A CLINICOPATHOLOGICAL STUDY OF OVARIAN TUMORS AND THE ROLE OF IMMUNOHISTOCHEMICAL PROLIFERATIVE MARKER Ki 67

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CERTIFICATE

This is to certify that the dissertation entitled  
“A CLINICOPATHOLOGICAL STUDY OF OVARIAN TUMORS AND  
THE ROLE OF IMMUNOHISTOCHEMICAL PROLIFERATIVE  
MARKER Ki 67 ” submitted by Dr. R.Lavanya to the Faculty of Pathology,  
The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfilment  
of the requirement for the award of M.D. Degree in Pathology is a bonafide  
work carried out by her during the period 2009 - 2011 under my direct  
supervision and guidance.

Place: Madurai

Date:

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Madurai.
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Introduction
INTRODUCTION

Like the everyform of cancer, early detection is what all about. It can be prevented with testing and it can be beaten if caught early!

-Rod Stewart

The ovarian tumors are not a single entity, but a complex wide spectrum of neoplasms involving a variety of histological tissues, ranging from epithelial tissues, connective tissues, specialized hormone secreting cells to germinal and embryonal cells.\(^{40}\)

The ovary is complex in its embryology, histology, steroidogenesis and has potential to develop malignancy\(^{40}\). Of all the gynecologic cancers, the ovarian malignancies represent the greatest challenge because the ovary gives rise to greater and larger variety of tumors than any other organ. A female’s risk at birth of having ovarian tumor sometime in her life is 6-7\%, of having ovarian cancer is almost 1.5\% and dying from ovarian cancer is 1\%\(^{49}\).

The incidence of ovarian cancer ranks below only to the carcinoma of cervix. The ovarian tumors constitute about 5\% of gynaecological admissions. About 75\% of them are benign and 25\% are malignant. In India, ovarian tumors account for 8\% of all gynecological malignancies\(^{43}\).

Different tumors tend to involve different age groups. They occur in perimenopausal and postmenopausal women, infrequently in children also. The risk of developing ovarian tumor peaks in the fifth decade of life\(^{88}\). The
ovarian tumors pose a special diagnostic and management problem in the postmenopausal women because of their late presentation, high risk of malignancy and poor prognostic outcome and in children pose a great challenge to the clinicians owing to the need of conservation of reproductive, endocrinal and menstrual function on one hand and malignant potential on the other.

Apart from primary tumors, ovaries are frequent site for metastatic involvement from organs like stomach, colon and breast.

Signs and symptoms of ovarian cancer are frequently absent or subtle early on, or persist for several months before being recognized and diagnosed. More than 50% of patients are diagnosed in the advanced stage of the disease.

This study is undertaken to analyze the histopathological spectrum and clinical features and to emphasize the importance of immunohistochemical markers in accurate diagnosis and to investigate the biological significance of Ki-67 antigen expression in benign, borderline and malignant ovarian tumors.
Aims & objectives
AIMS AND OBJECTIVES

1. To study the incidence of ovarian tumors in our institution during 2009-2011.

2. To study the age related occurrence and clinical presentation of various types of ovarian tumors.

3. To classify ovarian tumors based on gross and histopathological features and categorizing them into benign, borderline and malignant tumors.

4. To apply special stains like Reticulin, Periodic Acid Stain (PAS) in selected cases for differentiation of tumors.

5. Application of immunohistochemical markers in selected cases for final diagnosis.

6. To analyze the role of immunohistochemical proliferative marker Ki 67 in selected cases.
REVIEW OF LITERATURE

Historical aspects

A historical account of the ovary should begin with Herophilus of Chalcedon, a great anatomist of Alexandrian school of the fourth century B.C. “Hemophilus must be regarded as the first anatomist to describe the mammalian ovaries. He called it “female testis”.

FEMALE GENITAL TRACT

Fig. 1

ANATOMY OF OVARY

Ovary develops from the genital ridge by 5th week of gestation and oogonia develops by mid gestation.

The ovaries which are the site of oogenesis are paired organs lying on either side of the uterus adjacent to the lateral wall of the pelvis (Fig 1).
During active reproductive life, ovaries measure about 4x2.5x1cm in dimension. The ovary is divided into cortex and medulla. Follicles in varying stages of maturation are found within the outer cortex. These are numerous in infants and young adults, where they are estimated to total about 4,00,000 but the number progressively decreases with age and follicles disappear by menopause.

With each menstrual cycle, one follicle develops into a graffian follicle, which is transformed into a corpus luteum following ovulation.

The medulla of the ovary consists a loosely arranged mesenchymal tissue and contains remnants of both wolffian duct (rete ovarii) and small clusters of round to polygonal, epithelioid cells around vessels and nesves. The ovaries are also endocrine organs producing the hormones oestrogen and progesterone.

**HISTOLOGY**

Numerous ovarian follicles are seen in various stages of development in the stroma of cortex. Primordial follicles contain the immature small primary oocyte which gradually increases in size and develop into primary, secondary and mature follicles(Fig 2).
Follicles with antral cavities are called secondary follicles which exhibit a granulosa cell layer, a theca interna and an outer theca externa. The largest ovarian follicle is the mature graffian follicle which ultimately ruptures and the ovum is shed from the ovary (ovulation). After ovulation the remaining part of the follicle undergoes changes that convert it into Corpus Luteum. If the ovum is not fertilized, the corpus luteum degenerates into corpus albicans, and if fertilized it persists and secretes progesterone.
The series of changes that begin with the formation of an ovarian follicle and end with the degeneration of the Corpus Luteum constitutes the ovarian cycle.

The main function of the ovary is to produce ova to implant after fertilization in the endometrium, and as an endocrine gland in the development of secondary sexual characters. Thus the ovary is always in dynamic state. Ovaries serve as the main organ for maintaining the female fertility and at the same time, site of origin of the most complex as well as lethal neoplasms.

**OVARIAN CANCER**

Most primary ovarian neoplasms are derived from one of these components

1. Coelomic surface epithelium covering ovary.

2. The ovarian stroma, sex cord or both.

3. The germ cell.

**CLINICAL FEATURES**

Signs and symptoms of ovarian cancer are frequently absent early on and when they exist they may be subtle. Symptoms such as abdominal pain, mass, ascites, urinary urgency, constipation, abnormal vaginal bleeding, weight loss can occur. Functionally active ovarian tumors in young girls (Juvenile granulosa cell tumors) may produce precocious puberty. Occasionally they produce androgens, masculinizing the patient.
DIAGNOSIS OF OVARIAN CANCER

Histopathology

Histopathology is the most common diagnostic method used for the diagnosis of ovarian tumors. Tissue samples from ovariectomy specimens are fixed in 10% buffered neutral formalin and then processed. Sections made with the help of microtomes are routinely stained with hematoxylin and eosin and then studied microscopically in detail. Ascitic fluid cytology is helpful in the diagnosis of metastasis in advanced stage of ovarian tumors.

SPECIAL STAINS:

The most commonly used stains are PAS and Reticulin stain. PAS stain is an extremely useful and aesthetically pleasing technique to differentiate mucinous carcinoma from krukenberg tumor. Mucinous carcinoma of ovary shows PAS positive mucin pools, and krukenberg tumor show intracellular PAS positivity. Reticulin stain is useful to differentiate granulosa cell tumor from fibrothecoma. It shows fibrils surrounding the nests and large aggregates of granulosa cell tumor whereas in Fibrothecoma, it highlights an investment of individual cells by fibrils.
IMMUNOHISTOCHEMISTRY:

Diagnostic IHC markers for epithelial ovarian tumors are Epithelial membrane antigen (EMA) and Cytokeratins, for sex cord stromal tumors are Inhibin, vimentin, calretinin, CD 99, Melan A, WT 1 and for Germ Cell Tumors the markers are Placental Alkaline Phosphatase (PLAP), Alpha Feto Protein (AFP), Human Chorionic Gonadotrophin (HCG).

Role of anticytokeratin in distinguishing primary and secondary ovarian adenocarcinoma

Keratins are intermediate filament proteins that contribute to the cytoplasm of epithelial cells. Human cytokeratin have been classified according to their molecular weight and isoelectric pH. 20 epithelial cytokeratin polypeptides have been identified. Some of these have specific tissue distribution that can be exploited for the differential diagnosis of tumor.

CK7(+) / CK20 (-) : In all primary epithelial ovarian neoplasms,

CK 7(-) / CK20(+) : Secondary (metastatic) tumors except in intestinal type of mucinous carcinoma of ovary.
PROLIFERATIVE MARKERS:

The number of mitotic figures correlated with cancer stage and grade as well as with their progression. Immunohistochemical proliferative markers like Ki 67, proliferative cell nuclear antigen (PCNA), AgNOR count are used to assess mitotic activity. The number of mitotic figures increase progressively from benign to malignant tumors.

Ki 67 protein is a cellular marker for nuclear proliferation which is present in all phases of cell cycle (G1S,G2M) and is absent in resting phase (G0). Ki 67 is an excellent marker to determine the growth fraction of a given cell population. The determination of growth fraction using Ki 67 index is a simple method and has long been shown to have a prognostic value in a variety of malignancies like CNS tumors, Lymphoproliferative diseases, connective tissue tumors & breast tumors. The fraction of Ki 67 positive tumor cells (Ki 67 labelling index) is often correlated with clinical course of cancer.

Tumor markers in ovarian cancer

Tumor markers are biochemical indicators of presence of tumor. The term usually refers to a molecule that can be detected in plasma or other body fluids.
None of the tumor markers for ovarian carcinoma is 100% specific or 100% sensitive.

a) Tumor markers for epithelial ovarian cancer

Approximately 90% of ovarian cancers are coelomic epithelial carcinomas and contain a coelomic epithelium related glycoprotein, designated Cancer Antigen 125. This can be recognized in most serous, endometrial, and clear cell ovarian carcinomas.

The other serological tumor markers for epithelial ovarian cancer include carcinoembryonic antigen (CEA), CA 15-3, CA 19-9, LASA (lipid associated safe acid) and tissue peptide antigen.

b) Tumor markers in non-epithelial ovarian cancer:

Alpha fetoprotein and human beta HCG are the best known tumor markers in clinical practice and aid in treatment, follow-up of ovarian germ cell tumors. Serum placental alkaline phosphatase and lactate dehydrogenase are also sometimes useful as markers of dysgerminoma.

FLOW CYTOMETRY

The application of flow cytometry to ovarian tumor pathology may be considered principally in term of measuring the ploidy status of tumor. Most borderline tumors are diploid & if aneuploid it indicates progression.
differentiated tumors are diploid whereas poorly differentiated tumors are aneuploid and having worse prognosis.

**CYTOGENETICS:**

It has been shown that p53 gene is mutated in 30-80% of ovarian carcinomas. p53 overexpression is associated with increased probability of relapse and decreased survival. BRCA 1, and BRCA 2 are expressed in hereditary tumors. Teratomas show chromosomal aberrations.

**REVIEW OF INDIVIDUAL OVARIAN TUMORS**

**I) SURFACE EPITHELIAL TUMORS**

In 1870, Heinrich waldeyer wrote a paper on epithelial ovarian tumors. He was among the first to suggest a histogenesis similar to that which is now widely accepted for the most common form of ovarian tumor. These tumors are derived from the epithelium that normally lines the outer aspect of ovary, referred to as surface coelomic or germinal epithelium and the adjacent ovarian stroma.

These tumors comprise 58% of all ovarian neoplasms and more than 90% of malignant tumors. They are classified into benign, borderline and malignant. Epithelial neoplasm may occur in young women and are rare before menarche. This incidence increase especially after the age of 55 years.
A) SEROUS TUMORS:  
Constitute 30% of all ovarian tumors, making them the single most common group. About 50-70% are benign, 10-15% are borderline, while 25-35% are frankly malignant. About 30-50% are bilateral\textsuperscript{16}

**Benign Serous Tumors:**  
Commonest tumor making up about $\frac{1}{4}$ th of all ovarian tumors, occurs between 10-60 years of age, average being 45 years. Majority of them are unilateral and cystic. These include serous cystadenomas, serous cystadenofibroma, serous adenofibroma and serous surface papillomas.

**Gross:**  
Cystic, usually have a smooth pale yellow (or) gray white exterior with a prominent vascular pattern. It can be either unilocular or multilocular. They contain clear, thin serous fluid.

**Microscopy:**  
Cyst wall and papillae lined by single layer of a mixture of tall ciliated and non-ciliated columnar cells with elongated oval nuclei interspersed with a variable number of peg shaped cells and clear cells resembling the normal tubal epithelium. Psammoma bodies are calcific spherules, seen in 15% of cases\textsuperscript{82}

**Borderline Serous Tumors:**  
Howard C Taylor expanded on the concept of tumors intermediate between benign & malignant. He wrote a paper on borderline ovarian tumors.
These tumors are large usually multilocular, bilateral in 35-40% of cases. Coarse papillary excrescences arise from the cyst lining. Most common in fourth and fifth decades with average age of 46 years.

**Microscopy:**

The characteristic microscopic features of borderline serous tumors are Hierarchial branching papillary pattern of growth with variable cytologic atypia, Cellular stratification greater than 3 cells. Frank stromal invasion is absent, Stromal microinvasion (<3mm) is occasionally identified in a borderline serous tumor.

**Malignant serous tumors:**

Occurs in mean age 56 years, bilateral–in 2/3 of cases.

**Gross:**

These are large, often bilateral neoplasm in which there is a mixture of cystic, papillary and solid growth patterns. The solid areas are tan or white and contain foci of haemorrhage & necrosis.

**Microscopy:**

These tumors diffusely infiltrate a fibrotic stroma. Papillary growth is usually present at least focally. Tumor cells are arranged in solid nests and sheets. The papillae lined by stratified low columnar cells, show marked nuclear atypia and frequent mitotic figures in high grade tumors. The stroma may be scanty or desmoplastic with foci of necrosis.
B) MUCINOUS TUMORS:

Mucinous tumors account for 12-15% of all ovarian tumors of which 75% to 85% are benign, 10-15% borderline and remaining are frankly malignant. They attain largest size among ovarian neoplasms.

**Benign mucinous tumors:**

**Gross:** Mucinous cyanadenomas are cystic & generally unilateral. The average diameter is about 10cm. Cut surface reveals unilocular or multilocular mucin filled cysts of varying sizes.

**Microscopy:**

Characterized by a lining of tall columnar epithelial cells with apical mucin and the absence of cilia akin to benign cervical or intestinal epithelia.

**Borderline mucinous tumors:**

**Gross:**

These are large, with an average diameter of about 15cm. Most are multilocular, filled with mucin.

**Microscopy:**

Two types:

1. **INTESTINAL TYPE:** Most common type.

Crowding of complex glands, papillae supported by thin cores of fibrovascular connective tissue. Goblet cells are conspicuous, focal stratification of the cells into two or three layers. The tumor cells have round to oval vesicular nuclei with mild to moderate atypia, nucleoli may be prominent & occasional mitotic figures seen.
2. **ENDOCERVICAL LIKE**:  
These tumors comprise 5-15% of borderline mucinous tumors. Branching papillary growth pattern lined by columnar mucinous endocervical like cells and a variable number of cells with eosinophilic cytoplasm. Goblet cells are absent, mitotic figures infrequent, minimal nuclear atypia present.\(^{83}\)

**Malignant mucinous tumors:**  
Mucinous carcinoma are less frequent than their serous counterparts. They differ from borderline tumors having evidence of ovarian stromal invasion.

**Gross:**  
Large, multilocular cystic tumor averaging 15-20cm in diameter. Firm, fleshy, white or tan solid areas, often with foci of haemorrhage or necrosis. <10% bilateral\(^{11}\)

**Microscopy:**  
The glands and cysts are crossed and complex with irregular infoldings and protrusions into the surrounding stroma. Intestinal type cells predominate. The cells are columnar, have eosinophilic cytoplasm, and stratify into two or more layers. The nuclei are enlarged and vesicular with prominent nucleoli. Many typical and atypical mitotic figures, goblet cells and argyrophilic cells may be present.
Pseudomyxoma peritonei:

Occurs in tumors of intestinal type. It is seen in borderline or malignant mucinous tumors, but can occur with large benign tumors also. The cells produce mucin which fills the abdominal cavity.

C) ENDOMETRIOID TUMORS –

These tumors comprise 2-4% of all ovarian tumors. These tumors have an epithelial component that resembles proliferative hyperplastic or malignant endometrium. Occur most commonly in fifth and sixth decades. Benign & borderline tumors are rare. Endometroid Carcinoma account for about 20% of all ovarian cancers. 15-20% coexist with endometriosis. 15-30% are accompanied by carcinoma of endometrium.

Gross:

Cystic and solid or completely solid tumor measuring 10-20cm diameter. Firm or soft, gray or tan with haemorrhage and necrosis. Only 10-20% are bilateral.

Microscopy:

The growth pattern is glandular, papillary or mixture of two. The glands are small and relatively uniform in size and shape. The degree of atypia, nuclear stratification and the extent to which the glands coalesce into foci of solid growth increase as grade increases.
D) Clear Cell Tumors:

These tumors comprise 5% of all ovarian cancers, common in age group 40 - 70 years. Accompanied by both ovarian and pelvic endometriosis. More aggressive and more malignant than serous adenocarcinoma of ovary.

Gross:

These are unilateral and solid. They typically measure 10-15 cm in diameter. The cut surface is white gray or tan and contain small to medium sized cysts.

Microscopy:

Tubules and cysts are lined by cuboidal or hobnail cells with clear or eosniophilic cytoplasm. These cells are irregularly distributed in a fibrous stroma.

The epithelium is stratified or tufted or grows as small circumscribed nests. The presence of mild to moderate nuclear atypia and scattered mitotic figures (usually <1 per HPF) differentiates borderline clear cell tumors from a benign one. The absence of stromal invasion differentiates them from clear cell carcinoma.
E) TRANSITIONAL CELL TUMORS:

Ovarian tumors composed of epithelial elements histologically resembling urothelium and its neoplasms. Comprise 1–2% of all ovarian neoplasms. It comprises Brenner and Non Brenner type.

1) Brenner Tumor

In 1907 C Fritz Brenner was first to describe the cases of Brenner tumor which now bears his name.

Approximately 95% of Brenner tumors are diagnosed in women between ages of 30 & 70 yrs. It usually coexists with mucinous cystadenoma. Most Brenner tumors are benign, but borderline and malignant Brenner have been reported.

Gross:

Benign tumors are circumscribed, firm, pale yellow or gray white, solid fibrous or cystic tumors. Usually unilateral, average size 1-2 cm.

Microscopy:

The fibrous stroma is marked by sharply demarcated nests of epithelial cells resembling the transitional epithelial cells of urinary tract often with mucinous glands in the centre. The nuclei are round or oval and have small nucleoli. A longitudinal nuclear groove is characteristic.
2) Transitional cell carcinoma (Non-Brenner type)

**Gross:**

Transitional cell carcinoma is a partly cystic tumor that averages 10 to 15 cm in diameter.

**Microscopy:**

It is similar in appearance to malignant Brenner tumor except that Benign proliferating Brenner tumor is not identified and transitional cell carcinoma pattern must predominate (75%).

II) SEX – CORD – STROMAL TUMORS

Neoplasms derived from the sex cords or ovarian mesenchyme comprise 5-12% of all ovarian neoplasms.

A) GRANULOSA CELL TUMORS:

The tumor shows differentiation towards follicular granulosa cells and comprise 1-2% of all ovarian tumors. These tumors secrete oestrogen which stimulates the endometrium to proliferate. The presentation may be post menopausal bleeding, menorrhagia, metrorrhagia precocious puberty. It is associated with endometrial hyperplasia & endometrial carcinoma, cystic disease of breast. It has small (5-25%) but distinct hazard of malignancy (recurrence, extension)
Two types:
   Adult type occurs mainly in menopausal women and Juvenile type that occurs mainly in children.

a) Adult Granulosa Cell tumor:
   In 1914, Von Werdt proposed the term “Granulosa cell tumor”.

Gross:
   These range from few millimeter to 30 cm in diameter. Entirely solid but most are partly cystic. The solid portions are pink, tan, brown, light yellow and vary from soft to firm in consistency.

Microscopy
   The tumor cell resemble normal granulosa cells. Longitudinal folds or grooves are present in many nuclei giving a characteristic coffee bean appearance.

   Several histologic patterns like follicular, trabecular, insular, watered silk pattern have been described. Of these the microfollicular pattern is the most characteristic and are termed Call-exner bodies.

b) Juvenile Granulosa Cell tumor:
   The incidence of Juvenile Granulosa Cell tumor in children is <5%. Average age is 15 years. But it can occur at any age from infancy to old age but most arise in children.
The tumor consists of both cystic & solid areas. Macrofollicular, solid and cystic growth patterns are characteristic. Focal or extensive luteinization is a typical finding. The tumor cell nuclei lack grooves and contain conspicuous nucleoli.

B) FIBROMA – THECOMA GROUP

1) Thecoma
They account for 7% of sex cord stromal neoplasms. The average age is between 50 and 55 years. 5% bilateral.

Thecoma is a benign, firm tumor that varies in size from 1 - 20cm in diameter. The cut surface is gray or tan, with extensive yellow areas. The tumor is composed of fascicles or sheets of spindle or ovoid cells.

2) Fibroma
It is the most common sex-cord stromal tumor accounting for 1-5% of ovarian tumor. Average age is 50 years or more. Meig’s syndrome, in which ovarian fibroma is accompanied by ascites and hydrothorax.

Firm tumor with a smooth, lobulated surface. Size 1 - 10cm, solid white or tan cut surface. Fibromas are composed of thin spindle cells growing in whorled and anastamosing bundles. Mitotic figures are rare.

c) SERTOLI LEYDIG CELL TUMOR (ANDROBLASTOMA)
These tumors are seen in women of reproductive age, occurring unilaterally causing masculinization. Cut surface gray to golden yellow.
Microscopically well differentiated tumors show tubules composed of sertoli or leydig cells interspersed with stroma. The intermediate forms show only outlines of immature tubules & large eosinophilic leydig cells. Poorly differentiated tumors have a sarcomatous pattern with a disorderly disposition of epithelial cell cords. Leydig cells may be absent.

III) GERM CELL TUMORS

Germ cell tumors represent 15-20% of all ovarian tumors. They are composed of cells derived from oocyte. Most of these tumors are seen in children and young adults. Younger the patient, the more likely the germ cell tumor to be malignant.
A) Dysgerminoma:

Mayer first applied the name Dysgerminoma in 1931 to a solid carcinomatous ovarian tumor histologically resembling testicular seminoma. It is the most common (50%) of all malignant germ cell tumors of the ovary\textsuperscript{15}.

Dysgerminoma is a large solid tumor usually more than 10cm in diameter, with convoluted outer surface. Usually unilateral, cut surface shows haemorrhage and necrosis in 50% of cases. \textsuperscript{85}.

The tumor is composed of large round to polygonal uniform cells with vesicular nuclei and prominent nucleoli, abundant clear to finely granular cytoplasm that contains glycogen and separated by thin fibrous septa which shows lymphocytic infiltration\textsuperscript{85}.

B) Yolk sac tumor (Endodermal sinus tumor):

Yolk sac tumor is rare but it is the second most common malignant tumor of germ cell origin \textsuperscript{85}. Occurs in 2\textsuperscript{nd} and 3\textsuperscript{rd} decade. Prognosis is very poor.
**Gross:**

These are large, encapsulated, solid tumor with smooth and glistening external surface. The tumor has variegated cut surface.

**Microscopy:**

Yolk sac tumor shows variable microscopic appearance. The festoon pattern containing pseudopapillary processes with central vessel (ie) Schiller Duval bodies described by Schiller. Other patterns are microcystic (reticular), solid, polyvesicular vitelline pattern.

**C) Embryonal carcinoma:**

Embryonal carcinoma is seen more commonly in mixed germ cell tumors of ovary. Pure form is extremely rare. 5% of malignant germ cell tumors are of this category. Occurs in 2nd and 3rd decade of life.

**Gross:**

These tumors are large with smooth & glistening external surface and having variegated cut surface with extensive areas of haemorrhage and necrosis.

**Microscopy:**

These tumors are composed of solid sheets and nests of large primitive cells, syncytiotrophoblast like tumor cell and tumor giant cells are seen frequently. These are HCG positive immunohistochemically. Prognosis is very poor.
D) Choriocarcinoma:

These tumors are more commonly of placental origin. Primary ovarian choriocarcinoma is exceedingly rare. It is divided into gestational type from placental origin and nongestational type from germ cell origin. Ovarian gestational choriocarcinoma can be primary or metastatic from uterine or tubal pregnancy. As the tumor is associated with high HCG levels, its diagnosis especially in young women is most often confused with an ectopic pregnancy.

Gross:

The tumor has smooth or nodular external surface. The cut surface shows variegated appearance, gray white with areas of haemorrhage and necrosis.

Microscopy:

The tumor shows admixture of cytotrophoblast and syncytiotrophoblast, the latter form villous like structures around the cytotrophoblast in a necrotic or haemorrhagic background.

Prognosis is poor. Gestational Choriocarcinoma has better prognosis & respond to chemotherapy in contrast to non – gestational counterpart.

E) Teratoma:

Willis (1960) had given a vivid description the genesis of teratomas. According to him teratomas are the tumors arising from foci of pluripotent,
embryonic tissue that escapes from the influence of the primary organizer during embryonic development.

Teratomas form the commonest group of germ cell tumors in the ovarian neoplasm. They constitute 25.86% of all ovarian tumors. Depending upon the nature of the tissue component they are classified into mature and immature teratoma.

1. Mature cystic teratoma (Benign):

These are the most common variety of germ cell tumors accounting for more than 95% of ovarian teratomas and 15-20% of neoplasm in general. These are usually found in young women during the active reproductive years.

Gross:

They are unilateral in 88% of cases. Characteristically they are unilocular cysts containing greasy material composed of keratin, sebum and tuft of hair. Within the wall, tooth structures and areas of calcification may be seen.

Microscopy:

Blackwell et al (1946) found ectodermal derivatives in 100% of tumors, mesodermal derivatives in 93% and endodermal structure in 71% of cases. The tumor shows cyst lined by squamous epithelium in nearly all the cases with skin appendages and other elements like fat, cartilage, smooth
muscle and bone. Endodermal structures like bronchial & gastrointestinal epithelium are seen. Neural & thyroid tissue are also seen.

2. **Immature teratoma:**

These are rare tumors that differ from benign teratomas with component resembling embryonal and immature fetal tissue. Mean age of presentation is 18 yrs. Unilateral, large bulky with smooth external surface. Cut surface mostly solid with haemorrhage & necrosis. Microscopically varying amounts of immature epithelium, hair, cartilage, bone, calcification may be seen. Histological grading is done by assessing the amount of immature tissue and neuroepithelium.

3. **Monodermal or specialized teratomas:**

These specialized teratomas comprise a rare group, of which struma ovarii and carcinoid are the most common. They are always unilateral. Struma ovarii is composed entirely of mature thyroid tissue. The ovarian carcinoid presumably arises from the intestinal epithelium in a teratoma.

Secondary malignancies in benign cystic teratoma are rare. Cutaneous adnexal neoplasms, benign salivary gland type tumors, meningioma, glomus tumor. Invasive squamous cell carcinoma is common and comprises 85%. Other tumors are basal cell carcinoma, melanoma, adenocarcinoma, sarcoma etc.
METASTATIC TUMORS

The most common metastatic tumors of the ovary are derived from tumors of mullerian origin: uterus, fallopian tube, contralateral ovary or pelvic peritoneum. The most common extra mullerian tumors metastatic to ovary are carcinoma of breast and gastrointestinal tract including colon, stomach, biliary tract and pancreas. Comprises 10% of all ovarian cancers. The characteristic features of metastatic disease are bilateral presentation with smaller size than primary ovarian tumors, nodular growth pattern, surface involvement, infiltrative growth.

KRUKENBERG TUMOR:

A classical example of metastatic gastrointestinal neoplasia to the ovaries, characterized by bilateral metastases composed of mucin producing signet ring cells, most often of gastric origin.
Materials and Methods
MATERIAL AND METHODS

This prospective study is undertaken in the Department of Pathology, Madurai medical college, Madurai during the period 2009-2011. This study was conducted on 200 ovarian neoplasms (Ann.VI) out of 239 ovarian lesions received after exclusion of non-neoplastic lesions. This study was approved by the institutional ethical committee (Ann IV).

The tissue samples included in this study were 91 ovariotomy specimens and 109 hysterectomy with ovariotomy specimens received in buffered 10% neutral formalin from Government Rajaji Hospital, Madurai. A detailed history regarding clinical symptoms and signs were recorded and thorough gross examination in particular attention to laterality, size, consistency of the specimens were also done.(Ann I).

After adequate fixation, representative bits were taken. In cystic ovarian neoplasms, 4-5 bits were taken. In solid tumors, if <5cm, 3-4 bits were taken. If more than 5cm, 1 block per 1 cm of the tumors were taken across its greatest dimension, particularly if the appearance is variegated.

Tissue bits fixed in 10% buffered neutral formalin were processed in automated tissue processor. Sections were made manually with microtome of thickness 3-5 micrometer and routinely stained with hematoxylin and eosin stains. Special stains like Periodic Acid Schiff (PAS), Reticulin were done using standard procedures to study their different pattern of
expression in different tumors. Reticulin stain was done for all the Granulosa cell tumors (10 cases) and all Fibrothecomas (3 cases). PAS stain was done in all mucinous cystadenocarcinomas (8 cases) and all Krukenberg tumors (3 cases).

(Ann II). These tumors were then tumors were classified according to WHO classification of ovarian tumors (Ann III).

Ki 67 protein is a cellular marker for nuclear proliferation which is present in all phases of cell cycle (G1S,G2M) and is absent in resting phase (G0). It is an excellent marker to determine the growth fraction of a given cell population. The fraction of Ki 67 positive tumor cells (Ki 67 labelling index) is often correlated with the clinical course of cancer.

Ki 67 immunohistochemical proliferative marker study using peroxidase-antiperoxidase technique (Ann II) was done in 24 selected cases which comprised benign, borderline and malignant ovarian tumor.

Positive Ki 67 staining was observed as brown granular nuclear staining. For Ki 67 scoring the most positive area of the tumor was selected avoiding foci of inflammation. The number of positive nuclei is counted in 500 tumor cells in a high power field (x 400 magnification). The average of 3 counts over the same slide was taken and expressed as the percentage of Ki 67 positive cells in the tumor.
The expression of immunohistochemical markers like vimentin, inhibin, EMA, cytokeratin and chromogranin was studied in 10 ovarian tumors which were histopathologically diagnosed as Granulosa cell tumors.
Observation & results
OBSERVATION AND RESULTS

In the present study, a total of 7964 gynaecological specimens were received in the Department of Pathology, Madurai medical college, Madurai. Among them 882 cases were gynaecological malignancies including 239 ovarian lesions and in that after exclusion of non-neoplastic lesions, 200 were ovarian neoplasms constituting 2.5%.

THE DISTRIBUTION OF INDIVIDUAL OVARIAN TUMORS:

Among 200 cases of ovarian tumors studied, 155 cases were surface epithelial tumors (77.5%), 22 cases were germ cell tumors (11%), 15 cases were sex cord stromal tumors (7.5%), 5 cases were unclassified (2.5%), 3 were krukenberg tumors (1.5%).

Out of 200 cases, 124 were benign (62%), 11 were borderline (5.5%), 65 were malignant tumors (32.5%). Three patients had both benign and malignant tumors. They were included under malignant tumors.
The distribution of cases has been illustrated in table 1.

**Table 1: Diagnosis and type of tumor**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
<th>Type of tumor</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Benign</td>
<td>Borderline</td>
<td>Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>I. Surface epithelial</td>
<td>155</td>
<td>98</td>
<td>63.2</td>
<td>11</td>
<td>7.1</td>
<td>46</td>
</tr>
<tr>
<td>II. Sex cord stromal</td>
<td>15</td>
<td>15</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III. Germ cell tumor</td>
<td>22</td>
<td>13</td>
<td>59.1</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>IV. Metastasis</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>V. Unclassified</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
<td><strong>124</strong></td>
<td></td>
<td><strong>11</strong></td>
<td></td>
<td><strong>65</strong></td>
</tr>
</tbody>
</table>
AGE INCIDENCE OF OVARIAN TUMORS:

According to this study, ovarian neoplasms occur in the age group between 2 to 76 years. There was a high incidence of ovarian neoplasms in the age group of 41-50 years. The youngest patient in this study was 2 years old who presented with precocious puberty and was diagnosed as Juvenile granulosa cell tumor. The oldest patient was 76 years old, presented with mass abdomen (15x13x6) and was diagnosed as Fibrothecoma.

Benign tumors were more common in age group 21-30 years, Borderline in more than 60 years, malignant in age group 41-50 years. Benign tumor cases had lower mean age and borderline tumor cases had higher mean age. But the difference was not statistically significant.

Table - 2 : Age and type of tumor

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of cases</th>
<th>Type of tumor</th>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Upto 20 years</td>
<td>15</td>
<td>10</td>
<td>66</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21- 30 years</td>
<td>39</td>
<td>31</td>
<td>79.5</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>31- 40 years</td>
<td>46</td>
<td>27</td>
<td>58.7</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>41- 50 years</td>
<td>56</td>
<td>31</td>
<td>55.4</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>51- 60 years</td>
<td>29</td>
<td>18</td>
<td>62.1</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>15</td>
<td>7</td>
<td>46.7</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>124</td>
<td>62</td>
<td>11</td>
<td>5.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean SD</th>
<th></th>
<th>39.3 years</th>
<th>48.4 years</th>
<th>42.6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td>14.3 years</td>
<td>14.8 years</td>
<td>13.2 years</td>
</tr>
</tbody>
</table>
graph 2: Age and type of tumor

CLINICAL FEATURES

All the cases were evaluated clinically at the time of admission as in the following table. Abdominal mass was the most common clinical presentation (117 cases, 58.5%) followed by pain (101 cases, 50.5%). Other symptoms like menstrual disturbances, precocious puberty, weight loss, abdominal distention urinary frequency, constipation were present in 6 cases (3%). Many cases had more than one clinical features
### Table – 3: Clinical Features

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Mass</td>
<td>117</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>101</td>
</tr>
<tr>
<td>Menstrual disturbance</td>
<td>10</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>6</td>
</tr>
</tbody>
</table>

**Graph 3 Clinical Features**
SIZE OF THE OVARIAN TUMORS:

The largest ovarian tumor in this study was Benign mucinous cystadenoma measuring 30x25x10 cm and smallest tumor was a Benign serous cystadenoma measuring 2x2x0.5 cm. The size of the ovarian tumor in this study ranged from 2.5cm to 30cm. The average size was 9 cm.

Graph 4

Size
CONSISTENCY OF OVARIAN TUMORS:

The consistency of ovarian tumors was cystic in 115 tumors (57.5%), solid in 69 tumors (34.5%) and partly cystic and solid in 16 tumors (8%).

Consistency was cystic in majority (85.5%) of benign tumor cases. It was solid in 81.5% of malignant cases. Papillary lesions were seen in 31 ovarian tumors.

Graph 5

Type of tumor and consistency
LATERALITY OF OVARIAN TUMORS

In the present study, out of 200 cases 163 (81.5%) were unilateral and 37 were bilateral (18.5%). In that 90.3% of benign ovarian tumors were unilateral and 64.6% of malignant ovarian tumors were unilateral, whereas 9.7% of benign ovarian tumors were bilateral and 35.4% of malignant ovarian tumors were bilateral.

Bilaterality is more common in serous than mucinous tumors. Unilaterality is more common in sex cord stromal tumors (93.3%), bilaterality more common in metastatic tumors (66.7%). The more common surface epithelial tumors show unilaterality in 81.3% of cases and bilaterality in 18.7% cases.

Table 4

Diagnosis and Laterality

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
<th>Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>I. Surface epithelial tumors</td>
<td>155</td>
<td>126</td>
</tr>
<tr>
<td>II. Sex cord stromal</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>III. Germ cell tumor</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>IV. Metastasis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>V. Unclassified</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
<td><strong>163</strong></td>
</tr>
</tbody>
</table>

As severity of tumor increases, laterality becomes more bilateral.
METASTASIS OF OVARIAN TUMORS

Metastasis to omentum, ascites were present in 41.5% of malignant tumors.

Graph 6

Metastasis

27, 13%

173, 87%

PRESENT ABSENT
HISTOLOGICAL TYPES OF OVARIAN TUMORS

SURFACE EPITHELIAL STROMAL TUMORS

This was the commonest group encountered in the present study, 155 cases out of 200 were Surface Epithelial tumors (77.5%). 31 cases showed papillary pattern (fig 15). The distribution of Surface Epithelial tumors encountered in this study has been illustrated in the table 5.

Table 5

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Surface epithelial tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Cyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Benign serous cyst</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>ii) Benign mucinous cyst</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>b) Cyst adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Benign serous cystadenoma</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>ii) Benign mucous cystadenoma</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>44</td>
</tr>
<tr>
<td>c) Borderline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Borderline serous cystadenoma</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>ii) Borderline mucous cystadenoma</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>d) Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Serous adeno carcinoma</td>
<td>35</td>
<td>17.5</td>
</tr>
<tr>
<td>ii) Mucinous adnrcarcinoma</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>21.5</td>
</tr>
<tr>
<td>e) undifferentiated tumors</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>
SEX-CORD STROMAL TUMORS

15 sex cord stromal tumors which were encountered in the present study have been depicted in table 6.

Table 6

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>No. OF CASES</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Granulosa cell tumor</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>b) Fibrothecoma</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>c) Fibroma</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Among 15 cases, 10 were histopathologically diagnosed as Adult Granulosa cell tumor. These tumors showed microfollicular, insular and watered silk pattern with Call-Exner bodies (Fig21). A case of juvenile granulose cell tumor was reported (fig22). Two cases of fibroma and three cases of fibrothecoma were recorded in this series (1%).

In this study, we applied reticulin stain for all the Granulosa cell tumors (10 cases) and all the cases of fibrothecomas (3 cases). The stain shows fibrils surrounding the nests and large aggregates of granulosa cells in Granulosa cell tumors (fig 24). In Fibrothecoma, reticulin stain highlights an investment of individual cells by fibrils.
GERM CELL TUMORS

22 germ cell tumors which were encountered in the present study have been depicted in table 7.

Table 7

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>No. OF CASES</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Teratoma</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>b) Dysgerminoma</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>c) Yolk sac tumor</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>d) Embryonal carcinoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>11</td>
</tr>
</tbody>
</table>

In the present study out of 22 germ cell tumors, 15 cases were diagnosed as benign cystic teratoma (7.5%). Tumors showed presence of squamous epithelium and dermal appendages, fat, cartilage, respiratory and gastrointestinal epithelium (fig.29). One case of immature teratoma with neuroectodermal elements was encountered (fig.30).

Three cases of dysgerminoma were encountered. The tumor was grey white nodular external surface (cerebriform) with intact capsule (fig11). Four cases of yolk sac tumor encountered. Tumor arranged in
reticular pattern and endodermal sinus pattern with Schiller–Duval bodies (fig 28). Intracellular and extracellular hyaline globules were seen.

**METASTATIC TUMORS / KRUKENBERG TUMORS**

In the present study, 3 cases of krukenberg tumors were noted. Tumor was solid in consistency (fig 13). Histologically composed of signet ring cells admixed with benign appearing mucinous areas (fig 32).

Primary carcinoma were in stomach in 2 cases. In our study mucinous carcinoma of ovary shows extra cellular PAS positive mucin pools (fig 34) where as in Krukenberg tumor show intracellular PAS positivity in signet ring cells (fig 33).

**PROLIFERATIVE MARKER STUDY**

**RESULTS OF Ki 67 LABELLING INDEX**

Ki 67 labelling index was studied in 24 selected cases which comprised of 4 benign cystadenoma (2 serous, 2 mucinous), 4 borderline cystadenomas (2 serous, 2 mucinous), 4 carcinoma (2 serous, 2 mucinous adenocarcinoma), 2 germ cell tumors, all the 10 Granulosa cell tumors. One way analysis of variance test was used to assess the statistical difference between Benign, borderline & malignant epithelial ovarian tumors.

The comparative analysis of Ki 67 labelling index has been shown in table 8.
COMPARATIVE ANALYSIS OF Ki 67 LABELLING INDEX
Table 8

<table>
<thead>
<tr>
<th>s.no</th>
<th>TYPE OF CASES</th>
<th>NO.OF CASES</th>
<th>Ki67 INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BENIGN SEROUS CYSTADENOMA</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>BENIGN MUCINOUS CYSTADENOMA</td>
<td>2</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>BORDERLINE SEROUS CYSTADENOMA</td>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>4</td>
<td>BORDERLINE MUCINOUS CYSTADENOMA</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>5</td>
<td>SEROUS CYSTADENOCARCINOMA</td>
<td>2</td>
<td>29.1</td>
</tr>
<tr>
<td>6</td>
<td>MUCINOUS CYSTADENOCARCINOMA</td>
<td>2</td>
<td>32.4</td>
</tr>
<tr>
<td>7</td>
<td>DYSGERMINOMA</td>
<td>1</td>
<td>25.3</td>
</tr>
<tr>
<td>8</td>
<td>YOLK SAC TUMOR</td>
<td>1</td>
<td>31.3</td>
</tr>
</tbody>
</table>

The results were

a) Both cases of benign serous cystadenomas had a mean Ki 67 index of 2.8 % and both cases of benign mucinous cystadenomas had a mean Ki 67 index of 3 % (fig 36)

b) Two cases of borderline serous cystadenomas had a mean Ki 67 index of 8.3 % and both cases of borderline mucinous cystadenomas had a mean Ki 67 index of 6.1% (fig 38).

c) Both cases of malignant serous cystadenocarcinomas had a mean Ki 67 index of 29.1 % and both cases of mucinous cystadenocarcinomas had a mean Ki 67 index of 32.4 % (fig 40).
d) Both the cases of germ cell tumors showed an average Ki 67 index of 28.3% (fig42).

Benign tumors had a mean Ki 67 index of 2.9%, borderline tumors had a mean Ki 67 index of 7.2%, while the malignant tumors had a mean Ki 67 index of 29.9%.

The difference in the mean value between benign, borderline, and malignant epithelial tumors were statistically significant (p <= 0.001).

**IMMUNOHISTOCHEMICAL MARKER STUDY IN GRANULOSA CELLTUMORS (GCT):**

We received a total of 10 cases of Granulosa cell tumors in our study.

Out of the ten cases which were histopathologically diagnosed as Granulosa cell tumor, two cases turned out to be primary ovarian carcinoid and poorly differentiated carcinoma respectively after immunohistochemical study.

The results of expression of various immunomarker in all these tumors are shown in table 9.
Table 9

<table>
<thead>
<tr>
<th>S.N</th>
<th>case</th>
<th>vimentin</th>
<th>Inhibin</th>
<th>chromogranin</th>
<th>EMA</th>
<th>Ki 67 index</th>
<th>STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2955/09</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>5.4</td>
<td>I(a)</td>
</tr>
<tr>
<td>2</td>
<td>G4613/09</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>4.8</td>
<td>I(a)</td>
</tr>
<tr>
<td>3</td>
<td>G1879/10</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>4.4</td>
<td>I(a)</td>
</tr>
<tr>
<td>4</td>
<td>G1888/10</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>7.9</td>
<td>I(c)</td>
</tr>
<tr>
<td>5</td>
<td>G2652/10</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2.8</td>
<td>I(a)</td>
</tr>
<tr>
<td>6</td>
<td>G3169/10</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>3.4</td>
<td>I(a)</td>
</tr>
<tr>
<td>7</td>
<td>G3928/10</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>4.2</td>
<td>I(a)</td>
</tr>
<tr>
<td>8</td>
<td>G762/11</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>8.4</td>
<td>I(c)</td>
</tr>
<tr>
<td>9</td>
<td>G232/10</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>G1857/10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>25.1</td>
<td></td>
</tr>
</tbody>
</table>

DIAGNOSTIC SIGNIFICANCE OF IMMUNOHISTOCHEMICAL STUDY IN GRANULOSA CELL TUMORS:

1. **GCT TURNED OUT TO BE PRIMARY OVARIAN CARCINOID AFTER IHC:**

We received a clinically suspected specimen of ovarian tumor in a 55 year old postmenopausal woman. Grossly, it was a large yellowish tumor of size 12x11x11 cm with predominant solid areas. Initially histopathological diagnosis of Granulosa cell tumor/Carcinoid tumor were considered. With immunohistochemical study, tumor cells showed strong expression of
chromogranin and synaptophysin and was negative for vimentin. Final diagnosis of Ovarian Carcinoid was made.

(fig 25,26)

On retrospective analysis, no other tumor mass was detected elsewhere by abdominal ultrasonography and CT scan. Isolated Tricuspid regurgitation was incidentally found in pre-operative echocardiography.

In correlation with the above findings, we came to conclusion of Primary Ovarian Carcinoid tumor with Tricuspid regurgitation.

2. GCT TURNED OUT TO BE A POORLY DIFFERENTIATED CARCINOMA AFTER IHC:

In another case of ovarian tumor received, provisional diagnosis of Granulosa cell tumor was made based on histopathological features. On further evaluation with immunohistochemical markers Vimentin and Inhibin were negative and EMA was positive and so the final diagnosis of poorly differentiated carcinoma was made.

The remaining 8 cases showed vimentin positivity and EMA negative. These tumors were diagnosed as Granulosa cell tumors.

Ki 67 LABELLING INDEX IN GCT:

Mean Ki 67 index for 8 cases of histologically and immunohistochemically proven case of granulosa cell tumor was 5.1%.
In the present study, Ki 67 index was higher in 2 cases of Granulosa cell tumors (7.9% and 8.4%) which correlated clinically with higher stage (FIGO stage I(c) disease).

Ki 67 index in the rest of the Granulosa cell tumors was low which correlated clinically with FIGO stage I(a) disease.

Thus in the present study, Ki 67 index reflected more closely the clinical behavior and clinical stage of Granulosa cell tumors (fig 44).

**RETICULIN STAIN IN GRANULOSA CELL TUMOR:**

In this study, we applied reticulin stain for all granulosa cell tumors and fibrothecomas (3 cases). The stain shows fibrils surrounding nests and large aggregates of granulosa cells (fig 24). In Fibrothecoma, reticulin stain highlights an investment of individual cells by fibril.

**INTERESTING TUMORS:**

In this study we came across 7 interesting cases. They are as follows

1. **MIXED TUMORS:**
   2 cases of mixed epithelial tumors were observed. Combinations of mucinous cystadenoma of ovary with benign Brenner tumor in the same ovary in both cases (fig18)

2. **BILATERAL MALIGNANT BRENNER:**
One case of bilateral malignant Brenner tumor was observed in a 65 year old female who presented with abdominal mass. Grossly the tumor measured 10x8x5 cm and 4x3x2 cm on each side. The tumor was arranged in sheets with stromal invasion.(fig 20)

3. **JUVENILE GRANULOSA CELL TUMOR**:

One case of Juvenile granulosa cell tumor in a 2 year old girl who presented with precocious puberty (breast enlargement, vaginal bleeding). Grossly the tumor measured 8x6x5 cm. Both solid and cystic areas were seen(fig 10)

Microscopically the tumor showed predominantly macrofollicular pattern.(fig 22 )

4. **IMMATURE TERATOMA**:

One case of immature teratoma with neuroectodermal elements was encountered (fig.30).

5. **GCT WITH ASSOCATED ENDOMETRIAL CARCINOMA**:

One case of unilateral granulosa cell tumor in a 65 year old female was associated with well differentiated endometrial adenocarcinoma with omental metastatic deposits.
6. CYSTIC TERATOMA WITH MALIGNANT EPITHELIAL COMPONENT:

Secondary malignancies in benign cystic teratoma are rare. Invasive squamous cell carcinoma is common and comprises 85%. But we encountered a relatively rare association of adenocarcinoma occurring as a secondary malignancy in benign cystic teratoma in a 45 year female.

7. OVARIAN NEOPLASM WITH ASSOCIATED ENDOMETRIAL CANCER:

Out of 200 ovarian tumors, 5 were associated with endometrial carcinoma (2.5%). Among those 5 cases, 3 showed the same histologic pattern in both ovary and endometrium. One case was ovarian Granulosa cell tumor with endometrial adenocarcinoma and the other was bilateral mucinous cystadenoma with endometrioid type of endometrial adenocarcinoma.
**TABLE 10**

<table>
<thead>
<tr>
<th>S.No</th>
<th>BIOPSY NO</th>
<th>OVARIAN TUMOR TYPE</th>
<th>ENDOMETRIAL CARCINOMA TYPE</th>
<th>OTHER FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2575/09</td>
<td>b/l endometrioid carcinoma</td>
<td>endometrioid carcinoma</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>G2125/09</td>
<td>b/l mucinous cystadenocarcinoma</td>
<td>well differentiated mucin secreting adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>G4613/09</td>
<td>papillary cystadenocarcinoma</td>
<td>papillary adenocarcinoma</td>
<td>fallopian tubes tumor +</td>
</tr>
<tr>
<td>4</td>
<td>G762//11</td>
<td>u/l granulosa cell tumor</td>
<td>well differentiated adenocarcinoma</td>
<td>omentum tumor +</td>
</tr>
<tr>
<td>5</td>
<td>G695/11</td>
<td>b/l mucinous cystadenoma</td>
<td>endometrioid type of adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>
BENIGN PAPILLARY SEROUS CYSTADENOMA
Fig.3 G4026/09 Glistening cyst wall with papillary excrescences

BENIGN MUCINOUS CYSTADENOMA
Fig.4 G3577/10 Cystic mass filled with mucinous material
PAPILLARY SEROUS CYSTADENOCARCINOMA
Fig.5 G60/11 C/S solid and cystic with papillae

B/L ENDOMETRIOID CARCINOMA
Fig.6 G2575/09 C/S showing greyish-white solid areas
B/L MALIGNANT BRENNER TUMOR
Fig.7 G 476/11 C/S solid and yellowish white areas

FIBROMA
Fig.8 G1137/11 Cut surface showing uniformly whitish solid areas
ADULT GRANULOSA CELL TUMOR
Fig.9 G1888/10 C/S  solid yellowish areas with cystic degeneration

JUVENILE GRANULOSA CELL TUMOR
Fig.10 G3928/10 Cut surface solid and cystic with areas of hemorrhage
DYSGERMINOMA
Fig.11 G1920/10 Typical lobulated outer surface

BENIGN CYSTIC TERATOMA
Fig.12 G 2081/10 Admixture of sebum and hair within the cystic cavity
Fig. 13 G 1891/10 B/L KRU肯BERG TUMOR WITH OMENTAL DEPOSITS

OVARIAN CARCINOID TUMOR

Fig. 14 G232/10
Fig. 15: G1673/10 PAPILLARY SEROUS CARCINOMA
Tumor cells arranged in papillary pattern with fibrovascular core with insert showing psammoma bodies (H&E x 100x)

MUCINOUS CYSTADENOCARCINOMA
Fig.16 .G 934/11 Confluent pattern of growth with back-to-back glands with mucin lakes(H&E x 100X)
ENDOMETRIOID CARCINOMA
Fig. 17 G2575/09 Back-to-back glands lined by columnar cells with stratified hyperchromatic nuclei (H&E x 100X)

MIXED EPITHELIAL TUMOR-BRENNER TUMOR WITH MUCINOUS CYSTADENOMA
Fig. 18 G 884/10 (H&E x 100X)
Fig. 19 BRENNER TUMOR SHOWING EPITHELIAL NESTS EMBEDDED WITHIN FIBROUS STROMA  G 4175/11 (H&E x 100X)

BILATERAL MALIGNANT BRENNER
Nests and islands of tumor cells infiltrating the stroma. Fig. 20 G 476/11 (H&E x 100X)
ADULT GRANULOSA CELL TUMOR
Fig.21 G3713/11 Watered silk pattern with insert showing Call Exnerbodies(H&E x 100X)

JUVENILE GRANULOSA CELL TUMOR
Fig.22 G3928/10 Irregular macrofollicles filled with eosinophilic secretions and surrounded by neoplastic granulosacells(H&E x 100X)
ADULT GRANULOSA CELL TUMOR
Fig.23 G 3713/11 Vimentin positivity (H&E x 400X)

ADULT GRANULOSA CELL TUMOR
Fig.24 G 1888/10 Exhibiting reticulin wrapping around nests (H&E x 100X)
CARCINOID TUMOR
Fig.25 G232/10 Insular pattern (H&E x 100X)

CARCINOID TUMOR
Fig.26 G232/10 Chromogranin positivity (H&E x 100X)
FIBROTHECOMA
Fig.27 G4444/09 Pale lipid containing theca cells merge with spindle cell areas characteristic of fibroma (H&E x 100X)

YOLK SAC TUMOR WITH INSERT SHOWING SCHILLER- DUVAL BODIES
Fig.28 G3173/10 (H&E x 100X)
BENIGN CYSTIC TERATOMA
Fig. 29 G 2081/10 showing areas of cartilage, hair, squamous epithelial lining (H&E x 100x)

OVARIAN IMMATURE TERATOMA
With Primitive neuroepithelial elements
Fig. 30 G2016/10(H&E x 100X)
UNDIFFERENTIATED CARCINOMA
Fig. 31 Sheets of pleomorphic epithelial cells with marked nuclear atypia G 1644/10 (H&E x 100X)

KRUKENBERG TUMOR
Fig. 32 G1891/10 Insert showing signet ring cells. (H&E x 100X)
KRUKENBERG TUMOR
Fig. 33 G1891/10 Signet ring cells showing PAS positivity
(H&E x 400X)

MUCINOUS CYSTADENOCARCINOMA
Fig. 34 G934/11 Tumor Cells with extracellular mucin pools showing PAS positivity (H&E x 400X)
BENIGN MUCINOUS CYSTADENOMA
Fig. 35 G 3577/10 Cyst lined by columnar cells with bland basal nuclei and apical mucin (H&E x 100X)

BENIGN MUCINOUS CYSTADENOMA
Fig. 36 G 3577/10 Ki-67 index 3.1% (H&E x 400X)
BORDERLINE MUCINOUS CYSTADENOMA

Fig. 37 G4079/10 (H&E x 100X)

BORDERLINE MUCINOUS CYSTADENOMA

Fig. 38 G4079/10 (H&E x 100X) Ki-67 index 6% (H&E x 400X)
PAPILLARY SEROUS CYSTADENOCARCINOMA
Fig. 39 G 104/10 Tumor cells arranged in solid nests and papillary pattern (H&E x 100X)

PAPILLARY SEROUS CYSTADENOCARCINOMA
Fig. 40 G 104/10 (H&E x 400X) Ki-67 index 29%
DYSGERMINOMA

Fig. 41 G1920/10 Well defined nest of tumor cells separated by fibrous strands infiltrated by lymphocytes (H&E x 100X)

DYSGERMINOMA

Fig. 42 G1920/10 Ki-67 index 25.3%
Discussion
DISCUSSION

The tumors of the ovary pose a major problem to the gynaecologist due to their higher complication rate and they are the biggest diagnostic challenge in the field of gynaecological oncology. The absolute number of the new cancer patients in India is increasing rapidly due to an increase in the size of the population as well as an increase in the proportion of elderly persons due to improved life expectancy\textsuperscript{59}. The increased incidence of cases is partly due to more widespread screening programmes, improved certification and registration procedures in certain countries.

Though many authors have worked extensively in the field of ovarian tumor pathology, the wide variation in facts and figures from these studies causes the confusion in the area of tumor nomenclature and different morphological subtypes of tumor. In this study, an attempt has been made to study the histomorphology of ovarian tumors, and usefulness of immunohistochemical markers for accurate diagnosis and to assess the prognosis using Ki 67 immunoproliferative marker. These results are correlated with other studies.

INCIDENCE OF OVARIAN TUMORS:

The comparison of incidence rates of ovarian tumors in Indian registries are illustrated in table 11 and graph 7.
COMPARISON OF INCIDENCE RATES IN INDIAN REGISTRIES

Table 11

<table>
<thead>
<tr>
<th>Place of Study</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delhi</td>
<td>8.5%</td>
</tr>
<tr>
<td>Mumbai</td>
<td>6.5%</td>
</tr>
<tr>
<td>Chennai</td>
<td>5.4%</td>
</tr>
<tr>
<td>Mizoram</td>
<td>2.3%</td>
</tr>
<tr>
<td>Present study</td>
<td>8.05%</td>
</tr>
</tbody>
</table>
The incidence of ovarian malignant neoplasms among other gynaecological malignancies in this study period was 8.05%. This ranks next to Delhi, where the incidence was 8.5%. Mizoram has the lowest incidence 2.3%.

These observations suggest that the possible environmental and lifestyle factors have an influence on the incidence rate. Hence in urban areas like Mumbai, changes in lifestyle factors such as increase in age of marriage, delay in age at first birth, reduction in parity and improved socioeconomic conditions might have contributed to the increase in incidence in contrast with the rural area like Mizoram with the lower incidence.

As per the present study, ovarian carcinoma is the second most common gynaecologic malignancy in females (8.05%) next to cancer cervix (67%)(table 12)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Site</th>
<th>No. of malignancies</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cervix</td>
<td>593</td>
<td>67.23</td>
</tr>
<tr>
<td>2.</td>
<td>Ovary</td>
<td>71</td>
<td>8.05</td>
</tr>
<tr>
<td>3.</td>
<td>Endometrium</td>
<td>41</td>
<td>4.64</td>
</tr>
<tr>
<td>4.</td>
<td>Vulva</td>
<td>8</td>
<td>0.91</td>
</tr>
<tr>
<td>5.</td>
<td>Vagina</td>
<td>1</td>
<td>0.11</td>
</tr>
<tr>
<td>6.</td>
<td>Fallopian tube</td>
<td>0</td>
<td>0.11</td>
</tr>
</tbody>
</table>
AGE INCIDENCE OF OVARIAN TUMORS:

No age group was exempted from the occurrence of ovarian tumors including childhood. In the present study the majority of benign tumors occurred in the age group of 21-30 years (79.5%). This is in accordance with the studies conducted by Ramachandran et al (1972) and Jagadeeshwari N et al (1971). Majority of the malignant neoplasms occurred in the age group of 41-50 years in our study, which goes in hand with studies conducted by Jegadeeshwari N et al (1971) and Jha R and Karki S, but in contrast with the study conducted by Ramachandran et al (1972) wherein, the maximum malignant tumors occurred in age group between 31-40 years.

Table 13 Comparison of age in other studies

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Authors</th>
<th>&lt;20yrs</th>
<th>21-30yrs</th>
<th>31-40yrs</th>
<th>41-50yrs</th>
<th>51-60yrs</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tyagi SP</td>
<td>7.5</td>
<td>40.09</td>
<td>28.34</td>
<td>20.00</td>
<td>3.33</td>
<td>0.83</td>
</tr>
<tr>
<td>4.</td>
<td>Present study</td>
<td>7.5</td>
<td>19.5</td>
<td>23</td>
<td>28</td>
<td>14.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Benign tumor cases had lower mean age and borderline tumor cases had higher mean age. But the difference was not statistically significant.
As per the literature and studies conducted by various authors, borderline forms are detected after the age of 40 years and 30-40% of them after the age of 68 years \(^{82}\). In contrast, in our study borderline tumors stand in peak at the 3\(^{rd}\) decade.

**CLINICAL FEATURES OF OVARIAN TUMORS:**

The following table shows the occurrence of clinical features in the different studies in comparison with the present study.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Clinical Features</th>
<th>Gupta et al(^{33})</th>
<th>Couta F et al(^{21})</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pain in lower abdomen</td>
<td>46.2%</td>
<td>39.25%</td>
<td>50.2%</td>
</tr>
<tr>
<td>2.</td>
<td>Mass per abdomen</td>
<td>60.5%</td>
<td>90.20%</td>
<td>58.5%</td>
</tr>
<tr>
<td>3.</td>
<td>Menstrual disturbances</td>
<td>40.2%</td>
<td>31.70%</td>
<td>5%</td>
</tr>
<tr>
<td>4.</td>
<td>Others (Pressure symptoms)</td>
<td>34.5%</td>
<td>39.08%</td>
<td>3%</td>
</tr>
</tbody>
</table>

According to the studies of Gupta et al, the most common clinical feature was mass per abdomen which goes in accordance with our present study.

As per literature, menstrual irregularities were seen in 40.2% of cases (Gupta et al) whereas in our study only 5% of cases had similar symptoms.
CONSISTENCY OF OVARIAN TUMORS:

Table 15 comparison of Consistency of benign tumors with other studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cystic</th>
<th>Solid</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagadeeswari N et al 79</td>
<td>97.4</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>Gupta et al 33</td>
<td>76.2</td>
<td>2.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Kapas MM pal NC 51</td>
<td>82.0</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Chhanda et al 72</td>
<td>30.8</td>
<td>-</td>
<td>69.2</td>
</tr>
<tr>
<td>Present Study</td>
<td>6.2%</td>
<td>81.5%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

Table 16 comparison of Consistency of malignant tumors with other studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cystic</th>
<th>Solid</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagadeeswari N 91 et al</td>
<td>111</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>Gupta et al 73</td>
<td>2.4</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>Kapas MM pal NC 196</td>
<td>-</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Chhanda et al 72</td>
<td>-</td>
<td>69.2</td>
<td></td>
</tr>
<tr>
<td>Present Study</td>
<td>81.5%</td>
<td>12.3%</td>
<td></td>
</tr>
</tbody>
</table>

Various studies have shown that benign tumors are most often cystic in consistency while malignant tumors tend to be mixed (solid & cystic) or solid in consistency. This scenario has also been found in the present study.
LATERALITY OF OVARIAN TUMORS:

Table 17  Comparison of laterality of benign ovarian tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>Unilateral (%)</th>
<th>Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilli et al ⁷⁴</td>
<td>92.2%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Jha R &amp; Karki S ⁴⁹</td>
<td>93.3%</td>
<td>6.67%</td>
</tr>
<tr>
<td>Present Study</td>
<td>90.3%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

Table 18  Comparison of laterality of malignant ovarian tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>Unilateral (%)</th>
<th>Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prabhakar &amp; Maingi ⁷⁶</td>
<td>78.10%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Misra RK et al (1991) ⁶¹</td>
<td>82.98%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Couto et al (1993) ¹³</td>
<td>72.4%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Present Study</td>
<td>64.6%</td>
<td>35.4%</td>
</tr>
</tbody>
</table>

In our present study 90.3% of benign ovarian tumors were unilateral and 64.6% of malignant ovarian tumors were unilateral, whereas 9.7% of benign ovarian tumors were bilateral and 35.4% of malignant ovarian tumors were bilateral. These findings imply that bilaterality is more common in malignant tumors. This is in accordance with the findings of other studies.

According to the literature, bilaterality is more common in serous than mucinous tumors, which goes in accordance with the present study.
HISTOLOGICAL TYPES OF OVARIAN TUMORS:

SURFACE EPITHELIAL TUMORS

In our study, Surface epithelial tumor stands as the most common ovarian neoplasm (155/200 cases – 77.5%) followed by germ cell tumors (22/200 cases – 11%), sex cord stromal tumors (15/200 cases – 7.5%) and metastatic tumors (3/200 cases – 1.5%).

Of the surface epithelial tumors, serous epithelial tumors contribute 61.2% and mucinous epithelial tumors contribute 36.20%.

These findings are in accordance with the literature. In the study by katsube et al, koonings et al and Petterson et al, mucinous borderline tumors are less common than serous borderline tumors but in our study mucinous borderline tumors out number the serous borderline tumors in close correlation with the studies by Isarangkul in Thailand.

Brenner tumors are often associated with other tumors such as mucinous cystadenoma, mature cystic teratoma and transitional cell carcinoma of bladder. In our study 2 such associations with benign mucinous cystadenoma has been observed(fig18). Association may be due to overgrowth of metaplastic mucinous epithelium.

Other associations with mucinous cystadenoma commonly seen were with teratoma (4-5%) and carcinoid tumor.
One case of bilateral malignant Brenner tumor was observed in a 65 year old female who presented with abdominal mass. Grossly the tumor measured 10x8x5 cm and 4x3x2 cm on each side (fig 7). The tumor was arranged in sheets with stromal invasion (fig 20).

**GERM CELL TUMORS**

**Dysgerminoma:**

Three cases were diagnosed as dysgerminoma which accounted for 1.5% of all the tumors in the present study (fig 41). This was the third most common malignant germ cell tumor in our study in contrast to studies conducted by Kurman RJ et al, Bjorkholm et al and Mankad MH et al \(^55\) wherein, dysgerminoma was the most common.

**Yolk sac tumor:**

Yolk sac tumor was seen in 4 patients accounting for 2% of all ovarian tumors. Krigman et al highlighted the fact that this was the second commonest type of malignant germ cell tumor of the ovary with a median age of 19 years \(^54\). Which is in accordance with our study.

Microscopically tumor cells were arranged in microcystic reticulated pattern. PAS positive, diastase resistant intra and extra cellular hyaline globules and Schiller – duval bodies were seen (fig 28). Kurman et al \(^55\) observed that though reticular pattern is the common type, festoon pattern with Schiller – duval bodies was the easiest to identify.
3) Teratoma

This was the commonest germ cell tumor found in the present study constituting 7.5% of all the tumors. All were benign cystic teratomas (fig 29) except one immature teratoma. These findings were similar to those observed by Sahn L et al, Gupta SC et al and Couto F et al.¹³

One case of unilateral immature teratoma grade II tumor was observed in a 12 year girl who presented with mass per abdomen, tumor measuring 13x10x5 cm, cut surface was solid & cystic. Microscopically showed tissues derived from all germ cell layers and immature neuroectodermal elements (Fig 30).

We encountered a relatively rare association of adenocarcinoma occurring as a secondary malignancy in Benign cystic teratoma in a 45 year female.

Two cases of mixed epithelial tumors were observed. Combinations of mucinous cystadenoma of ovary with benign Brenner tumor was observed in the same ovary in both cases (fig.18).

SEX – CORD STROMAL TUMORS

Granulosa cell tumor is the commonest sex cord stromal tumor. Further it is also the commonest functional ovarian tumor with hormone (oestrogen) production. In the present study 8 cases (4%) were reported as granulosa cell tumor.
Tyagi SP, Tyagi GK and Logani KP found an incidence of 3.3% in a pathological study of 120 cases. Jagadeswari N, Reddy RS and Rao found an incidence of 3.7% while Ramachandran G et al found an incidence of 2.7% as shown in table.

**Table 19 Incidence of Granulosa Cell Tumors In Different Studies**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Authors</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tyagi SP et al 104</td>
<td>3.30</td>
</tr>
<tr>
<td>2.</td>
<td>Jagadeswari et al 107</td>
<td>3.70</td>
</tr>
<tr>
<td>3.</td>
<td>Ramachandran G et al 106</td>
<td>2.70</td>
</tr>
<tr>
<td>4.</td>
<td>Gupta SC et al</td>
<td>4.40</td>
</tr>
<tr>
<td>5.</td>
<td>Present Study</td>
<td>4.0</td>
</tr>
</tbody>
</table>

The commonest presenting symptom in the granulosa cell tumor was menorrhagia, similar symptom was encountered by Stenwit JT et al, while this was the second commonest symptom in the study by Pancratz E et al.

**Microscopy:**

Microscopically a mixture of microfollicular, trabecular and diffuse patterns were seen along with typical Call-Exner bodies (Fig 21). Though Stenwing et al observed that these characteristic bodies were found only in 60% of the cases. Well differentiated tumor has a longitudinal nuclear groove. Presence of 3 or more mitosis / 10HPF and degree of cellular atypia correlated with a worst prognosis in the study by Stenwing was JT et al. In this study, we applied reticulin stain for granulosa cell tumors and fibrothecoma. The stain shows fibrils surrounding the nests and large
aggregates of granulosa cells (fig. 24). In thecoma reticulin stain highlights an investment of individual cells by fibrils.

2) **Fibroma:**

2.35% of all tumors were fibromas in the studies by Gupta SC et al. These percentage was higher than 1% in the present study.

3) **Fibrothecoma:**

According to the Evan AT et al, the peak age of occurrence was 51–60 yrs. This goes in accordance with the present study wherein the mean age incidence was 50.2 years. Cut section of the tumor was solid grey – yellow, this feature according to Evans AT et al. helps to distinguish grossly, thecoma from fibroma which have greyish white appearance.

**METASTATIC TUMORS**

Three cases of Krukenberg tumor were found among the 200 cases of ovarian tumors (fig 32). This was lower than study reports by Holt ZF and Hart WR (1982) (3-5%).

PAS stain is an extremely useful and aesthetically pleasing technique. In our study mucinous carcinoma of ovary shows PAS positive mucin pools (fig 34), and Krukenberg tumor show intracellular PAS positivity(fig 33). In a study by Powari M et al, out of 19 metastatic tumors, 31.5% (6 cases) were Krukenberg tumors. The incidence is much higher compared to the present study.
IMPORTANCE OF IMMUNOHISTOCHEMICAL CONFIRMATION IN GRANULOSA CELL TUMORS:

During the study period, out of 200 cases 10 were histopathologically diagnosed as granulosa cell tumor. We did immunohistochemical marker study in all these cases for confirmation. Surprisingly, in one case tumor cells showed strong expression of chromogranin and synaptophysin and negative for vimentin. Final diagnosis of ovarian Carcinoid was made.

On retrospective analysis, no other tumor mass was detected elsewhere by abdominal ultrasonography and CT scan, Isolated Tricuspid regurgitation was incidentally found in preoperative echocardiography.

In correlation with the above findings, we came to conclusion of Primary ovarian Carcinoid tumor with isolated Tricuspid regurgitation.

And in another case Vimentin and Inhibin were negative and EMA was positive. And so the final diagnosis of poorly differentiated carcinoma was made. The significance of differentiating Granulosa cell tumor and poorly differentiated carcinoma lies in the fact that the treatment modalities of both these tumors vary markedly. Granulosa cell tumor is a benign in which case total abdominal hysterectomy with bilateral salpingo oopherectomy (TAH-BSO) alone would suffice whereas in a case of poorly
differentiated tumors of ovary along with TAH-BSO, chemotherapy is mandatory.

The remaining 8 cases showed vimentin positivity and were negative for EMA. These tumors were diagnosed as Granulosa cell tumors.

Thus Immunohistochemical confirmation is always necessary in Granulosa cell tumors to rule out other differential diagnosis which simulate them histopathologically. This is very important because treatment protocol varies for each.

**Ki-67 LABELLING INDEX:**

The rate at which a tumor proliferates has long been considered to bear a relationship with its clinical course. The determination of growth fraction using Ki-67 index is a simple method and has long been shown to have a prognostic value in a variety of malignancies like CNS tumors, Lymphoproliferative diseases, connective tissue tumors and breast tumors.\(^ {69}\)

Ki67 expression in different ovarian tumors has long been studied by various authors across the world. However, there is a paucity of such a study in the Indian literature. Few literature clearly document the importance of Ki 67 proliferative marker in assessing the prognosis of ovarian cancers.

We evaluated Ki 67 expression in 24 selected cases which included 4 benign cystadenoma(2 serous, 2 mucinous), 4 borderline cystadenomas (2
serous, 2 mucinous), 4 carcinoma (2 serous, 2 mucinous adenocarcinoma), 2 Germ cell tumors, 8 granulosa cell tumors.

**1) Ki 67 INDEX IN BENIGN, BORDERLINE AND MALIGNANT OVARIAN TUMORS:**

The Ki 67 index gradually increase from benign to malignant tumors. We observed the same in our study with ki-67 marker. Benign tumors had a mean Ki 67 index of 2.9%, borderline tumors had a mean Ki 67 index of 7.2%, while the malignant tumors had a mean Ki 67 index of 29.9%.

A statistically significant difference (p ≤ 0.001) was obtained between the mean Ki 67 indices of benign, borderline & malignant tumors. These findings are in close agreement with Garzetti et al. and with Monisha Chowdhury et al.

Ki 67 index is especially useful in borderline epithelial ovarian tumors of low malignant potential. These are seen in younger premenopausal women between 30-50 years of age. They remain confined to ovary for a longer time. Overall about 15-25% of borderline tumors behave in a malignant fashion, invading locally and even metastasizing. It is thus important to identify those borderline neoplasms which are likely to behave in a malignant fashion, for it is possible that histological grading of the
degree of severity of the epithelial proliferation and atypia may prove to have some prognostic benefits.\(^7\)

\(b)\) **Ki 67 INDEX IN GRANULOSA CELL TUMORS:**

Granulosa cell tumors behave unpredictably. Histopathologic evaluation of Granulosa cell tumors offers only few clues. It is difficult to predict their prognosis by pathologic means. Tumors larger than 15 cm, bilateral tumors, spread beyond ovary (FIGO stage >1A) or ruptured have less favourable prognosis. The ‘stage’ is the single most powerful prognostic indicator.\(^17\)

Ki 67 index provide insight into nuclear proliferation and to predict the clinical behavior of Granulosa cell tumors\(^19\).

In this study Ki 67 immunohistochemistry was assessed in all the Granulosa cell tumors (8 cases) and the results were correlated with tumor stage at presentation. Mean Ki 67 index for 8 cases of histologically and immunohistochemically proven case of granulosa cell tumor was 5.1\%.(fig 44).

In the present study, Ki 67 index was higher in 2 cases of Granulosa cell tumors (7.9\% and 8.4\%) which correlated clinically with higher stage (FIGO stage I(c) disease). This is in correlation with the study conducted by Costa MJ,Walls J et al\(^19\).
who also proved that higher Ki 67 index in GCT was associated with worst prognosis.

Ki 67 index in the rest of the Granulosa cell tumors was low which correlated clinically with FIGO stage I(a) disease. This goes in hand with study conducted by Costa MJ, Walls J et al who also proved that lower Ki 67 index in GCT was associated with better prognosis.

Thus in the present study, ki 67 index was higher in advanced stage tumors, and thereby pointing toward the aggressive clinical behavior and poorer clinical outcomes.

Even though Granulosa cell tumor usually has good prognosis, it is a tumor of unquestionable malignant potential and has a tendency for late relapse. Case series and reports suggest that post operative chemotherapy is of most benefit in advanced diseases and long term follow-up is recommended.100-102

**OVARIAN CANCER WITH ASSOCIATED ENDOMETRIAL CANCER:**

The simultaneous development of multiple primary cancers in the upper female genital tract is a well known phenomenon. Of these the commonest is the endometrioid carcinoma of the ovary and the uterus. Diagnosis of this type of tumor either as a separate independent primary or as a metastatic tumor is difficult. A careful consideration of a number of gross, histological and immunohistochemical features may be helpful in the
distinction between metastatic and synchronous primary tumors which have different therapeutic and prognostic implications.\textsuperscript{45,104,68}

Out of 200 ovarian tumors, 5 were associated with endometrial carcinoma (2.5%). Among those 5 cases, 3 showed the same histologic pattern in both ovary and endometrium. One was bilateral mucinous cystadenoma with endometrioid type of endometrial adenocarcinoma. Other case was ovarian Granulosa cell tumor with endometrial adenocarcinoma. It is due to estradiol overproduction which continuously stimulates endometrium. Endometrial cancer occurs in association with Granulosa cell tumor in at least 5% of cancer and 25% to 50% are associated with endometrial hyperplasia.\textsuperscript{7}
Summary
SUMMARY

In the present prospective study of 200 ovarian neoplasms evaluated with clinical, histopathological, histochemistry and immunohistochemistry, the following conclusions are made.

1. The incidence of ovarian neoplasms was 8.05% and ranked second among the malignancies of female genital tract.

2. The incidence of ovarian neoplasms was highest during the 5th decade. The peak age incidence of benign tumors was 3rd decade and that for borderline and malignant tumors was 4th and 5th decade respectively.

3. The most common symptom was mass per abdomen (58%), followed by pain (51%) and menstrual disturbances(5%).

4. 81.5% of ovarian tumors were unilateral and 18.5% were bilateral.

5. 85.5% of benign tumors were predominantly cystic and 81.5% of malignant tumors were predominantly solid and cystic or purely solid.

6. The size of the ovarian tumors varied from 2 to 30 cm.

7. 77.5% were Surface Epithelial tumors, 7.5% were Sex Cord Stromal tumors, 11% were Germ Cell tumors, 1.5% were metastatic tumors and 2.5% were undifferentiated tumors.

8. In Surface epithelial tumors, benign serous cystadenoma was the most common (25%).
9. In Sexcord stomal tumors, Granulosa cell tumor was the most common (5%).

10. In Germ cell tumors, benign cystic Teratoma was the most common (7.5%).

11. 62% of ovarian tumors were benign, 5.5% were borderline and 32.5% were malignant.

12. Reticulin stain plays a vital role in distinguishing between Fibrothecoma and Granulosa cell tumor. PAS stain is used to differentiate between krukenberg tumor and mucinous cystadeno carcinoma.

13. In this study, 2 cases which were histolopathologically diagnosed as ovarian granulosa cell tumor was finally diagnosed as Primary ovarian Carcinoid tumor and Poorly differentiated carcinoma respectively after immunohistochemical study.

14. Benign ovarian tumors had a mean Ki 67 index of 2.9%, borderline tumors had a mean Ki 67 index of 7.2%, while the malignant tumors had a mean Ki 67 index of 29.9%.

   The difference in the mean value between benign, borderline, and malignant epithelial tumors were statistically significant (p =<0.001).

15. In Granulosa cell tumors, the mean Ki 67 index was 5.1%. (fig 44) and it was higher in two cases with higher clinical stage.
16. Several interesting cases which we encountered were

A. Two cases of mixed epithelial tumors composed of mucinous cystadenoma of ovary and benign Brenner tumor (fig 18)

B. One case of bilateral malignant Brenner tumor in a 65 year old female (fig 20)

C. One case of juvenile granulosa cell tumor in a 2 year old girl with precocious puberty (fig 22)

D. A case of unilateral granulosa cell tumor associated with well differentiated endometrial adenocarcinoma and omental metastatic deposits.

E. A rare association of adenocarcinoma occurring as a secondary malignancy in Benign cystic teratoma.

F. One case of immature teratoma with neuroectodermal elements.

G. 2.5% (5 cases) ovarian tumors were associated with endometrial carcinoma.
CONCLUSION

Accurate diagnosis of ovarian tumors can be rendered in most of the cases by correlating the clinical presentation, gross and microscopic features. Histochemistry and immunohistochemistry are essential in certain ovarian tumors with doubtful diagnosis. In our study, immunohistochemical markers were very useful in accurate diagnosis of Granulosa cell tumors.

Ki 67 immunostaining is a simple method which provides robust prognostic information for patients with ovarian cancers. This biomarker is very much useful to identify borderline tumors which are likely to behave in a malignant fashion, to assess the prognosis in Granulosa cell tumors and may define subgroups of patients who would be more likely to benefit from cell-cycle dependent chemotherapy regimens, and may guide the development of future therapeutic strategies.
Annexure – I
PROFORMA

Name : 
Age : 
IP.No / Unit : 
Biopsy No. : 
Clinical Features : Pain / Mass Abdomen / Acute Abdomen / Menstrual Irregularity 
Clinical Diagnosis : 
Gross : 
Laterality : Unilateral / Bilateral 
Size : 
Consistency Cystic : Solid / Solid & Cystic 
Microscopy :
1. Tumor differentiation : Benign / Borderline / Malignant 
2. Histological Types : Surface Epithelial / sexcord stromal I Germ Cell 
3. Subtypes : 
Metastasis : 
IHC / Special Stain/ Ki67 index : 
Clinical & Histological Correlation : 

Annexure – II
PROCEDURES

HEMATOXYLIN AND EOSIN

1. Bring the sections to water.
2. Stain in Harris Hematoxylin for 5 minutes
3. Wash well in tap water
4. Differentiate in 1% acid alcohol
5. Wash in running tap water for 10-15 minutes
6. Stain in 1% eosin for 1 to 2 minutes
7. Wash in tap water for 1 to 5 minutes

Dehydrate with alcohol, clear in Xylene and mount in DPX.

SPECIAL STAINS

PERIODIC ACID SCHIFF STAIN: modified McMannus 1946

Periodic acid solution

Periodic acid : 1 gm
Distilled water : 100 ml

PREPARATION OF SCHIFF REAGENT

Dissolve 1gm of basic fuchsin and 1.9gm of sodium metabisulfite in 100ml of 0.15N Hydrochloric acid. Shake the solution at intervals, until it is clear and yellow to light brown in colour. Add 500mg of activated charcoal and shake for 1 to 2 mins. Filter the solution through a No.1 Whatman filter. The filtered solution should be clear and colourless. Store at 4 degree centigrade.

Method:

1. Bring the sections to water
2. Treat with periodic acid for 5 minutes
3. Wash well with several changes of distilled water
4. Cover with schiff’s reagent for 15 minutes
5. Wash in running tap water 5-10 minutes
6. Stain nuclei with Harris Hematoxylin. Differentiate in acid alcohol and blueing in tapwater for 5 minutes.
7. Wash in water
8. Rinse in absolute alcohol
9. Clear in Xylene and mount with DPX

RESULTS

Glycogen : Magenta
Nuclei : Blue

RETICULIN STAIN (GOMORI’S METHOD)
Preparation of silver solution:

To 10ml of 10% potassium hydroxide solution add 40ml of 10% silver nitrate solution. Allow the precipitate to settle and decant the supernatant. Wash the precipitate several times with distilled water. Add ammonia drop by drop until the precipitate has just dissolved. Add further 10% silver nitrate solution until a little precipitate remains. Dilute to 100 ml and filter. Store in a dark bottle.

Method:

1. Deparaffinize sections and bring to water.
2. Treat with 1% potassium permanganate solution, 2 minutes.
3. Rinse in tap water.
4. Bleach in 2% potassium metabisulfate solution.
5. Rinse in tap water.
6. Treat with 2% iron alum, 2 minutes.
7. Wash in several changes of distilled water.
8. Place in Coplin jar of silver solution, 1 minute.
9. Wash in several changes of distilled water.
10. Reduce in 4% aqueous formalin solution, 3 minutes.
11. Rinse in tap water.
12. Tone in 0.2% gold chloride solution, 10 minutes.
13. Rinse in tap water.
14. Treat with 2% potassium metabisulfite solution, 1 minute.
15. Rinse in tap water.
16. Treat with 2% sodium thiosulfate solution, 1 minute.
17. Rinse in tap water.
18. Counterstain as desired (Van Gieson or eosin is suitable.)
19. Dehydrate
20. Clear in xylene and mount in permanent mounting medium.

Results:

- Reticular fibers: black
- Nuclei: Gray
- Other tissues: according to counterstain

**IMMUNOHISTOCHEMISTRY:**

An assay that shows specific antigens in tissues by the use of markers that are either fluorescent dyes or enzymes (such as horseradish peroxidase)

Visualising an antibody-antigen interaction can be accomplished in a number of ways.
Immunoperoxidase staining: an antibody is conjugated to an enzyme, such as peroxidase, that can catalyse a colour-producing reaction.

Immunofluorescence staining: the antibody can also be tagged to a fluorophore, such as FITC, rhodamine, Texas Red, Alexa Fluor, or DyLight.

Sample preparation
In the procedure, either thin (about 4-40 µm) slices are taken of the tissue of interest, or if the tissue is not very thick and is penetrable it is used whole.

Direct and indirect IHC

DIRECT METHOD: One labelled antibody, which binds directly to the antigen being stained for

INDIRECT METHOD: One antibody against the antigen being probed for, and a second, labelled, antibody against the first

In a common procedure, a biotinylated secondary antibody is coupled with streptavidin-horseradish peroxidase. This is reacted with 3,3'-Diaminobenzidine (DAB) to produce a brown staining wherever primary and secondary antibodies are attached in a process known as DAB staining. The reaction can be enhanced using nickel, producing a deep purple/gray staining.
Annexure – III
WHO CLASSIFICATION OF OVARIAN TUMORS

Surface epithelial-stromal tumors
Serous tumors
  Malignant
    Adenocarcinoma
    Surface papillary Adenocarcinoma
    Adencarcinofibroma (malignant adenofibroma)
  Borderline tumor
    Papillary cystic tumor
    Surface papillary tumor
    Adenofibroma, cystadenofibroma
  Benign
    Cystadenoma
    Papillary cystadenoma
    Surface papilloma
    Adenofibroma and cystadenofibroma

Mucinous tumors
  Malignant
    Adenocarcinoma
    Adenocarcinofibroma (malignant adenofibroma)
  Borderline tumor
    Intestinal type
    Endocervical – like
  Benign
    Cystadenoma
    Adenofibroma and cystadenofibroma
    Mucinous cystic tumor with mural nodules
    Mucinous cystic tumor with pseudomyxoma peritonei

Endometrioid tumors including variants with squamous differentiation
  Malignant
    Adenocarcinoma not otherwise specified
    Adenocarcinofibroma (malignant adenofibroma)
    Malignant mullerian mixed tumor
      (carcinosarcoma)
    Adenosarcoma
    Endometrioid stromal sarcoma (low grade)
    Undifferentiated ovarian sarcoma
  Borderline tumor
Cystic tumor
  Adenofibroma and cystadenofibroma

Benign
  Cystadenoma
  Adenofibroma and cystadenofibroma

Clear cell tumors

Malignant
  Adenocarcinoma
  Adenocarcinofibroma (malignant adenofibroma)

Borderline tumor
  Cystic tumor
  Adenofibroma and cystadenofibroma

Benign
  Cystadenoma
  Adenofibroma and cystadenofibroma

Transitional cell tumors

Malignant
  Transitional cell carcinoma (non-Brenner type)
  Malignant Brenner tumor

Borderline
  Borderline Brenner tumor
  Proliferating variant

Benign
  Brenner tumor

Metaplastic variant

Squamous cell tumors
  Squamous cell carcinoma
  Epidermoid cyst

Mixed epithelial tumors (specify components)
  Malignant
  Borderline
  Benign

Undifferentiated and unclassified tumors
  Undifferentiated carcinoma
  Adenocarcinoma, not otherwise specified

Sex cord-stromal tumors

Granulosa-stromal cell tumors
  Granulosa-stromal cell tumor group
  Adult granulosa cell tumor
  Juvenile granulosa cell tumor
  Thecoma-fibroma group
Thecoma, not otherwise specified
  Typical
  Luteinized
Fibroma
Cellular fibroma
Fibrosarcoma
Stromal tumor with minor sex cord elements
Sclerosing stromal tumor
Signet-ring stromal tumor
Unclassified (fibrothecoma)

Sertoli-stromal cell tumors
  Sertoli – Leydig cell tumor group (androblastomas)
    Well differentiated
    Of intermediate differentiation
      Variant with heterologous elements (specify type)
    Poorly differentiated (sarcomatoid)
      Variant with heterologous elements (specify type)
    Retiform
      Variant with heterologous elements (specify type)
Sertoli cell tumor
Stromal-Leydig cell tumor

Sex cord-stromal tumors of mixed or unclassified cell type
  Sex cord tumor with annular tubules
  Gynandroblastoma (specify components)
  Sex cord-stromal tumor, unclassified

Steroid cell tumors
  Stromal luteoma
Leydig cell tumor group
  Hilus cell tumor
  Leydig cell tumor, non-bilar type
  Leydig cell tumor, not otherwise specified
Steroid cell tumor, not otherwise specified
  Well differentiated
  Malignant

Germ cell tumors
Primitive germ cell tumors
  Dysgerminoma
Yolk sac tumor
  Polyvesicular vitelline tumor
Glandular variant
Hepatoid variant
Embryonal carcinoma
Polyembryoma
Non-gestational choriocarcinoma
Mixed germ cell tumor (specify components)
Biphasic or triphasic teratoma
Immature teratoma
Mature teratoma
   Solid
   Cystic
       Dermoid cyst
       Fetiform teratoma (homunculus)
Monodermal teratoma and somatic-type tumors associated with dermoid cysts
   Thyroid tumor group
       Struma ovarii
           Benign
           Malignant (specify type)
Carcinoid group
   Insular
   Trabecular
   Mucinous
   Strumal carcinoid
   Mixed
Neuroectodermal tumor group
   Ependymoma
   Primitive neuroectodermal tumor
   Medulloepithelioma
   Glioblastoma multiforme
   Others
Melanocytic group
   Malignant melanoma
   Melanocytic naevus
Sarcoma group (specify type)
Sebaceous tumor group
   Sebaceous adenoma
   Sebaceous carcinoma
Pituitary–type tumor group
Retinal anlage tumor group
Others
Germ cell sex cord-stromal tumors
  Gonadoblastoma
    Variant with malignant germ cell tumor
  Mixed germ cell-sex cord-stromal tumor
    Variant with malignant germ cell tumor

Tumors of the rete ovarii
  Adenocarcinoma
  Adenoma
  Cystadenoma
  Cystadenofibroma

Miscellaneous tumors
  Small cell carcinoma, hypercalcemic type
  Small cell carcinoma, pulmonary type
  Large cell neuroendocrine carcinoma
  Hepatoid carcinoma
  Primary ovarian mesothelioma
  Wilms tumor
  Gestational choriocarcinoma
  Hydatidiform mole
  Adenoid cystic carcinoma
  Basal cell tumor
  Ovarian wolffian tumor
  Paraganglioma
  Myxoma
  Soft tissue tumors not specific to the ovary
  Others

Tumor-like conditions
  Luteoma of pregnancy
  Stromal hyperthecosis
  Stromal hyperplasia
  Fibromatosis
  Massive ovarian oedema
  Others

Lymphoid and haematopoetic tumors
  Malignant lymphoma (specify type)

  Leukaemia (specify type)
  Plasmacytoma

Secondary tumors
Annexure – IV
Minutes of the Ethical Committee meeting held on 19.8.2010—regarding

The following members of the committee were present and the following points were decided in the meeting:

1. Dr. S. M. Sivalakumaran, MS., Medical Superintendent, Govt. Rajaji Hospital, Madurai.
2. Dr. N. Vijayanakaran, M.Ch(Uro.)
3. Dr. T. Meena, M.D., Prof. of Physiology
4. Dr. Moses K. Daniel, M.D., "Madurai Medical College Professor of Medicine"
5. Dr. M. Gobinath, MS(Gen. Surgery)
6. Dr. S. S. Dilath, M.D(O&G)
7. Dr. B. K. Mohan Prasad, M.Ch, Professor of Surgery
8. Shri M. Srikanth, B.Sc., B.L.
10. Shri S. Sivalakumaran, M.A. (Social), M.PHIL., Plot No. 51, F.F.

a) The Committee has considered the revised study-specific informed Consent Document version of 30 Apr, 2010, pertaining to the previously approved clinical trial “H3E-MC- S103: A Randomized phase 2 study comparing Erlotinib-Pemetrexed, Pemetrexed alone, and Erlotinib alone, as second-line treatment for Non-smoker patients with locally advanced or Metastatic Nonsquamous Non-Small cell lung cancer”, and finds it satisfactory. The same is approved.

b) The Committee has considered the revised Tamil Translation of study-specific informed Consent document version of 20 May 2010, pertaining to the previously approved clinical trial “HeE-MC-S103: A Randomized phase 2 study comparing Erlotinib-Pemetrexed, Pemetrexed alone, and Erlotinib alone, as second-line Treatment for Non-Smoker Patients with locally Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer”, and finds it satisfactory. The same is approved.
c) The committee reviewed the clinical trial proposal submitted by Dr. J. Jebasingh, Principal Investigator, Dept of Medical Oncology, Govt. Rajaji Hospital, Madurai. "Phase II study of Coagulation Factor VIIa Inhibitor PCI-27483 in Pancreatic Cancer patients Receiving Treatment with Gemcitabine"-Protocol #PCYC-1001 (Considered by the Committee in its meeting of 04 Mar 2010) along with the letter of Undertaking received from the sponsors confirming that the study patients' samples will not be used for purposes other than that specified in the clinical trial protocol. The clinical trial proposal is found to be satisfactory, and is approved.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the applicant</th>
<th>Course</th>
<th>Name of the Project</th>
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<td>1.</td>
<td>B.Sc. (N) IV Year Students</td>
<td>College of Nursing Madurai Medical College Madurai.</td>
<td>Statistical data from MRD and various departments in GRH Madurai.</td>
<td>Approved</td>
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<tr>
<td>2.</td>
<td>Dr. K. Preetha Rani, PG.Student in MS, MMC, Madurai.</td>
<td>Role of Laparoscopic Surgery Versus open surgery for colorectal cancers.</td>
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<td>3.</td>
<td>Dr. N. Mohanraj, PG.Student in MS/MMC, Madurai.</td>
<td>Role of Diagnostic Laparoscopy Preoperatively in Assessing the Operability in Various Intra-Abdominal Malignancies.</td>
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<td>5.</td>
<td>Dr. C. Baskar. PG. in MS. Ortho. MMC, Madurai.</td>
<td>A study on Functional outcome of Intraarticular Distal Radius Fractures fixed with locking compression plate.</td>
<td>&quot;</td>
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<td>6.</td>
<td>Dr. S. Suresh. PG. Student, MS. Ortho. MMC, Madurai.</td>
<td>A study on Functional outcome of Proximal Humerus Fractures Fixed with Proximal Humerus locking compression plate.</td>
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<td>7</td>
<td>Dr.V.Anandkumar</td>
<td>PG.Student in MS.Ortho,MMC,Madurai</td>
<td>A Study of Functional outcome of Translaminar Facetal Screw fixation for Grade 1 Lumbar spondylolisthesis.</td>
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<td>8</td>
<td>Dr.K.Subathra</td>
<td>PG.in Pathology, MMC, Madurai</td>
<td>Histopathological study of prostate lesions, Assessment of Premalignant and Malignant Conditions &amp; Statistical Evaluation.</td>
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<td>9</td>
<td>Dr.R.Lavanya</td>
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<td>A Clinico Pathological study of Ovarian Tumors.</td>
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<td>Dr.S.Dilshath, MD, DGO</td>
<td>Prof.of OG, GRH, Madurai</td>
<td>Evaluation of progesterone vaginal ring (PVR) as a new contraceptive option in India study.</td>
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<td>Dr.P.Sangaia Raja</td>
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<td>Limb Salvage Procedures in Diabetic Foot Ulcers.</td>
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<td>Dr.R.Ashok kumar</td>
<td>PG.Student, MS.Ortho, MMC, Madurai</td>
<td>Natural History of Obstetric Brachial plexus palsy - A Prospective study of 25 cases.</td>
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<td>Dr.S.Frathiba</td>
<td>PG.in MD, DVL, MMC, Madurai</td>
<td>A Clinicopathological study of Perforating Dermatoses.</td>
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<td>14</td>
<td>Dr.Jayanthi, OR</td>
<td>-do-</td>
<td>Study and Analysis of Cutaneous small Vessel Vasculitis.</td>
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<td>G.Jayanthi</td>
<td>M.Sc. Nursing, II Year, Appollo college of Nursing, Chennai</td>
<td>An Experimental study to Assess the Effectiveness if changing positions upon serum bilirubin level among newborn under phototherapy at GRH, Madurai.</td>
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<td>17.</td>
<td>Dr. Aneesh B. Rahiman, PG in MD, MMC, Madurai.</td>
<td>TIMI Risk Score-A Convenient, Bedside, Clinical Score for Risk Assessment in ST Elevation Myocardial infarction.</td>
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<td>Dr. A. Tamilvanan, PG in GM, III Unit, MMC, Madurai.</td>
<td>Study of Etiological Profile of Late (Adult) Onset Seizures.</td>
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<td>Dr. P. Sivasubramania Barathi, PG in MD (GM) MMC, Madurai.</td>
<td>Anemia in Type 2 Diabetes Mellitus Risk Factor for the presence and the severity of Micro Vascular Complication (Diabetic Retinopathy)</td>
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<td>Dr. Prasanth S, PG in MD (GM) MMC, Madurai.</td>
<td>Pulmonary manifestations in Rheumatoid Arthritis Patients.</td>
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<td>Dr. Mageesh B, PG in GM, MMC, Madurai.</td>
<td>An Epidemiological study of Poisonous Snake bite in and Around Madurai from December 2009 to December 2010</td>
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<td>Dr. A. Jeya Jancy Selvi, MD.</td>
<td>Asst. Professor, Institute Physiology, MMC, Madurai</td>
<td>Cord Blood Prolactin Birth Weight Respiratory compliance in Newborns.</td>
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<td>Dr. P. Balamanikandan, PG in G.M.MC, Madurai</td>
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<td>A study of Cardiac Function in Non Diabetic Non-Smoker Chronic Kidney Disease patients from July 2010 to December 2010</td>
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<td>25</td>
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<td>Cardiovascular Autonomic Neuropathy in type 2 Diabetes Mellitus.</td>
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Please note that the investigator should adhere the following:

1) She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

2) She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.

3) She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.

4) She/He should not deviate for the area of the work for which applied for Ethical clearance.

5) She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.

6) She/he should abide by the rules and regulations of the institution.

7) She/He should complete the work within the specific period and apply for if any extension of time is required. She should apply for permission again and do the work.

8) She/He should submit the summary of the work to the Ethical Committee on completion of the work.

9) She/He should not claim any funds from the institution while doing the work or on completion.

10) She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

MEDICAL SUPERINTENDENT.
Annexure – V
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ABSTRACT

BACKGROUND AND OBJECTIVES

The ovarian tumors manifest a wide spectrum of clinical, morphological and histological features. Their complex nature, unpredictable behaviour, prognosis and varying therapeutic strategies, necessitates an accurate diagnosis.

Hence this study was undertaken to correlate the clinical and pathological parameters and to analyse the role of Ki 67, a nuclear protein expressed by mitotic cells, as a prognostic marker in ovarian tumors and also to evaluate the usefulness of immunohistochemical markers for confirmatory diagnosis of Granulosa cell tumors.

METHODS

This study was done in the Department of Pathology, Madurai Medical College, Madurai, for a period of two years (2009-2011), on 200 ovarian neoplasms out of 239 ovarian lesions received after exclusion of non-neoplastic lesions. A detailed history regarding the clinical symptoms and signs were recorded. Representative bits were processed and stained with hematoxylin and eosin. Special stains like PAS, reticulin were done in selected cases.

Immunostaining was performed on 24 selected cases with proliferative marker Ki 67 using peroxidase-antiperoxidase technique and immunohistochemical marker study was done in all cases of Granulosa cell tumors with vimentin, inhibin and for selected cases with chromogranin and EMA.
RESULTS

The incidence of ovarian neoplasms was 8.05% and ranked second among the female genital tract malignancies. The peak age incidence was fifth decade. Mass per abdomen was the most common clinical presentation (58%). 81.5% were unilateral and 18.5% were bilateral. Surface epithelial tumors were the commonest (77.5%), sex cord stromal tumors 7.5% and germ cell tumors 11%. Out of 200 cases, benign tumors constituted 62%, borderline tumors constituted 5.5% and malignant tumors 32.5%. There were 3 cases (1.5%) of Krukenberg’s tumor. The difference in the mean Ki 67 index between benign (2.9%), borderline (7.2%) and malignant tumors (29.9%) was statistically significant. In Granulosa cell tumors the mean Ki 67 index was 5.1% and it was higher in two cases with higher clinical stage.

In this study, two cases which were histopathologically diagnosed as Granulosa cell tumors were finally diagnosed as Primary ovarian carcinoid tumor and Poorly differentiated carcinoma respectively after immunohistochemical study.

CONCLUSION

Accurate diagnosis of ovarian tumors can be rendered in most of the cases by correlating the clinical and pathological parameters. Immunohistochemistry is essential in Granulosa cell tumors with doubtful diagnosis. Ki 67 immunostaining provides robust prognostic information and is very much useful to identify borderline ovarian tumors which are likely to behave in a malignant fashion and also to assess the prognosis of Granulosa cell tumors.

Key words:

ovarian tumors, surface epithelial tumors, germ cell tumors, granulosa cell tumors, immunoproliferative marker Ki 67.
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115 51376/6/10 24952 13 MASS P 3X5X1.5 P P BENVN MUCINOUS CYSTADENOMA

116 51365/6/10 28614 40 MASS, PAIN P 15X2X2 P P IMPLANT SEROSITY CYSTADENOCARCINOMA OVARY

117 51474/5/10 3684 30 MASS P 15X2X2 P P F PAPILLARY CYSTADENOMA

118 51492/5/10 31014 54 PAIN P 4X8X2 P P F PAPILLARY CYSTADENOMA

119 51401/5/10 4188 PAIN P 15X2X2 P P BENVN MUCINOUS CYSTADENOMA

120 51571/5/10 4610 25 PAIN P 10X5X2 P P BENVN SEROSITY CYSTADENOCARCINOMA

121 51646/5/10 3389 41 MASS, PAIN P 8X5X3 P P BENVN MUCINOUS CYSTADENOMA

122 51646/5/10 3127 41 MASS P 8X5X3 P P BENVN MUCINOUS CYSTADENOMA

123 51673/6/10 3119 14 MASS, PAIN P 8X5X3 P P F P PAPILLARY SEROSITY CYSTADENOMA

124 51708/6/10 36389 37 MASS P 15X2X2 P P F BENVN CYSTIC TERTOMA, 2 MUCINOUS CYSTADENOCARCINOMA 32.60%

125 51806/6/10 3814 40 MASS, PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOCARCINOMA

126 51876/6/10 37644 19 MENSUAL DISTURBANCES P 10X6X4 P P POORLY DIFFERENTIATED SEROSITY CYSTADENOMA

127 51901/6/10 4440 40 MASS, PAIN P 10X6X4 P P BENVN ADENOCARCINOMA

128 51886/6/10 3962 23 MASS P 15X11X7 P P ADULT GRANULOSITY CEL TUMOR

129 51895/6/10 3673 50 mass ABDOMEN P 4X1X1 P P KRUENBERG TUMOR

130 51916/6/10 414 41 PAIN P 8X5X3 P P XAMINTUM TATOMA GARDI 11

131 52033/7/10 2925 27 PAIN P 8X5X3 P P DERMOPY CYST

132 52047/7/10 3835 21 MASS P 8X5X3 P P XAMINTUM MELLITIC CSDIDEP

133 52057/7/10 4021 27 MASS P 8X5X3 P P BENVN MUCINOUS CYSTADENOMA

134 52083/7/10 43121 30 PAIN P 8X5X3 P P ENDOMIOETIC CYST

135 52087/7/10 44276 40 MASS P 17X10X8 P P FIBROMA

136 52112/7/10 41448 12 PAIN P 8X5X3 P P BENVN PAPILLARY SEROSITY CYSTADENOMA

137 52218/7/10 4752 40 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

138 52277/7/10 4699 50 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

139 52313/7/10 4708 55 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

140 52356/7/10 52171 23 PAIN P 8X5X3 P P BENVN CYSTIC TERTOMA

141 52338/7/10 51161 45 PAIN P 8X5X3 P P (both) F (both) CYSTIC TERTOMA WITH ADENOCARCINOMA

142 52394/8/10 4065 46 PAIN P 8X5X3 P P BENVN CYSTIC CYS

143 52417/8/10 43214 48 MASS, PAIN P 12X3X2 P P F PASCITES= PAPPILLARY CYSTADENOCARCINOMA

144 52493/8/10 46144 40 PAIN P 8X5X3.5 P P BENVN SEROSITY CYSTADENOMA

145 52597/8/10 30857 42 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

146 52505/8/10 52118 35 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

147 52565/8/10 54651 47 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA OF BORDERLINE MALIGNANCY 8.30%

148 52655/8/10 53245 48 MASS P 12X3X2 P P BENVN SEROSITY CYST

149 52659/8/10 55458 17 MENSUAL DISTURBANCES P 15X2X2 P P GRANULOSITY CEL TUMOR

150 52703/8/10 46326 50 PAIN P 8X5X3 P P F ASCITE= SEROSITY ADENOCARCINOMA

151 52821/8/10 44617 50 MASS P 8X5X3 P P BENVN MUCINOUS CYSTADENOMA

152 52908/8/10 43158 55 PAIN P 8X5X3 P P BENVN SEROSITY CYST

153 52930/9/10 52164 50 MASS P 8X5X3 P P F PASCITES= MUCINOUS CYSTADENOCARCINOMA

154 52951/8/10 43114 42 PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

155 53046/9/10 43141 45 MASS, PAIN P 8X5X3 P P BENVN SEROSITY CYSTADENOMA

156 53046/9/10 54028 67 PAIN P 8X5X3 P P F ASCITE= PAPPILLARY CYSTADENOCARCINOMA

157 53120/10/10 5698 48 PAIN P 4X8X2 P P F PAPPILARY MUCINOUS CYSTADENOCARCINOMA

158 53169/10/10 1193 28 MASS P 8X5X3 P P F BENVN CYSTIC TERTOMA

159 53177/10/10 5656 15 MASS, PAIN P 15X2X4 P P F ASCITE= VOLK SAC TUMOR

160 53377/10/10 5656 15 MASS P 15X2X4 P P F BENVN SEROSITY CYSTADENOMA

161 53377/10/10 5656 15 MASS, PAIN P 15X2X4 P P F BENVN MUCINOUS CYSTADENOMA

162 53377/10/10 5656 15 MASS, PAIN P 15X2X4 P P F BENVN MUCINOUS CYSTADENOMA

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169 53377/10/10 5656 15 MASS, PAIN P 15X2X4 P P F BENVN MUCINOUS CYSTADENOMA

170 53377/10/10 5656 15 MASS, PAIN P 15X2X4 P P F BENVN MUCINOUS CYSTADENOMA
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