THE STUDY OF CLINICOPATHOLOGICAL SIGNIFICANCE OF C-KIT EXPRESSION IN GERM CELL TUMOURS OF OVARY WITH SPECIAL REFERENCE TO DYSGERMINOMA

Dissertation submitted in partial fulfilment of

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CERTIFICATE

This is to certify that this Dissertation entitled "**THE STUDY OF CLINICO PATHOLOGICAL SIGNIFICANCE OF C-KIT EXPRESSION IN GERM CELL TUMOURS OF OVARY WITH SPECIAL REFERENCE TO DYSGERMINOMA**" is the bonafide original work of **Dr. K. MAHA LAKSHMI**, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University will be held in April 2013.

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DECLARATION

I, **Dr.K.MAHALAKSHMI,** solemnly declare that the dissertation titled "**THE STUDY OF CLINICO PATHOLOGICAL SIGNIFICANCE OF C-KIT EXPRESSION IN GERM CELL TUMOURS OF OVARY WITH SPECIAL REFERENCE TO DYSGERMINOMA**" is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of **Dr.M.P.KANCHANA, M.D.**, Professor of Pathology, Institute of Obstetrics & Gynaecology, Madras Medical College. The dissertation submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place: Chennai

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ABBREVIATIONS

AFP	-	Alpha feto protein
β HCG	-	Human chorionic gonadotrophin
B/L	-	Bilateral
BSO	-	Bilateral salphingo oopherectomy
CML	-	Chronic myeloid leukemia
CSF	-	Colony stimulating factor
CT	-	Computerized tomography
DNA	-	de-oxy ribonucleic acid
FIGO	-	International Federation of Gynaecology and Obstetrics
IHC	-	Immunohistochemistry
HRP	-	Horse-Radish Peroxidase
LDH	-	Lactate dehydrogenase
LSO	-	Left salphingo oopherectomy
MGCT	-	Mixed germ cell tumour
PAS	–	Periodic acid Schiff
PDGFR	-	Platelet derived grpwth factor
PGP9.5	-	Protein gene product
PLAP	-	Placental Alkaline Phosphatase
RSO	-	Right salphingo oopherectomy
TAH	-	Total abdominal hysterectomy
TTF	-	Thyroid Transcription Factor

CONTENTS

INTRODUCTION

Ovaries are paired organs measuring 4 x 2.5 x 1.5 cm each in dimension[1] situated one on either side of the uterus close to lateral pelvic wall.

Pathology of ovary is most difficult gynaecological disease to evaluate clinically[2].

Ovarian cancers account for 25% of all gynaecological malignancies and fourth most common cause of death from cancers of female genital tract in western world[3].

Ovaries are subjected to monthly endocrine and traumatic insult and hence it becomes a prime site of carcinogenesis.

The primary and secondary carcinomas of ovary are frequent with variety of histological pattern, which is seen in all age and ethnic groups[2].

50% of ovarian tumours are benign tumours, of malignant tumours 90% are epithelial tumours.[4]

AIMS AND OBJECTIVES

* To study the incidence of ovarian germ cell tumours in patients admitted in Institute of Obstetrics and Gynaecology (MMC), Egmore, Chennai during the period of 2007, January to 2012, October.

* To study the histo-morphological features of germ cell tumours including tumour size, macroscopic appearance, histological type, stage.

* To study the immunohistochemical expression of CD117 in germ cell tumours of ovary.

* To determine the correlation of CD117 expression with known prognostic factors such as tumor size, histological type, stage and also with the outcome of the disease.

REVIEW OF LITERATURE

ANATOMY:

EMBYOLOGY:

Ovaries are almond shaped structures measuring 4 x 2.5 x 1.5cm[1] located in the ovarian fossa in the pelvic wall. They are attached to the broad ligament and held in situ by the by suspensory ligament containing ovarian vessels and nerves. They are grayish pink in colour with smooth exterior surface before ovulation. The surface becomes distorted by scarring due to degeneration of successive corpora lutea.

The gonads appear as genital or gonadal ridges, formed by proliferation of coelomic epithelium. The primitive germ cells in the wall of the yolk sac migrate along the mesentery of the lined gut to reach the primitive gonads by 5^{th} week and invade the genital ridges by 6^{th} week[5].

Shortly before the arrival of germ cells, the coelomic epithelium proliferate and penetrate the underlying mesenchyme in the form of primitive sex cords which are connected to the surface epithelium. This stage is known as indifferent gonad. The primitive sex cords dissociate in to irregular cell clusters, which are replaced by vascular stroma forming the ovarian medulla.

The cortex constituting one half to 2/3rd of depth of ovary, thus appearing primarily a cortical structure unlike testis. The epithelial cells proliferate forming cortical cords which penetrate the underlying mesenchyme. These cell cords split in to isolated cell clusters with each clusters surround one/more primitive germ cell. The germ cells develop in to oogonia while surrounding cells become the follicular cells[6].

HISTOLOGY:

The surface of the ovary is covered by single layer of cuboidal cells, which forms the germinal epithelium. This is continuous with the mesothelial covering, the mesovarium. Beneath the epithelium, there is tough tissue coat called tunica albuginea under which lies the thick cortex and thin medulla.

The cortex makes the major part of the ovary surrounding the medulla. The follicles are surrounded by dense stroma composed of thin collagen fibres and numerous fusiform like fibroblasts forming characteristic whorls. The boundary between the cortex and medulla is indistinct. The medulla is richly vascular composed of spiral arteries and numerous veins in a loose connective tissue stroma made of smooth muscles and elastic fibres.

The ovarian follicles of varying sizes surround the developing ova.

Primordial follicle:

At birth, the cortex contains a superficial zone of primordial follicles, consisting of primary oocytes, each surrounded by a single layer of flat follicular cells. During childhood and even in child bearing period, many degenerate forming atretic follicle.

Primary follicle:

The follicular cells undergo rapid mitotic proliferation to form a multilayered membrane granulosa, surrounding the oocyte. The stromal cells immediately surrounding the follicle differentiate into theca internal being spindle shaped and later accompanied by fibrous theca externa. As the oocyte grows, it secretes a homogenous proteoglycan rich acidophilic refractile layer, the zona pellucida.

Secondary follicles:

A hyaluronic acid rich fluid called the liquor folliculi begins to form between the follicular cells. A large fluid filled space is formed –antrum folliculi, surrounded by a thin layer of granulosa cells, thickened at one pole of follicle to encompass the oocyte in a mound of cells, the cumulus oophorus. The theca interna becomes more prominent and cells start producing estrogenic hormone.

Tertiary follicles:

Only one follicle from the two ovaries proceeds to the tertiary stage and remaining become atretic. This follicle increases in size to 2mm by taking up fluid to form Graffian follicle. The oocyte and its surrounding ring of cells break away from the wall and float freely in follicular fluid. The primary oocyte which has remained in first meiotic prophase since fetal life, complete its meiotic division to form the secondary oocyte and first polar body. The secondary oocyte begins second meiotic division, which is again arrested in metaphase until fertilization occurs. The follicle moves to the surface of cortex causing the ovarian surface to bulge. The tunica albuginea and epithelium are eroded and the follicle develops an aperture to release its contents into peritoneal cavity.

Atretic follicles:

These are formed by degeneration of follicles at all stages of oocyte development from the embryonic period onwards. The follicular remnants are invaded by blood vessels, macrophages and connective tissue, which ultimately converts it in to a small white fibrous body.

Corpus luteum:

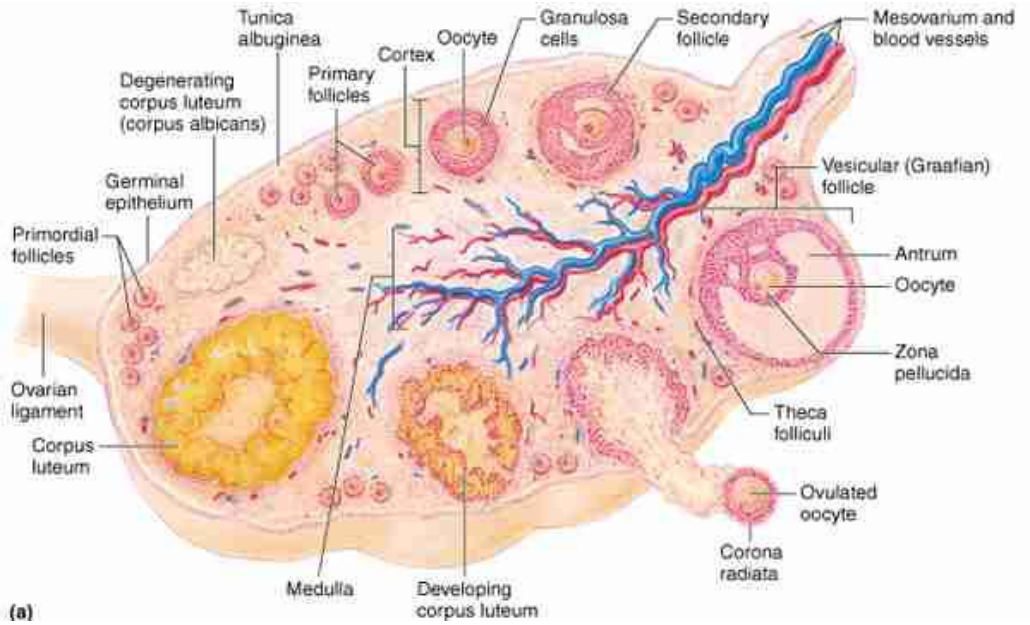
After ovulation, the walls of the empty follicle collapse and fold. The remaining granulosa cells increase in size and synthesize a cytoplasmic pigment (lutein). These granulosa lutein cells form most of corpus luteum, smaller, more numerous cells, derived from theca lutein cells, infiltrate the cellular mass. Lutein cells are grouped into small clusters, each of which is surrounded by a little connective tissue. These secrete estradiol, progesterone and testosterone. If the oocyte is not fertilized, the corpus luteum functions for 12 to 14 days then atrophies into corpus luteum of menstruation. The lutein cells undergo fatty degeneration and fibrosis to form a scar like corpus albicans. If fertilization does occur, the corpus luteum of menstruation grows to form the corpus luteum of pregnancy, which is then metabolically active till 2 months of gestation[7].

Corpus albicans:

Regressing corpus luteum invaded by connective tissue forms corpus albicans.

In early stage it may contain hemosiderin laden macrophages. Mature corpus albicans is well circumscribed structure with convoluted borders almost entirely of densely packed collagen fibers with a few admixed fibroblasts.

Most of them are eventually resorbed and replaced by ovarian stroma, although corpora albicantia often persists in medulla of post menopausal women.



Hilus cells:

Found in ovarian hilus. Cells measuring 15-25µm in diameter, oval to round cells with abundant eosinophilic cytoplasm with vesicular nuclei and 2 or more prominent nucleoli. The cytoplasm may contain reinke's crystal, lipids, lipochrome pigment.

These cells are morphologically similar to testicular Leydig cells.

Rete ovary:

Ovarian homologue of rete testes, consisting of a network of tubules with intra luminal polypoidal proliferation lined by columnar to flat epithelium. These tubules are surrounded by spindle cell stroma.

Risk factors:

The aetiology of ovarian cancers are multifactorial, with genetic, environmental, and reproductive factors directly or indirectly involved in carcinogenesis.

Genetic factors:

A family history of ovarian cancer is the most significant risk factor. Approximately 10% of all ovarian cancers can be associated with a familial genetic predisposition. The risk depends on the number of their first and second degree relatives with ovarian cancer and their age at diagnosis.

Some of the genes implicated in causation of ovarian cancers are P53, BRCA-1, and BRCA-2.

Hereditary syndromes associated with ovarian cancers are Lynch-II syndrome, hereditary site specific ovarian cancer syndrome and sweyer syndrome is associated with dysgerminoma.

Environmental factors:

Consumption of coffee and tobacco has an association with etiology of ovarian cancers. Obesity is an also important factor.

Reproductive factors:

Multiparous women are at increased risk than parous women. First pregnancy at an early age offers protection against ovarian cancers. Breast feeding offers protection against ovarian cancer.

Infertility is an independent risk factor for ovarian cancer.

Oral contraceptive pills use offers protection.

Clinical presentation:

Ovarian tumours are known to present with variable clinical features, these range from patient being absolutely asymptomatic, accidental detection during

laporotomy for other reasons, caesarian section to patient presenting as acute abdomen due to torsion or rupture.

The commonest symptoms are those due to asymptomatic slow growing abdominal or pelvic mass, with or without pain and tenderness. Nowadays, most cases are detected on USG done for other reasons.

Epidemiology:

Early knowledge of the ovary and the gradual evolution of use of the word 'ovary' refering to the female gonad have been reviewed by Gruhn[8].

Worldwide, ovarian cancer is the sixth most common cancer in women and the seventh most common cause of cancer death. There are about 2 lakh and four thousand new cases and 1 lakh and 25 thousand deaths were reported annually [3].

Ovarian carcinoma is the fifth most common malignancy in most western countries and fourth common cause of cancer mortality.

In the Western hemisphere, it accounts for 4% of cancer in women and is the most frequent cause of death due to gynecological cancers.

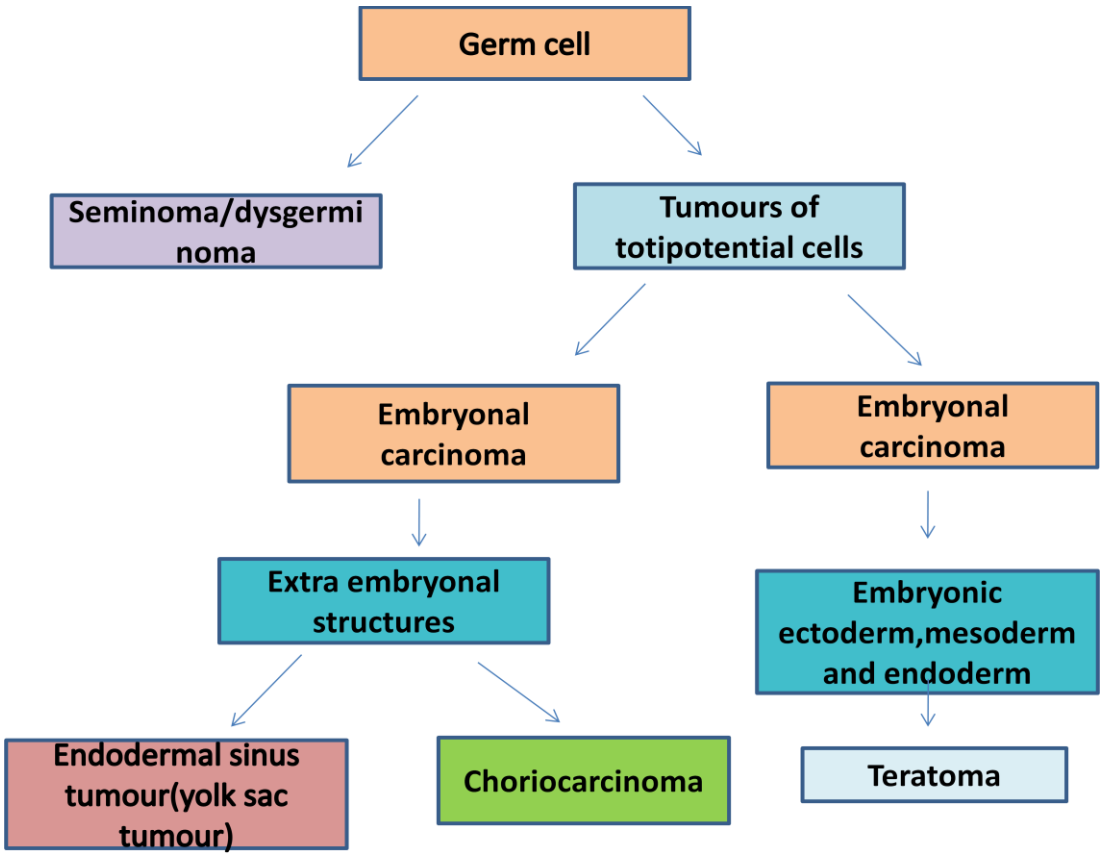
In general, the disease is more common in industrialized nations where parity is lower, but there are notable exceptions such as Japan which has a low

parity and low rate of ovarian cancer. The incidence varies widely among different ethnic groups. The lifetime risk varies widely from 0.45% in Japan to 1.7% in Sweden.

Germ cell tumours constitute the second largest group of ovarian neoplasms, comprises 20% of all ovarian neoplasms.

It's only after studies by Teilum [9,10] on the homology of ovarian and testicular neoplasms and studies by Friedman, Moore [11]and Dixon[12], Moore[13] on testicular tumors, and those by Friedman [14] on related extragonadal neoplasms group of neoplasm belonging to germ cell origin was proposed. These views were also supported by the embryologic studies of Witschi [5]and Gillman [15], and later by experimental studies of Stevens [16-18] and Pierce et al[19,20.] on germ cell tumors in rodents.

TEILUM'S HYPOTHESIS



Robert Meyer coined the term 'disgerminoma' (soon changed it as dysgerminoma) Schiller made important contributions, writing his earliest papers on dysgerminoma in 1934 [21]. He also pointed about the granulomatous infiltrate of dysgerminoma, which had previously been mistaken as representing tuberculosis, was unrelated to that infectious disease.

Ovarian surface epithelial neoplasms are common followed by germ cell neoplasms.

WHO classification of ovarian tumours is given in Annexure II.

Germ cell tumours are encountered at all ages from infancy to old age, but are seen most frequently from first to 6^{th} decades of life.

In children and adolescents, more than 60% of ovarian neoplasms are of germ cell origin and one third are malignant.

DYSGERMINOMA:

The term dysgerminoma was first introduced by Meyer in 1931.

In view of strong resemblance to their testicular counterpart seminoma, Masson called it as ovarian seminoma[22].

HISTOGENESIS:

Dysgerminoma is a tumour composed almost entirely of cell population that resembles primordial germ cells[23]. These cells are believed to be arrested at developmental stage at which they have not yet gained the ability for further differentiation. The amount of DNA in the nuclei of dysgerminoma cells is twice that of lymphocyte nuclei in all the cases studied.

In most cases studied, dysgerminoma is not associated with endocrine symptoms.

PREVALENCE:

Dysgerminoma accounts for 1-2% of primary ovarian malignant tumours[24,25]. Until 1950, only 427 cases recorded in literature.

Dysgerminoma is the most common germ cell malignancy occurring in pure form.

CLINICAL FEATURES:

Dysgerminoma is reported from ages of 7months to 70yrs[24]. Common in second and third decades of life.50% of patients are under 20 years of age, 80% of

patients are under 30 yrs of age[24,26,27,28]. Duration of symptoms is short, presenting symptoms are lower abdominal mass and abdominal pain.

Dysgerminoma is one of the common ovarian neoplasm observed during pregnancy, the others are benign serous cystadenoma and benign cystic teratoma.

GROSS:

Dysgerminoma is usually unilateral. It is more common in right side of the ovary (approximately 50% of cases)[24].

They are usually solid in nature with a lobulated contour with a smooth grey white slightly glistening fibrous capsule, red brown or yellow discoloration caused by haemorrage or necrosis is also seen. Cystic areas are very rare in pure dysgerminomas.

MICROSCOPY:

Histologically identical to classical seminoma of testis. It consists of islands, strands or aggregates of large uniform cells, surrounded by connective tissue stroma rich in lymphocytes.Cells are round to oval with vesicular nucleus, sharp nuclear membrane, two prominent eosinophilic nucleoli, abundant granular eosinophilic or clear cytoplasm. Mitotic activity is almost always present.

Cytoplasm contains glycogen demonstrated by PAS. They may show positive alkaline phosphatase reaction beneath the cytoplasmic rim.

The stroma that surrounds the tumour cells is almost always infiltrated by lymphocytes. Occasionally lymphoid follicles with germinal centres may be seen. Rarely a granulomatous reaction can also be observed.

CLINICAL BEHAVIOUR:

Dysgerminoma is a malignant neoplasm capable of both metastatic and local spread. Tumours are highly sensitive to radiotherapy. Dysgerminoma similar to seminoma, associated with elevated levels of LDH.

Placental alkaline phosphatase produces membranous staining of dysgerminoma, can be used to diagnose dysgerminoma immunohistochemically.

Patients with pure dysgerminoma carry very favourable prognosis.

5yr survival rate of patients with unilateral encapsulated dysgerminoma is 90%.

TREATMENT:

Dysgerminoma like its counterpart in testis, seminoma is highly sensitive to radiotherapy. It responds well to combination chemotherapy of bleomycin, etoposide and cisplatin.

Patients with bilateral or disseminated dysgerminoma and patients with unilateral encapsulated tumours no longer desirous of having children were treated by hysterectomy and bilateral salphingo oopherectomy followed by radiation to abdominal and to mediastinal lymph nodes.

Nowadays, such patients are treated with three to four cycles of combination chemotherapy with good results.

YOLK SAC TUMOUR:

Yolk sac tumour is a malignant germ cell neoplasm, thought to arise from undifferentiated and multipotential embryonal carcinoma by selective differentiation towards yolk sac or vitelline structures[29,30,31].

AFP is elevated grossly in yolk sac tumours.AFP has been identified in cells of yolk sac tumour, embryonal carcinoma and eosinophilic PAS positive, diastase resistance globules.

PREVALENCE:

Second most common malignant ovarian germ cell neoplasm[32] after dysgerminoma. Most frequent in second and third decades.

CLINICAL FEATURES:

Most patients present with abdominal enlargement pain, lower, abdominal or pelvic mass. They are not associated with endocrine symptoms.

GROSS:

They tend to be large with an average size of 16cm.Cut surface is tan white or gray with small cysts and areas of haemorrhage and necrosis.

HISTOPATHOLOGY:

Two most common pattern.

- Reticular or microcystic pattern
- Endodermal sinus pattern[34].

Endodermal sinuses or perivascular formations (also known as Schiller–Duval bodies) are hallmark of this tumor. These structures are also known as sinuses of Duval, Schiller–Duval bodies, or glomerulus-like structures and

resemble superficially the structure of immature renal glomeruli. When sectioned longitudinally, the perivascular structures consist of a central connective tissue core containing a longitudinal vessel surrounded by epithelial-like cells that often form small papillary formations that projects into the surrounding capsular sinusoid space.

Reticular pattern consists of loose meshwork of microcystic spaces lined by single layer of flattened or cuboidal cells. Cells have clear or amphophilic cytoplasm and atypical hyperchromatic nucleus.

Other patterns:

Alveolar glandular pattern.

Solid pattern

Hepatoid pattern

Glandular pattern-with zone of endometrioid glands or glands of intestinal type.

Eosinophilic PAS positive, diastase resistant hyaline globules are characteristic finding in yolk sac tumours, most often found in reticular and

endodermal sinus patterns. They are composed of laminin and collagen IV that resembles basement membrane ultrastucturally[35,36].

IHC:

Most important immunohistochemical finding in yolk sac tumour is positive staining for AFP, α1 antitrypsin[37] and PLAP. Extra cellular hyaline material is laminin positive[36].

Yolk sac tumour is cytokeratin positive but epithelial membrane antigen negative.

EMBRYONAL CARCINOMA:

It occurs almost exclusively in children and young women[35,36]. The typical presentation is with pelvic or abdominal pain or palpable abdominal mass. Most patients have positive pregnancy test, or an elevated serum β HCG concentration, 50% of patients have precocious pseudopuberty[38].Embryonal carcinoma is virtually never bilateral, unilateral salphingo oopherectomy is the appropriate treatment.

Before effective combination chemotherapy was available, embryonal carcinoma was often rapidly fatal. At present patients with completely resected

embryonal carcinoma are treated with post-operative cisplatin based adjuvant chemotherapy with nearly complete success.

GROSS:

Embryonal carcinoma is a large solid neoplasm with an average diameter of 15-17cm.The cut surface is fleshy and tan or gray with small cysts and areas of haemorrhage and necrosis.

HISTOPATHOLOGY:

Tumour cells have large vesicular nuclei with coarse chromatin and one or two prominent nucleoli. The cytoplasm is abundant and amphophilic or clear. The tumour cells grow in nests, sheets, punctuated by occasional clefts, glands or papillae. Stroma is loose and edematous.

IHC:

Immunostains for CK and CD30 are positive with a membranous pattern of staining.

It shows nuclear staining for OCT4 but staining for CD117 and EMA are negative.

POLYEMBRYOMA:

Rare form of malignant germ cell tumour with features intermediate between embryonal carcinoma and more differentiated forms of malignant germ cell tumours[39,40].

Microscopically is composed of numerous embryoid bodies growing in a primitive embryonal stroma. Embryoid bodies resembles 14-20wks embryo. They contain an embryonal disc composed of tall columnar cells with hyperchromatic nuclei, on one side of disc is an amniotic cavity and on other side yolk sac lined by α fetoprotein positive cells.

CHORIOCARCINOMA:

Pure primary ovarian choriocarcinoma of germ cell origin is extremely rare.

CLINICAL FEATURES:

Choriocarcinoma of ovary occurs in children and young women[41].The clinical presentation is abdominal pain and abnormal vaginal bleeding.

Pregnancy test is positive and serum β HCG is elevated[42].

Choriocarcinoma of ovary is unilateral and is treated by salphingo oopherectomy. Surgery is followed by combination chemotherapy with platinum based regimen. Chemotherapy and prognosis differ in gestational choriocarcinoma .There are no morphological differences between gestational choriocarcinoma and choriocarcinoma of germ cell origin.

GROSS:

Choriocarcinoma is unilateral soft, purple red tumour with a haemorrhagic and necrotic cut surface.

HISTOLOGY:

Much of the tumour is haemorrhagic and necrotic. Cytotrophoblastic and syncytiotrophoblastic giant cells grow in a plexiform pattern. Cytotrophoblastic cells have abundant clear cytoplasm and well defined cell borders. Nuclei are irregular and vesicular and some contain macronucleoli. Syncytiotrophoblastic giant cells have abundant vacuolated basophilic or amphophilic cytoplasm in which there are multiple hyperchromatic nuclei.

IHC:

All trophoblastic cells are cytokeratin positive with dense staining of cytoplasm of syncytiotrophoblastic giant cells. Immunostains for β HCG mark the cytoplasm of syncytiotrophoblastic giant cells[42].

TERATOMA:

BENIGN CYSTIC TERATOMA:

Benign Cystic Teratoma is the most common ovarian neoplasm, comprising 25% or more of all ovarian tumours.

They are cystic or merely solid tumours that contain various mature tissues derived from one or more of the embryonic germ layers, ectoderm, mesoderm and endoderm.

CLINICAL FEATURES:

Peak incidence is between 20 and 29yrs.Symptoms such as pelvic pressure or pain appear when tumour attains larger size. The most common serious complications are torsion, found in 3-10% of cases. Cystectomy performed laporoscopically or at laporotomy is adequate treatment.

GROSS:

They are nearly always cystic tumours average diameter 7-8cm on cross section, there is unilocular or multilocular cyst with solid protuberance called dermoid papilla in the wall. The cyst contains hair, grumous material or oily or serous liquid. Cartilage, bone or teeth may be found.

HISTOLOGY:

Benign teratomas contain a varied mixture of ectodermal, mesodermal and endodermal structures distributed in an organised fashion. Ectodermal derivatives such as skin, hair follicle and sebaceous and sweat glands are most common, when they dominate, tumour is refered to as dermoid cyst.

IMMATURE TERATOMA:

Immature Teratoma is one of the most common malignant germ cell tumours of ovary.

CLINICAL FEATURES:

It occurs predominantly in children and young women. Patients present with pelvic or abdominal pain, mass. Serum α-fetoprotein level can be elevated in patients with pure immature teratoma, often modest elevation of tumour markers

CA125[43-46]. Bilaterality is exceptional. Spreads mainly by implantation on pelvic and abdominal peritoneum in the omentum.

Patients with localized stage1A tumours are treated by unilateral salphingo-oopherectomy, a few patients have been treated by cystectomy followed by chemotherapy. Cisplatin containing regimens such as BEP are highly effective forms of adjuvant chemotherapy for patients with no residual tumour after, surgery with survival rates of 90-100 percent.

GROSS:

Immature teratoma is predominantly solid unilateral tumour that averages 18cm in diameter. Solid component are gray or brown and can be soft or hard and gritty, scattered small cysts are typically seen on the cut surface.

HISTOPATHOLOGY:

Tissues derived from all three germ cell layers are present and a mixture of mature and immature elements is found in most tumours. Ectodermal and mesodermal derivatives typically predominate among immature elements.

STRUMA OVARII:

Struma ovarii is a teratoma in which thyroid tissue predominates. More than 50% of thyroid tissue[47] should be present to call it as struma ovarii.

CLINICAL FEATURES:

Occurs mainly in women older than 40 yrs, only 10% of patients present with hyperthyroidism.

GROSS:

Struma ovarii is red, green or tan with a glairy meaty appearance.

MICROSCOPY:

It is composed of follicles lined filled with eosinophilic colloid and lined by cuboidal or columnar cells with uniform round nuclei.

IHC:

Immunostains for thyroglobulin positive in colloid and follicular cells are positive for TTF-1.

TREATMENT:

Cystectomy is adequate treatment.

MALIGNANT MIXED GERM CELL TUMOUR:

They contain a mixture of various types of pure germ cell tumours. They constitute 5-20% of all malignant germ cell tumours.

CLINICAL FEATURES:

They occur in children and young women. Average age group is 16 yrs. They present with abdominal pain or palpable abdominal mass.

About one third of patients present with precocious puberty.

50% of patients present with positive pregnancy test.

GROSS:

They tend to be large averages about 15cm in diameter. Dysgerminoma is fleshy and gray, tan or white, yolk sac tumour varies in colour contains small cysts and often have areas of necrosis.

MICROSCOPY:

There are two elements in 80% of germ cell tumours. Dysgerminoma is the most frequent element followed by yolk sac tumour and immature teratoma.Embryonal carcinoma, choriocarcinoma and polyembryoma are less common.

TREATMENT:

Encapsulated unilateral tumours (stageIA) are best treated by salphingo oopherectomy. More advanced cases are treated by abdominal hysterectomy, B/L salphingo oopherectomy. Chemotherapy is administered to most patients except stage I.

C-KIT:

The proto-oncogene c-kit encodes for a 145–160 kDa, type III transmembrane tyrosine kinase receptor known as c-kit or CD117[48,49,] which belongs to the same family of receptors as platelet-derived growth factor(PDGFR) and colony-stimulating factor-1(CSF-1).[50.]

The binding of stem cell factor, the ligand for this receptor, leads to the dimerization of c-kit proteins, thus initiating a signaling cascade that ultimately

induces cell growth. Expression of c-kit is essential in the development of some cell types, including germ cells, melanocytes, mast cells, erythrocytes, and interstitial cells of Cajal[48,51-53].

In addition, expression of this receptor may be seen in other histologically normal cell types, such as breast epithelial cells, astrocytes, renal tubule cells, purkinje cells, parotid acini, and endometrial cells[53-55.]

Aberrant expression of this C-kit has also been implicated in the development of a number of human cancers, including malignancies of the lung, breast, skin, uterus, endometrium, urinary bladder, and ovary, as well as in certain types of leukemia, gastrointestinal stromal tumors (GISTs), ewing's sarcoma and germ cell tumors[55–75]. The advent of therapies targeted to c-kit have proven highly effective in treating some of the cancers that over express this receptor, such as CML and GISTs.[76-79]

M Sever et al[80] studied the c-kit expression in 30 cases of dysgerminoma. Immunohistohemical staining done with a polyclonal anti-CD117 antibody. Staining was graded in a semiquantitative manner as follows:

no staining	-	NEGATIVE
1-10% staining	-	1+

10-29% staining - 2+

30-50% staining - 3+

> 50% staining - 4+

In his studies 26 (87%) showed immunoreactivity for CD117. In total, 33% of cases (26) demonstrated 4+ staining, 30% of cases(9) demonstrated 3+ staining,10% of cases (3) demonstrated 2+ staining; 13% of cases(4) demonstrated 1+ staining; and 13% of cases (4) demonstrated no staining. In conclusion, CD117 positivity was detected in 87% of ovarian dysgerminomas, a finding that is correlating with previously reported frequencies of CD117 expression in seminomas about 78–100%. Thus, antibodies to c-kit may be a useful diagnostic marker for ovarian dysgerminoma. Though prognosis of patients with dysgerminoma is generally good, this receptor could potentially serve as a target for site-specific immunotherapy as an alternative and or complement to conventional treatment options.

IMMUNOHISTOCHEMISTRY:

Albert Coons et al in 1941 first labeled antibodies directly with fluorescent isocyanate. Nakane and Pierce et al in 1966, introduced indirect labeling technique in which unlabeled antibody is followed by second antibody or substrate. Various stages of development of Immunohistochemistry include peroxidase –

antiperoxidase method (1970), alkaline phosphatase labeling (1971), avidin biotin method (1977) and two layer dextrin polymer technique (1993)[81].

ANTIGEN RETRIEVAL:

Antigen retrieval can be done by the following different techniques to unmask the antigenic determinants of fixed tissue sections.

1. Proteolytic enzyme digestion
2. Microwave antigen retrieval
3. Pressure cooker antigen retrieval
4. Microwave and trypsin antigen retrieval

PROTEOLYTIC ENZYME DIGESTION:

Huank et al in 1976 introduced this technique to breakdown formalin cross linkages and to unmask the antigen determinants. The most commonly used enzymes include trypsin and proteinase[82]. The disadvantages include over digestion, under digestion and antigen destruction.

MICROWAVE ANTIGEN RETRIEVAL:

This is a new technique most commonly used in current practice.

Microwave oven heating involves boiling formalin fixed paraffin sections in various buffers for rapid and uniform heating. Antibodies against CD117 work well after heat pretreatment in this method[81].

PRESSURE COOKER ANTIGEN RETRIEVAL:

Miller et al in 1995 compared and proved that pressure cooking method has fewer inconsistencies, less time consuming and can be used to retrieve large number of slides than in microwave method[83].

PITFALLS OF HEAT PRETREATMENT:

Drying of sections at any stage after heat pretreatment destroys antigenicity. Nuclear details are damaged in poorly fixed tissues. Fibers and fatty tissues tend to detach from slides while heating. Not all antigens are retrieved by heat pretreatment and also some antigens like PGP 9.5 show altered staining pattern.

DETECTION SYSTEMS:

After addition of specific antibodies to the antigens, next step is to visualize the antigen antibody reaction complex. The methods employed are direct and indirect methods.

In the direct method, primary antibody is directly conjugated with the label. Most commonly used labels are flouro-chrome, horse radish peroxidase and alkaline phosphatase. Indirect method is a two-step method in which labeled secondary antibody reacts with primary antibody bound to specific antigen. The use of peroxidase enzyme complex or avidin biotin complex further increases the sensitivity of immunohistochemical stains[81].

In 1993, Pluzek et al introduced enhanced polymer one step staining, in which large numbers of primary antibody and peroxidase enzymes are attached to dextran polymer back bone. This is the rapid and sensitive method[84].

Dextran polymer conjugate two step visualization system is based on dextran technology in Epos system. This method has greater sensitivity and is less time consuming.

MATERIALS AND METHODS

This study is a retrospective descriptive study of germ cell tumours of ovary conducted in the Institute of obstetrics and gynaecology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during the period between January 2007 and October 2012. A total of 725 ovarian neoplasms were received over the study period, out of which 487 cases were benign, 34 cases were border line and 204 cases were malignant.

SOURCE OF DATA:

All cases of ovarian neoplasm received in Institute of Obstetrics and Gynaecology, Madras Medical College and Rajiv Gandhi Government General Hospital were studied.

INCLUSION CRITERIA:

All malignant germ cell tumours of ovary.

EXCLUSION CRITERIA:

- Benign germ cell tumours of ovary.
- Surface epithelial , sex cord stromal and metastatic tumours.

METHOD OF DATA COLLECTION:

The detailed history of cases including age, presenting complaints, duration of complaints, USG and CT findings, any hormonal elevation (AFP, β-HCG, LDH), were taken.

In macroscopy, the appearance of external surface and cut surface of the tumours are studied.

In microscopy, type of tumour, if mixed germ cell tumour, components of MGCT, omental infiltration by tumour, malignant cells in ascitic fluid, and peritoneal washings, all were studied.

The follow up data of these patients including the details of months of follow up, number of chemotherapy cycles given and outcome of the patient are studied.

The proforma for obtaining clinical details from the patient is given in Annexure I.

Representative formalin fixed paraffin embedded tissue samples of all the 30 cases of were subjected to immunohistochemistry (CD117).

IMMUNOHISTOCHEMICAL EVALUATION:

Immuohistochemical analysis of a panel of marker CD117 were done in paraffin embedded tissue samples using Super-sensitive30 polymer HRP system based on non-biotin polymeric technology. 4 μ thick sections from formalin fixed paraffin embedded tissue samples were transferred on to gelatin coated slides. Heat induced antigen retrieval was done. The antigen was bound with mouse monoclonal antibody (Biogenex) against CD117 protein and then detected by the addition of secondary antibody conjugated with horse radish peroxidase-polymer and diaminobenzidine substrate. The step by step procedure of Immunohistochemistry is given in Annexure IV.

INTERPRETATION AND SCORING SYSTEM:

Immunohistohemical staining with a anti-CD117 antibody was done tumours show a peri membranous positivity of CD117.

Staining was graded in a semiquantitative manner as follows:

no staining	-	NEGATIVE
1-10% staining	-	1+
10-29% staining	-	2+
30-50% staining	-	3+
> 50% staining	-	4+

STASTISTICAL PACKAGE:

The statistical analysis was performed using statistical package for social science software version 11.5 which consisted computing the frequency counts and percentages for qualitative variables and mean for the quantitative variables. The expression of CD 117 is correlated with different histological subtypes of germ cell tumours, stage of the disease, USG findings and also with outcome of the disease using pearson chi square test.

The various clinical parameters like gross, USG findings, HPE subtypes, type of surgical procedure ,chemotherapy given are also correlated with outcome of the disease.

OBERVATION AND RESULTS

* In our institute, a total of 725 ovarian neoplasms were received. Out of which 487 cases were benign, 34 cases were borderline and 204 cases were malignant (TABLE 1 and CHART 1).

TABLE – 1

DISTRIBUTION OF BENIGN, BORDERLINE AND MALIGNANT CASES

Tumour type	No of cases	Percentage
Benign	487	67.13%
Borderline	34	4.7%
Malignant	204	28%

* Out of 725 cases surface epithelial tumours (75.5%) were common followed by germ cell tumours (16.5%) followed next by sex cord stromal tumours (7.2%) and finally metastatic tumours which account for 0.8% (TABLE 2 and CHART 2).

TABLE – 2

DISTRIBUTION OF OVARIAN TUMOURS ACCORDING TO HISTOLOGICAL TYPE

TUMOUR TYPE	NO OF CASES	PERCENTAGE
Surface epithelial tumours	547	75.5%
Germ cell tumours	120	16.5%
Sex cord stromal tumours	52	7.2%
secondaries	6	0.8%
TOTAL	725	100%

* In surface epithelial tumours, commonest is benign serous cystadenoma. In germ cell tumours benign cystic teratoma is common.
* In malignant tumours, papillary serous cystadenocarcinoma was very common (90cases). 6 cases of clear cell carcinoma has been reported.
* In 120 germ cell tumours, 88 were benign cystic teratoma, 2 cases were struma ovarii and 30 were malignant germ cell tumours (TABLE 3 and CHART 3).

TABLE - 3

SUBCLASSIFICATION OF GERM CELL TUMOURS BASED ON HISTOLOGICAL TYPE

Tumour type	No of cases	Percentage.
Mature cystic teratoma	88	73.33%
Struma ovarii	2	1.67%
Malignant germ cell tumours	30	25%
TOTAL	120	100%

* In malignant germ cell tumours, dysgerminoma is very common accounting for 11 cases out of 30 malignant germ cell tumours, followed by mixed germ cell tumours which constitute about 10.

* In sex cord stromal tumours, granulosa cell tumours were common which constituted 27 cases out of which 5 cases were malignant. Rare cases like steroid cell tumour (2), sclerosing stromal tumour (1) has also been reported.

* In the malignant germ cell tumours, 11 were dysgerminoma, 10 were mixed germ cell tumour, 4 were yolk sac tumour and 5 were immature teratoma.

TABLE – 4

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS

ACCORDING TO TUMOUR TYPE

TYPE	NUMBER	PERCENTAGE
DYSGERMINOMA	11	36.66%
YOLK SAC TUMOUR	4	13.34%
IMMATURE TERATOMA	5	16.66%
MIXED GCT	10	33.34%
TOTAL	30	100%

* Dysgerminoma is the most common germ cell tumour in the current study, which constitutes about 11 cases followed by mixed germ cell tumours which constitute about 10 cases (TABLE 4 and CHART 4).

TABLE – 5

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS

ACCORDING TO AGE GROUP

AGE	NUMBER	PERCENTAGE
11-15	3	10%
16-20	12	40%
21-25	6	20%
26-30	6	20%
31-35	1	3.34%
36-40	2	6.66%
TOTAL	30	100%

* Our patients age range from 13 to 40 yrs, with mean age of occurrence is 22.4 yrs.

* The maximum number of patients present in second decade (50%) followed by third decade (40%) (TABLE 5 and CHART 5).

TABLE - 6

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS

ACCORDING TO LATERALITY OF TUMOURS

SIDE	NUMBER	PERCENTAGE
RIGHT	18	60%
LEFT	11	36.66%
BILATERAL	1	3.34%

* In 30 cases studied 18 cases are right sided, 11 cases are left sided and 1 case is bilateral (TABLE 6 and CHART 6).

TABLE - 7

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS

ACCORDING TO SIZE OF THE TUMOURS

SIZE	NUMBER	PERCENTAGE
5-10 cm	5	16.66%
11-15cm	13	43.34%
16-20cm	4	13.34%
21-25cm	6	20%
26-30cm	2	6.66%
TOTAL	30	100%

* The maximum diameter of tumour is taken in to account and the average is calculated. The largest diameter is about 30cm and smallest is about 8cm.

* The average size of tumours is about 15.7 cm. Most of the tumours fall within a range of 5-15cm (about 60%) (TABLE 7 and CHART 7).

TABLE – 8

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO GROSS FINDINGS

GROSS FINDINGS	NUMBER	PERCENTAGE
SOLID	8	26.7%
CYSTIC	2	6.7%
MIXED	20	66.6%
TOTAL	30	100%

* In macroscopy, purely solid tumours were 8, purely cystic tumours were 2 and mixed solid and cystic tumours were 20 (TABLE8).

* From our observation dysgerminoma presents as purely solid lesions and mixed germ cell tumours presents as variegated appearance. One of the case of dysgerminoma presented with cystic change which is give in (Fig.11)

TABLE – 9

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO USG FINDINGS

USG FINDINGS	NO OF CASES	PERCENTAGE
Solid	8	26.7%
Cystic	2	6.7%
Mixed echoes	20	66.6%

* In ultra sound findings, out of the 30 germ cell tumours, 8 cases showed solid lesions, 2 cases showed purely cystic shadows and 20 cases were mixed lesions (TABLE 9 and CHART 8).

TABLE – 10

DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO STAGE

STAGE	NO OF CASES	PERCENTAGE
I	11	36.7%
II	2	6.7%
III	17	66.6%
IV	0	0%
TOTAL	30	100%

* FIGO staging system is followed, which is given in Annexure III.

* In current study, stage III disease is more common constitutes about 17 cases followed by stage I which is about 11 cases and stage II constitutes about 2 cases (TABLE10 and CHART 9).

TABLE - 11

PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT MALIGNANT GERM CELL TUMOURS

Tumour type	No of cases	Cases showing c-kit positivity	Percentage
Dysgerminoma	11	10	90.9%
Yolk sac tumour	4	2	50%
Immature teratoma	5	1	20%
Mixed germ cell tumour	10	7	70%
TOTAL	30	20	

* The percentage of positivity in histological subtypes of germ cell tumours were compared.C –kit positivity is more in cases of pure dysgerminoma compared to other tumours (TABLE 11 and CHART 10)

TABLE – 12

PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT STAGES OF MALIGNANT GERM CELL TUMOURS

STAGE	NO OF CASES	C-KIT POSITIVITY	PERCENTAGE
I	11	8	72.7%
II	2	1	50%
III	17	11	64.7%
IV	0	0	0
TOTAL	30	20	66.6%

* In current study positivity rate more in stage I tumours (72.7%) followed by stage III (64.7%) (TABLE 12 and CHART 11).

TABLE – 13

COMPARISION OF C-KIT POSITIVITY IN MIXED GERM CELL TUMOURS WITH AND WITHOUT DYSGERMINOMA COMPONENT

TUMOUR TYPE	NO OF CASES	CASES SHOWING C-KIT POSITIVITY	PERCENTAGE
Mixed germ cell tumours with dysgerminoma	6	6	100%
Mixed germ cell tumours without dysgerminoma	4	1	25%
TOTAL	10	7	

* The percentage of c-kit positivity in mixed germ tumours with and without dysgerminoma was compared. The positivity rate is more in the group with dysgerminoma component (TABLE 13 and CHART 12).

TABLE – 14

CORRELATION OF EXPRESSION OF CD117 WITH USG FINDINGS

CD117	SOLID	CYSTIC	MIXED	TOTAL	Pearson chi square test
0	1(12.5%)	2(100%)	7(35%)	10(33.3%)	P=0.614
1	1(12.5%)	0(0%)	3(15%)	4(13.3%)	
2	1(12.5%)	0(0%)	3(15%)	4(13.3%)	
3	3(37.5%)	0(%)	4(20%)	7(23.3%)	
4	2(25%)	0(%)	3(15%)	5(16.7%)	
TOTAL	8(100%)	2(100%)	20(100%)	100%	

* CD117 expression is more common in solid tumours than cystic and lesions with mixed echoes, but the correlation is not statistically significant.

TABLE – 15

CORRELATION OF EXPRESSION OF CD117 WITH HPE DIAGNOSIS

CD117	DYSGERMI-NOMA	YOLK SAC TUMOUR	IMMATURE TERATOMA	MIXED GERM CELL TUMOUR	TOTAL	PEARSON CHI SQUARE TEST
0	1(9.0%)	2(50%)	4(80%)	3(30%)	10(33.3%)	
1	1(9.0%)	1(25%)	0(%)	2(20%)	4(13.33%)	
2	3(27.3%)	0(%)	0(%)	1(10%)	4(13.33%)	
3	3(27.3%)	1(25%)	1(20%)	2(20%)	7(23.33%)	P=0.367
4	3(27.3%)	0(%)	0(%)	2(20%)	5(16.67%)	
TOTAL	11(100%)	4(100%)	5(100%)	10(100%)	30(100%)	

* **CD117** expression is more common in dysgerminoma than other germ cell tumour subtypes, but the correlation is not statistically significant. Out of 20 cases showing positivity, 7 cases are showing 3+ positivity. Out of the 5 cases showing strong c-kit positivity (4+) 3 were dysgerminoma.

TABLE - 16

CORRELATION OF AGE WITH CD117 EXPRESSION

CD 117	AGE<20	AGE>20	TOTAL	PEARSON CHI SQUARE TEST
0	3(30%)	7(35%)	10(33.3%)	
1+	2(20%)	4(20%)	6(20%)	
2+	1(10%)	1(5%)	2(6.66%)	
3+	3(30%)	4(20%)	7(23.3%)	P=0.559
4+	1(10%)	4(20%)	5(16.7%)	
TOTAL	10(100%)	20(100%)	30(100%)	

* Patients in age group <20 yrs exhibit more CD117 (70%) positivity than patients under age >20 (65%), but the correlation is not statistically significant.

TABLE – 17

CORRELATION OF SIZE OF THE TUMOURS WITH CD117 EXPRESSION

CD 117	SIZE<20cm	SIZE>20cm	TOTAL	PEARSON CHI SQUARE TEST
0	8(36.3%)	2(25%)	10(33.3%)	P=0.631
1+	2(9.1%)	2(25%)	4(13.3%)	
2+	3(13.6%)	1(12.5%)	4(13.3%)	
3+	5(22.7%)	2(25%)	7(23.3%)	
4+	4(18.2%)	1(12.5%)	5(16.7%)	
TOTAL	22(100%)	8(100%)	30(100%)	

* Tumours with size more than 20 cm are showing more positivity (75%) than tumours with size less than 20 cm (63.6%), but the correlation is not statistically significant.

TABLE - 18

CORRELATION OF EXPRESSION OF CD117 WITH STAGE OF THE DISEASE

CD117	STAGE I	STAGE II	STAGE III	TOTAL	PEARSON CHI SQUARE TEST
0	3 (27.3%)	1 (50%)	6(35.3%)	10(33.3%)	P=0.792
1	1(9.1 %)	0(0.0%)	3(17.6%)	4 (13.3%)	
2	2(18.2%)	0(0.0 %)	2 (11.8%)	4(13.3 %)	
3	4(36.4%)	0(0.0 %)	3(17.6%)	7(23.3 %)	
4	1(9.1%)	1(50.0%)	3(17.6 %)	5(16.7%)	
TOTAL	11(100%)	2(100%)	17(100%)	30(100%)	

* Stage I tumours show more positivity than stage III tumours, but the correlation is not statistically significant.

TABLE – 19

CORRELATION OF EXPRESSION OF CD117 WITH OUTCOME OF THE DISEASE

CD 117	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
0	4(23.5%)	2(100%)	1(100%)	7(35%)	
1	2(11.8%)	0(0%)	0(0%)	2(10%)	
2	2(11.8%)	0(0%)	0(0%)	2(10%)	
3	3(35.3%)	0(0%)	0(0%)	3(30%)	P=0.585
4	6(17.6%)	0(0%)	0(0%)	6(15%)	
TOTAL	17	2	1	20	

* Out of the 30 patients of malignant germ cell tumours, follow up available for 20 patients, 9 patients defaulted and for one patient chemotherapy cycles are pending.

* The median months of follow up is 24.5, maximum being 64 months and minimum being 3 months.

* In the 20 patients followed, 17 patients were symptom free,2 patients presented with recurrent abdominal mass and 1 patient expired

* All the tumours showing CD117 positivity were symptom free. Symptoms recurred and one patient expired only in group showing negativity for CD117

TABLE - 20

CORRELATION OF GROSS FINDINGS WITH OUTCOME OF THE DISEASE

GROSS	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
Solid	7(41.2%)	0(0%)	0(0%)	7	P=0.577
Cystic	2(11.8%)	0(0%)	0(0%)	2	
Mixed	8(47.1%)	2(100%)	1(100%)	11	
TOTAL	17(100%)	2(100%)	1(100%)	20(100%)	

* All the solid and cystic tumours were free of symptoms, only mixed germ cell tumour showed recurrence of the disease, but the correlation is not statistically significant.

TABLE – 21

CORRELATION OF LATERALITY OF TUMOURS WITH OUTCOME OF THE DISEASE

SIDE	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
RIGHT	8(47.1%)	2(100%)	1(00%)	11(55.0%)	
LEFT	9(52.9%)	0(0%)	0(0%)	9(45%)	P=0.236
TOTAL	17(100%)	2(100%)	1(100%)	20(100%)	

* All left sided were free of symptoms, the disease recurrence and death occurred only in tumours of right side, but the correlation is not statistically significant.

TABLE – 22

CORRELATION OF USG FINDINGS WITH OUTCOME OF THE DISEASE

USG FINDINGS	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
Solid	5(29.4%)	0(0%)	0(0%)	5(25%)	P=0.754
Cystic	2(11.8%)	0(0%)	0(0%)	2(10%)	
Mixed	10(58.8%)	2(100%)	1(100%)	13(65%)	
TOTAL	17(100%)	2(100%)	1(100%)	20(100%)	

* The tumours which are solid and cystic in USG were asymptomatic, tumour recurrence and death occurred only in lesions showing mixed echogenicity, but the correlation is not statistically significant.

TABLE - 23

CORRELATION OF HPE DIAGNOSIS WITH OUTCOME OF THE DISEASE

HPE	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
DYSGERMINOMA	7(41.2%)	0(0%)	0(%)	7(35%)	P=0.221
YOLK SAC TUMOUR	3(17.6%)	0(0%)	0(%)	3(15%)	
IMMATURE TERATOMA	4(23.5%)	0(0%)	0(%)	4(20%)	
MIXED GERM CELL TUMOUR	3(17.6%)	2(100%)	1(100%)	6(30%)	
TOTAL	17	2	1	20(100%)	

* All dysgerminomas, yolk sac tumour and immature teratoma were free of tumour, symptoms persists in patients of mixed germ cell tumours, but the correlation is not statically significant.

TABLE – 24

CORRELATION OF STAGE WITH OUTCOME OF THE DISEASE

STAGE	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
I	7(41.2%)	1(50%)	0(0%)	8(45%)	P=0.906
II	1(5.9%)	0(0%)	0(0%)	1(5%)	
III	9(52.9%)	1(50%)	1(100%)	11(55%)	
TOTAL	17(100%)	2(100%)	1(100%)	20(100%)	

* All patients in stage I and stage II tumours are free of symptoms, only stage III tumours presents with recurrence and one patient expired. But this correlation is not statistically significant.

TABLE – 25

CORRELATION OF CHEMOTHERAPY WITH OUTCOME OF THE DISEASE

CHEMO THERAPY	SYMPTOM FREE	SYMPTOM PERSISTS	EXPIRED	TOTAL	PEARSON CHI SQUARE TEST
GIVEN	13(%)	2(100%)	1(100%)	16(%)	P=0.643
NOT GIVEN	4(%)	0(0%)	0(0%)	4(%)	
TOTAL	17(100%)	2(100%)	1(100%)	20(100%)	

* Disease recurrence and death occurred only in patients who were given chemotherapy, whereas all patients who were not given chemotherapy are symptom free but the correlation is not statistically significant.

CHART : 1- DISTRIBUTION OF BENIGN, BORDERLINE AND MALIGNANT CASES.

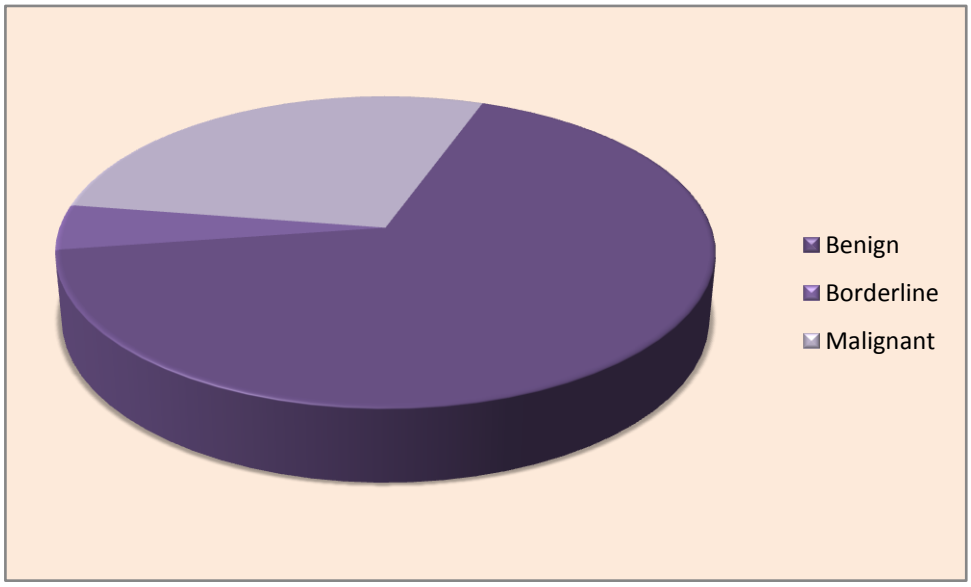


CHART : 2 - DISTRIBUTION OF OVARIAN TUMOURS ACCORDING TO HISTOLOGICAL TYPE.

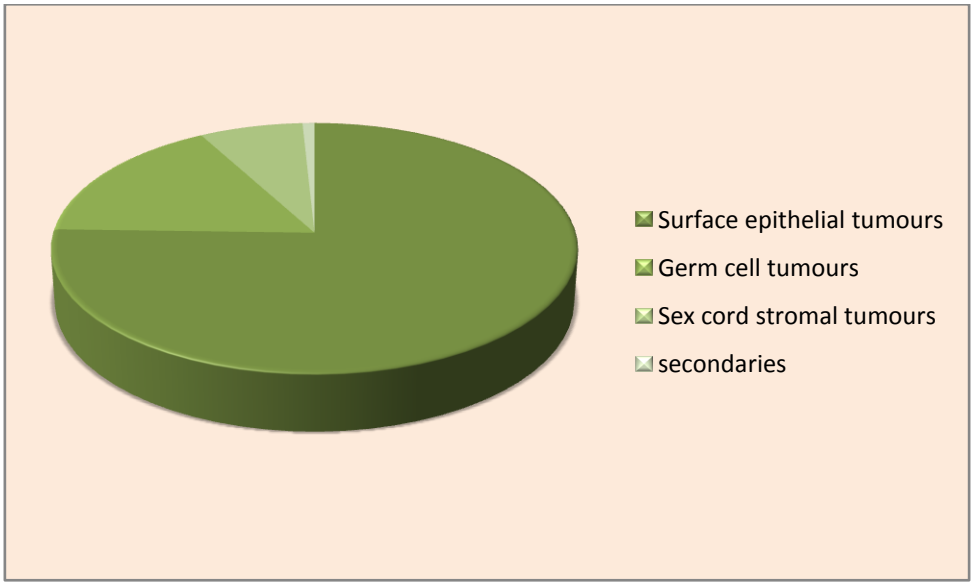


CHART : 3 - COMPARISION OF INCIDENCE OF BENIGN AND MALIGNANT GERM CELL TUMOURS.

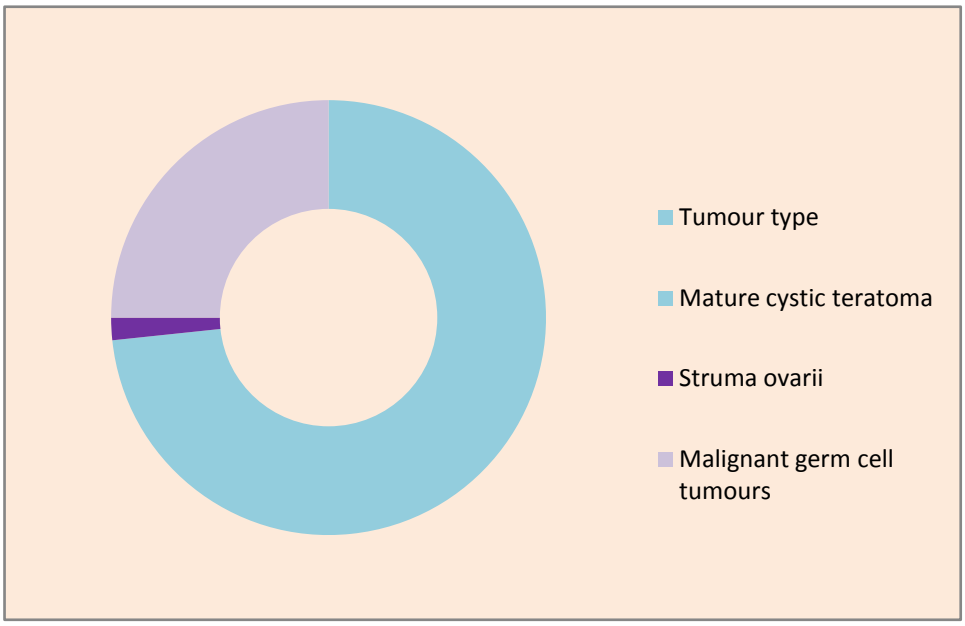


CHART : 4 - DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO TUMOUR TYPE.

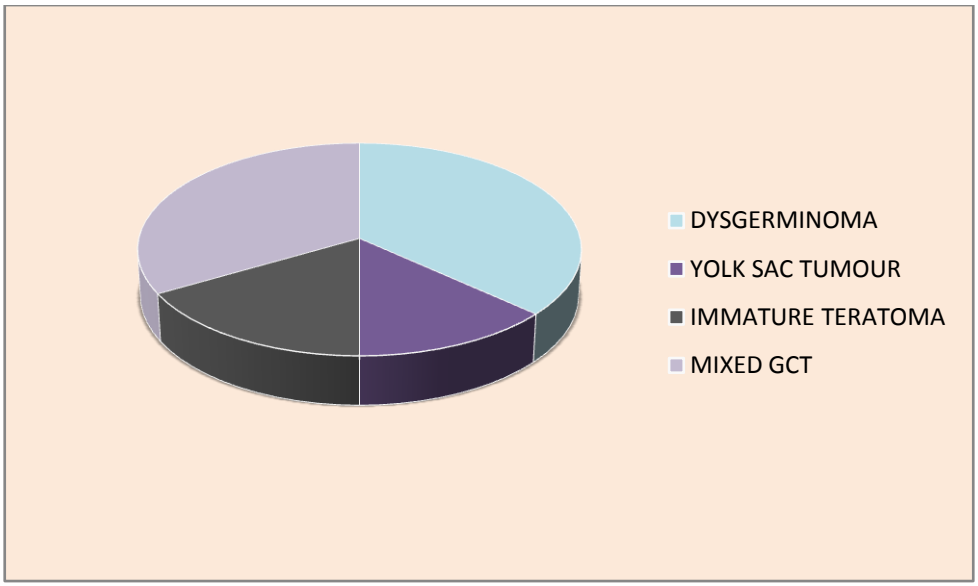


CHART : 5 - DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO AGE GROUP

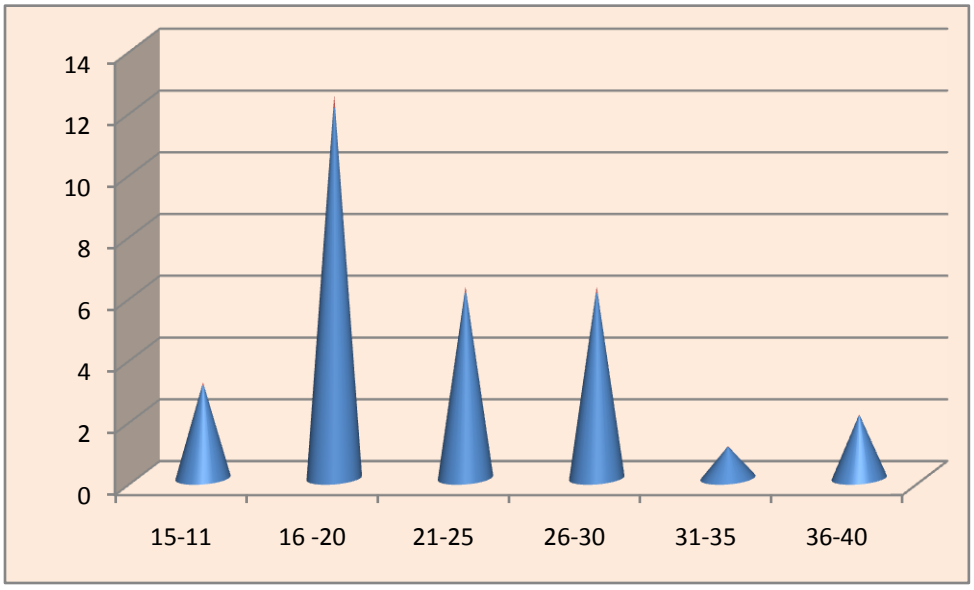


CHART : 6 - DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO LATERALITY OF TUMOURS.

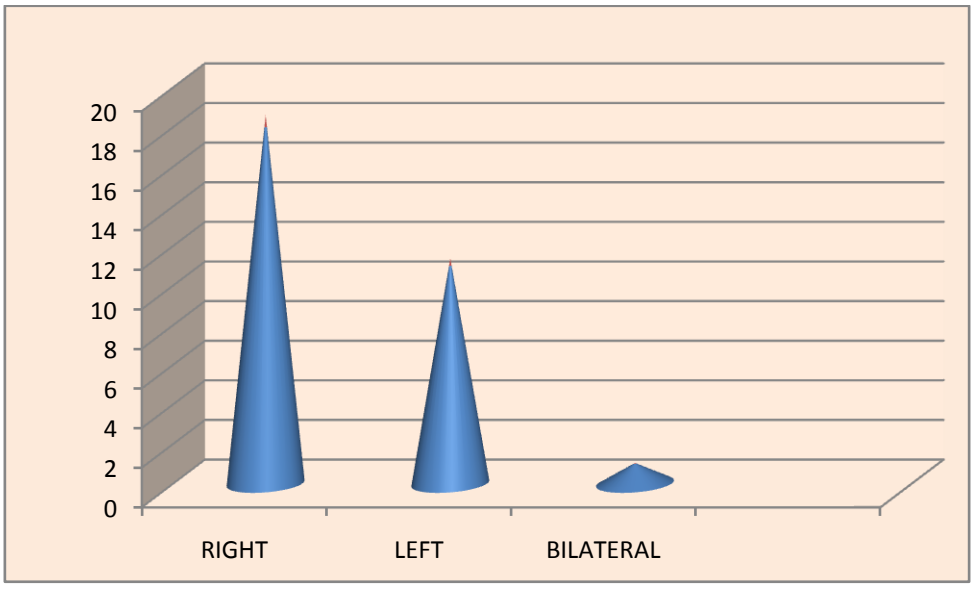


CHART : 7 - DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO SIZE OF THE TUMOURS.

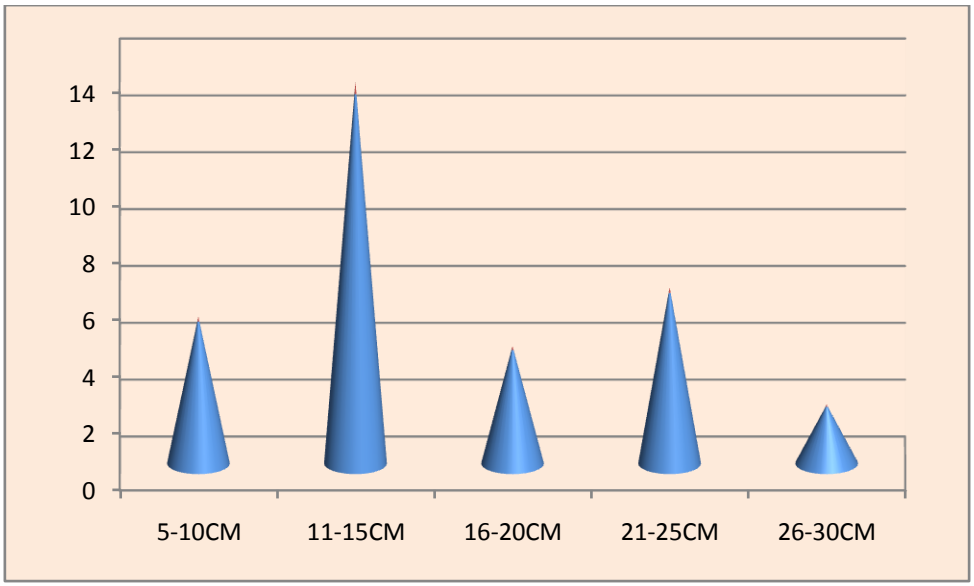


CHART : 8 - COMPARISON OF MALIGNANT GERM CELL TUMOURS BASED ON USG FINDINGS

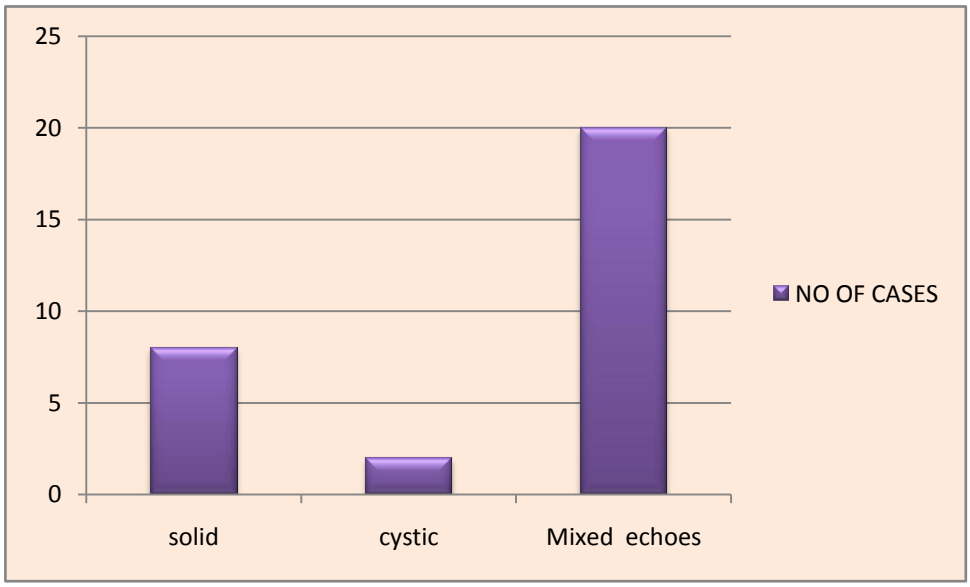


CHART: 9 - DISTRIBUTION OF MALIGNANT GERM CELL TUMOURS ACCORDING TO STAGE.

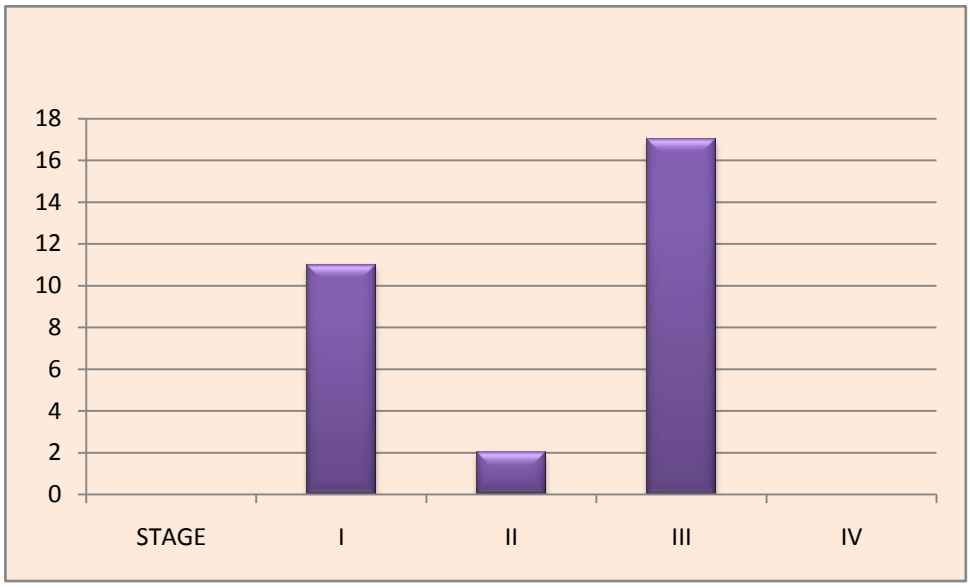


CHART : 10 - PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT MALIGNANT GERM CELL TUMOURS.

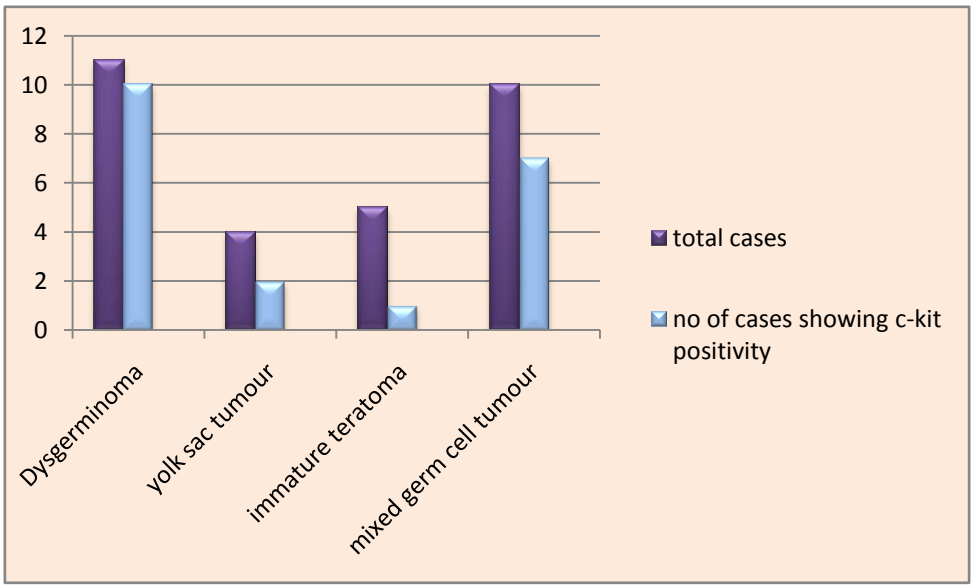


CHART: 11 - PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT STAGES OF MALIGNANT GERM CELL TUMOURS.

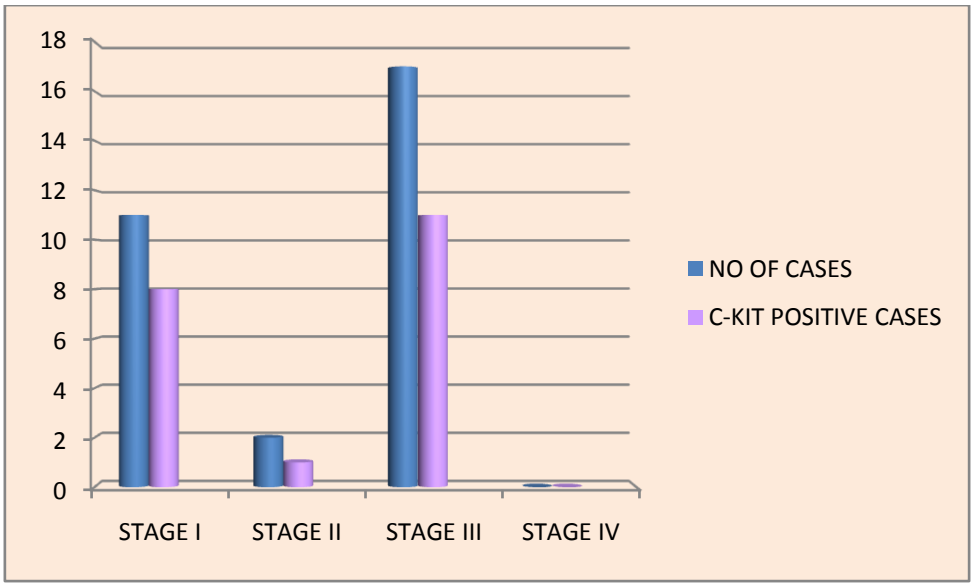


CHART : 12 COMPARISION OF C-KIT POSITIVITY IN MIXED GERM CELL TUMOURS WITH AND

WITHOUT DYSGERMINOMA COMPONENT

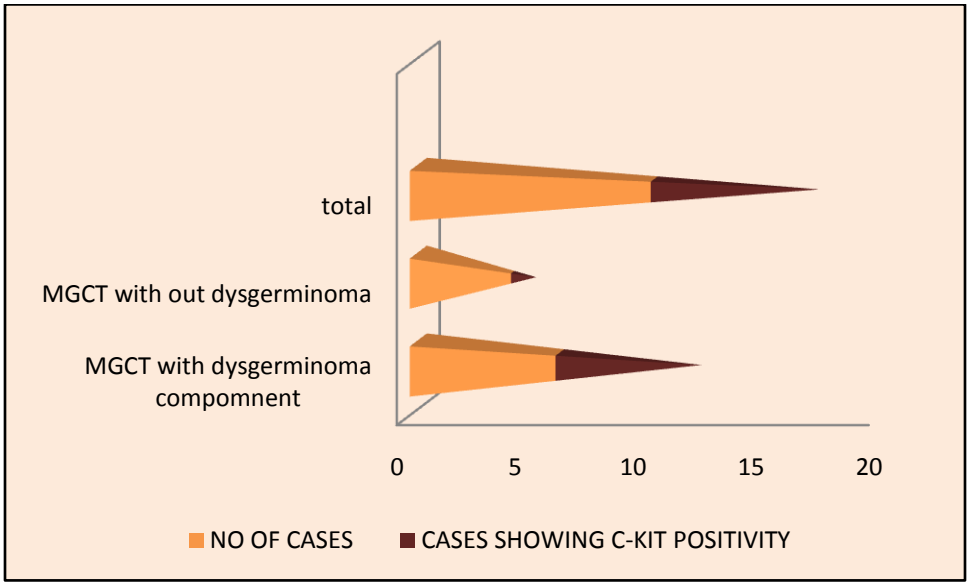


CHART: 13 - COMPARISION OF PROPORTION OF BENIGN, BORDERLINE AND MALIGNANT CASES IN DIFFERENT STUDIES.

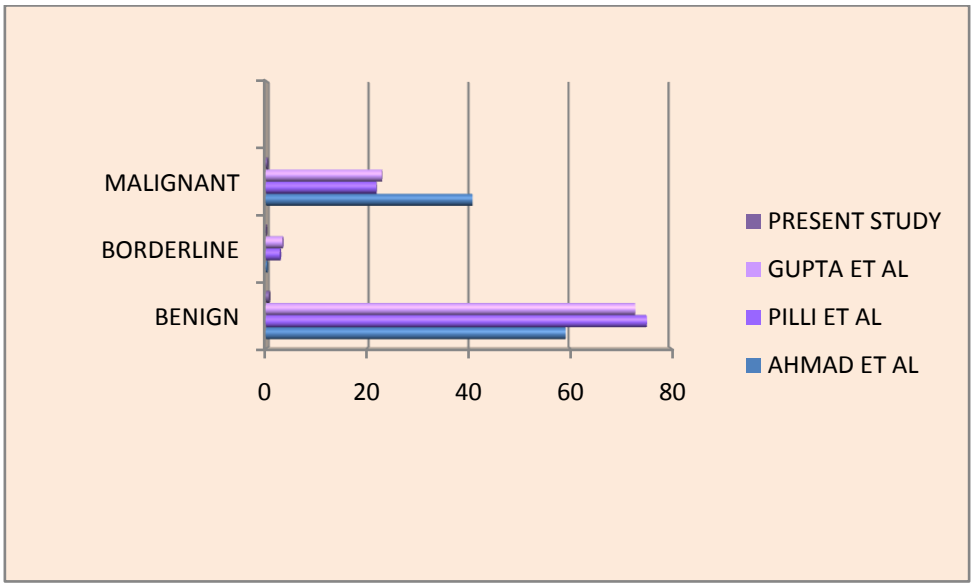


CHART: 14 - COMPARISION OF HISTOLOGICAL TYPE OF OVARIAN TUMOURS IN DIFFERENT STUDIES.

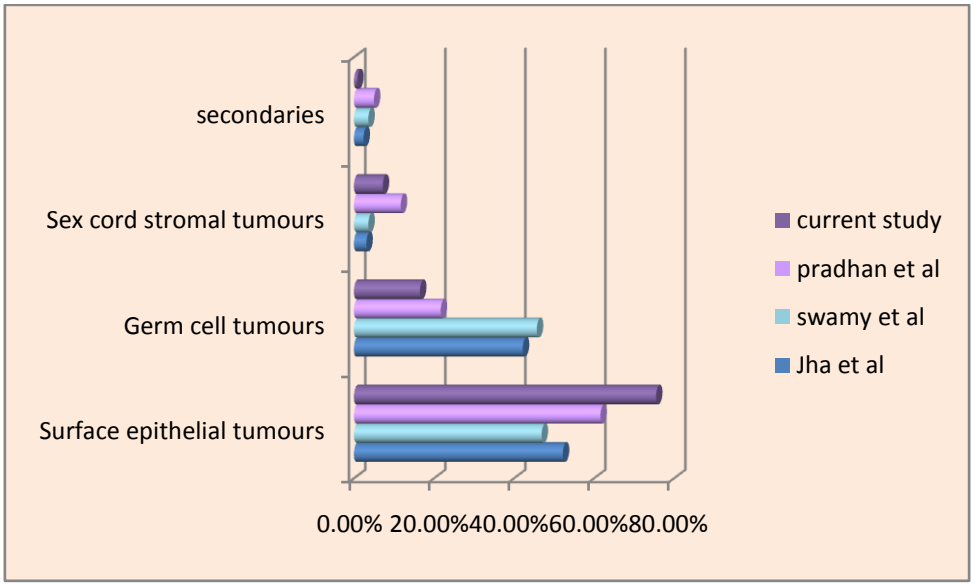


CHART: 15 - COMPARISION OF HISTOLOGICAL TYPES OF MALIGNANT GERM CELL TUMOURS IN DIFFERENT STUDIES

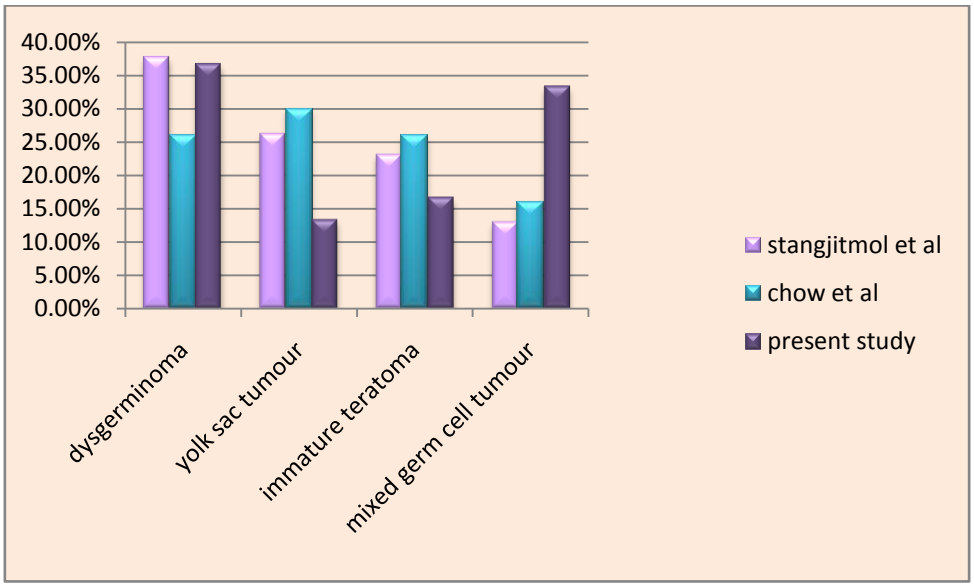


CHART: 16 - COMPARISION OF STAGE OF DISEASE IN DIFFERENT STUDIES.

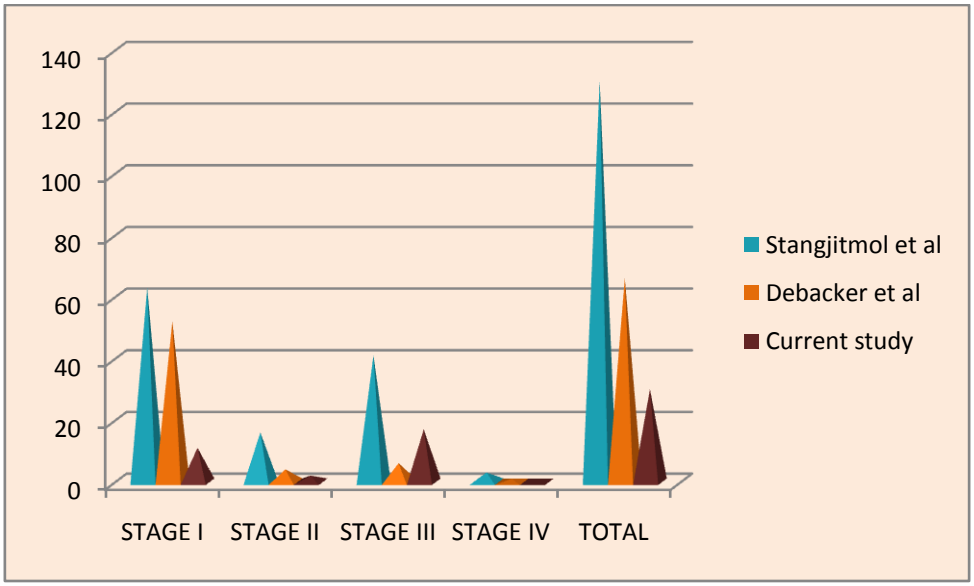


CHART: 17- COMPARISION OF LATERALITY OF GERM CELL TUMOURS.

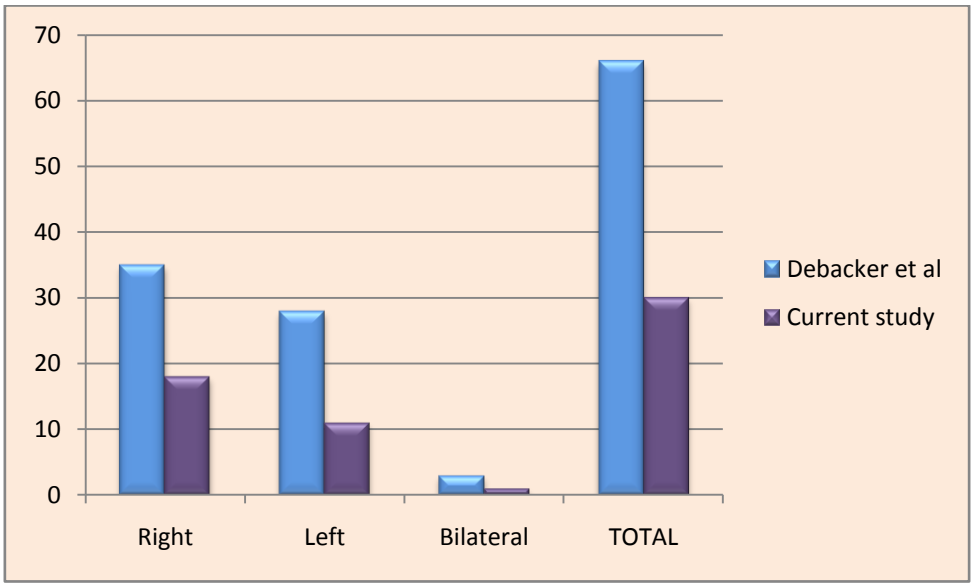


CHART: 18 - PERCENTAGE OF C-KIT POSITIVITY IN DYSGERMINOMA IN DIFFERENT STUDIES

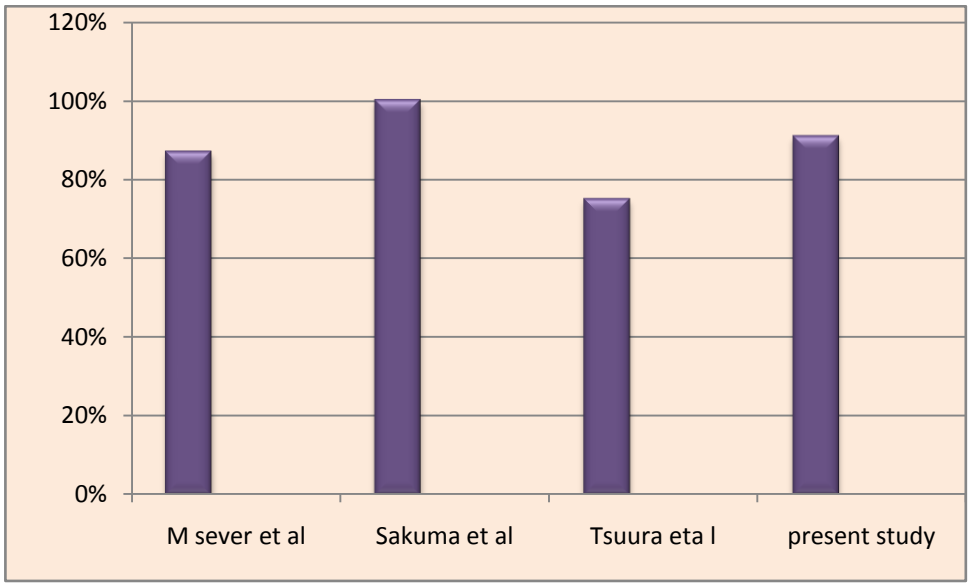


CHART : 19 - PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT GERM CELL TUMOURS IN DIFFERENT STUDIES

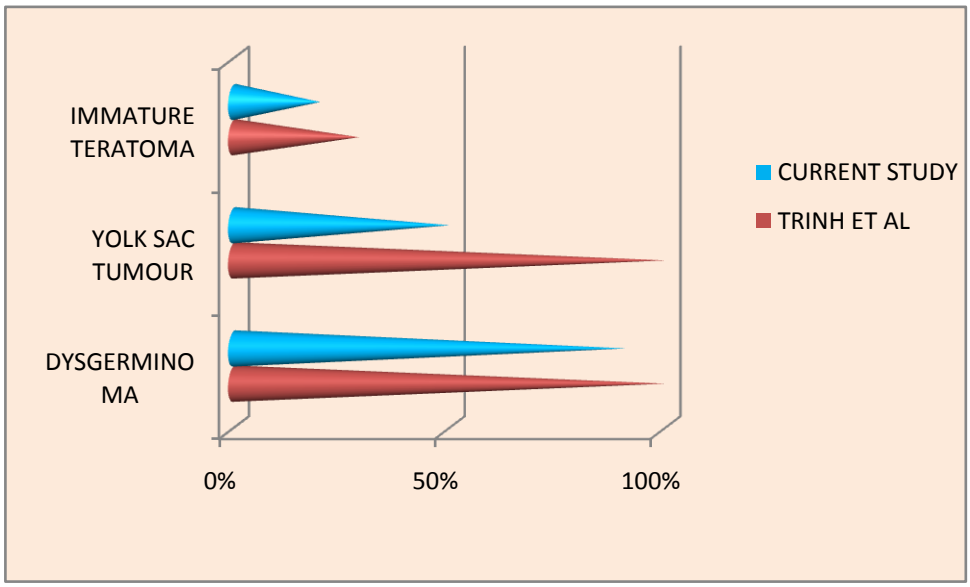


FIG.1- 145/11-DYSGERMINOMA.

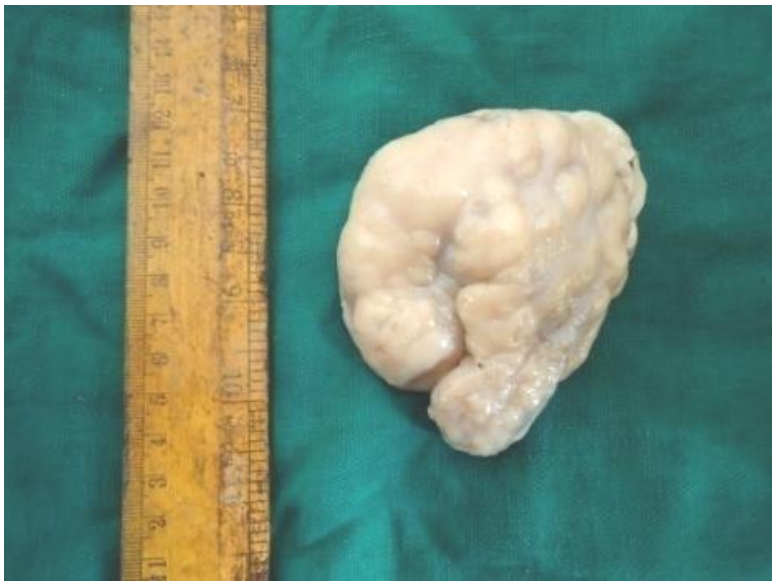


FIG.2- 145/11-DYSGERMINOMA.

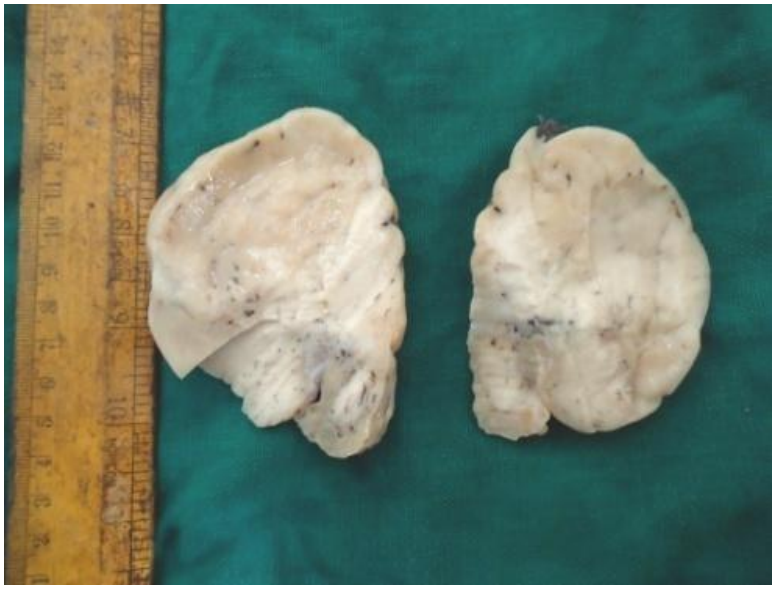


FIG.3- 2046/12-BILATERAL DYSGERMINOMA.

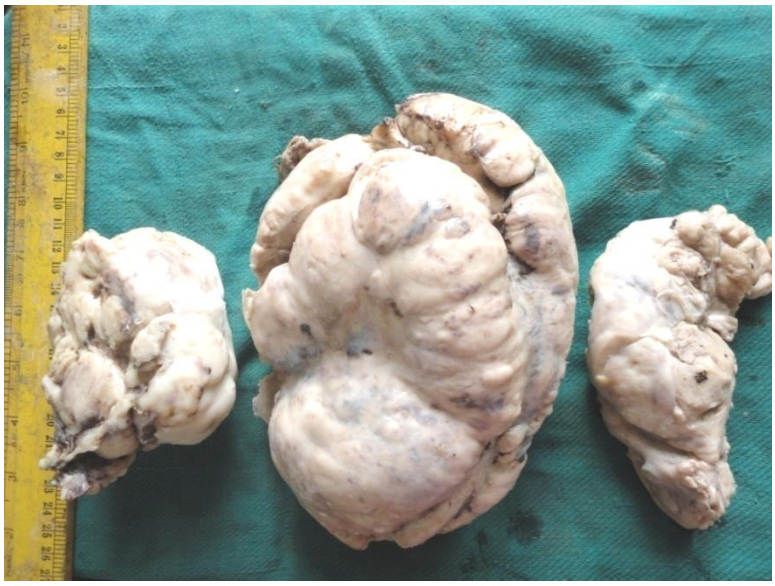


FIG.4-1439/12-DYSGERMINOMA

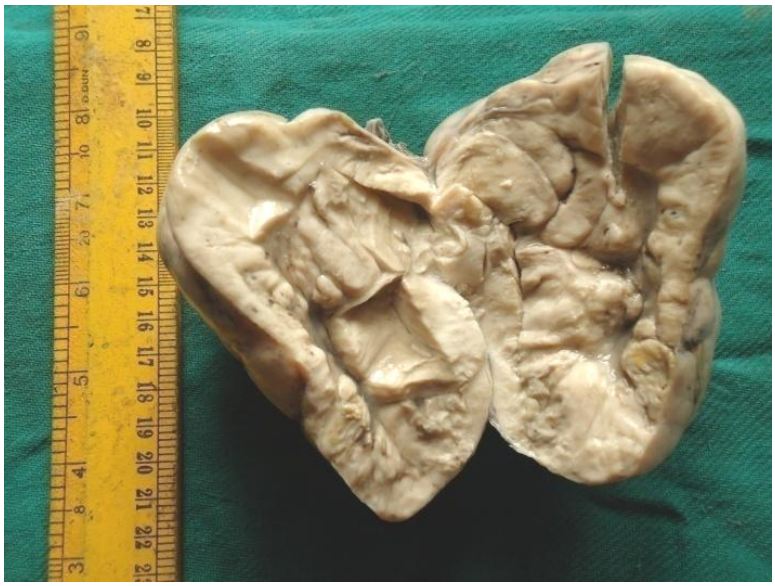


FIG.5-4280/07-YOLK SAC TUMOUR

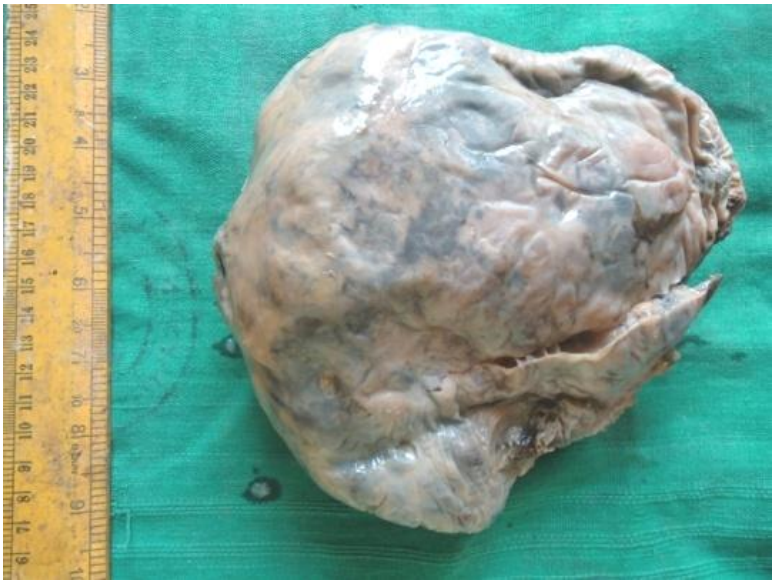


FIG.6- 4280/07-YOLK SAC TUMOUR

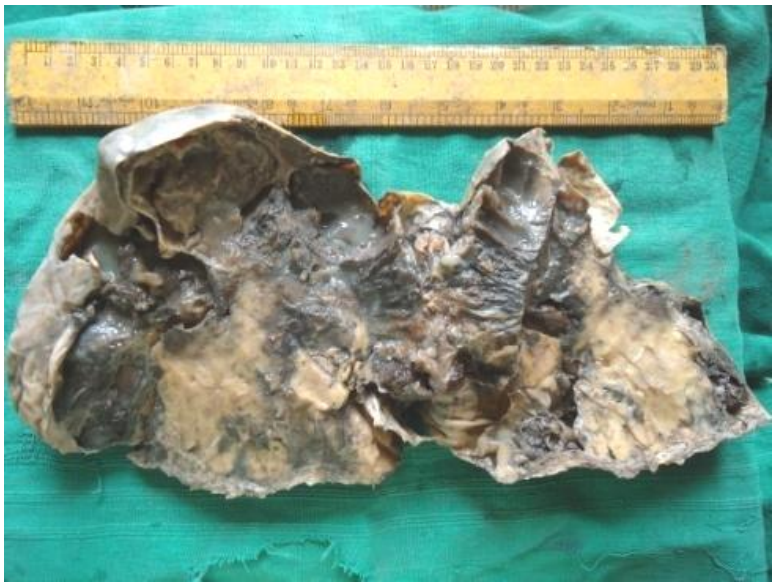


FIG.7-2094/09-IMMATURE TERATOMA

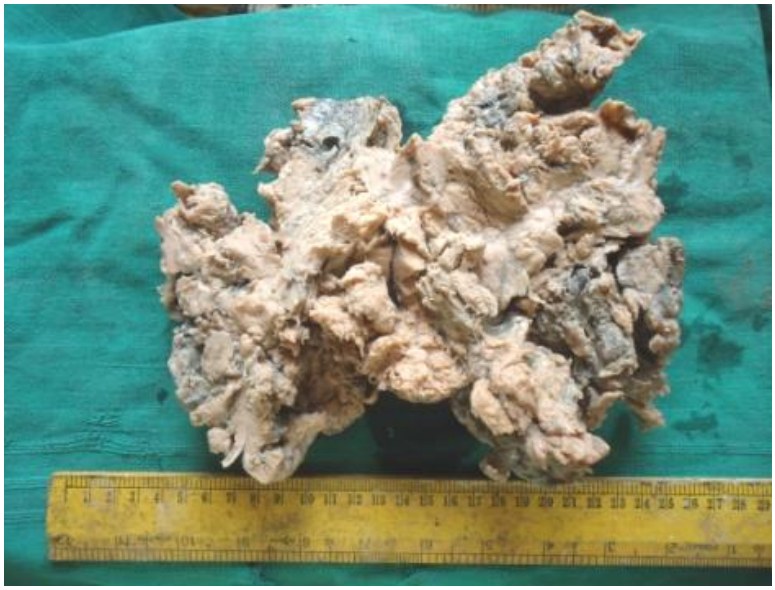


FIG.8- 3600/08-MIXED GERM CELL TUMOUR

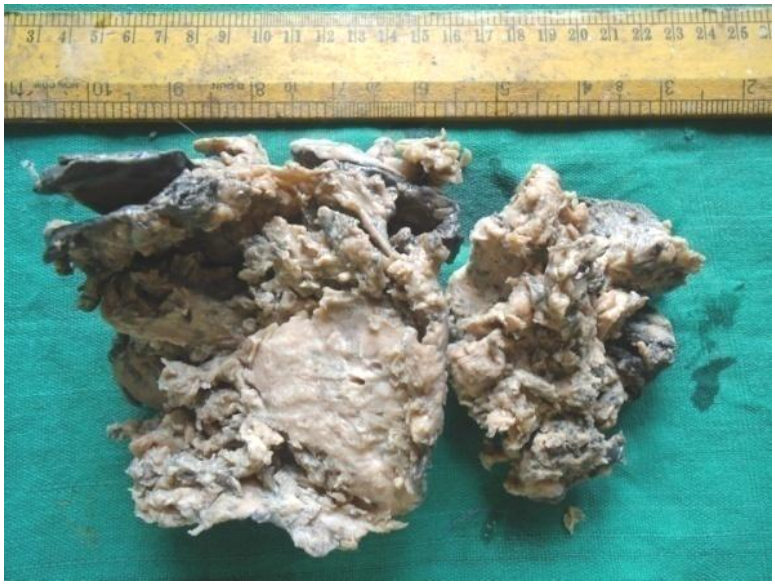


FIG.9- 2349/11-STRUMA OVARII.

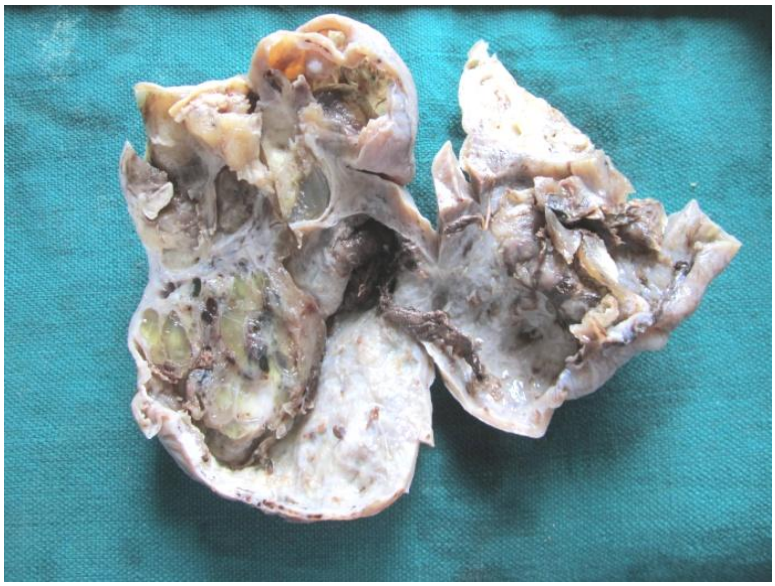


FIG.10 3286/11-DYSGERMINOMA

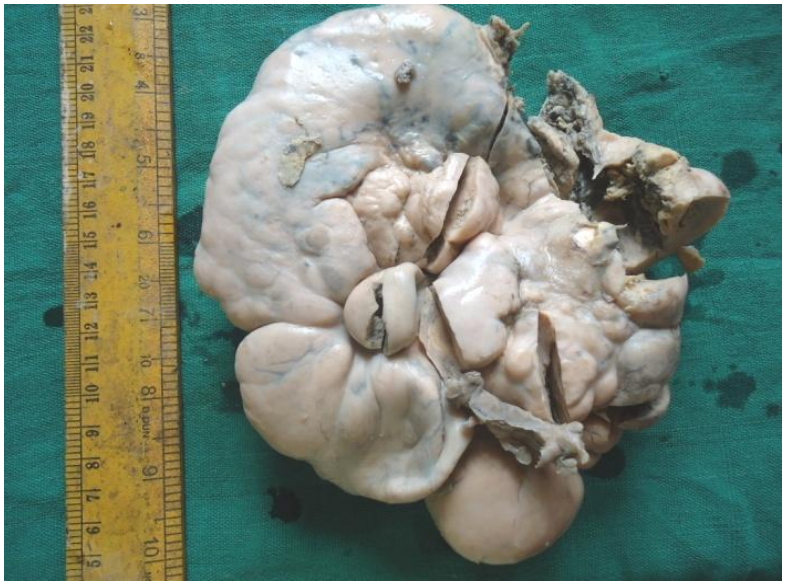


FIG.11- 3286/11-DYSGERMINOMA WITH CYSTIC CHANGE

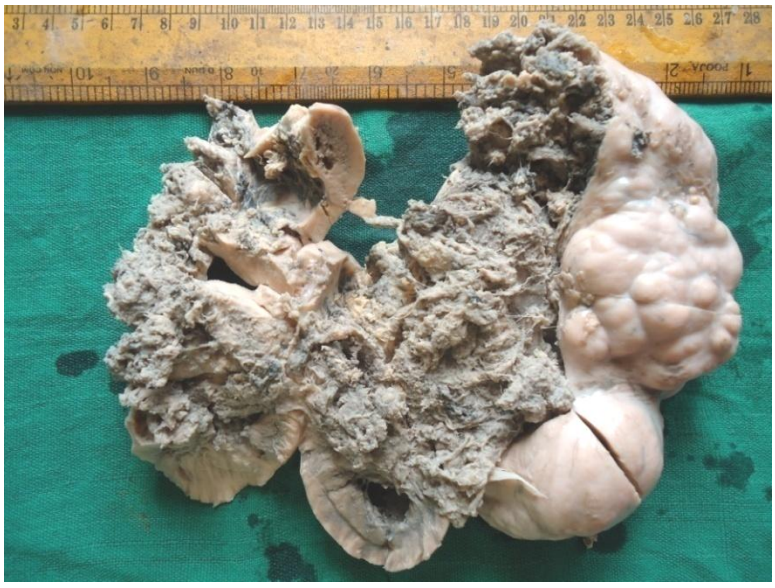


FIG.12--DYSGERMINOMA X 10

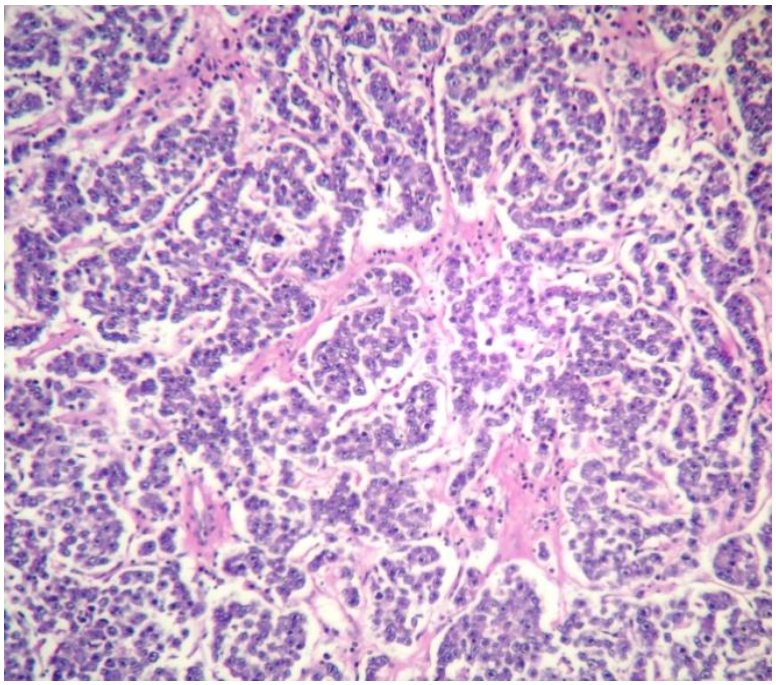


FIG.13--DYSGERMINOMA X40

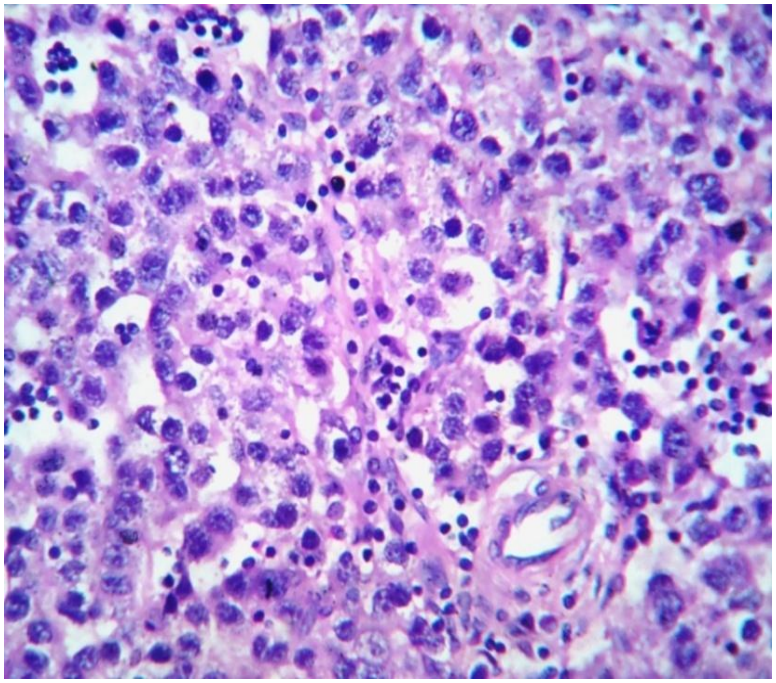


FIG.14--DYSGERMINOMA X10

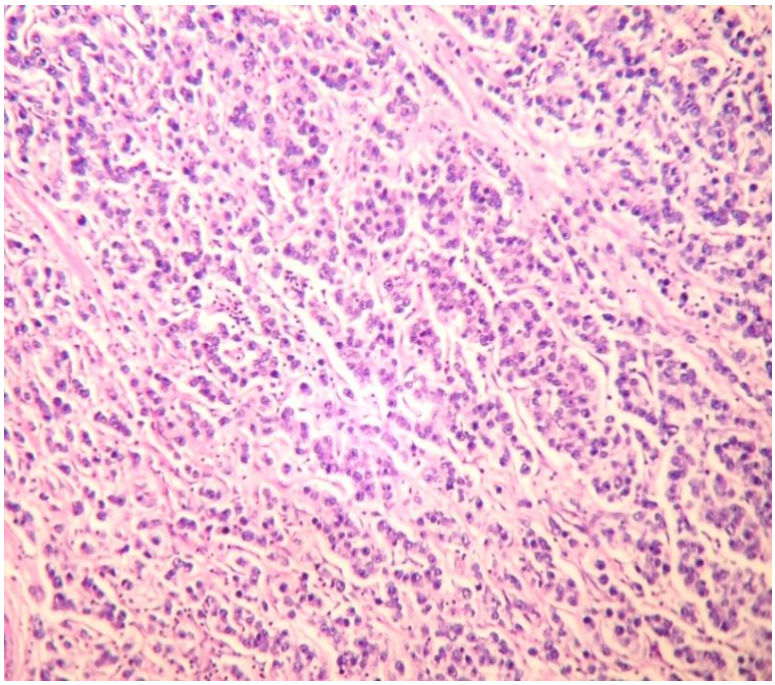


FIG.15--DYSGERMINOMA X40

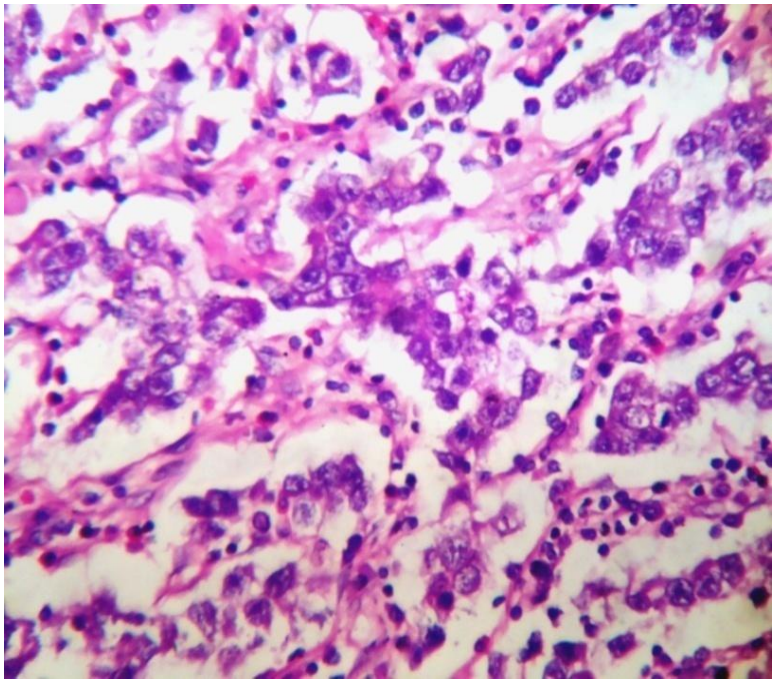


FIG.16--YOLK SAC TUMOUR X 10

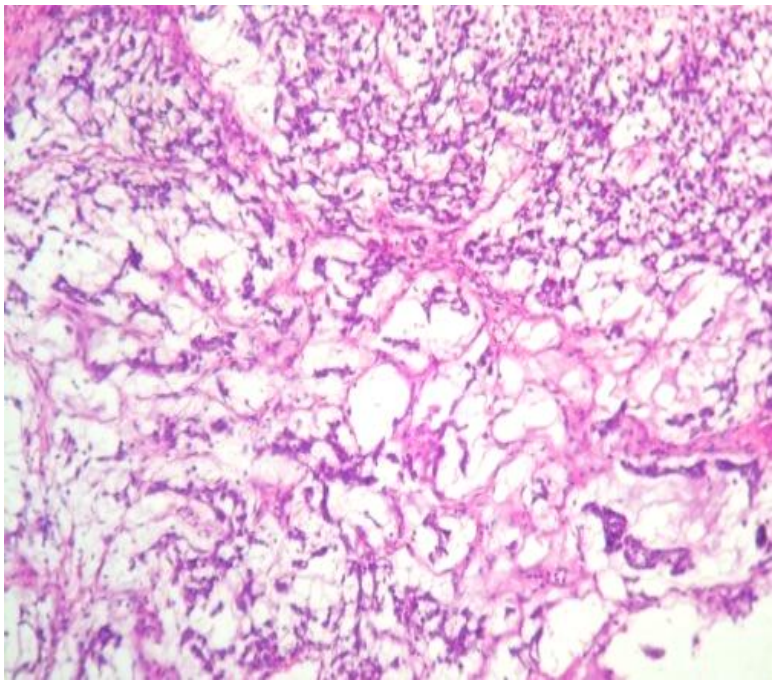


FIG.17--MIXED GERM CELL TUMOUR (YST IN LEFT AND DYSGERMINOMA IN RIGHT) X 10

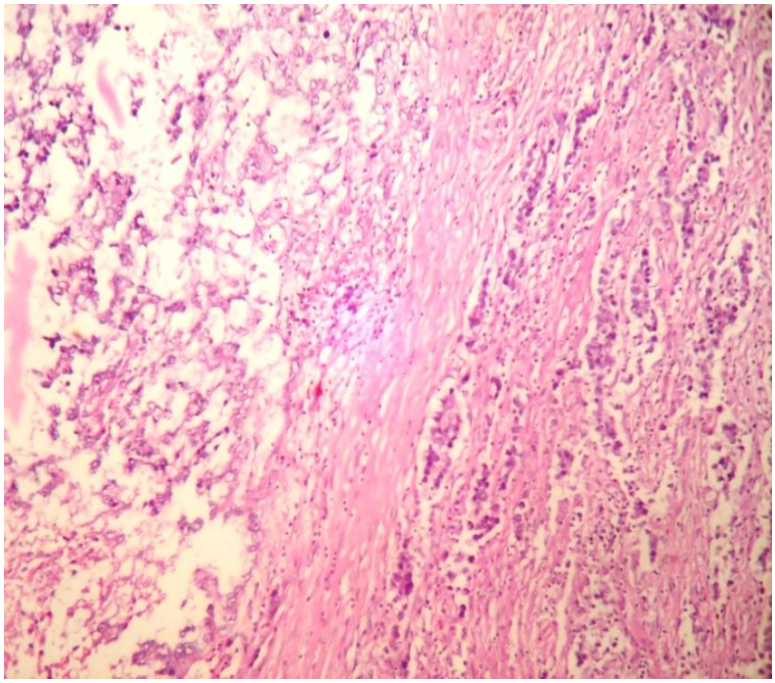


FIG.18-IMMATURE TERATOMA SHOWING IMMATURE NEURAL ELEMENTS X 10

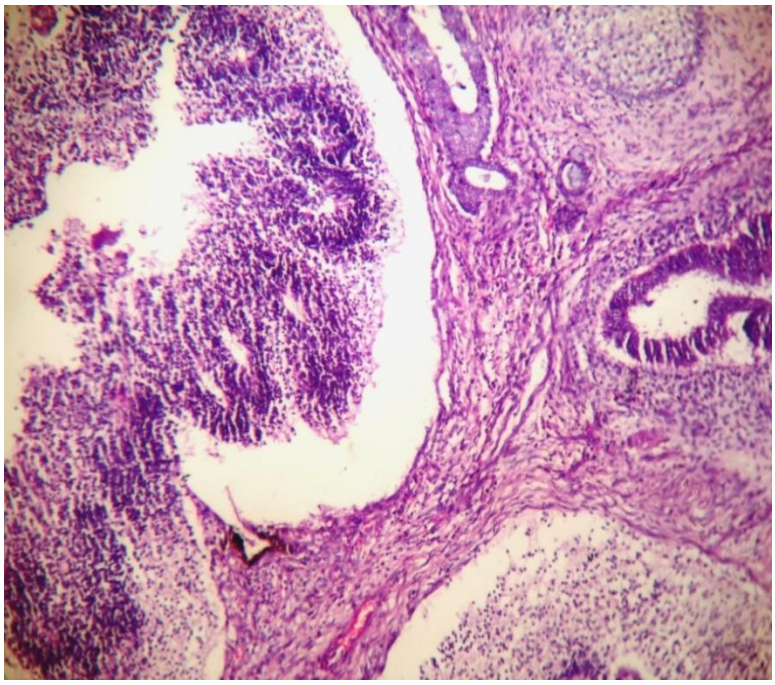


FIG.19-IMMATURE TERATOMA SHOWING IMMATURE NEURAL ELEMENTS X 40

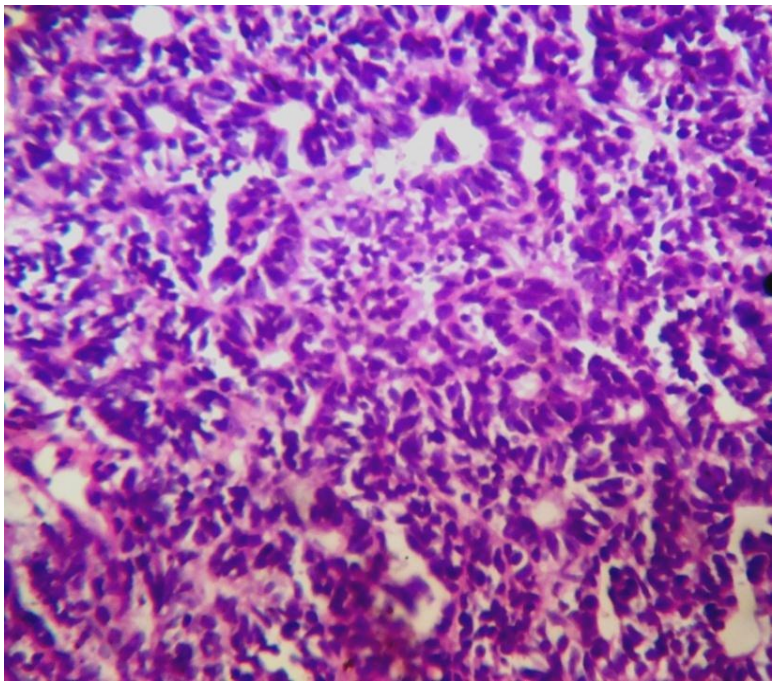


FIG.20-MIXED GERM CELL TUMOUR CONTAINING YST AND IMMATURE TERATOMA X 40

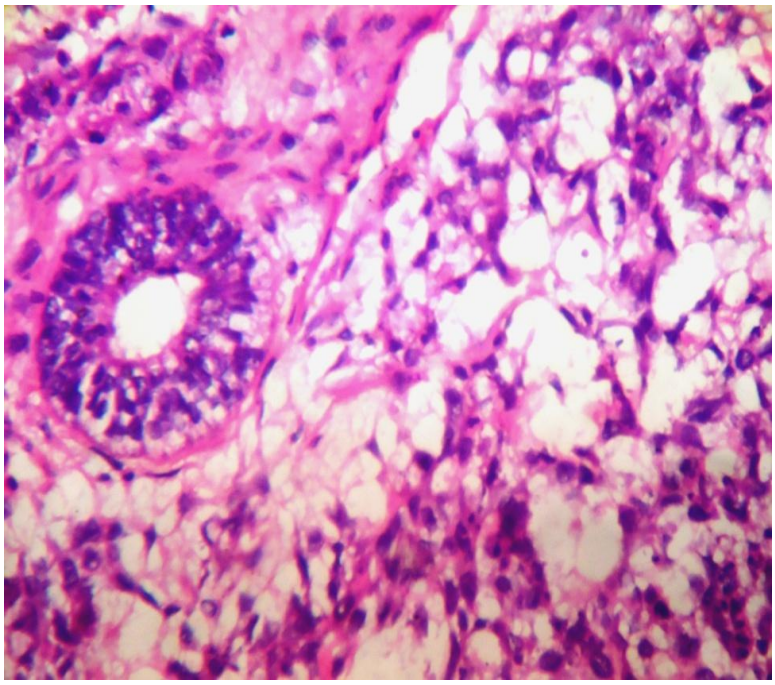


FIG.21-C-KIT POSITIVITY IN DYSGERMINOMA (4+ STAINING) X 10

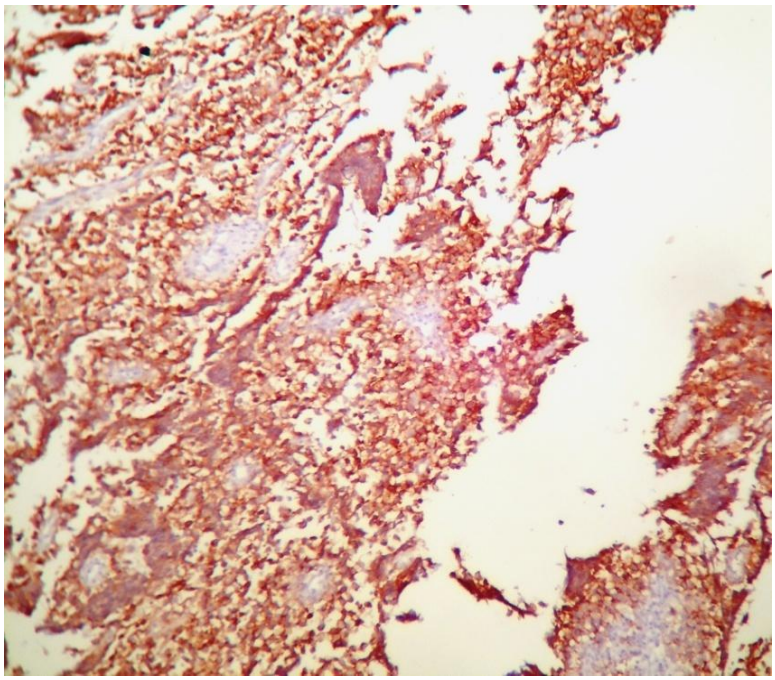


FIG.22-C-KIT POSITIVITY IN DYSGERMINOMA (4+ STAINING) X 10

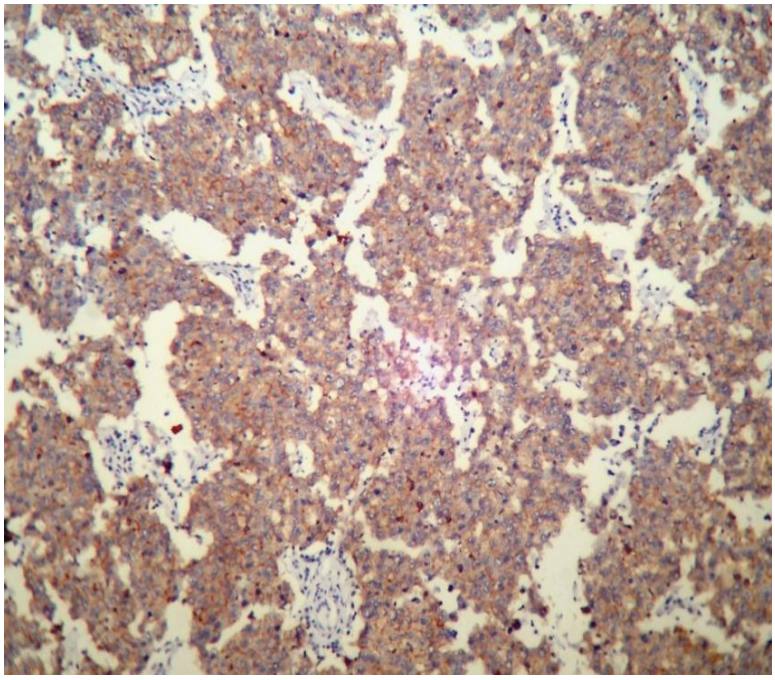


FIG.23-C-KIT POSITIVITY IN DYSGERMINOMA (4+ STAINING) X 10

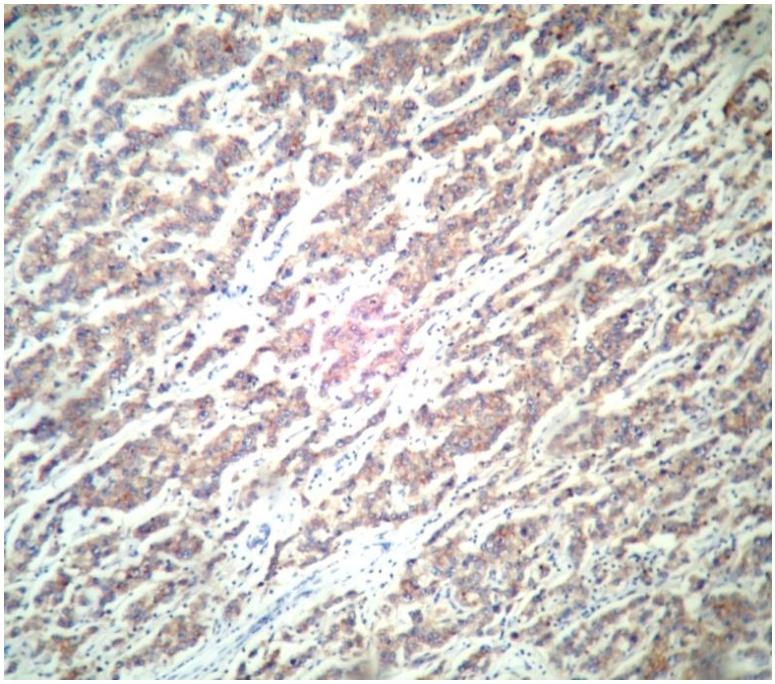


FIG.24-C-KIT POSITIVITY IN DYSGERMINOMA (4+ STAINING) X 40

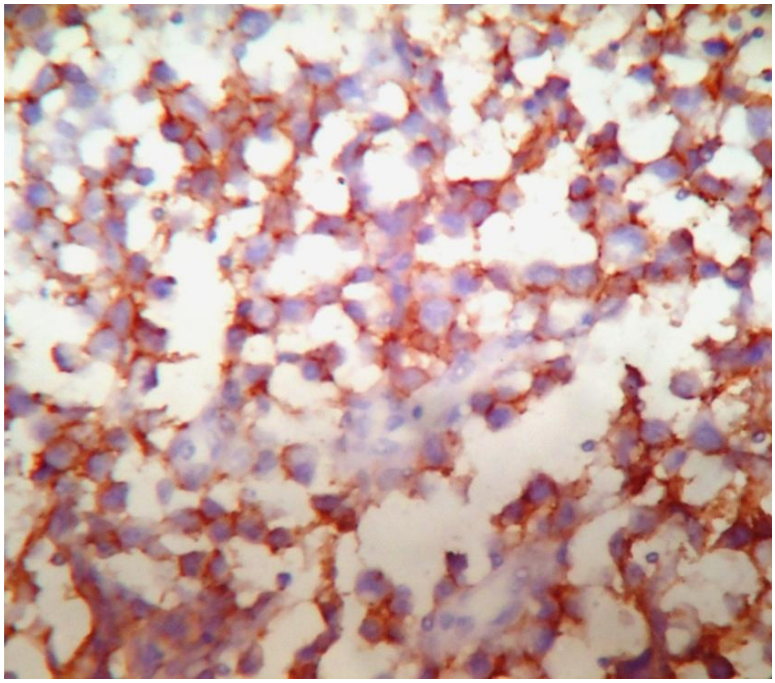


FIG.25-C-KIT POSITIVITY IN DYSGERMINOMA (4+ STAINING) X 40

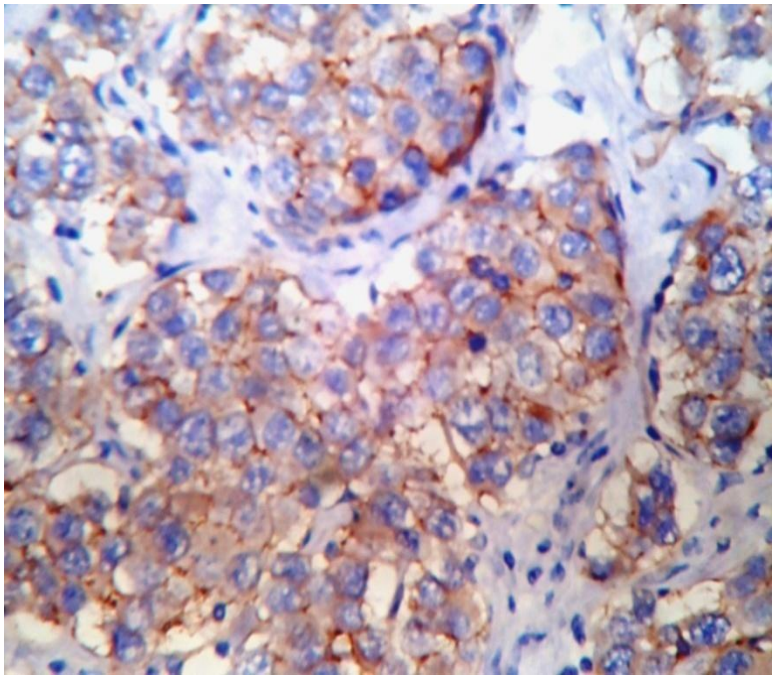


FIG.26-C-KIT POSITIVITY IN DYSGERMINOMA (1+ STAINING) X 40

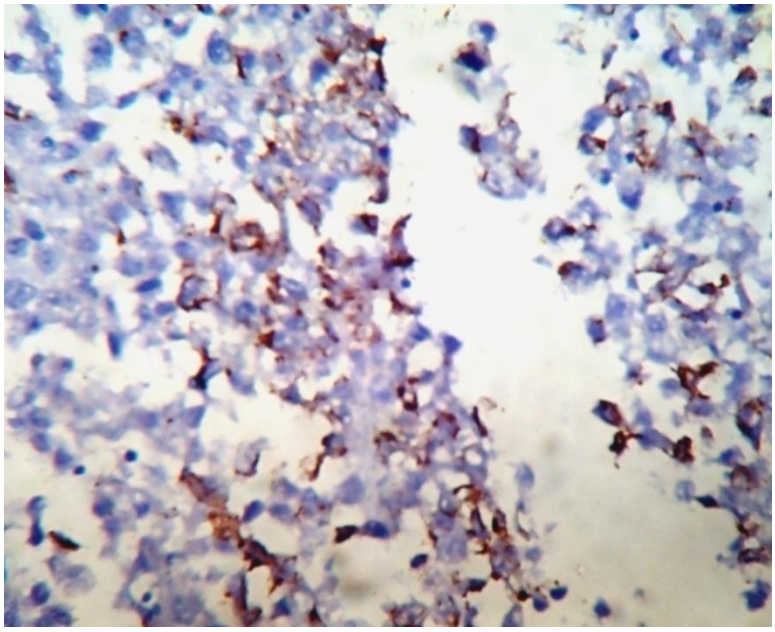


FIG.27-C-KIT NEGATIVE CELLS IN DYSGERMINOMA (0 STAINING) X 40

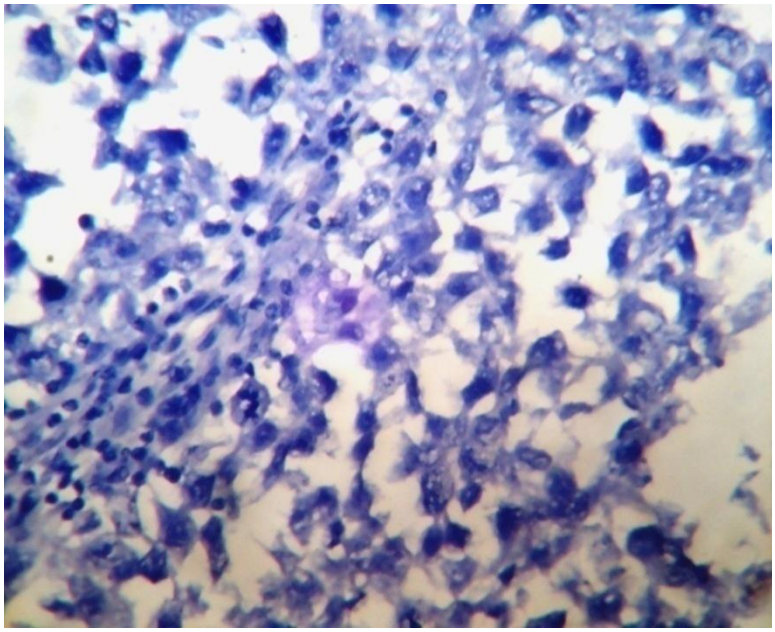


FIG.28-C-KIT POSITIVITY IN YOLK SAC TUMOUR (4+ STAINING) X 10

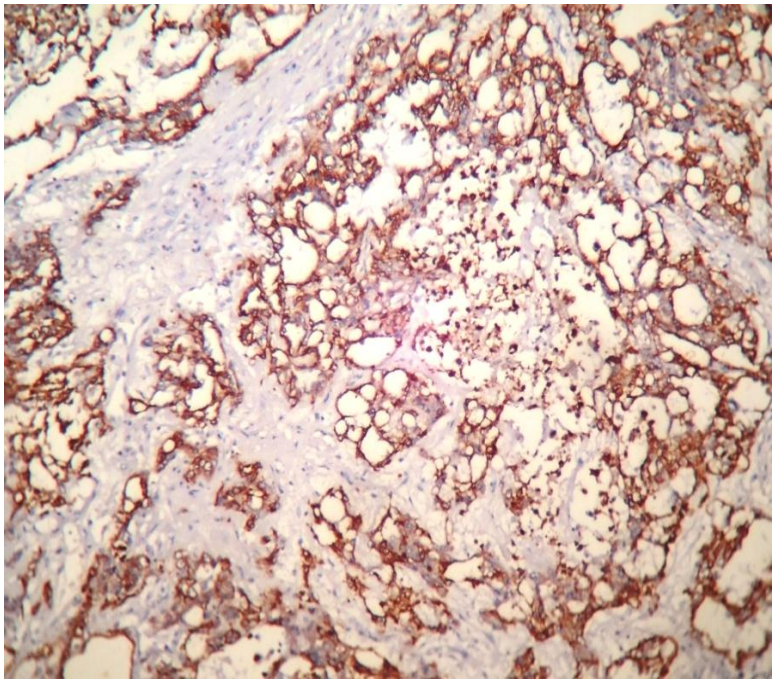


FIG.29-C-KIT POSITIVITY IN YOLK SAC TUMOUR (4+ STAINING) X 40

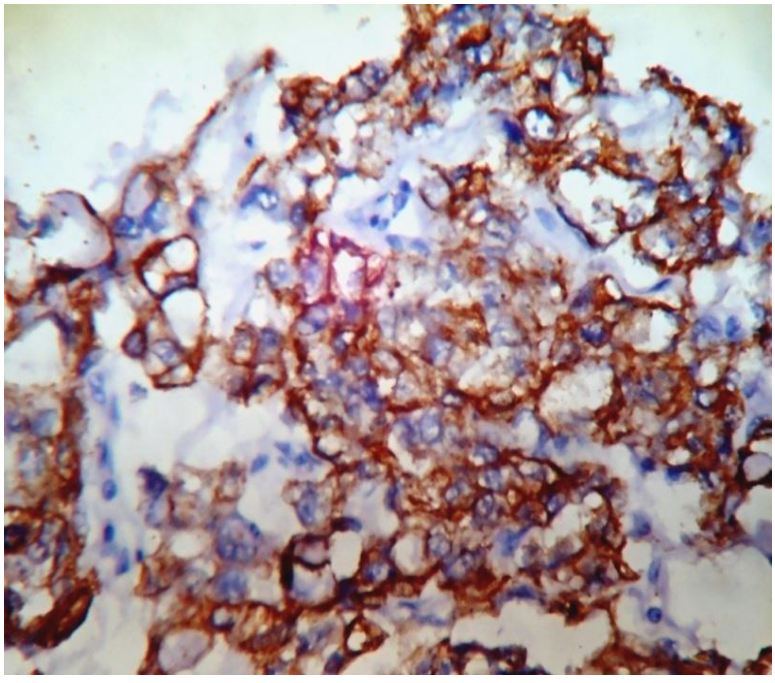


FIG.30-C-KIT NEGATIVITY IN YOLK SAC TUMOUR (0 STAINING) X 40

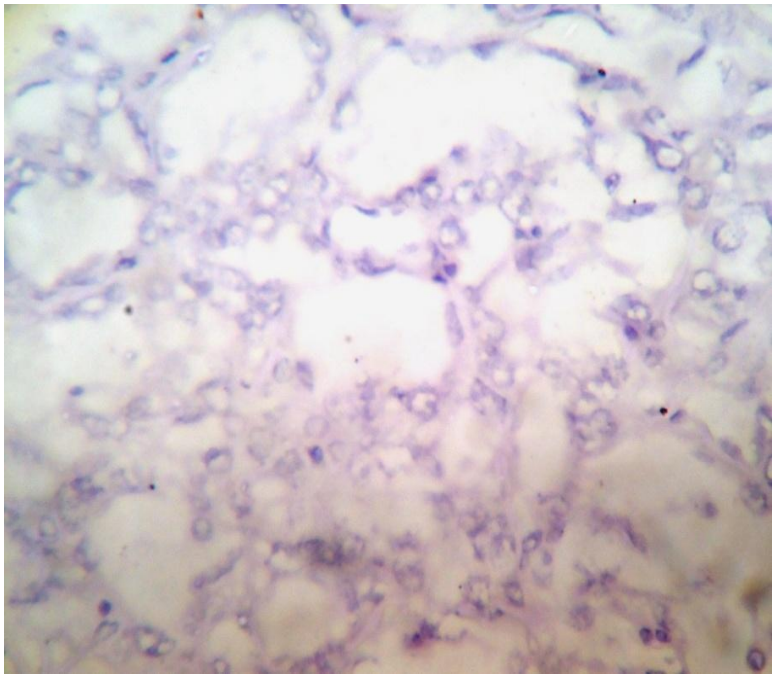


FIG.31-C-KIT POSITIVITY IN MIXED GERM CELL TUMOUR (BOTH YST AND DYSGERMINOMA ELEMENTS SHOWING POSITIVITY (4+ STAINING) X 40

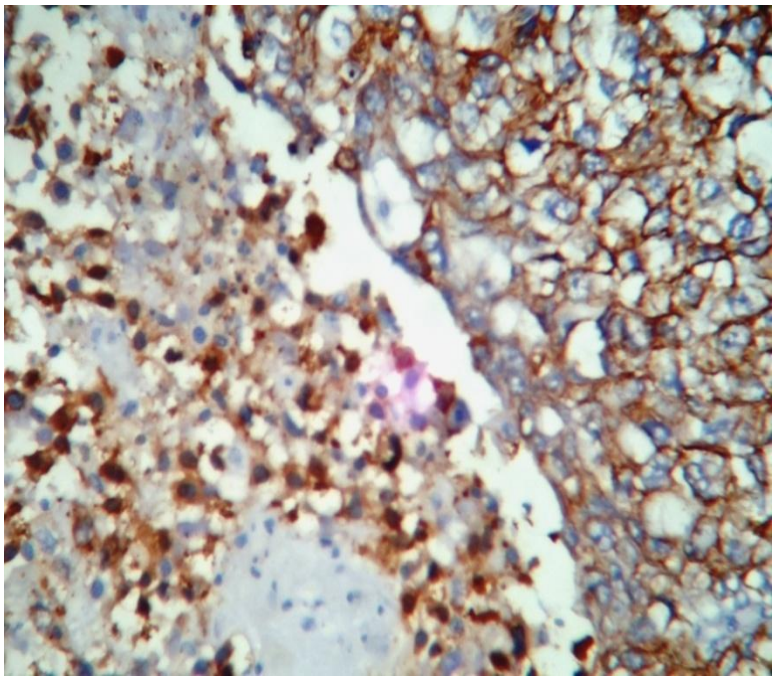


FIG.32-C-KIT POSITIVITY IN IMMATURE TERATOMA X 10

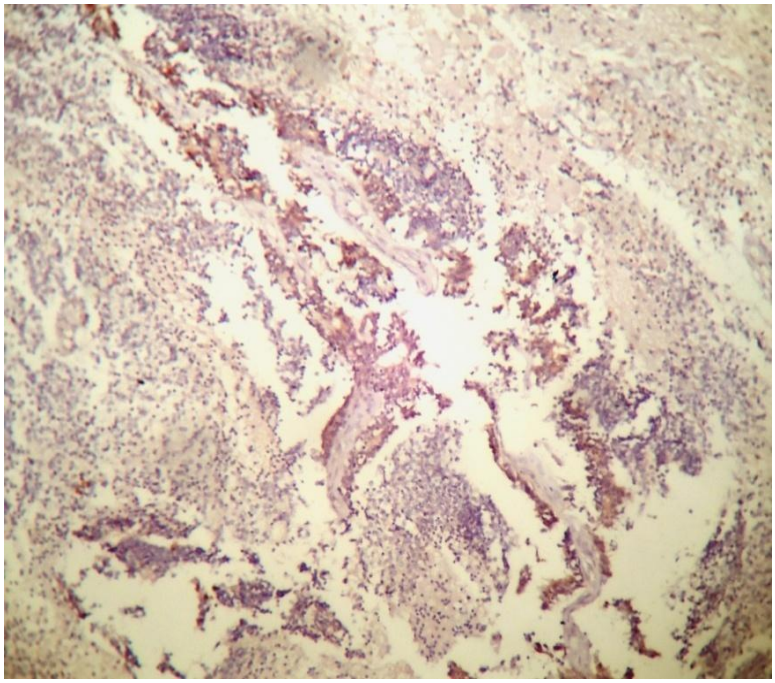
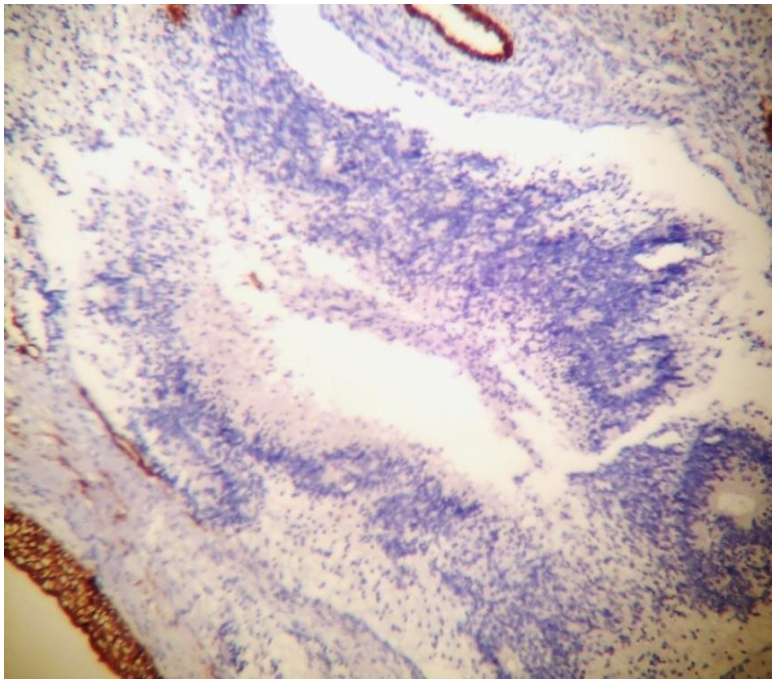


FIG.33-C-KIT NEGATIVITY IN IMMATURE TERATOMA X 10.



DISCUSSION

* Ovarian cancers are important gynecological cancers having variable presentation. They tend to affect all age groups. Different histological type of tumours occurs in different age groups.

* Germ cell malignancies generally affect younger women.

* In our study, clinical and histopathological features of malignant germ cell tumours were studied and their immunohistochemical expression of c-kit is studied.

* In our institute of obstetrics and gynecology, madras medical college we received a total of 725 ovarian neoplasms during a period of 70 months (from January 2007 - October 2012).

TABLE – 26

COMPARISION OF PROPORTION OF BENIGN, BORDERLINE AND MALIGNANT CASES IN DIFFERENT STUDIES

	Ahmad et al[85]	Pilli et al[86]	Gupta et al[87]	Current study
Benign.	59.18	75.2	72.9	67.13%
Borderline	0.2	2.8	3.3	4.7%
Malignant.	40.81	21.8	22.9	28.17%

* Out of 725 cases 487 cases were benign, 34 cases were borderline tumours and 204 cases were malignant. The distribution of benign, borderline and malignant cases in different studies by Ahmad et al[85], Pilli et al[86] and Gupta et al[87] were studied (TABLE 26 and CHART 13). Current study incidence is more similar to study by Gupta et al.

TABLE – 27

COMPARISION OF HISTOLOGICAL TYPE OF OVARIAN TUMOURS IN DIFFERENT STUDIES

TUMOUR TYPE	Jha et al[88]	Pradhan et al[89]	Swamy et al[90]	Current study
Surface epithelial tumours	52.2%	46.9%	61.6%	75.5%
Germ cell tumours	42.2%	45.7%	21.7%	16.5%
Sex cord stromal tumours	3.1%	3.6%	11.7%	7.2%
Metastasis	2.4%	3.6%	5.0%	0.8%

* The different histological types of ovarian tumours were compared with different studies by Jha eta l[88], Pradhan et al[89], Swamy et al[90] (TABLE 27 and CHART 14). Current study incidences are more correlating with study of Swamy et al.

TABLE – 28

COMPARISION OF HISTOLOGICAL TYPES OF MALIGNANT GERM CELL TUMOURS IN DIFFERENT STUDIES

Tumour type	S tangjitgamol et al[91] (n-130)	Chow et al[92] (n-50)	Present study (n-30)
Dysgerminoma	37.7%	26%	36.66%
Yolk sac tumour	26.2%	30%	13.34%
Immature teratoma	23.1%	26%	16.66%
Mixed germ cell tumour	13%	16%	33.34%
TOTAL	100%	100%	100%

* In germ cell tumours distribution of different histological subtypes was compared with studies by Stangjitgamol et al[91] and Chow et al[92] (TABLE.28 and CHART15) compared to both these studies incidence of yolk sac tumour is less in current study and incidence of mixed germ cell tumour is more.

TABLE – 29

COMPARISION OF MEAN AGE OF MALIGNANT GERM CELL TUMOURS IN DIFFERENT STUDIES

	Stangjitgamol et al[91]	Lai et al[93]	Chow et al[92]	Current study
Mean age	21 yrs	23 yrs	21.5yrs	22.4yrs

* The mean age of patients in current study group is 22.4 yrs which almost similar to studies by Stangjitgamol et al [91] (21 yrs), Lai et al[93] (23 yrs) and Chow et al[92] (21.5 yrs) (TABLE 29).

* The mean size of all tumours is 15.7cm which is similar to study by Chow et al[92] which is about 16cm.

TABLE – 30

COMPARISION OF STAGE OF DISEASE IN DIFFERENT STUDIES

STAGE	Stangjitgamol et al[91]	Debacker et al[94]	Current study
I	63	52	11
II	16	4	2
III	41	6	17
IV	3	1	0

* The stage at presentation of tumours were compared with studies by Stangjitgamol et al[91] and Debacker et al[94] (TABLE.30 and CHART.16). In both these studies presentation in stage I is common, but in our study presentation in stage III is more common.

TABLE – 31

COMPARISION OF LATERALITY OF MALIGNANT GERM CELL TUMOURS

LATERALITY	Debacker et al[94]	Current study
Right	35	18
Left	28	11
Bilateral	3	1
TOTAL	66	30

* The laterality of germ cell tumours is compared with Debacker et al[94] (TABLE.31 and CHART.17) which is similar to our study, more tumours on right side.

TABLE – 32

PERCENTAGE OF C-KIT POSITIVITY IN DIFFERENT GERM CELL TUMOURS IN DIFFERENT STUDIES

TUMOUR TYPE	TRINH et al[95]	CURRENT STUDY
DYSGERMINOMA	100%	90.9%
YOLK SAC TUMOUR	100%	50%
IMMATURE TERATOMA	29%	20%

Percentage of c-kit positivity in germ cell tumour subtype is compared with study by Trihn et al[95] (TABLE.32 and CHART.18) Trihn et al[95] reported 100% positivity of C-kit in both dysgerminoma and yolk sac tumour and a positivity of 29% in cases of immature teratoma. Current study also showed similar results except lower positivity rate in cases of yolk sac tumour.

TABLE – 33

PERCENTAGE OF C-KIT POSITIVITY IN DYSGERMINOMA IN DIFFERENT STUDIES

Author	No of cases studied (dysgerminoma)	% of cases showing c-kit positivity
M sever et al[80]	30	87%
Sakuma et al[96]	16	100%
Tsuura et al[52]	884	75%
Present study	11	90.9%

Since current study emphasize more interest on dysgerminoma the percentage of C-kit positivity in various studies were compared (TABLE.33 and CHART 19). Results of current study (81.8%) are closer to the percentage obtained by M sever et al[80] (87%)

SUMMARY

* A total of 725 ovarian neoplasms were reported in our institution, benign cases were 487, borderline 34 cases and 204 malignant cases.

* Surface epithelial tumours were common followed by germ cell tumours.

* Common surface epithelial tumour is benign serous cystadenoma and common germ cell tumour is benign cystic teratoma.

* In malignant ovarian tumours serous cystadenocarcinoma is the commonest tumour.

* Among malignant germ cell tumours dysgerminoma is commonly observed.

* The age incidence of germ cell tumours in current study ranges from 13 yrs to 40 yrs.

* The mean age of the patients with malignant germ cell tumours is 22.4 yrs.

* The average size of tumours is about 15.7 cm.

* The mean age and size are correlating with various other studies.

* Dysgerminoma exhibits solid morphology in most cases. Mixed germ cell tumours and immature teratoma presents with mixed or variegated morphology.

* Compared to other studies, in current study more patients are presented in stage III, whereas in other studies stage I presentation is more common followed by stage III.

* The immunohistochemical expression of c-kit is more in dysgerminoma (90.9%) than the other malignant germ cell tumours.

* In mixed germ cell tumours also, tumours having dysgerminoma as a component are expressing more c-kit positivity than tumours without dysgerminoma.

* Yolk sac tumours show 50% positivity in current study which is comparatively compared to other studies.

* In Immature teratoma c-kit positivity is about 20% in our study, which is almost to similar to other studies.

* Out of the 20 patients followed up 17 patients were alive and symptom free, 2 patient have recurrent abdominal mass, 1 patient expired.

* The correlation between the Immunohistochemical expression of c-kit and the clinical parameters is not statistically significant.

CONCLUSION

Malignant germ cell tumours are the second common group of ovarian malignancy after surface epithelial malignancies.

Since they are affecting the reproductive age group people, preserving the fertility with cure of the patient is a big challenge.

Dysgerminoma, the ovarian counterpart of seminoma is the common germ cell malignancy occurring in younger age group with a peak incidence in second and third decades.

Expression of c-kit in dysgerminoma is similar to its counterpart seminoma.

Though the germ cell malignancies are responding better to platinum based chemotherapy given in our institutional set up, the possible risk of infertility is there.

Targeted therapy against c-kit is available for disease like chronic myeloid leukemia, GIST, it can be of use in germ cell tumours too.

But even in a tertiary hospital like IOG, MMC the incidence of germ cell tumours is only 30 cases for a period of 70 months period.

Hence trials involving a large group of people with germ cell tumours should be done for evaluation of c-kit expression and positive c-kit cases should be tried with anti-c kit compounds like imatinib so that it could be effective alternative for conventional platinum based regimens.

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ANNEXURE I

PROFORMA.

Name:

Age:

Address:

Ip no:

Biopsy no:

Presenting complaints:

Obstetric history:

USG/CT/MRI Findings:

Hormonal levels (AFP,CEA,β-HCG,LDH):

Surgical procedure done:

FIGO STAGE:

HPE Diagnosis:

Chemotherapy details:

- Chemo given or not
- If given , no of cycles and regimen used.

Months of follow up:

Outcome of the patient:

ANNEXURE II

WHO classification of ovarian tumours.

Surface epithelial–stromal tumors

Serous tumors

- Malignant
  - Adenocarcinoma
- Borderline tumor
- Benign
  - Cystadenoma, adenofibroma, cystadenofibroma

Mucinous tumors

- Malignant
  - Adenocarcinoma
- Borderline tumor
- Benign
  - Cystadenoma, adenofibroma, cystadenofibroma
- Mucinous cystic tumor with pseudomxoma peritonei

Endometrioid tumors including variants with squamous differentiation

- Malignant
  - Adenocarcinoma
  - Malignant mixed müllerian tumor (carcinosarcoma)
  - Endometrioid stromal sarcoma (low grade)
  - Undifferentiated ovarian sarcoma
- Borderline tumor
- Benign
  - Cystadenoma, adenofibroma, cystadenofibroma

Clear cell tumors

- Malignant
  - Adenocarcinofibroma
- Borderline tumor
- Benign

- Cystadenoma, adenofibroma, cystadenofibroma

Transitional cell tumors

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

Squamous cell tumors

- Squamous cell carcinoma

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 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
  - 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 types
- 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, nonhilar type
  - Leydig cell tumors, not otherwise specified
- Steroid cell tumor, not otherwise specified
  - Well differentiated
  - Malignant

Germ cell tumors

Primitive germ cell tumors

Dysgerminoma

Yolk sac tumor

Embryonal carcinoma

Polyembryoma

Nongestational choriocarcinoma

Mixed germ cell tumor (specify components)

Biphasic or triphasic teratoma

Immature teratoma

Mature teratoma

- Solid
- Cystic
- Fetiform teratoma (homunculus)

Monodermal teratoma and somatic-type tumors associated with dermoid cysts

Thyroid tumor group

- Struma ovarii
  - Benign
  - Malignant (specify type)

Cardinoid group

Neuroectodermal tumor group

Carcinoma group

Melanocytic group

- Malignant melanoma
- Melanocytic nevus

Sarcoma group (specify type)

Sebaceous tumor group

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

Tumorlike conditions

Luteoma of pregnancy

Stromal hyperthecosis

Stromal hyperplasia

Fibromatosis

Massive ovarian edema

Others

Lymphoid and hematopoetic tumors

Malignant lymphoma (specify type)

Leukemia (specify type)

Plasmacytoma

Secondary tumors

ANNEXURE III

FIGO STAGING OF OVARIAN CANCERS.

Stage I -Growth limited to the ovaries.

IA -Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact.

IB- Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surface; capsule intact.

IC- Tumor classified as either Stage IA or IB but with tumor on the surface of one or both ovaries; or with ruptured capsule(s); or with ascites containing malignant cells or with positive peritoneal washings.

Stage II -Growth involving one or both ovaries, with pelvic extension.

IIA -Extension and/or metastases to the uterus and/or tubes.

IIB- Extension to other pelvic tissue.

IIC- Tumor classified as either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites containing malignant cells or with positive peritoneal washings.

Stage III- Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis

equals Stage III.Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.

IIIA- Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.

IIIB -Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative.

IIIC- Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV -Growth involving one or both ovaries, with distant metastases. If pleural effusion is present, there must be positive cytological findings to allot a case to Stage IV.Parenchymal liver metastasis equals Stage IV.

ANNEXURE IV

IMMUNOHISTOCHEMISTRY PROCEDURE

1. 4µ thick sections were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.

2. The slides were incubated at 58ºC for overnight.

3. The sections were deparaffinized in xylene for 15 minutes x 2 changes.

4. The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.

5. The sections were washed in tap water for 10 minutes.

6. The slides were then immersed in distilled water for 5 minutes.

7. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.

8. The slides were then cooled to room temperature and washed in running tap water for 5 minutes.

9. The slides were then rinsed in distilled water for 5 minutes.

10. Wash with appropriate wash buffer (citrate buffer) for 5 minutes x 2 changes.

11. Apply peroxidase block over the sections for 10 minutes.

12. Wash the slides in citrate buffer for 5 minutes x 2 changes.

13. Cover the sections with power block for 15 minutes.

14. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 1 hour (CD117).

15. The slides were washed in citrate buffer for 5 minutes x 2 changes.

16. The slides were covered with Super Enhancer for 30 minutes.

17. The slides were washed in citrate buffer for 5 minutes x 2 changes.

18. The slides were covered with SS Label for 30 minutes.

19. Wash in citrate buffer for 5 minutes x 2 changes.

20. DAB substrate was prepared by diluting 1 drop of DAB chromogen to 1 ml of DAB buffer.

21. DAB substrate solution was applied on the sections for 8 minutes.

22. Wash with citrate buffer solution for 5 minutes x 2 changes.

23. The slides are washed well in running tap water for 5 minutes.

24. The sections were counterstained with Hematoxylin stain for 2 seconds (1 dip).

25. The slides are washed in running tap water for 3 minutes.

26. The slides are air dried, cleared with xylene and mounted with DPX

S.NO	BX NO	AGE IN YRS	SEX	SIDE	P/D	SIZE	USG	GROSS	HPE	STAGE	CHEMO	CD117	FOLLOW UP	COURSE
1	456/07	20	F	LFT	L.OVAR	25 X 25 X15 CM	MIXED	MIXED	MGCT	III C	4BEC	4+	62mths	sym free
2	730/07	29	F	RT	TAH,R.OVAR	30 X 30 X 10 CM	MIXED	MIXED	MGCT	III	4BEC	3+	60mths	sym free
3	1923/07	17	F	LFT	L.OVAR	15 X10 CM	MIXED	MIXED	IMM.TER	I C	3BEC	3+	55mths	sym free
4	2651/07	27	F	LFT	LSCS,LSO	22 X20 CM	SOLID	SOLID	MGCT	III	4BEC	3+	10mths	sym free
5	3072/07	16	F	RT	R.OVAR	12 X 10 X7 CM	CYS	MIXED	IMM.TER	I C	NO CHEMO	NEG	24mths	sym free
6	4046/07	20	F	RT	R.OVAR	30 X 23 X 7 CM	MIXED	MIXED	MGCT	III	NO CHEMO	1+	DEF	-
7	4280/07	40	F	LFT	TAH,BSO	15 X15 X 7 CM	MIXED	MIXED	YST	I C	4BEC	1+	19 mths	sym free
8	156/08	18	F	LFT	L.OVAR	16 X 12 X 6 CM	MIXED	CYST	IMM.TER	II	4 BEC	NEG	51 mths	sym free
9	165/08	16	F	RT	B/L OVAR	21 X 11 CM	MIXED	MIXED	YST	IIIC	4 BEC	NEG	55 mths	sym free
10	2993/08	25	F	LFT	TAH,BSO	12 X 6 X 6 CM	MIXED	SOLID	MGCT	III A	4BEC	4+	16mths	sym free
11	3600/08	20	F	RT	R.OVAR	12 X 10 X 4 CM	MIXED	MIXED	IMM.TER	III	3BEC	NEG	DEF	-
12	7509/08	13	F	RT	TAH,BSO	8 X 7 X 5 CM	SOLID	SOLID	DYSG	I A	NO CHEMO	3+	DEF	-
13	361/09	18	F	RT	R.OVAR	21 X 18 X 12 CM	MIXED	MIXED	MGCT	I A	4BEC	2+	DEF	-
14	2212/08	25	F	LFT	TAH,BSO	12 X6 X 6 CM	MIXED	SOLID	DYSG	IIIA	1 BEC	4+	DEF	-
15	2094/09	28	F	RT	TAH,BSO	15 X 12 X 5 CM	MIXED	MIXED	MGCT	III C	4 BEC	NEG	6 mths	RECUR

S.NO	BX NO	AGE IN YRS	SEX	SIDE	P/D	SIZE	USG	GROSS	HPE	STAGE	CHEMO	CD117	FOLLOW UP	COURSE
16	2780/09	28	F	RT	TAH,BSO	15 X 12 X 5 CM	MIXED	MIXED	MGCT	III C	I BEC	NEG	4mths	Expired
17	3141/09	32	F	RT	R.OVAR	20 X 20 X15 CM	MIXED	SOLID	MGCT	IIIC	NO CHEMO	1+	DEF	-
18	3399/09	28	F	RT	TAH,BSO	25 X 20 X 15 CM	MIXED	MIXED	YST	III C	NO CHEMO	NEG	DEF	-
19	3909/09	18	F	LFT	L.OVAR	11 X 10 X 8 CM	SOLID	SOLID	DYSG	I A	NO CHEMO	NEG	DEF	-
20	4A/10	13	F	RT	DEBULK	13 X 10 CM	MIXED	MIXED	YST	III	3BEC	3+	30 mths	sym free
21	824/10	22	F	LFT	L.OVAR	11 X11 X 7 CM	SOLID	SOLID	DYSG	I	4 BEC	2+	25 mths	sym free
22	1231/10	15	F	RT	R.OVAR	16 X 10 X 6 CM	MIXED	SOLID	DYSG	III C	4 BEC	2+	27 mths	sym free
23	1431/10	21	F	RT	R.OVAR	10 X 9 X 6CM	MIXED	SOLID	DYSG	IA	2 BEC	3+	22 mths	sym free
24	2513/10	38	F	RT	TAH,BSO	8 X 7 X 7 CM	MIXED	MIXED	MGCT	I C	4 BEC	NEG	5 mths	RECUR
25	3286/10	17	F	RT	R.OVAR	14 X 12 X 5 CM	SOLID	MIXED	DYSG	III C	4BEC	1+	5mths	sym free
26	101/11	30	F	LFT	LSO	9 X 5 X 3 CM	CYS	CYS	IMM.TER	III C	NO CHEMO	NEG	3mths	sym free
27	145/11	23	F	LFT	LSO	9 X 7 X 3 CM	SOLID	SOLID	DYSG	I A	NO CHEMO	3+	14 mths	sym free
28	3201/11	20	F	RT	RSO	11 X7 X 5 CM	MIXED	SOLID	DYSG	III C	3 BEC	2+	DEF	-
29	1439/12	16	F	RT	RSO	15 X10 X9 CM	SOLID	SOLID	DYSG	I	NO CHEMO	4+	3mths	sym free
30	2046/12	21	F	B/L	DEBULK	19 X 13 X 6 CM	SOLID	SOLID	DYSG	II B	2BEC	4+	chemo pend	-

KEY TO MASTER CHART

Bx no-biopsy number.

F-female.

RT- right.

LFT-left.

B/L-bilateral.

P/D-procedure done.

R.OVAR-right ovariotomy.

L.OVAR-left ovariotomy.

RSO-right salphingo oopherectomy.

LSO-left salphingo oopherectomy.

TAH-total abdominal hysterectomy.

BSO-bilateral salphingo oopherectomy.

DEBULK-debulking.

CM-centimeter.

CYS-cystic.

HPE-histopathological examination.

DYSG-dysgerminoma.

IMMAT.TER-immature teratoma.

YST-yolk sac tumour.

MGCT-mixed germ cell tumour.

BEC-bleomycin,etoposide,cisplatin.

NEG-negative.

Mths-months.

DEF-default.

Chemo pen-chemo pending.

Sym free-symptom free.

REC-recurrence.

ABSTRACT.

AIM:

The aim of current study is to know about the incidence of ovarian cancers, study about the histomorphological features of malignant germ cell tumours and also the immunohistochemical expression of CD117 with special emphasis on dysgerminoma of ovary, in patients admitted in Institute of Obstetrics and Gynaecology, Egmore, Madras Medical College.

MATERIALS AND METHODS:

The detailed case history of all the ovarian cancers were collected retrospectively and the paraffin blocks of 30 cases of malignant germ cell tumours were collected and subjected for immunohistochemical study of CD117 expression. The expression of CD117 is correlated with various clinico pathological parameters using pearson chi square test.

OBSERVATION AND RESULTS:

A total of 725 cases of ovarian neoplasms are observed, out of which 487 cases are benign, 34 cases are borderline and 204 cases are malignant. Among the malignant germ cell tumours observed, 11cases were dysgerminoma, 10 cases were mixed germ cell tumour, 5cases were immature teratoma and 4 cases were yolk sac tumour.90.9% of dysgerminoma, 70% of mixed germ cell tumour, 50% of yolk sac tumour and 20% of immature teratoma were positive for CD117.

CONCLUSION:

The incidence of malignant germ cell tumours is very less even in a tertiary hospital like MMC, hence trials involving a large group of people with germ cell tumours should be done for evaluation of c-kit expression and positive c-kit cases should be tried with anti-c kit compounds like imatinib so that it could be effective alternative for conventional platinum based regimens.

Key words: malignant germ cell tumours, dysgerminoma, CD117.

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THE STUDY OF CLINICOPATHOLOGICAL SIGNIFICANCE OF C-KIT EXPRESSION IN GERM CELL TUMOURS OF OVARY WITH SPECIAL REFERENCE TO DYSGERMINOMA

Dissertation submitted in partial fulfilment of the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH – III

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