated using graded alcohols
4. Washed in tap water.
5. Staining with Harris hematoxylin for 10 minutes to stain all the nuclei.
6. Sections were then washed for 5 minutes under running tap water for blueing
7. Counterstained in 1% aqueous Eosin - 8 dips washed in tap water.
8. The sections were dehydrated, cleared and mounted.

Sections stained with haematoxylin and eosin were used for histological typing of ovarian tumors. The studied 61 cases of ovarian tumors were classified according to WHO histological classification as serous tumors, mucinous tumors, endometrioid tumors, clear cell tumors, Brenner tumors and seromucinous tumors and others. Each group of tumors were subclassified as Benign, Borderline and Malignant. The pathological tumor staging was performed according to the American Joint Committee on cancer by grouping the various TNM components. The tumor stage (T) was determined by the presence or absence of tumor cells in the adjacent organs, presence or absence of capsular breech and level of extension outside the pelvis by studying the corresponding representative sections. The nodal status (N) was also recorded from the corresponding sections and any metastasis was reported from the file and accompanying specimens.

Steroid receptor status such as estrogen and progesterone (ER and PR), index of tumor cell proliferation (Ki-67), and carcinoma antigen ( CA 125) were studied by doing immunohistochemistry with corresponding ER, PR, Ki67 and CA 125 antibody.

An analysis was done by correlating the ER, PR, Ki67 and CA125 with the stage and grade of the tumor in these 61 cases of ovarian tumors.

**IMMUNOHISTOCHEMISTRY FOR ER, PR, KI67 AND CA125**

Special positively charged or coated slides are used for IHC. Thin sections of about

3-4µm size was cut on the charged slides.

**STEPS IN IHC[66]**

1. Charged slides with 3-4µm thick section are incubated at 60-70$^{o}$ C for 1 hour for dewaxing.
2. Sections were deparaffinized, hydrated through descending grades of alcohol and then brought to water.
3. Antigen Retrieval was done in Pressure Cooker by keeping the slides in a pre-heated Tris-EDTA retrieval buffer of pH -9 at 60$^{o}$ C for 20 minutes. The dilution used for Tris – EDTA retrieval buffer was 1 in 50. Then the slides were washed with distilled water for two minutes.
4. Slides were treated with Tris-Wash buffer of pH 7.6 at room temperature for 5 minutes. The dilution of Tris-Wash Buffer was 1 in 20.
5. Slides were treated with peroxidase blocking reagent for 15 minutes.
6. Then washed in Tris-Wash buffer for 5 minutes.
7. Slides were treated with ER, PR, Ki-67 and CA125 primary antibody for 30 minutes.
8. Then washed in Tris -Wash buffer for 5 minutes.
9. Slides were treated with HRP Polymerase, secondary antibody for 30 minutes.
10. Then washed in Tris-Wash buffer for 5 minutes.
11. Slides are covered with substrate buffer containing DAB (Diaminobenzidine tetrachloride) chromogen for 10 minutes.
12. Then washed in Tris-Wash Buffer for 5 minutes.

13. Slides were then washed with Distilled water two changes.
14. Counterstaining was done with Mayer's Haematoxylin for 30 seconds to impart background staining.
15. Running tap water wash given.
16. Xylene, 2 changes 5 minutes each was done.
17. Dehydration in 100% alcohol for 5 minutes.
18. Then the sections were mounted with DPX. (Dextrene Phthalate Xylene)

**ESTIMATION OF SERUM CA 125.**

1. 4 ml of blood was collected preoperatively in a Red top plastic tube as per the standard procedures
2. The blood was spun in a centrifuge machine and the obtained serum was measured for serum CA 125.
3. Using a Chemi-Luminiscence Immuno assay analyser (Beckmann & coulter inc) and by using Access II kits and calibrators.

**CALCULATION OF IMMUNOHISTOCHEMISTRY SCORE FOR STEROID HORMONE RECEPTOR STATUS (ER AND PR)**

The nuclear staining of the tumor cells was considered as a positive expression for ER and PR. Grading of nuclear ER and PR staining was performed using an Immunoreactive H-Scoring obtained by the product of intensity of staining and the percentage of positively stained cells.

IMMUNOREACTIVITY H- SCORE[19]

| **PROPORTION OF POSITIVE CELLS** | **SCORE** | **STAINING INTENSITY** | **INTENSITY SCORE** |
|---|---|---|---|
| 0 | 0 | NEGATIVE | 0 |
| <10% | 1 | WEAK | 1 |
| 11-50% | 2 | MODERATE | 2 |
| 51-80% | 3 | STRONG | 3 |
| >80% | 4 | | |

INTERPRETATION

| **TOTAL SCORE** | **RESULTS** | |
|---|---|---|
| 0-1 | 0 | NEGATIVE |
| 2-3 | 1+ | WEAK POSITIVE |
| 4-8 | 2+ | MODERATE POSITIVE |
| 9-12 | 3+ | STRONG POSITIVE |

## CALCULATION OF KI67 INDEX[7]

Ki-67 is expressed during all active phases of the cell cycle and the monoclonal Ki-67 antibody MIB -1 binds to the nuclear Ki-67 antigen. The labelling index was calculated for the entire lining epithelium and expressed as percentage of positive cells by counting atleast 1000 tumor cells in atleast 4-5 high power fields.

Every stained nucleus was considered positive, irrespective of intensity. The percentage of positively stained cells was recorded as Ki-67 – labelling index.

$$\text{Ki67 labelling index} = \frac{\text{Number of positive stained nucleus}}{\text{Number of tumor cells counted}} \times 100$$

The cut-off limit was set to 20%. The number of positively stained cells with cut-off value more than 20% is considered as over expression or high expression. The Number of positively stained cells with cut- off value less than 20% is considered as underexpression or low expression.

## CALCULATION OF IMMUNOHISTOCHEMICAL EXPRESSION OF CA125

The immunostaining was scored semi-quantitatively by means of a modified histoscore method, taking into account the staining intensity and the percentage of positive tumor cells. Briefly for each stained section the estimated percentage of tumor cells was multiplied by the intensity value and the result named

Immunohistochemical Score (IS) was obtained.

| SCORE | PROPORTION OF POSITIVITY OF CELLS | RESULTS |
|---|---|---|
| 0 | <5% | NEGATIVE |
| 1+ | 5-30% | SLIGHTLY POSITIVE |
| 2+ | 30-80% | MODERATE POSITIVE |
| 3+ | >80% | STRONG POSITIVE |

**STATISTICAL ANALYSIS**

The data were coded and entered in MS-excel office 2010. The data were analyzed using Graph Pad Prism version 5. The categorical data were represented as n (%).

Sensitivity and specificity were calculated by constructing the 2 x 2 table. Fischer's Exact test was used to compare the frequency between the groups. $P < 0.05$ was Considered statistically significant.

## OBSERVATION

A total of 61 patients who were diagnosed clinically, radiologically and histopathologically as ovarian tumors were included in this study. Blood samples of these patients and their corresponding formalin fixed ovarian tumors were included in our study.

Among these 61 cases 58 fall under surface epithelial tumors, 1 case under pure stromal tumor and other 2 cases are non neoplastic lesions.

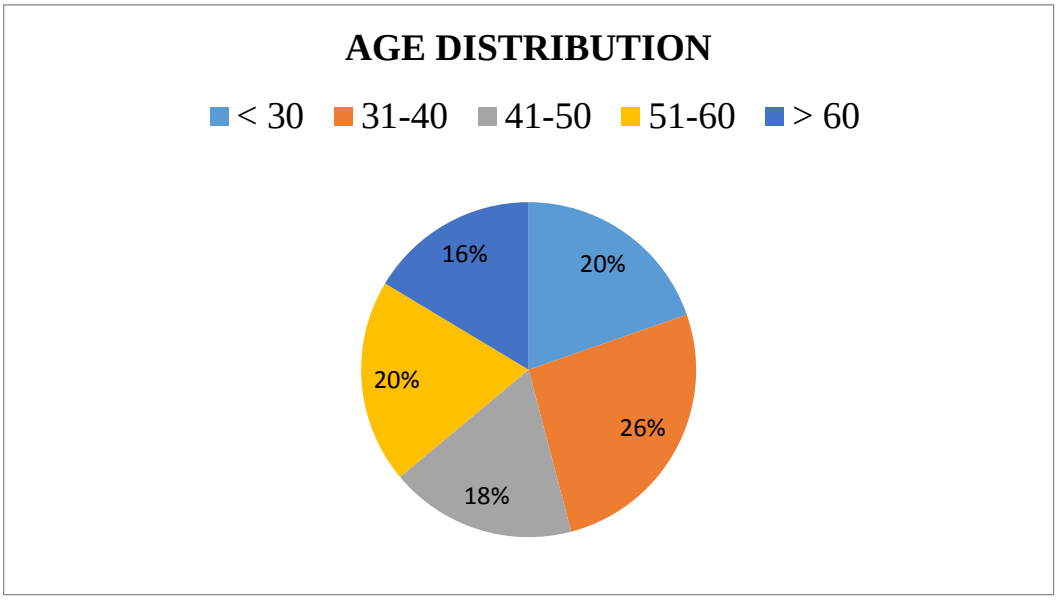
### DISTRIBUTION OF CASES ACCORDING TO AGE

Among the 61 cases the minimum age of presentation was 24 years and the maximum age of presentation was 80 years. The mean age of presentation was 45.59 years. In the 61 patients, 12 patients were below 30 years , 16 patients were between the age group of 31 to 40 years, 11 were between 41 to 50 years, 12 were between 51 to 60 years and 10 patients fall under > 60 years age group ( Table 1 & chart 1).

TABLE 1: DISTRIBUTION OF CASES ACCORDING TO AGE

| AGE IN YEARS | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| < 30 | 12 | 20% |
| 31-40 | 16 | 26% |
| 41-50 | 11 | 18% |
| 51-60 | 12 | 20% |
| > 60 | 10 | 16% |
| | Total = 61 | |

CHART 1: DISTRIBUTION OF CASES ACCORDING TO AGE



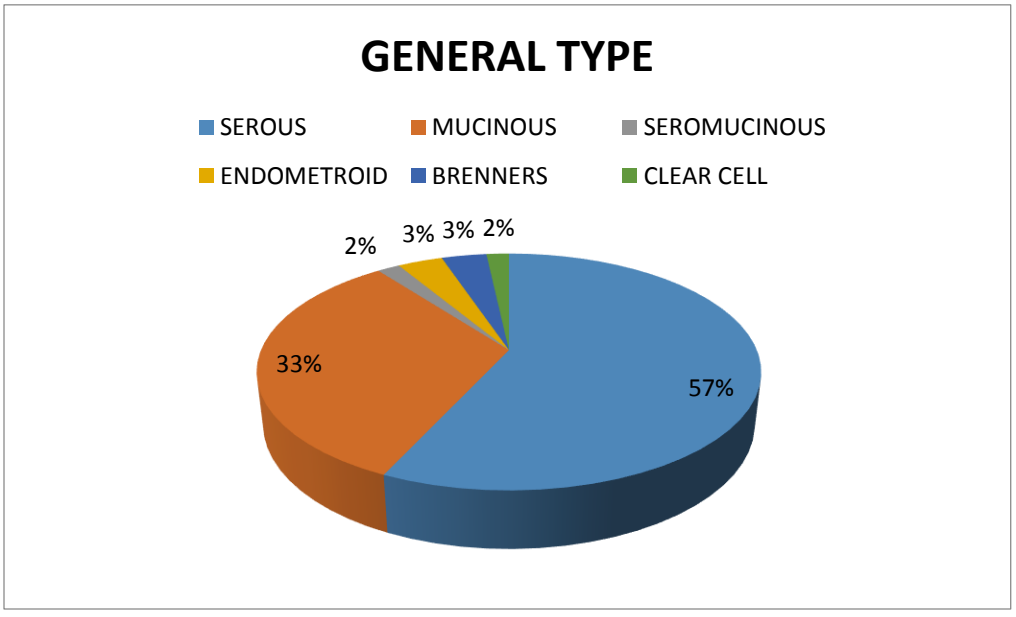
**DISTRIBUTION OF TUMOR ACCORDING TO HISTOLOGICAL TUMOR TYPE**

Out of 61 cases, 33 cases are Serous tumor, 19 cases are Mucinous tumor, 2 cases are Endometrioid tumor, 1 case of clear cell tumor, 2 cases are Brenner tumor and 1 case of Seromucinous tumor ( Table 2 & Chart 2)

TABLE 2: DISTRIBUTION OF TUMOR ACCORDING TO HISTOLOGICAL TUMOR TYPE

| GENERAL TYPE | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| SEROUS | 33 | 57% |
| MUCINOUS | 19 | 33% |
| SEROMUCINOUS | 1 | 2% |
| ENDOMETROID | 2 | 3% |
| BRENNERS | 2 | 3% |
| CLEAR CELL | 1 | 2% |
| | TOTAL = 61 | |

CHART 2:DISTRIBUTION OF TUMOR ACCORDING HISTOLOGICAL TUMOR TYPE



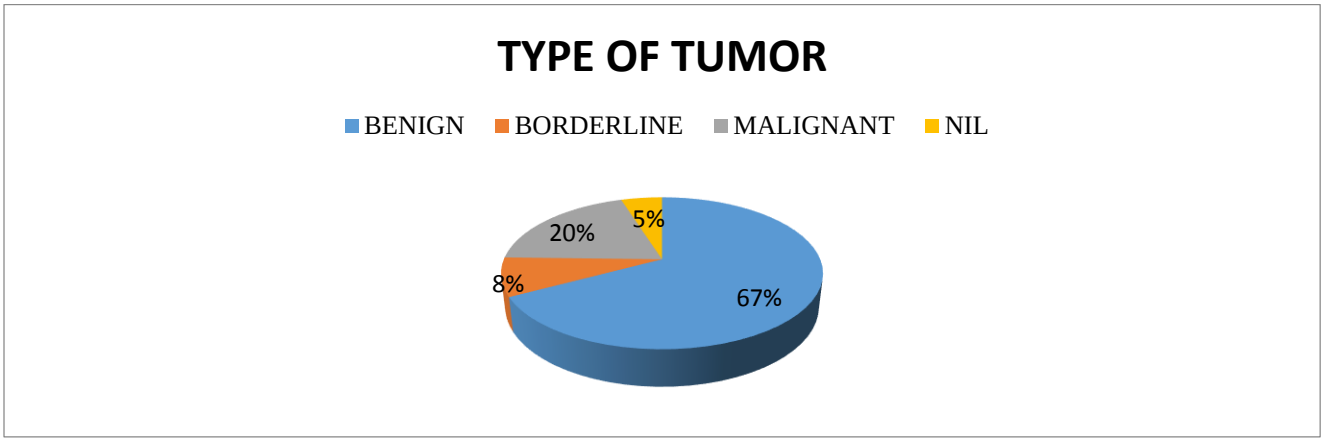
## DISTRIBUTION OF CASES ACCORDING TO THE TYPE OF TUMOR

Out of the 61 cases, 41 cases are benign tumor, 5 cases are borderline tumor, 12 cases are malignant tumor and 3 cases are non neoplastic lesions ( Table 3 & chart 3)

TABLE 3: DISTRIBUTION OF CASES ACCORDING TO THE TYPE OF TUMOR

| TYPE OF TUMOR | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| BENIGN | 41 | 67% |
| BORDERLINE | 5 | 8% |
| MALIGNANT | 12 | 20% |
| NON-NEOPLASTIC LESION **( NIL)** | 3 | 5% |
| | Total = 61 | |

CHART 3: DISTRIBUTION OF CASES ACCORDING TO THE TYPE OF TUMOR



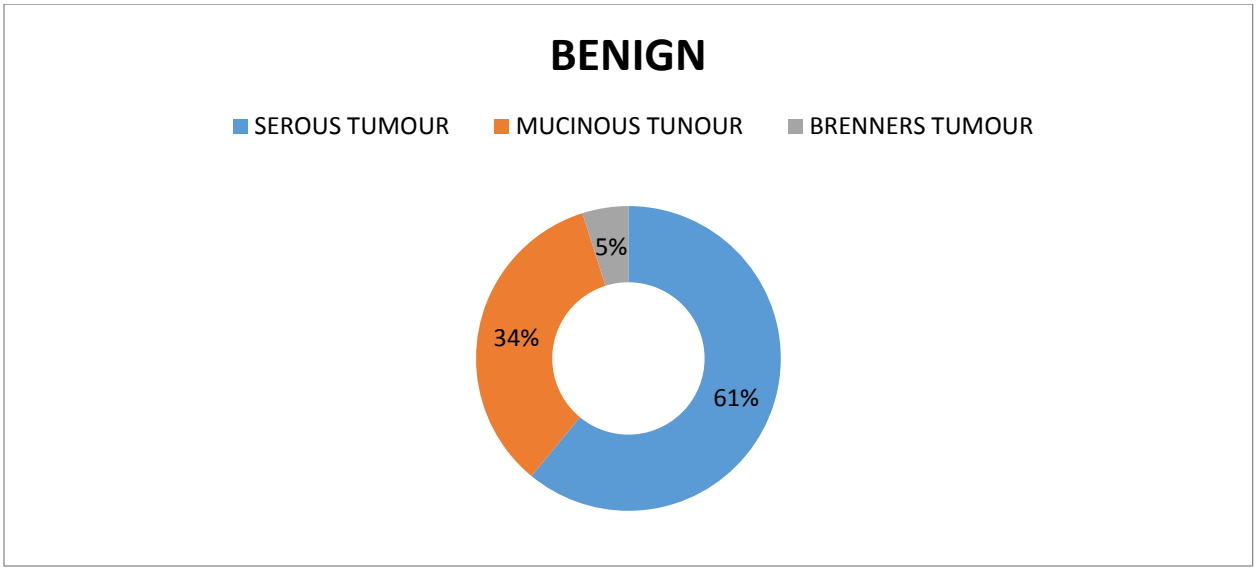
**DISTRIBUTION OF CASES ACCORDING TO HISTOLOGICAL TUMOR TYPE – BENIGN TUMORS.**

Out of 61 cases, 41 cases are benign which includes 25 serous tumors, 14 mucinous tumors and 2 brenner tumor ( Table 4 & Chart 4)

TABLE 4: DISTRIBUTION OF BENIGN TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE.

| BENIGN (N=41) | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| SEROUS TUMOUR | 25 | 61% |
| MUCINOUS TUNOUR | 14 | 34% |
| BRENNERS TUMOUR | 2 | 5% |
| | TOTAL = 41 | |

CHART 4: DISTRIBUTION OF BENIGN TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE.



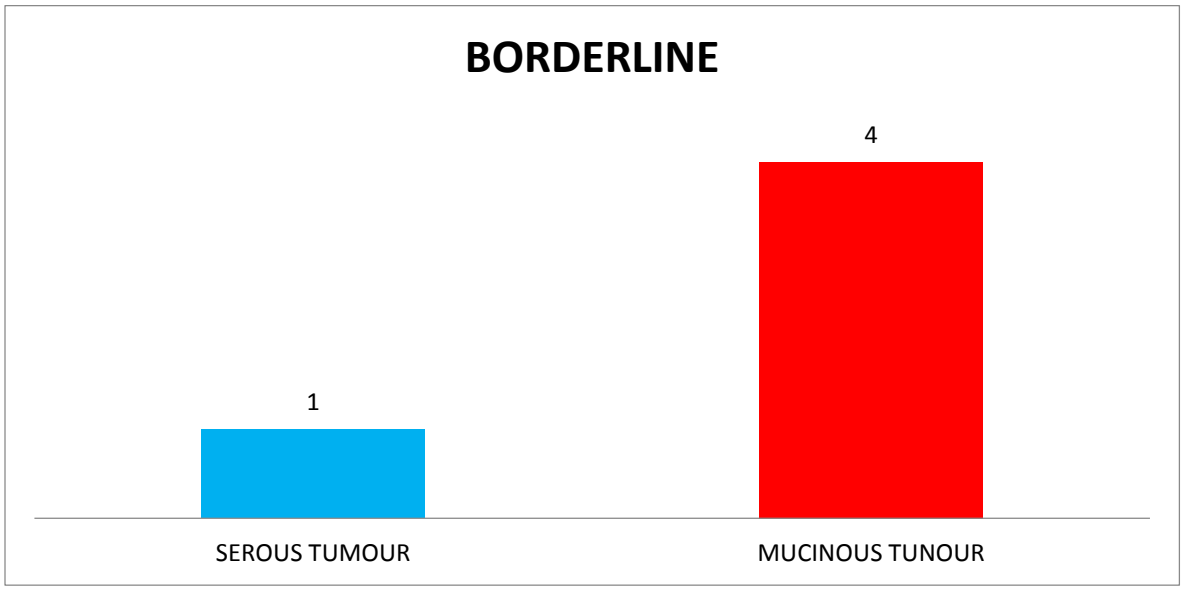
**DISTRIBUTION OF BORDERLINE TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE.**

Of the 61 cases, 5 cases are borderline tumors. Among them 1 case fall under serous tumor and 4 are mucinous tumor ( Table 5& Chart5).

TABLE 5: DISTRIBUTION OF BORDERLINE TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE.

| BORDERLINE (N=5) | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| SEROUS TUMOUR | 1 | 20% |
| MUCINOUS TUMOUR | 4 | 80% |
| | TOTAL = 5 | |

CHART 5: DISTRIBUTION OF BORDERLINE TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE.



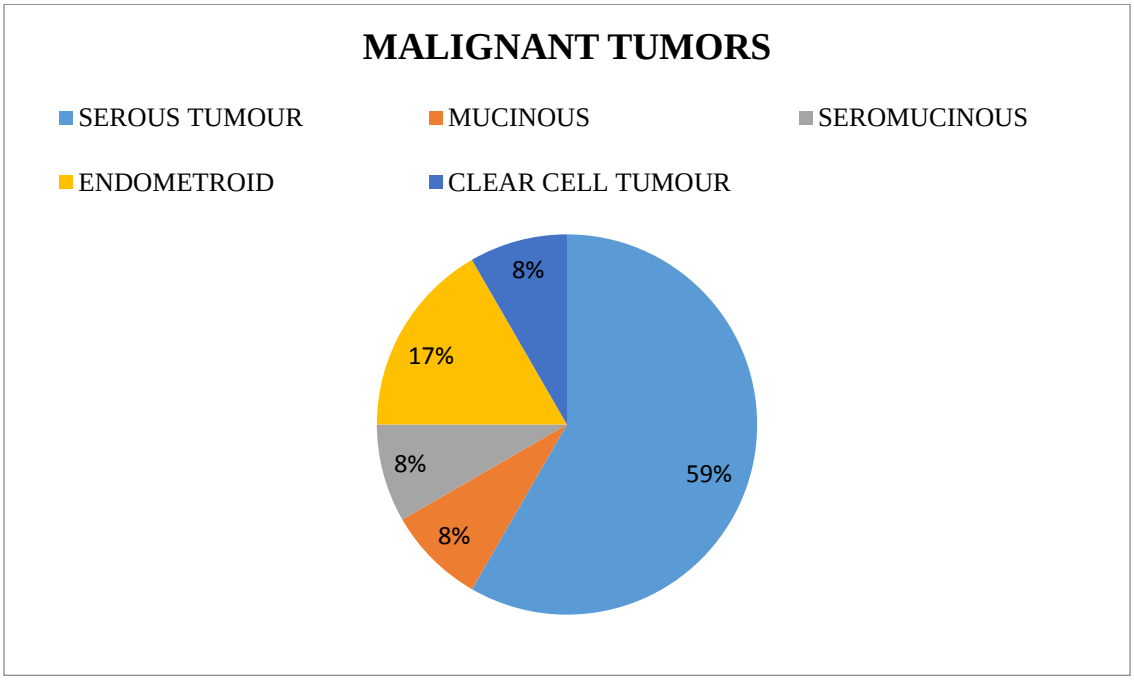
**DISTRIBUTION OF MALIGNANT TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE**

Out of 61 cases , 12 cases are malignant tumors which includes 7 serous tumors, 1 mucinous tumor, 1 clear cell tumor, 2 Endometrioid tumors and 1 Seromucinous tumor.

TABLE 6: CHART 6: DISTRIBUTION OF MALIGNANT TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE

| MALIGNANT (N=12) | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| SEROUS TUMOUR | 7 | 59% |
| MUCINOUS TUMOUR | 1 | 8% |
| SEROMUCINOUS | 1 | 8% |
| ENDOMETROID | 2 | 17% |
| CLEAR CELL TUMOUR | 1 | 8% |
| | TOTAL = 12 | |

CHART 6: DISTRIBUTION OF MALIGNANT TUMORS ACCORDING TO HISTOLOGICAL TUMOR TYPE



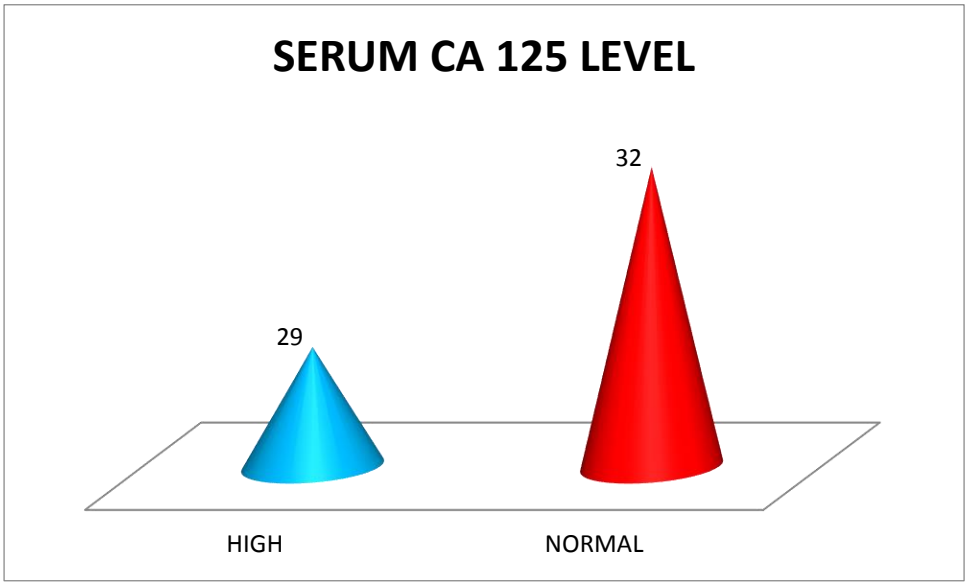
**DISTRIBUTION OF LEVELS OF SERUM CA125.**

Out of 61 cases, 29 cases are found to have high levels of serum CA125 and32 cases have normal CA 125 levels. The cut off value is 35 IU/ml (Table 7 & Chart 7)

TABLE 7: DISTRIBUTION OF LEVELS OF SERUM CA125.

| SERUM CA 125 LEVEL | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| HIGH | 29 | 48% |
| NORMAL | 32 | 52% |
| | TOTAL = 61 | |

CHART 7: DISTRIBUTION OF LEVELS OF SERUM CA125.



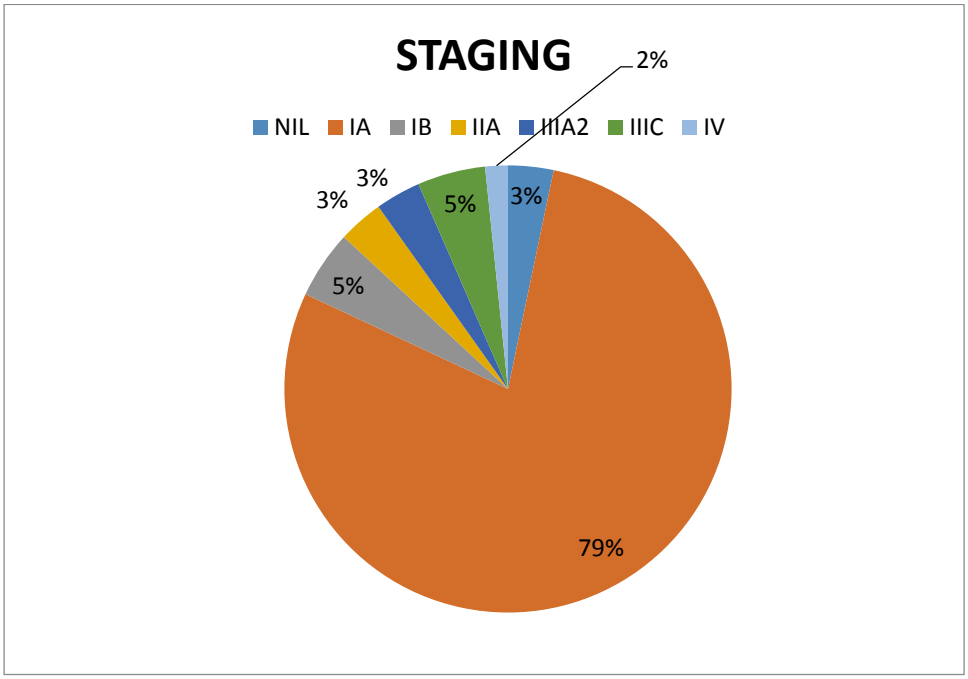

**DISTRIBUTION OF CASES ACCORDING TO TNM STAGING OF THE DISEASE.**

Out of 61 cases, 48 cases fall under Stage IA, 3 cases under Stage IB, 2 cases under Stage IIA, 2 cases under Stage IIIA2, 3 cases fall under Stage IIIC, 1 case under Stage IV and 2 cases are non-neoplastic lesion (not placed under TNM staging) (Table 8 & Chart 8).

TABLE 8: DISTRIBUTION OF CASES ACCORDING TO TNM STAGING OF THE DISEASE.

| STAGING | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| NIL | 2 | 3% |
| IA | 48 | 79% |
| IB | 3 | 5% |
| IIA | 2 | 3% |
| IIIA2 | 2 | 3% |
| IIIC | 3 | 5% |
| IV | 1 | 2% |

CHART 8: DISTRIBUTION OF CASES ACCORDING TO TNM STAGING OF THE DISEASE.



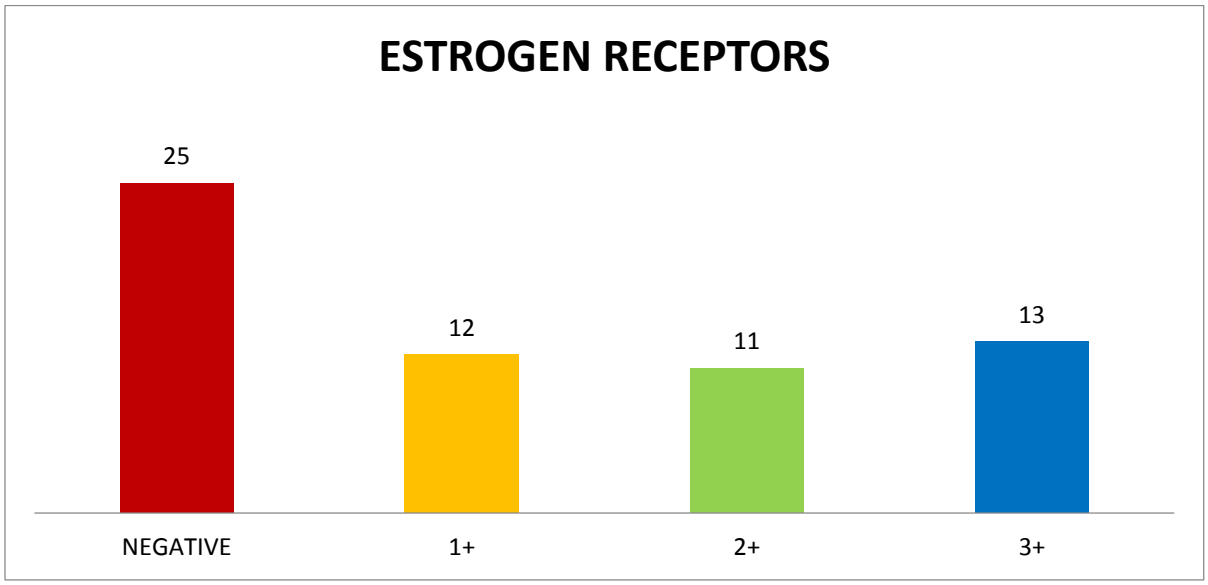
**DISTRIBUTION OF CASES ACCORDING TO ESTROGEN RECEPTOR POSTIVITY.**

Out of 61 cases, 25 cases are ER negative, 12 cases are weak positive (1+), 11 cases are moderate positive (2+) and 13 cases are strong positive (3+) (Table 9 & Chart 9).

TABLE 9: DISTRIBUTION OF CASES ACCORDING TO ESTROGEN RECEPTOR POSTIVITY.

| ESTROGEN RECEPTOR | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| NEGATIVE | 25 | 42% |
| 1+ | 12 | 19% |
| 2+ | 11 | 18% |
| 3+ | 13 | 21% |

CHART 9: DISTRIBUTION OF CASES ACCORDING TO ESTROGEN RECEPTOR POSTIVITY.



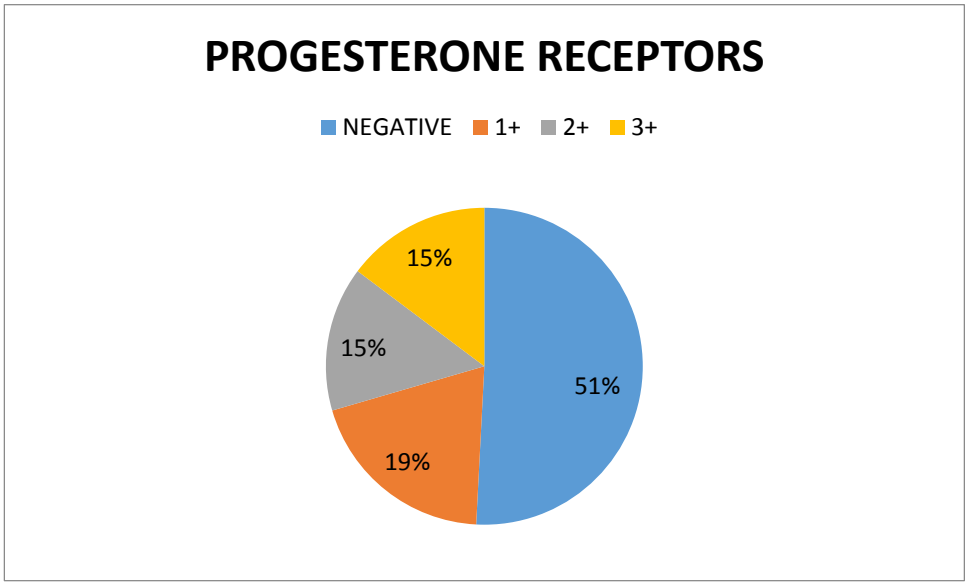
**DISTRIBUTION OF CASES ACCORDING TO PROGESTERONE RECEPTOR POSTIVITY.**

Out of 61 cases, 31 cases are Progesterone receptor negative, 12 cases weak positive (1+), 9 cases moderate positive (2+) and 9 cases strong positive (3+) (Table 10 & Chart 10).

TABLE 10: DISTRIBUTION OF CASES ACCORDING TO PROGESTERONE RECEPTOR POSTIVITY.

| PROGESTERONE RECEPTOR | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| NEGATIVE | 31 | 51% |
| 1+ | 12 | 19% |
| 2+ | 9 | 15% |
| 3+ | 9 | 15% |

CHART 10: DISTRIBUTION OF CASES ACCORDING TO PROGESTERONE RECEPTOR POSTIVITY.



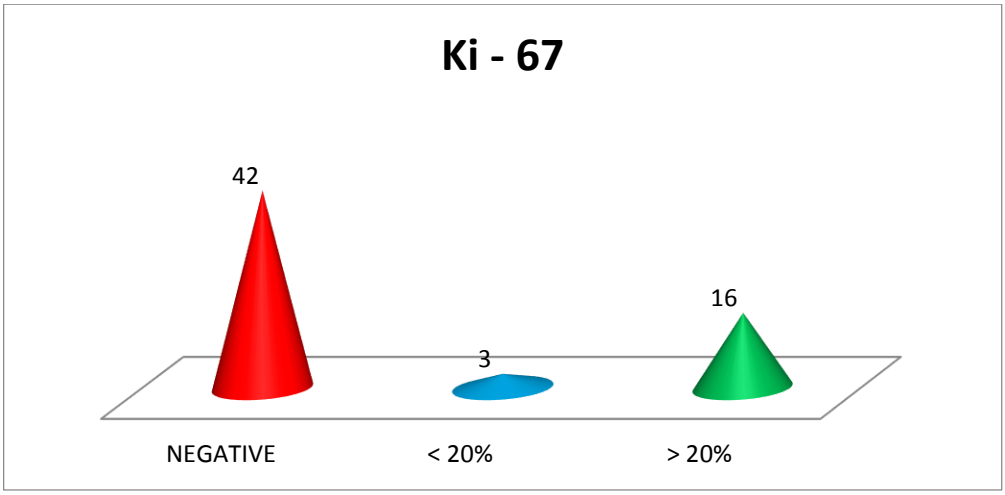
## DISTRIBUTION OF TUMORS ACCORDING TO Ki-67 POSITIVITY

Out of 61 cases, 42 cases are Ki-67 negative, 3 cases show under expression (< 20%) and 16 cases show overexpression of Ki-67 (>20%) (Table 11 & Chart 11).

TABLE 11: DISTRIBUTION OF TUMORS ACCORDING TO Ki-67 POSITIVITY.

| Ki - 67 | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| NEGATIVE | 42 | 69% |
| < 20% | 3 | 5% |
| > 20% | 16 | 26% |

CHART 11: DISTRIBUTION OF TUMORS ACCORDING TO Ki-67 POSITIVITY



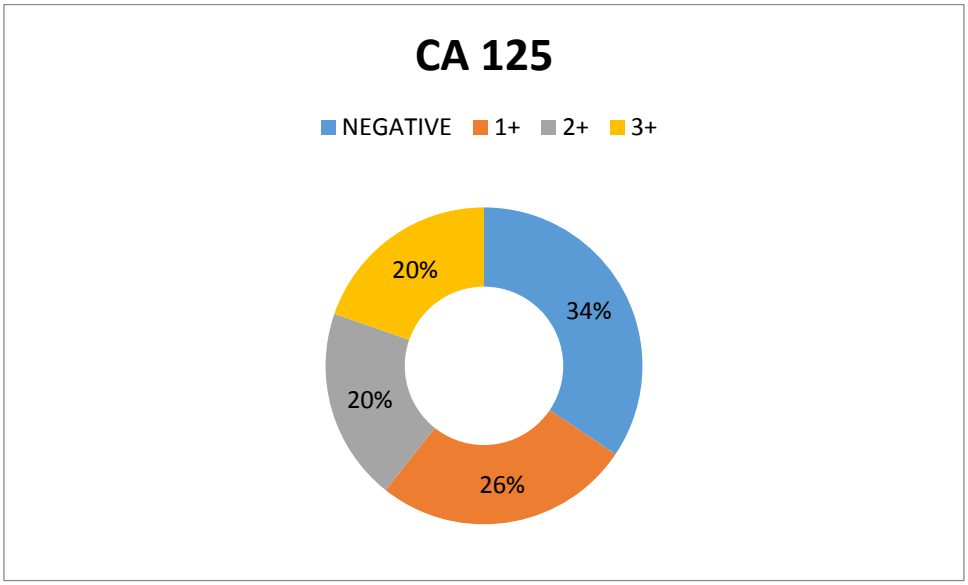
**DISTRIBUTION OF CASES OF ACCORDING TO CA-125 POSITIVITY**

Out of 61 cases, 21 cases are CA 125 negative, 16 cases show weak positivity (1+), 12 cases show moderate positivity (2+) and 12 cases show strong Positivity (3+) ( Table & chart 12)

TABLE 12: DISTRIBUTION OF CASES OF ACCORDING TO CA-125 POSITIVITY

| CA 125 | NO OF PATIENTS | PERCENTAGE |
|---|---|---|
| NEGATIVE | 21 | 34% |
| 1+ | 16 | 26% |
| 2+ | 12 | 20% |
| 3+ | 12 | 20% |

CHART 12: DISTRIBUTION OF CASES OF ACCORDING TO CA-125 POSITIVITY



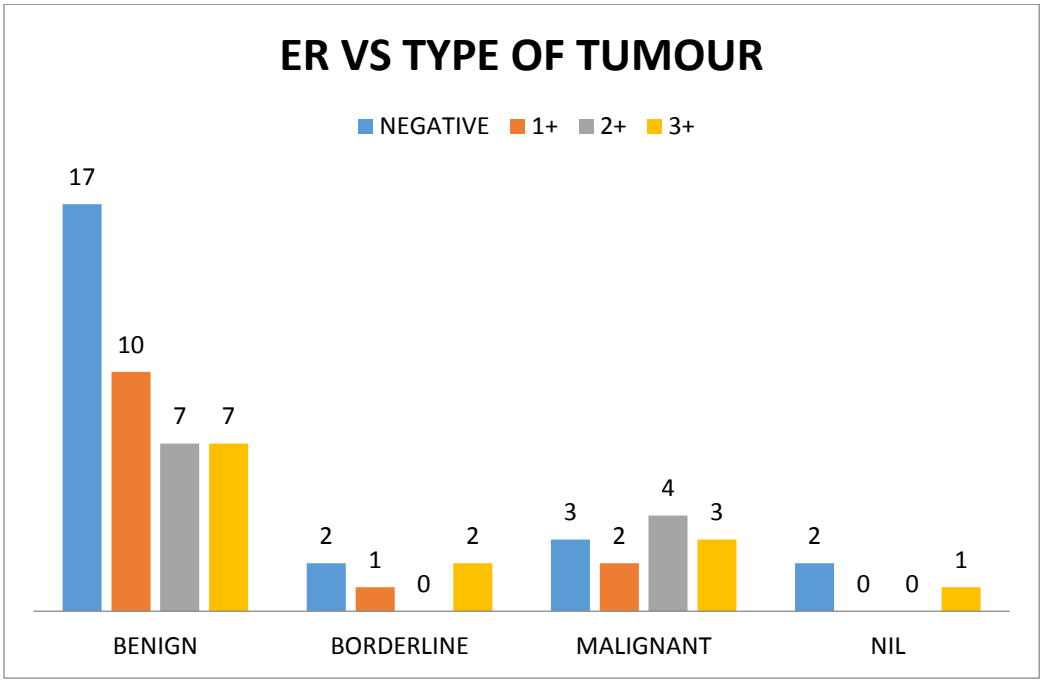
**DISTRIBUTION OF ESTROGEN RECEPTOR POSITIVITY ACCORDING HISTOLOGICAL TUMOR TYPE.**

Out of 61 cases, Estrogen receptor (ER) negativity is seen in 17 benign tumors, 2 Borderline tumors, 3 malignant tumor and 2 non neoplastic lesion. Weak positivity (1+) observed in 10 benign ,1 borderlineand 2 malignant Tumors. Moderate positivity(2+) seen in 7 benign and 4 malignant tumors. Strong positivity (3+) seen in 7 benign, 2 borderline, 3 malignant tumors and 1 non- neoplastic lesion (considered nil) ( Table 13 & Chart 13).

TABLE 13: TOTAL DISTRIBUTION OF ESTROGEN RECEPTOR POSITIVITY ACCORDING HISTOLOGICAL TUMOR TYPE

| ESTROGEN RECEPTOR | BENIGN | BORDERLINE | MALIGNANT | NIL | TOTAL |
|---|---|---|---|---|---|
| NEGATIVE | 17 | 2 | 3 | 2 | 24 |
| 1+ | 10 | 1 | 2 | 0 | 13 |
| 2+ | 7 | 0 | 4 | 0 | 11 |
| 3+ | 7 | 2 | 3 | 1 | 13 |

CHART 13: DISTRIBUTION OF ESTROGEN RECEPTOR POSITIVITY ACCORDING HISTOLOGICAL TUMOR TYPE



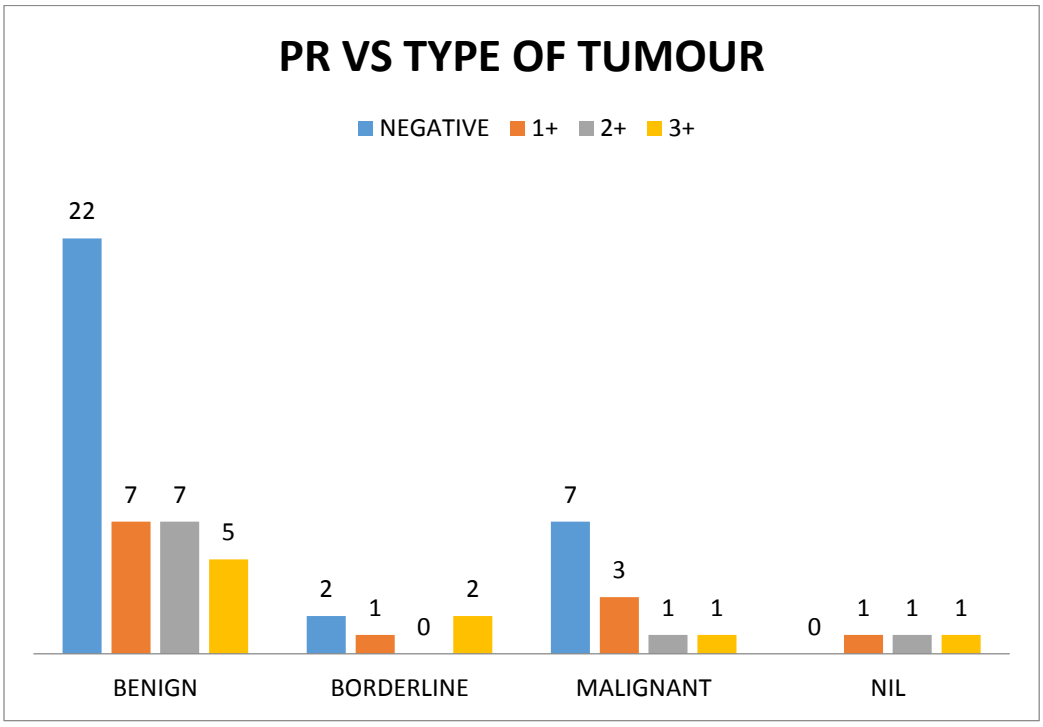

**DISTRIBUTION OF PROGESTERONE RECEPTOR POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE**

Out of 61 tumors, Progesterone Receptor Negativity is seen in 22 benign tumors, 2 borderline tumors and 7 malignant tumors. Weak positivity (1+) is observed in 7 benign tumors, 1 borderline tumor, 3 malignant tumors and 1 non neoplastic lesion (nil). Moderate positivity (2+) seen in 7 benign tumors, 1 malignant tumor and 1 non neoplastic lesion. Strong positivity (3+) is seen in 5 benign tumors, 2 borderline tumors, 1 malignant tumor and 1 non neoplastic lesion (nil).

TABLE 14: DISTRIBUTION OF PROGESTERONE RECEPTOR POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE

| PROGESTERONE RECEPTOR | BENIGN | BORDERLINE | MALIGNANT | NIL | TOTAL |
|---|---|---|---|---|---|
| NEGATIVE | 22 | 2 | 7 | 0 | 31 |
| 1+ | 7 | 1 | 3 | 1 | 12 |
| 2+ | 7 | 0 | 1 | 1 | 9 |
| 3+ | 5 | 2 | 1 | 1 | 9 |

CHART 14: DISTRIBUTION OF PROGESTERONE RECEPTOR POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE



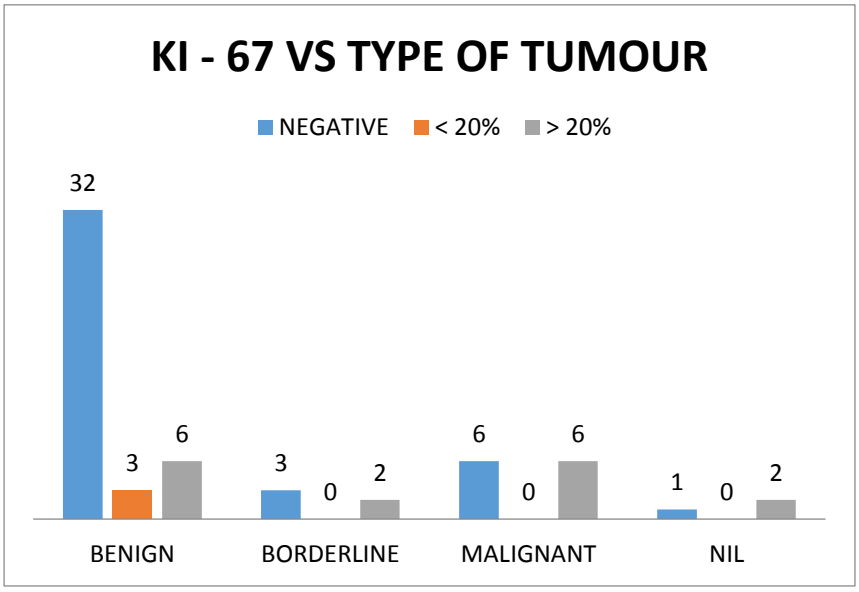
**DISTRIBUTION OF Ki-67 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE**

Out of 61 cases, Ki-67 positivity seen in 32 benign, 3 borderline, 6 malignant tumors and 1 non-neoplastic lesion (considered as nil). Low expression (<20%) seen in 3 benign tumors only. Over-expression (>20%) observed in 6 benign, 2 borderline ,6 malignant tumors and 2 non-neoplastic lesion (considered as nil) (Table & chart 16).

TABLE 15 : DISTRIBUTION OF Ki-67 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE.

| Ki - 67 | BENIGN | BORDERLINE | MALIGNANT | NIL | TOTAL |
|---|---|---|---|---|---|
| NEGATIVE | 32 | 3 | 6 | 1 | 42 |
| < 20% | 3 | 0 | 0 | 0 | 3 |
| > 20% | 6 | 2 | 6 | 2 | 16 |

CHART 15 : DISTRIBUTION OF Ki-67 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE



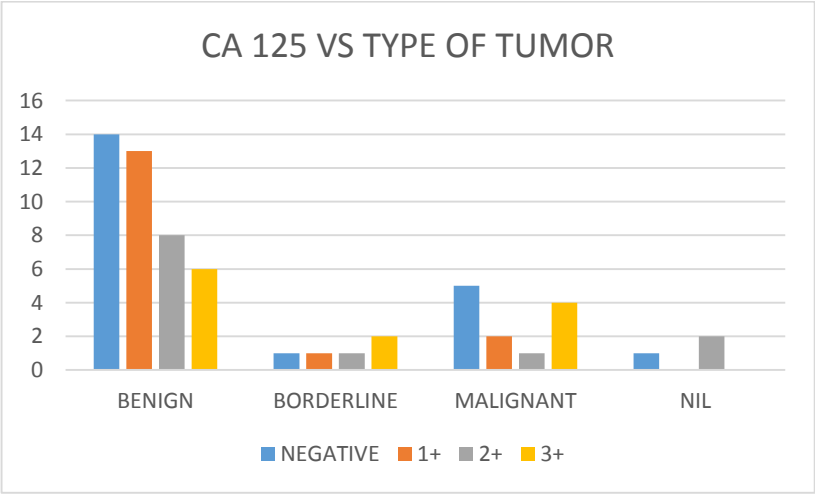
**DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE**

Out of 61 cases, CA 125 negativity seen in 14 benign, 1 borderline, 5 malignant tumors and 1 non- neoplastic lesion. Weak positive (1+) expressed by 13 benign, 1 borderline and 2 malignant tumors. Moderate positivity (2+) expressed by 8 benign, 1 borderline, and 1 malignant tumor, 2 non-neoplatic lesion. Strong positivity (3+) expressed by 6 benign, 2 borderline and 4 malignant tumors ( Table & Chart 16).

TABLE 16: DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE.

| CA 125 | BENIGN | BORDERLINE | MALIGNANT | NIL | TUMOR |
|---|---|---|---|---|---|
| NEGATIVE | 14 | 1 | 5 | 1 | 21 |
| 1+ | 13 | 1 | 2 | 0 | 16 |
| 2+ | 8 | 1 | 1 | 2 | 12 |
| 3+ | 6 | 2 | 4 | 0 | 12 |

CHART 16: DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL TUMOR TYPE.



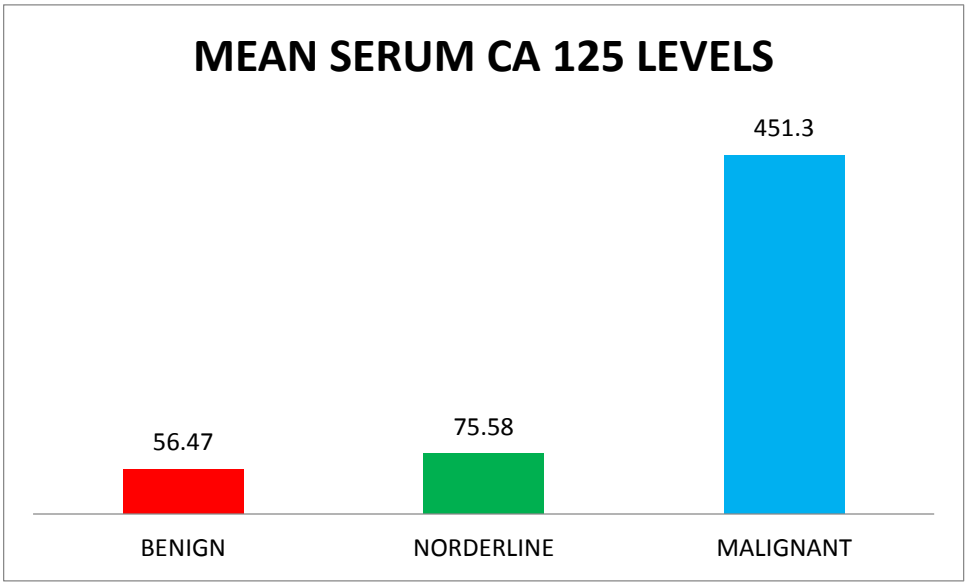
**DISTRIBUTION OF MEAN CA 125 LEVEL ACCORDING TO TYPE OF TUMOR**

Table 17 & chart 17 shows mean level of CA 125 according to the type of tumor.

TABLE 17: MEAN CA 125 LEVEL ACCORDING TO TYPE OF TUMOR

| TYPE OF TUMOUR | SERUM CA 125 LEVELS | |
|---|---|---|
| | MEAN | SD |
| BENIGN | 56.47 | 280.3 |
| NORDERLINE | 75.58 | 214.3 |
| MALIGNANT | 451.3 | 190.2 |
| P VALUE - 0.001 | | |
| ANOVA | | |
| SIGNIFICANT | | |

CHART 17: MEAN CA 125 LEVEL ACCORDING TO TYPE OF TUMOR



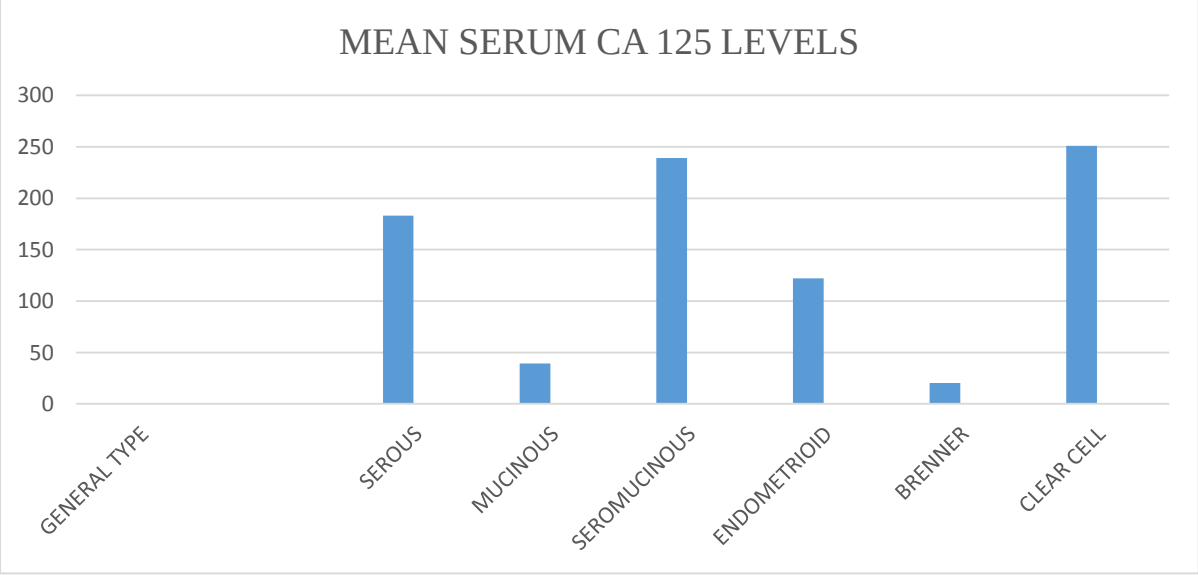

**DISTRIBUTION OF MEAN CA 125 LEVEL ACCORDING TO HISTOLOGICAL TYPE OF TUMOR**

Table & chart 18 shows mean CA 125 level according to the histological type – serous, mucinous, endometrioid, clear cell, Brenner and seromucinous Tumor.

TABLE 18: DISTRIBUTION OF MEAN CA 125 LEVEL ACCORDING TO HISTOLOGICAL TYPE OF TUMOR

| GENERAL TYPE | SERUM CA 125 LEVELS | |
|---|---|---|
| | MEAN | SD |
| SEROUS | 183.23 | 280.13 |
| MUCINOUS | 39.36 | 219.21 |
| SEROMUCINOUS | 239 | 0 |
| ENDOMETRIOID | 122.1 | 92.3 |
| BRENNER | 20.5 | 10.2 |
| CLEAR CELL | 251 | 0 |
| P VALUE - 0.001 | | |
| ANOVA | | |
| SIGNIFICANT | | |

CHART: 18 : DISTRIBUTION OF MEAN CA 125 LEVEL ACCORDING TO HISTOLOGICAL TYPE OF TUMOR.



**DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL SUBTYPE OF TUMOR**

Out of 61 cases, CA 125 negativity expressed by 1 non- neoplastic lesion (nil), 13 serous, 6 mucinous and 2 endometrioid tumors. Weak positivity (1+) by 8 serous, 6 mucinous, 1 brenner and 1 clear cell tumor. Moderate positivity (2+) by 2 non-neoplastic lesion, 4 serous, 1 seromucinous and 1 clear cell tumor. Strong positivity (3+) by 9 serous and 3 mucinous tumors ( Table 19 and Chart 19).

CHART 19: DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL SUBTYPE OF TUMOR

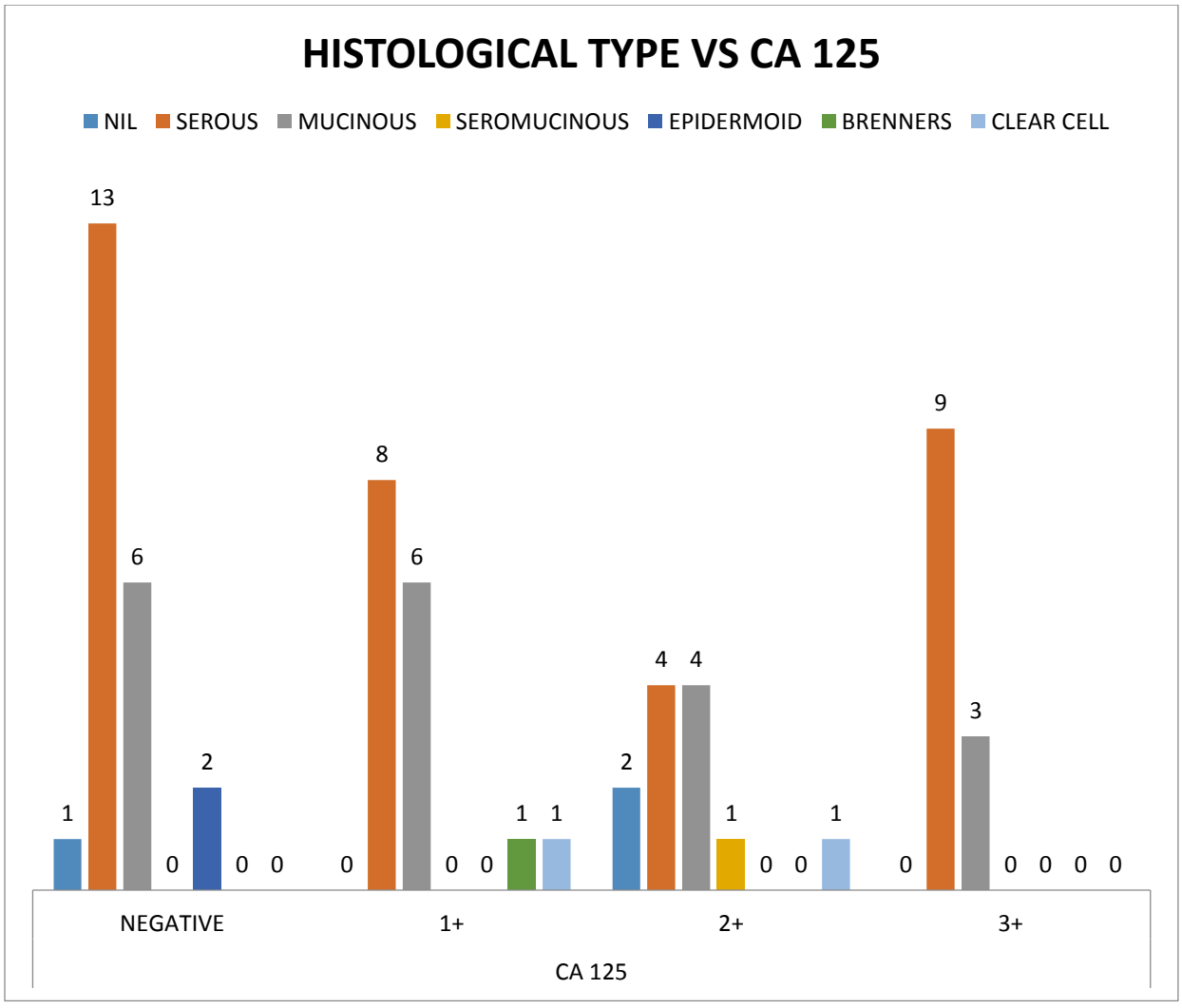


TABLE :19 DISTRIBUTION OF CA 125 POSITIVITY ACCORDING TO HISTOLOGICAL SUBTYPE OF TUMOR.

| GENERAL TYPE | CA 125 | | | |
|---|---|---|---|---|
| | NEGATIVE | 1+ | 2+ | 3+ |
| NIL | 1 | 0 | 2 | 0 |
| SEROUS | 13 | 8 | 4 | 9 |
| MUCINOUS | 6 | 6 | 4 | 3 |
| SEROMUCINOUS | 0 | 0 | 1 | 0 |
| ENDOMETRIOID | 2 | 0 | 0 | 0 |
| BRENNERS | 0 | 1 | 0 | 0 |
| CLEAR CELL | 0 | 1 | 1 | 0 |
| TOTAL | 22 | 16 | 12 | 12 |

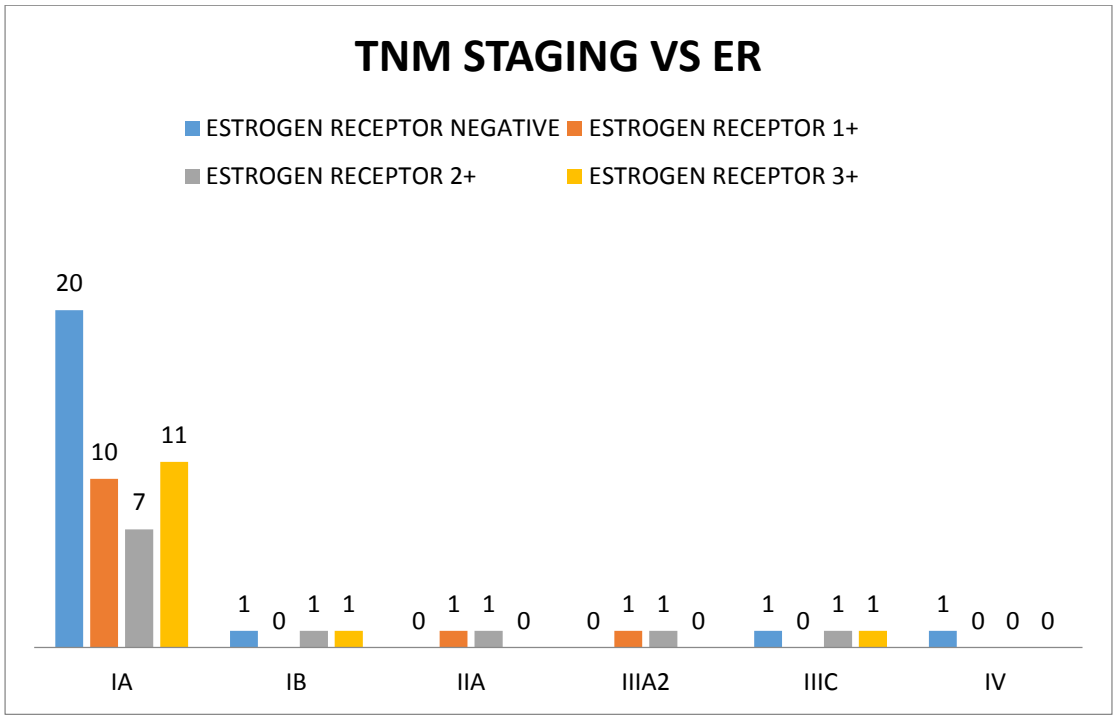
**DISTRIBUTION OF ESTROGEN RECEPTOR POSITIVITY ACCORDING TO TNM STAGING OF THE TUMOR**

Out of 61 cases, ER negativity expressed by 20 stage IA tumors, 1 stage IB tumor, 1 stage IIIC tumor and 1 stage IV tumor. Weak positivity ( 1+) seen in one stage IA tumor, one stage IIA tumor and one stageIIIA2 tumor. Moderate positivity (2+) showed by 7 stage IA tumor, one stage IB tumor, one stage IIIA2 tumor and one stage IIIC tumor. Strong positivity (3+) showed by tumor 11 stage IA tumor, one stage IB tumor and one stage IIIC tumor.

TABLE 20: TNM STAGING VS ESTROGEN RECEPTOR

| TNM STAGING | ESTROGEN RECEPTOR | | | | |
|---|---|---|---|---|---|
| | NEGATIVE | 1+ | 2+ | 3+ | TOTAL |
| IA | 20 | 10 | 7 | 11 | 48 |
| IB | 1 | 0 | 1 | 1 | 3 |
| IIA | 0 | 1 | 1 | 0 | 2 |
| IIIA2 | 0 | 1 | 1 | 0 | 2 |
| IIIC | 1 | 0 | 1 | 1 | 3 |
| IV | 1 | 0 | 0 | 0 | 1 |
| TOTAL | 23 | 12 | 11 | 14 | 59 |

CHART 20: TNM STAGING VS ESTROGEN RECEPTOR



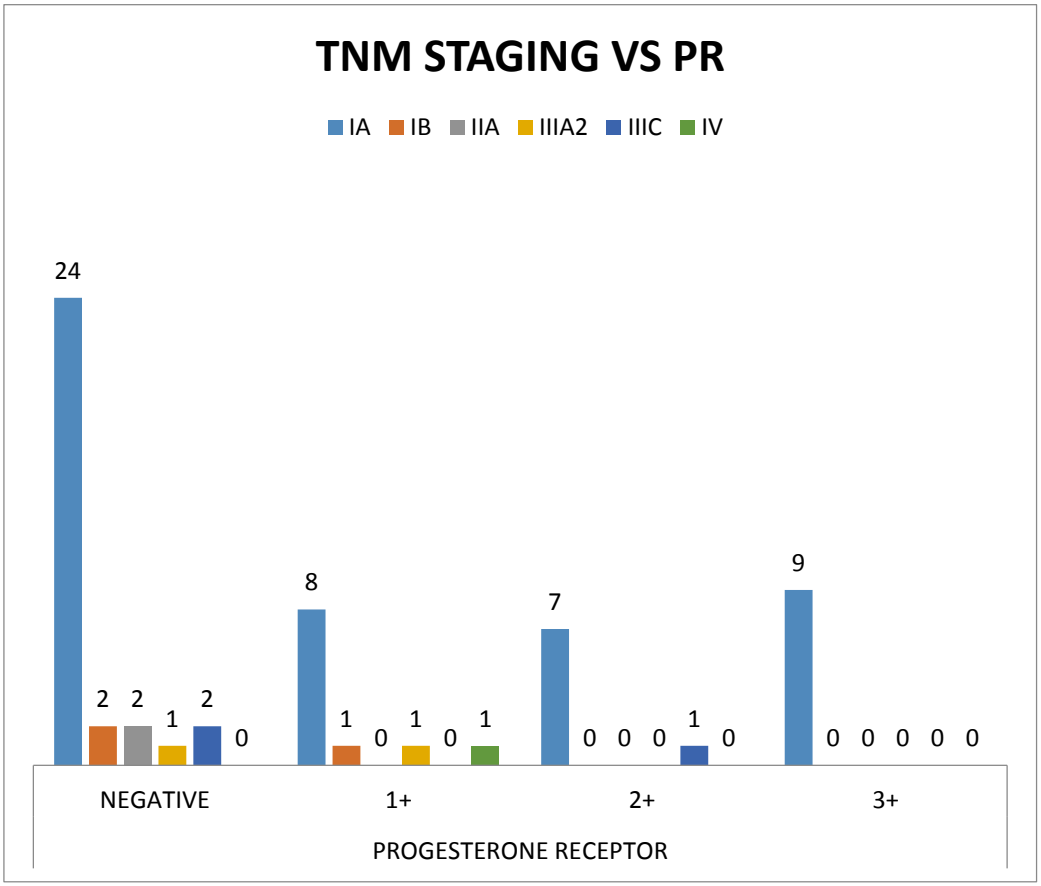
**DISTRIBUTION OF PROGESTERONE RECEPTOR POSITIVITY ACCORDING TO TNM STAGING OF THE TUMOR**

Out of 61 cases, PR negativity expressed by 24 stage IA tumors, 2 stage IB tumor, 2 stage IIA, 1 stage IIIA2 tumor and 2 stage IIIC tumor. Weak positivity (1+) showed by 8 stage IA tumor, one stage IB tumor, one stage IIIA2 tumor and one stage IV tumor. Moderate positivity (2+) showed by 7 stage IA tumor and one stage IIIC tumor. Strong positivity (3+) showed by tumor 9 stage IA tumors only (Table 20 and chart 20) .

TABLE 21: TNM STAGING VS PROGESTERONE RECEPTOR

| **TNM STAGING** | **PROGESTERONE RECEPTOR** | | | | |
|---|---|---|---|---|---|
| | **NEGATIVE** | **1+** | **2+** | **3+** | **TOTAL** |
| IA | 24 | 8 | 7 | 9 | 48 |
| IB | 2 | 1 | 0 | 0 | 3 |
| IIA | 2 | 0 | 0 | 0 | 2 |
| IIIA2 | 1 | 1 | 0 | 0 | 2 |
| IIIC | 2 | 0 | 1 | 0 | 3 |
| IV | 0 | 1 | 0 | 0 | 1 |
| TOTAL | 31 | 11 | 8 | 9 | 59 |

CHART 21: TNM STAGING VS PROGESTERONE RECEPTOR



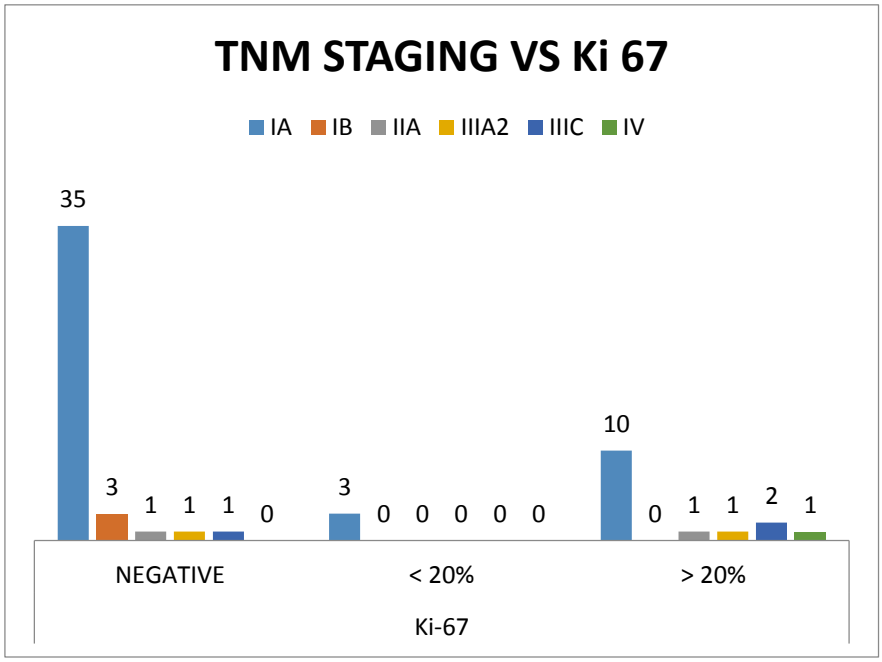

**DISTRIBUTION OF Ki-67 RECEPTOR POSITIVITY ACCORDING TO TNM STAGING OF THE TUMOR**

Out of 61 cases, Ki-67 negativity expressed by 35 stage IA tumors, 3 stage IB tumor, one stage IIA, one stage IIIA2 tumor and one stage IIIC tumor. Low expression or under expression (<20%) showed by 3 stage IA tumor only. Over expression (> 20%) showed by 10 stage IA tumor and one stage IIA tumor, one stage IIIA2 tumors , 2 stage IIIC tumor and one stage IV tumor.

TABLE : 22 TNM STAGING VS Ki-67 RECEPTOR POSITIVITY

| TNM STAGING | Ki-67 | | | |
|---|---|---|---|---|
| | NEGATIVE | < 20% | > 20% | TOTAL |
| IA | 35 | 3 | 10 | 48 |
| IB | 3 | 0 | 0 | 3 |
| IIA | 1 | 0 | 1 | 2 |
| IIIA2 | 1 | 0 | 1 | 2 |
| IIIC | 1 | 0 | 2 | 3 |
| IV | 0 | 0 | 1 | 1 |
| TOTAL | 41 | 3 | 15 | 59 |

CHART : 22 TNM STAGING VS Ki-67 RECPTOR POSITIVITY



**DISTRIBUTION OF CA 125 RECEPTOR ACCORDING TO TNM STAGING OF THE TUMOR.**

Out of 61 cases, CA125 negativity is observed in 17 stage IA tumors, one stage IB tumor, one stage IIA and one stage IIIA2 tumor .weak positivity (1+) showed by 14 stage IA tumor, one stage IB tumor and one stageIIIC tumor. Moderate positivity (2+) showed by 9 stage IA tumor and one stage IB tumor and one stage IV tumor. Strong positivity (3+) showed by 8 stage IA tumors , one stage IIA tumor, one stage IIIA2 and 2 stage IV tumor.

TABLE 23: TNM STAGING VS CA 125 POSITIVITY

| **TNM STAGING** | **CA 125** | | | | |
|---|---|---|---|---|---|
| | **NEGATIVE** | **1+** | **2+** | **3+** | **TOTAL** |
| IA | 17 | 14 | 9 | 8 | 48 |
| IB | 1 | 1 | 1 | 0 | 3 |
| IIA | 1 | 0 | 0 | 1 | 2 |
| IIIA2 | 1 | 0 | 0 | 1 | 2 |
| IIIC | 0 | 1 | 0 | 2 | 3 |
| IV | 0 | 0 | 1 | 0 | 1 |
| TOTAL | 20 | 16 | 11 | 12 | 59 |

CHART: 23 TNM STAGING VS CA 125 POSITIVITY

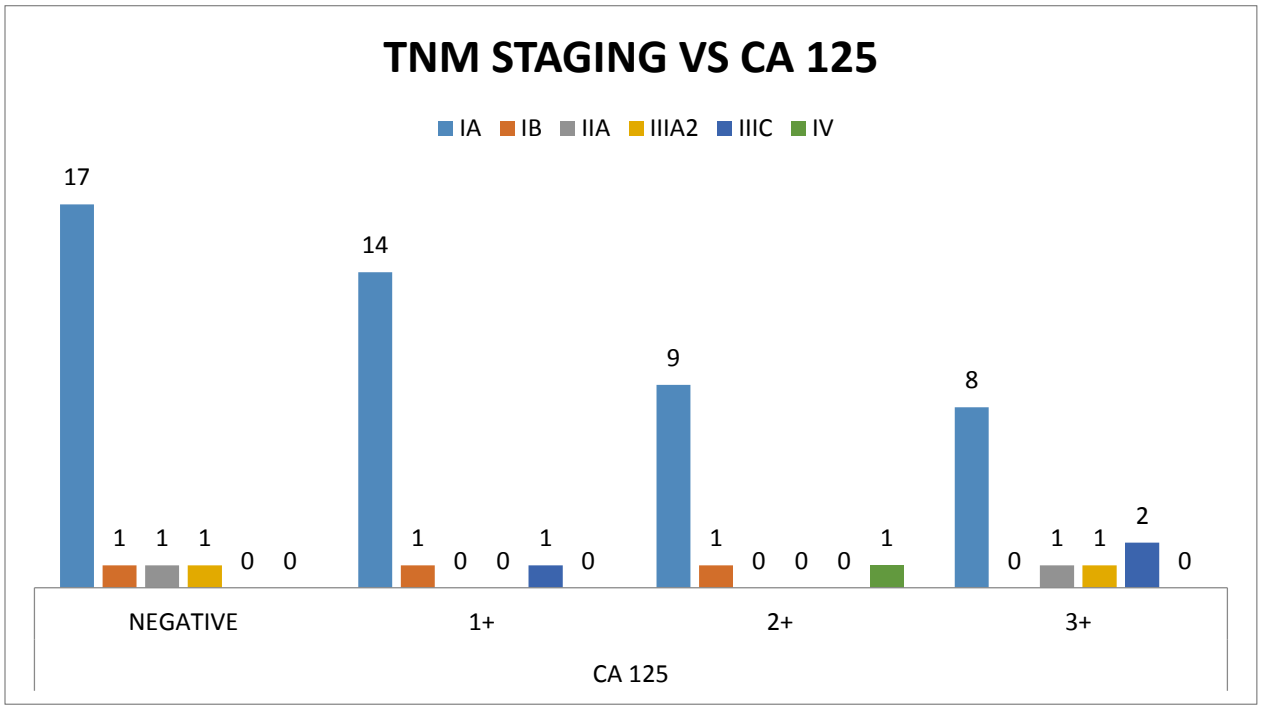


TABLE 24: SUMMARY OF NUMBER OF TUMORS ACCORDING TO HISTOLOGIC SYBTYPE

| **Type of tumors** | **Serous tumor** | **Mucinous tumor** | **Endometrioid tumor** | **Brenner tumor** | **Clear cell tumor** | **Seromucinous tumor** |
|---|---|---|---|---|---|---|
| Total No of tumors | 33 | 19 | 2 | 2 | 1 | 1 |
| No of Benign Tumors | 25 | 14 | 0 | 2 | 0 | 0 |
| No of Borderline Tumors | 1 | 4 | 0 | 0 | 0 | 0 |
| No of Malignant Tumors | 7 | 1 | 2 | 0 | 1 | 1 |

TABLE 25: SUMMARY OF IMMUNOHISTOCHEMICAL EXPRESSION OF ALL TUMORS

| IHC | ER & POSITIVITY PERCENTANGE | | | | PR & POSITIVITY PERCENTANGE | | | | KI67 & POSITIVITY PERCENTANGE | | | CA125 & POSITIVITY PERCENTANGE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NEG | 1+ | 2+ | 3+ | NEG | 1+ | 2+ | 3+ | NEG | <20% | >20% | NEG | 1+ | 2+ | 3+ |
| BENIGN (41) | 17 | 10 | 7 | 7 | 22 | 7 | 7 | 5 | 32 | 3 | 6 | 14 | 13 | 8 | 6 |
| | 39.34% | | | | 31.14% | | | | 14.75% | | | 44.26% | | | |
| BORDERLINE (5) | 2 | 1 | 0 | 2 | 2 | 1 | 0 | 2 | 3 | 0 | 2 | 1 | 1 | 1 | 2 |
| | 4.91% | | | | 4.91% | | | | 3.27% | | | 6.55% | | | |
| MALIGNANT (12) | 3 | 2 | 4 | 3 | 7 | 3 | 1 | 1 | 6 | 0 | 6 | 5 | 2 | 1 | 4 |
| | 14.75% | | | | 8.196% | | | | 9.83% | | | 11.47% | | | |
| NIL (3) | 2 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 2 | 0 |
| | 1.67% | | | | 4.91% | | | | 1.67% | | | 11.47% | | | |

## RESULTS

This is a prospective study conducted over a period of 2 years in the Department of Pathology, TVMC .61 cases diagnosed clinically and radiologically as ovarian tumor were Included. Blood samples were collected from the patients and their corresponding tumor tissue with the histopathological diagnosis were studied.

Out of 61 cases, the histopathological diagnosis of 58 tumors fall under category of surface epithelilal tumors, one turned out to be pure sex cord tumor and the rest of 2 were non-neoplastic lesion (stromal hyperthecosis and cystic follicles).

In this study the maximum number of patients fall under the age group of 31-40 years (26%) followed by age group of < 30 years (20%) and 51- 60 years (20%). Minimum number of patients fall under the age group of more than 60 years (16 %). According to the histopathological diagnosis, in this study the maximum tumor category belongs to Serous tumor 57% followed by mucinous tumors 33% and the minor contributions are from other tumors in the order endometrioid 3%, Brenner 3%, clear cell 2% and seromucinous 2%. In our study most of the ovarian tumors were benign (41) which constitutes 67% followed by 12 malignant tumors (20%). Among the benign tumors maximum cases fall under serous group 25 tumors which constitutes 61% followed by mucinous 34% and Brenner 5%. Within borderline category the high number of tumors fall under mucinous group, constitutes 4 tumors (80%), while most of the malignant tumors belongs to Serous tumors that constitutes 7 (59%).

Also in our study out of 61 cases, maximum number of cases (48) fall under stage IA which constitutes 79% followed by stage IB three tumors (5%), stage IIIC three tumors (5%), stage IIA two tumors (3%), Stage IIIA2 two tumors (3%) and stage IV one tumor (2%), while two non-neoplastic lesion occupies 3%.

**IMMUOHISTOCHEMICAL EXPRESSION**

In our present study the immunohistochemical expression of four important markers are studied which are Estrogen Receptor, Progesterone Receptor, proliferative marker Ki-67 and carcinoma antigen CA125.

Estrogen receptor positivity is expressed by 36 tumors which constitutes 58% and negativity is shown by 25 tumors (42%). ER positivity by benign tumors are 39.34%, borderline tumors show 4.91% and malignant tumors show 14.75 %. The maximum number of ER positivity is expressed by stage IA tumors 45.90% followed by stage IB to stage IIIC.

Progesterone receptor positivity is expressed by 30 tumors which constitutes 49.18% and negativity by 31 tumors (51%). PR positivite expression by benign tumors are 31.14%, borderline tumors are 4.91% and malignant tumors are 8.19 %. The maximum number of PR positivity was expressed by stage IA tumors 39.34% followed by stage IB to stage IIIC each (1.63%) except stage IIA which shows complete absence.

Ki-67 receptor positivity is expressed by 19 tumors which constitutes 31 % and no proliferative activity is shown by 42 tumors (69 %). Ki-67 positive expression by benign tumors are 14.75 %, borderline tumors are 3.27 % and malignant tumors are 9.83 %. The maximum number of Ki-67 positivity was expressed by stage IA tumors 21.31% followed by stage IIIC tumors 3.27%, stage IIA, stage IIIA2 and stage IV tumors each contributes 1.63% except stage IB which shows complete absence.

CA125 receptor positivity is expressed by 40 tumors that constitutes 66% and negativity by 21 tumors (34 %). CA 125 positive expression by benign tumors are 44.26%, borderline tumors are 6.55 % and malignant tumors are 11.47 %. The maximum number of CA125 positivity is expressed by stage IA tumors 50.81% followed by stage IIIC 4.91% tumors, stage IB 3.27% and by stage IIA tumors, stage IIIA2 tumors and stage IV tumors each contributes 1.63%

**SERUM CA 125**

In our study out of 61 patients, higher values of serum CA 125 is seen in 29 patients (48%) and normal values are shown by 32 patients (52%).

Also mean elevation of serum CA 125 values is observed in the higher order of frequency as benign 56.47, borderline 75.58 and malignant 451.3. The p value is significant $p < 0.05$. And the elevation of serum CA 125 in histological subcategory falls accordingly in the order serous tumors, mucinous tumors, endometrioid tumors, clear cell tumors, seromucinous tumors and Brenner tumor. The p value is significant $p < 0.005$.

# DISCUSSION

Ovarian cancer is the sixth most common cancer in women[1] and ranks third among the female genital tract malignancy in India with age standardized ratio 6.7/1,00,000. There are about 2,04,000 new cases and 1,25,000 death annually[2]. The most recent, surveillance epidemiology and end results (SEER) calculation of life time risk for ovarian cancers are that 1 in 55 women will develop ovarian cancer over their lifetime[3]. World health organization (WHO) classifies ovarian tumor according to their most probable cell of origin and histomorphological features[4]. Most of the tumors are epithelial in origin. Surface epithelial tumors accounts for about 2/3$^{rd}$ of all ovarian neoplasm[5].

About 80% tumors are benign and occur in younger women and 10% among them are hereditary in nature[6]. Malignant epithelial ovarian tumor occurs most commonly in older women and accounts for approximately 3% of all cancers [7] Ovarian surface epithelial tumor cells are characterized by increased expression of steroid hormone receptors (ER&PR), CA125 and shows high proliferative activity[8]. Greater than 80%of patients with epithelial ovarian cancer have elevated serum CA125 levels at diagnosis and serial serum CA125 levels correlate with changes in disease status in most cases[9].

Serum CA125 is routinely monitored in ovarian cancers and many studies haveproven their value in guiding treatment, but the immunohistochemical expressions are not clearly made out[10].

So, in this study we studied 61 cases of ovarian tumors. Out of 61 cases, 59 turned out to be ovarian neoplasms and 2 were non neoplastic lesion of ovary (cystic follicles and stromal hyperthecosis). Hence the incidence of ovarian neoplasm is almost 30 times the incidence of Non-neoplastic lesions. Similar studies were done by SO Sharadha, T.A Sridevi With 205 patients with ovarian masses at ESIC Medical College and PGIMSR[116]. And their conclusion says that the incidence of ovarian neoplasm were twice that of non neoplastic lesion[116].

In our study out of 61 cases, 59 are ovarian neoplasms and within that 58 turned out to be surface epithelial tumors, and 1 case of pure sex cord tumor. Hence it is made clear that surface epithelial tumor is the most common tumor (96.72%) among ovarian tumors. Similar study results were concluded by L.G buchynska, N.P Iurchenko at national institute of cancer at Uttar Pradesh [109], Bhagora R and Malik R at department of pathology Madhya Pradesh [ 117] and Santosh Kumar Mondal, Ranjana Banyopadhayay at deparment of pathology, Medical collge kolkatta[119]. Thus their observation correlates with our study.

In our study out of 58 surface epithelial tumor, the **incidence of serous tumor** was high, totally 33 Tumors (57%) followed by incidence of mucinous tumors -19 tumors (33%) which correlates with the studies of Dr. Yogambal, Dr. P.Arunalatha, Dr.V.Palaniappan at department of pathology, Stanley medical college [3].

The ovarian tumors are well known for their **bilateral** involvement. The likelihood of bilateral involvement by primary ovarian tumors varies with histologic subtype.

In our study out of 59 ovarian neoplasms only 4 tumors are bilateral 2 benign & 1 malignant serous tumors and 1 benign mucinous tumor]. Hence unilateral involvement of serous tumors (30 tumors) are more common than their bilaterality. Similar results were reported by Santosh Kumar Mondal, Ranjana Banyopadhayay at department of pathology, Medical college kolkatta[119]. Their observation correlates with our study.

In our study out of 61 cases, 41 tumors are benign (67%), 5 are borderline (8%), 13 cases are malignant (20%) and 2 non neoplastic lesions. Hence the occurence of benign tumor is more common followed by malignant tumors and borderline tumors. This observation correlates with the studies carried out by Pilli et el and Suneeta [118] and SO Saradha, T.A.Sridevi [116].

In our study within the 41 benign tumors, the occurrence of benign serous tumors (61%) are common than benign mucinous tumors (14%). Similarly malignant serous tumors occurrence is more common, totally 7 tumors (59%) which correlates with the studies

carried out by Dr. Yogambal, Dr. P.Arunalatha, Dr.V.Palaniappan at department of pathology, Stanley medical college [3].

In our study, we reported 5 borderline tumors with the incidence rate of 8 %. Among the 5 tumors, borderline mucinous tumor (4 tumors, 80%) is more common than borderline serous tumor (1 tumor, 20%). This observation does not correlate with the studies carried out by Dr. Yogambal, Dr. P.Arunalatha, Dr.V.Palaniappan at department of pathology, Stanley medical college [3], which concludes that frequency of borderline serous is more than mucinous.

The age of presentation of ovarian tumors in our study is between the age group of 20-40 years (46%) and 54% in the age group of 41-65 years. So the median age of presentation of ovarian tumors is 40 years, which is similar to the study by Santosh Kumar Mondal, Ranjana Banyopadhayay at department of pathology, Medical college kolkatta[119]. Their observation correlates with our study.

In our study, the age of presentation of most benign tumors is between 20 and 40 years. Whereas the median age of presentation of malignant tumor is 48 years, which correlates with the study carried out by Santosh Kumar Mondal, Ranjana Banyopadhayay at department of pathology, Medical college kolkatta[119]. Hence the indication towards an

earlier presentation of malignant lesion in our study warrants a prompt and thorough investigation of any vague abdominal complaint.

In our study out of 59 ovarian neoplasm, the other 2 were non-neoplastic lesion, maximum number of cases (48) fall under stage IA Which constitutes an incidence of 79% followed by stage IB three tumors (5%), stage IIIC three tumors (5%), two stage IIA tumors (3%), two Stage IIIA2 tumors (3%) and one stage IV tumor (2%). This observation is contrary against the study conducted by Miriam Lenhard, Lennervo tereza at Ludwig- Maximilians University of Munich[120] , according to which stage III tumors have more incidence. But this observation correlates with the study carried out by Shilpa Garg, Nisha Marwah at university of medical sciences Haryana [108] .

In our study Estrogen receptor positivity is expressed by 36 tumors which constitutes 58% and negativity is shown by 25 tumors (42%). ER positivity by benign tumors are 39.34%, borderline tumors are 4.91% and malignant tumors are 14.75 %. The maximum number of ER positivity is expressed by stage IA tumors 45.90% followed by stage IB to stage IIIC. ER negativity is observed more in the higher stage of the tumor (Stage III to Stage IV).

Similarly in our study Progesterone receptor positivity is expressed by 30 tumors which constitutes 49.18% and negativity is shown by 31 tumors (51%). PR positivity by benign tumors are 31.14%, borderline tumors are 4.91% and malignant tumors are 8.19 %. The

maximum number of PR positivity is expressed by stage IA tumors 39.34% followed by stage IB to stage IIIC each (1.63%) except stage IIA which shows complete absence. Hence PR negativity is also observed in the higher stage of tumor (stage II, Stage III and stage IV). Both of these steroid Hormone receptor positivity and negativity correlates to the study conducted by Buchynska LG1, Iurchenko NP at department of oncopathology, uttar Pradesh [109]. Their was study conducted with 81 ovarian tumor patients and their corresponding 81 tissue samples with the conclusion that, group of stage III - IV patients show high number of steroid receptor negative tumors and it is 3 fold increased [109]. Similarly stage I-II ovarian tumors showed steroid hormone receptor positivity of 43% in their study. Which also correlates with our study showing 52.45 % ER positivity and 40.97 % of PR positivity among Stage I-II tumors.

In our study Ki-67 receptor positivity is expressed by 19 tumors which constitutes 31 % and no proliferative activity is shown by 42 tumors (69 %). Ki-67 positivity by benign tumors are 14.75 %, borderline tumors are 3.27 % and malignant tumors are 9.83 %. The maximum number of Ki-67 positivity is expressed by stage IA tumors 21.31% followed by stage IIIC tumors 3.27% , stage IIA, stage IIIA2 and stage IV tumors each contributes 1.63% except stage IB which shows complete absence. So, in this study benign tumors shows increased proliferative index compared to Borderline and malignant tumors, also maximum number of Ki-67 positivity was expressed by stage IA and lower proliferative index was shown by higher stage of tumors. This observation is contrary to the studies carried by Buchynska LG1, Iurchenko NP at department of oncopathology, uttar Pradesh

[109], Pooja S. Naik, Sanjay Deshmukh [10] and Lavanya Rajagopal and Ramesh s at SRM medical College, Chennai [14]. All these studies concludes that high proliferative index is observed only in malignant and higher stage of ovarian tumors. In our study, CA125 receptor positivity is expressed by 40 tumors which constitutes 66 % and negativity is shown by 21 tumors (34 %). CA 125 positivity by benign Tumors are 44.26%, borderline tumors are 6.55 % and malignant tumors are 11.47 %.

Serous tumors shows maximum CA125 positivity (34.42%), followed by mucinous tumors (21.31%). This observation correlates with the study by Divya Kriplani and Mandakini M. Patel [106]. The maximum number of CA 125 positivity was expressed by stage IA tumors 50.81% followed by stage IIIC 4.91% tumors, stage IB 3.27% and by stage IIA tumors, stage IIIA2 tumors and stage IV tumors each contributes 1.63%

In our study out of 61 patients, higher values of serum CA 125 is seen in 29 Patients (48%) and normal values are shown by 32 patients (52%). Also mean elevation of serum CA 125 values is observed in the higher order of frequency as benign 56.47, borderline 75.58 and malignant 451.3. And the elevation of serum CA 125 in histological subcategory falls accordingly in the order serous tumors, mucinous tumors , endometrioid tumors, clear cell tumors, seromucinous tumors and Brenner tumor. The p value is significant $p < 0.005$. This observation correlates with the study by Kristein pepin MD, Marcela del Camen et al [115].

In our study out of 61 patients, higher values of serum CA 125 is seen in 29 Patients. 8 benign & 5 malignant serous tumors, 2 benign & 3 borderline mucinous tumors and 1 malignant clear cell tumor showed both elevated serum CA 125 values and tissue expression of CA125. This observation correlates with the study by Channdana das et al [104] where they carried out study with 50 ovarian tumor Patients, out of those only 19 patients showed elevation and 14 cases only showed Corresponding tissue CA 125 expression [104].

Also in our study 3 benign & 2 malignant serous tumor, 1 borderline & 1 malignant mucinous tumor, 2 malignant endometrioid tumor and 1 benign Brenner tumor had elevated serum CA 125 level but did not reveal tissue expression of CA125. Possible explanations for this phenomenon are loss of CA 125 in tissues during formalin fixation and paraffin embedding [104]. Significant higher level of CA125 expression is seen in mostly malignant tissues in our study.

## CONCLUSION

In conclusion, the current study shows higher incidence of surface epithelial ovarian tumors. And higher incidence of benign and malignant serous surface epithelial tumors. Whereas in borderline category mucinous tumor incidence is more. Unilateral involvement of serous tumors are higher.

The median age of presentation of all ovarian tumor is 40 years. In our study, the median age of presentation of malignant tumor is 48 years. An earlier presentation of malignant lesion is thus confirmed from this study, hence a thorough investigation should be done for any vague abdominal complaints. Maximum steroid receptor (ER and PR) positivity is observed in stage I-II tumors whereas maximum negativity is observed in stage III-IV tumors. This receptor expression depends on the tumor histologic grade and varies between tumors of same grade and plays an important role in prognostic significance. In this study high proliferative activity was observed in stage I-II tumors of benign and borderline category tumors rather than Stage III-IV and malignant tumors. Tissue expression of CA 125 is observed in all stages of tumors with majority expression in Stage I tumors, thus CA 125 can be used as a cardinal IHC marker to differentiate between surface epithelial tumors of ovary from metastatic tumors to ovary. Serum CA 125 value is significantly elevated in most of the patients, some shows near normal values. Hence it can be used a useful screening marker to rule out ovarian neoplasms. Serum CA 125 and tissue coexpression of CA 125 also correlates in this study.

Significant higher level of CA 125 expression both in serum and tissue is seen in most of the malignant tissue. Hence the detection of ovarian tumors at early stage by screening with serum CA 125 level and immunohistochemical expression by CA125 can impact greatly on patient survival[104].

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# TITLE: SERUM CA125 IN OVARIAN TUMORS

| | | |
|---|---|---|
| NAME | : | |
| AGE /SEX | : | |
| IP NO | : | |
| WARD | : | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | Study ID | | | Hospital ID | | |
| 2 | Personal Details | | | | | |
| | a. Name | | | | | |
| | b. Age | | c. Gender | | d. Ward | |
| | e. Address | | | | | |
| | f. Block | | | g. District | | |
| | h. Occupation | | | i.Income pa | | |
| | j. Home | Joint | Nuclear | Single | Old Home | Homeless |
| 3 | Presenting Symptoms | | | | | |
| 4 | Presenting History | | | | | |
| 5 | Past History | | | | | |
| | Obstetric History | | | | | |

| | | | | |
|---|---|---|---|---|
| | Menstrual History | | | |
| 6 | Treatment & Drug History (DM/HT/CAD/Cancer/Others)<br><br>H/O Allergy<br>Current Medication if any | | | |
| 7 | Family History | | | |
| 8 | Occupation & Socio-economic status | | | |
| 9 | Personal History<br>Smoking Alcohol Tobacco Chewing Drugs<br>Vegetarian / Non vegetarian | | | |
| 10 | Examination | Pulse | BP | Resp |
| | | | | |
| | Ht in cms | Wt in kg | Mid Arm Cir | Hip/Waist |
| | | | | |
| | Skin Color & Texture | Iris Color | Hair Color | Hair Texture |
| | | | | |
| | Nail Texture | Pallor : Y/ N | Cyanosis: Y/ N | Oedema: Y / N |
| | | | | |

| | | | | |
|---|---|---|---|---|
| | Jaundice: Y/ N | Clubbing: Y/ N | | |
| | | | | |
| | Sensorium : | Conscious/ Drowsy / Comatose | | |
| | | | | |
| 11 | **Systemic Examination:** (Respiratory system/ Cardiovascular system/ Central Nervous system/ Alimentarysystem/ Genito-urinary system/ Musculoskeletal system/ Endocrine system/ Lymphatic system) | | | |
| | | | | |
| | Other Examination | | | |

| | | | | |
|---|---|---|---|---|
| 14 | Clinical Investigation Reports | | | |
| | **Test** | Test Value | Standard Value | |
| | RBCC | | | |
| | WBCC | | | |
| | PLC | | | |
| | DC | | | |
| | HCt | | | |
| | MCV | | | |
| | Hb | | | |
| | B. Urea | | | |
| | S. Creatinine | | | |
| | S. ALP | | | |
| | **Urine** | | | |
| | Sugar | | | |
| | Albumin | | | |
| | Deposits | | | |
| | **A) Peripheral Blood Film** | | | |
| | **B) FNAC** | | | |
| | **C) Ascitic fluid** | | | |

| | |
|---|---|
| | **D) Sonology: U S G** |
| | **E) C T Scan** |
| | **F) M R I** |
| | **G) OVARIAN BIOPSY** |

| | |
|---|---|
| | **H) Biopsy** |
| | **I. Gross** |
| | **II. Histopathology** |
| | **III. Special stain** |
| | **Treatment Protocol**<br><br>**NEO ADHOVANT CHEMOTHERAPY**<br><br>**SURGICAL CYTOREDUCTION** |

| | Before Chemotherapy | Before 1st Cycle | Before 2nd Cycle | Before 3rd Cycle | Before 4th Cycle | Before 5th Cycle | Before 6th Cycle |
|---|---|---|---|---|---|---|---|
| **Serum ca 125** | | | | | | | |
| **FDNA** | | | | | | | |
| **PCR BASED TEST** | | | | | | | |

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பதற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

| | | பங்கு பெறுவர் இதனை ✓ குறிக்கவும் |
|---|---|---|
| 1. | நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன். | ☐ |
| 2. | நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். | ☐ |
| 3. | இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். | ☐ |
| 4. | இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன். | ☐ |
| 5. | இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்டஅறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்றேன். | ☐ |

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....
கட்டைவிரல் ரேகை
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் /..... இடம் .....
ஆய்வாளரின் பெயர் .....
மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் /..... இடம் .....
பெயர் மற்றும் விலாசம் ..... .....

| SL.NO. | PATH NO | AGE/ SEX | HISTOPATHOLOGICAL DIAGNOSIS | SERUM CA125 | ER | PR | Ki-67 | CA 125 | TNM STAGING | STAGING GROUP |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2309/17 | 66/F | STROMAL HYPERTHECOSIS | 964.5 | NEGATIVE | 1+ | NEGATIVE | NEGATIVE | T0N0M0 | NIL |
| 2 | 3697/17 | 32/F | BORDERLINE MUCINOUS TUMOR | 37.7 | NEGATIVE | 1+ | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 3 | 3956/17 | 75/F | BENIGN MUCINOUS CYSTADENOMA | 49.5 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 4 | 4541/17 | 34/F | BORDERLINE MUCINOUS TUMOR WITH CAPSULAR BREECH | 234.8 | 1+ | NEGATIVE | >20% | 3+ | T2aN0M0 | STAGE IIA |
| 5 | 4675/17 | 44/F | CYSTIC FOLLICLES | 6.8 | NEGATIVE | 2+ | >20% | 2+ | T0N0M0 | NIL |
| 6 | 7/18. | 36/F | BENIGN SEROUS CYSTADENOMA | 42.2 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 7 | Gy 106/18 | 54/F | ADULT TYPE GRANULOSA CELL TUMOR | 16.6 | 3+ | 3+ | >20% | 2+ | T1aN0M0 | STAGE IA |
| 8 | Gy 125/18 | 31/F | BORDERLINE SEROUS TUMOR CONFINED TO THE CAPSULE | 13 | 3+ | 3+ | >20% | 3+ | T1aN0M0 | STAGE IA |
| 9 | Gy 130/18 | 30/F | HEMORRHAGIC SEROUS CYST | 315.2 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 10 | Gy169/18 | 50/F | BENIGN MUCINOUS CYSTADENOMA | 141.5 | 1+ | 1+ | >20% | 1+ | T1aN0M0 | STAGE IA |
| 11 | Gy 376/18 | 27/F | BENIGN SEROUS ADENOFIBROMA | 16.3 | 3+ | NEGATIVE | >20% | 2+ | T1aN0M0 | STAGE IA |
| 12 | 430/18 | 75/F | BENIGN SEROUS CYSTADENOMA | 60.2 | NEGATIVE | NEGATIVE | >20% | 1+ | T1aN0M0 | STAGE IA |
| 13 | Gy 452/18 | 35/F | BENIGN MUCINOUS CYSTADENOMA | 3.1 | 3+ | 3+ | >20% | NEGATIVE | T1aN0M0 | STAGE IA |
| 14 | Gy 454/18 | 44/F | INVASIVE LOW GRADE SEROUS CARCINOMA | 101.6 | 3+ | 3+ | >20% | 1+ | T1aN0M0 | STAGE IA |
| 15 | Gy 528/18 | 38/F | BENIGN MUCINOUS CYSTADENOMA | 30.86 | 3+ | 2+ | >20% | 1+ | T1aN0M0 | STAGE IA |
| 16 | Gy 548/18 | 59/F | FIBROTHECOMA WITH SEROUS CYSTADENOMA | 144.4 | 1+ | 1+ | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 17 | 676/18 | 38/F | MUCINOUS CARCINOMA EXPANSILE INFILTRATIVE PATTERN | 776 | 1+ | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 18 | Gy 722/18 | 57/F | BENIGN SEROUS CYSTADENOFIBROMA | 3.3 | 1+ | 1+ | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 19 | 884/18 | 80/F | SIMPLE SEROUS HEMORRHAGIC CYST | 7.3 | 1+ | 1+ | <20% | 1+ | T1aN0M0 | STAGE IA |
| 20 | 1067/18 | 45/F | BENIGN MUCINOUS CYSTADENOMA | 1.3 | 3+ | 3+ | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 21 | 1131/18 | 53/F | BILATERAL HIGH GRADE SEROUS CARCINOMA OF OVARY | 1100 | 3+ | 2+ | >20% | 3+ | T3cN1M0 | STAGE IIIC |
| 22 | 1214/18 | 62/F | PRIMARY OVARIAN ENDOMETRIOID CARCINOMA -GRADE II WITH CAPSULAR BREECH | 229.7 | 2+ | 1+ | NEGATIVE | NEGATIVE | T3aN1M0 | STAGE IIIA2 |
| 23 | Gy1226/18 | 31/F | BENIGN SEROUS CYSTADENOMA | 19.7 | 1+ | 1+ | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 24 | Gy 1401/18 | 37/F | BENIGN SEROUS CYSTADENOMA | 22.3 | 1+ | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 25 | Gy 1447/18 | 47/F | BENIGN MUCINOUS CYSTADENOMA | 21.9 | 1+ | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 26 | 1449/18 | 28/F | MIXED SURFACE EPITHELIAL TUMOR-PAPILLARY SEROUS,MUCINOUS AND ENDOMETRIOID | 239 | NEGATIVE | 1+ | >20% | 2+ | TM1bN1 | STAGE IV |
| 27 | Gy 1531/18 | 26/F | BILATERAL BENIGN  MUCINOUS CYSTADENOMA | 4.8 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1bN0M0 | STAGE IB |
| 28 | Gy1640/18 | 45/F | BENIGN SEROUS CYSTADENOMA | 13.2 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 29 | 1855/18 | 60/F | BENIGN SEROUS CYSTADENOFIBROMA | 50.8 | 2+ | 2+ | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 30 | 1975/18 | 63/F | WELL DIFFERENTIATED ENDOMETRIOID CARCINOMA OF OVARY- GRADE I | 15.1 | 2+ | 1+ | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 31 | Gy 2206/18 | 28/F | BENIGN SEROUS CYSTADENOFIBROMA | 13 | 1+ | 1+ | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 32 | 2466/18 | 45/F | HIGH GRADE PAPILLARY SEROUS CYSTADENOCARCINOMA | 64.1 | 2+ | NEGATIVE | NEGATIVE | NEGATIVE | T2aN0M0 | STAGE IIA |
| 33 | 2493/18 | 40/F | BENIGN SEROUS CYSTADENOMA | 150.2 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 34 | Gy 2522/18 | 58/F | BENIGN SEROUS CYSTADENOFIBROMA | 11 | 2+ | NEGATIVE | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 35 | 2816/18 | 70/F | BENIGN SEROUS CYSTADENOMA | 62.5 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 36 | 3172/18 | 65/F | BORDERLINE MUCINOUS TUMOR | 40.8 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 37 | 3475/18 | 36/F | BENIGN SEROUS CYSTADENOMA | 81.3 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 38 | 3917/18 | 51/F | HIGH GRADE PAPILLARY SEROUS CYSTADENOCARCINOMA WITH CAPSULAR BREECH | 453.1 | 1+ | NEGATIVE | >20% | 3+ | T3aN0M0 | STAGE IIIA2 |
| 39 | 4483/18 | 62/F | BENIGN SEROUS CYSTADENOMA | 8.2 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 40 | 4488/18 | 36/F | BENIGN SEROUS CYSTADENOMA | 14.7 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 41 | Gy 27/19 | 27/F | BENIGN MUCINOUS CYSTADENOMA | 10.8 | NEGATIVE | NEGATIVE | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 42 | Gy 32/19 | 30/F | BENIGN MUCINOUS CYSTADENOMA | 9.2 | NEGATIVE | NEGATIVE | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 43 | Gy 100/19 | 37/F | BENIGN SEROUS CYSTADENOMA | 8.1 | 2+ | 3+ | <20% | NEGATIVE | T1aN0M0 | STAGE IA |

| SL.NO. | PATH NO | AGE/ SEX | HISTOPATHOLOGICAL DIAGNOSIS | SERUM CA125 | ER | PR | Ki-67 | CA 125 | TNM STAGING | STAGING GROUP |
|---|---|---|---|---|---|---|---|---|---|---|
| 44 | Gy 213/19 | 52/F | BENIGN MUCINOUS CYSTADENOMA WITH BENIGN BRENNER TUMOR | 22.2 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 45 | GY 249/19 | 60/F | LOW GRADE PAPPILLARY SEROUS CYSTADENOCARCINOMA - GRADE I | 1401.1 | NEGATIVE | NEGATIVE | >20% | NEGATIVE | T1aN0M0 | STAGE IA |
| 46 | Gy 308/19 | 50/F | BENIGN SEROUS CYSTADENOMA | 15.2 | 3+ | 3+ | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 47 | Gy 400/19 | 26/F | BENIGN SEROUS CYSTADENOFIBROMA | 13.1 | 3+ | 2+ | NEGATIVE | NEGATIVE | T1aN0M0 | STAGE IA |
| 48 | Gy 485/19 | 52/F | BENIGN BRENNER TUMOR | 10.7 | NEGATIVE | NEGATIVE | <20% | 1+ | T1aN0M0 | STAGE IA |
| 49 | Gy 511/19 | 30/F | BENIGN SEROUS CYSTADENOMA | 44.8 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 50 | Gy 579/19 | 50/F | BENIGN MUCINOUS CYSTADENOMA | 21.9 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T1aN0M0 | STAGE IA |
| 51 | Gy 789/19 | 65/F | LOW GRADE PAPPILLARY SEROUS CYSTADENOCARCINOMA -CAPSULE INTACT | 701.4 | 3+ | NEGATIVE | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 52 | Gy 944/19 | 29/F | BORDERLINE MUCINOUS TUMOR | 51.6 | 3+ | 3+ | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 53 | Gy 1083/19 | 34/F | BENIGN SEROUS CYSTADENOMA | 9.2 | 2+ | 2+ | >20% | 2+ | T1aN0M0 | STAGE IA |
| 54 | Gy 1362/19 | 30/F | BENIGN MUCINOUS CYSTADENOMA | 17.6 | 2+ | 2+ | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |
| 55 | Gy 1379/19 | 39/F | BILATERAL BENIGN SEROUS CYSTADENOMA | 42.1 | 3+ | 1+ | NEGATIVE | 1+ | T1bN0M0 | STAGE IB |
| 56 | Gy 1403/19 | 40/F | CLEAR CELL CARCINOMA -TUMOR INFILTRATES ACROSS THE CAPSULE | 251 | NEGATIVE | NEGATIVE | NEGATIVE | 1+ | T3cN1M0 | STAGE IIIC |
| 57 | Gy 1408/19 | 58/F | BENIGN BRENNER TUMOR | 30.2 | 2+ | 2+ | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 58 | 1984/19 | 55/F | BILATERAL BENIGN PAPILLARY SEROUS CYSTADENOFIBROMA | 43.2 | 2+ | NEGATIVE | NEGATIVE | 2+ | T1bN0M0 | STAGE IB |
| 59 | 2152/19 | 50/F | HIGH GRADE PAPILLARY SEROUS CYSTADENOCARCINOMA-CAPSULE INTACT | 408.3 | 2+ | NEGATIVE | >20% | 3+ | T3cNxM0 | STAGE IIIC |
| 60 | 2193/19 | 50/F | BENIGN MUCINOUS CYSTADENOMA | 7.2 | NEGATIVE | 3+ | NEGATIVE | 2+ | T1aN0M0 | STAGE IA |
| 61 | 2546/19 | 24/F | BENIGN MUCINOUS PAPILLARY CYSTADENOMA | 1.8 | 1+ | 2+ | NEGATIVE | 3+ | T1aN0M0 | STAGE IA |