HISTOPATHOLOGICAL ANALYSIS OF UTERINE CORPUS MALIGNANCIES AND THE ROLE OF IMMUNOHISTOCHEMISTRY IN DISTINCTION BETWEEN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA.

DISSERTATION

SUBMITTED FOR M.D. (PATHOLOGY)

BRANCH III

APRIL 2016

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CERTIFICATE

This is to certify this dissertation titled **"HISTOPATHOLOGICAL ANALYSIS OF UTERINE CORPUS MALIGNANCIES AND THE ROLE OF IMMUNOHISTOCHEMISTRY IN DISTINCTION BETWEEN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA.** is the bonafide record work done by **Dr. UMADEVI SRINIVASAN** submitted as partial fulfillment for the requirements of **M.D Degree Examinations** Branch III **Pathology** to be held in **April 2016**

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Date : .09.2015

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This is to certify that this dissertation entitled **"HISTOPATHOLOGICAL ANALYSIS OF UTERINE CORPUS MALIGNANCIES AND THE ROLE OF IMMUNOHISTOCHEMISTRY IN DISTINCTION BETWEEN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA."** is the original and bonafide work done by **Dr. UMADEVI SRINIVASAN** under my guidance and supervision at the Thanjavur Medical College & Hospital, Thanjavur, during the tenure of her course in M.D Pathology from June 2013 to April 2016 held under the regulation of the Tamilnadu Dr. M.G.R Medical University, Guindy, Chennai – 600032.

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Date : .09.2015

DECLARATION.

I Dr. UMADEVI SRINIVASAN solemnly declare that this Dissertation **HISTOPATHOLOGICAL ANALYSIS OF UTERINE CORPUS MALIGNANCIES AND THE ROLE OF IMMUNOHISTOCHEMISTRY IN DISTINCTION BETWEEN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA "" ** is a bonafide record of work done by me in the Department of Pathology, Thanjavur Medical College and Hospital, Thanjavur under the Guidance and Supervision of my Professor **Dr.AL.SANTHI, M.D.,D.G.O**, The Head of the Department, Department of Pathology, Thanjavur Medical College, Thanjavur between 2013 and 2016.

This Dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University , Chennai in partial fulfilment of University regulations for the award of M.D Degree (Branch – III) in Pathology to be held in April 2016.

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submitted by Dr. UMADEVI SRINIVASAN **of**

Dept. of PATHOLOGY **Thanjavur Medical College, Thanjavur**

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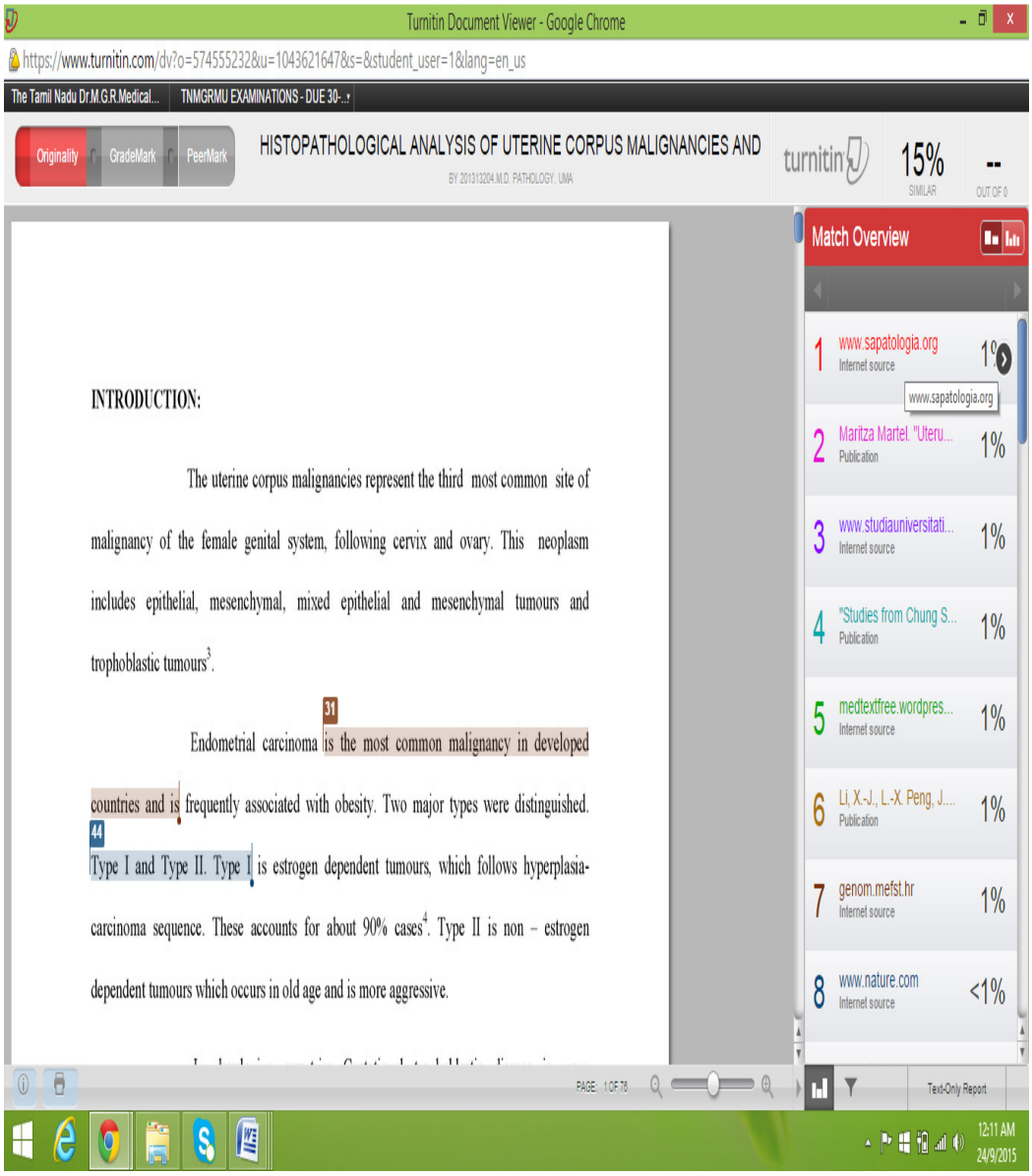
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The uterine corpus malignancies represent the third most common site of malignancy of the female genital system, following cervix and ovary. This neoplasm includes epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and trophoblastic tumours[3].
Endometrial carcinoma is the most common malignancy in developed countries and is frequently associated with obesity. Two major types were distinguished. Type I and Type II. Type I is estrogen dependent tumours, which follows hyperplasia-carcinoma sequence. These accounts for about 90% cases[4]. Type II is non – estrogen dependent tumours which occurs in old age and is more aggressive.
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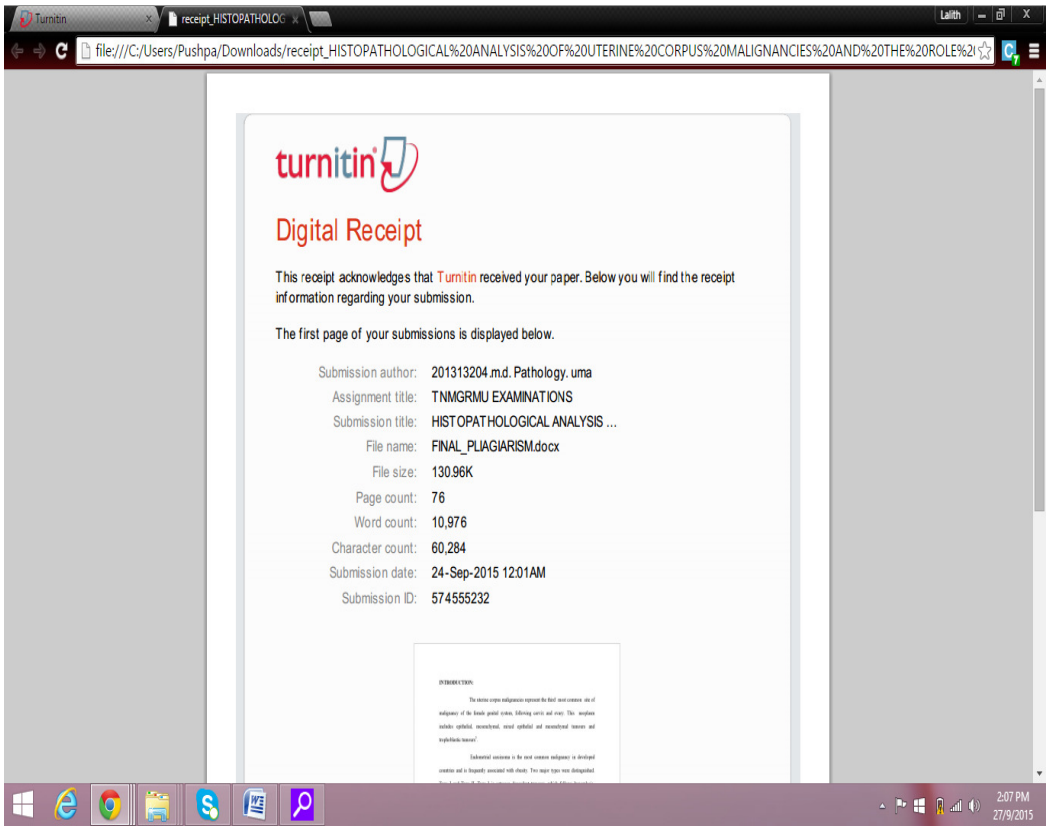
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CONTENTS

ABSTRACT

TITLE: HISTOPATHOLOGICAL ANALYSIS OF UTERINE CORPUS MALIGNANCIES AND THE ROLE OF IMMUNOHISTOCHEMISTRY TO DISTINGUISH BETWEEN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA.

The study was carried out in Thanjavur Medical college and Hospital in Tamil Nadu over a period of three and half years. In a total of 7910 gynaecological specimens received, 761 cases (9.6%) were reported to be uterine corpus neoplasms including benign and malignant neoplasms. There are 60 malignant uterine corpus neoplasms reported out of 761 cases (7.8%). The following histopathological diagnosis were reported within this given period of time are 49 cases of endometrial carcinoma, 4 cases of leiomyosarcoma, 4 cases of choriocarcinoma, 1 case of endometrial stromal sarcoma, 1 case of germ cell tumors and 1 case of carcinosarcoma. The inference is that endometrial carcinoma is the most common malignancy observed in our study as seen in other literatures. In endometrial adenocarcinoma, Endometriod adenocarcinoma NOS type is the most common pattern noted. 76% of cases are exhibiting grade I features which is not in concordance with other studies, where Grade II features is prevalent. Around 80 % of tumors are Stage I tumors and hence simple hysterectomy is sufficient. Although stage II, III and higher grade tumors require Radical Hysterectomy with lymphadenectomy.

The other histologic variants documented in our study are 1 case of uterine papillary serous carcinoma, 1 case of clear cell adenocarcinoma, 1 case of squamous cell carcinoma in an elderly women presenting with pyometra, and 2 cases of poorly differentiated carcinoma.

The Immunohistochemical stains used in our study are ER and P16 . The expression of both the markers were studied in a total of 20 small biopsy / curettings which includes 10 cases of endometrial adenocarcinoma and 10 cases of endocervical adenocarcinoma. 90% of endocervical adenocarcinoma expressed P16 and 40% of endometrial adenocarcinoma expressed P16.

ER expression was 60% in endometrial adenocarcinoma and 30 % in endocervical adenocarcinoma.Both markers were positive in 30% of cases and no single marker is diagnostic to distinguish endometrial adenocarcinoma from endocervical adenocarcinoma. Various literatures rtecomment panel of IHC markers to distinguish this two. The panel should include ER, PR, Vimentin, CEA, P16.

ER, PR, and vimentin is predominantly positive in Endometrial adenocarcinomas whereas CEAand P16 is positive in Endocervical adenocarcinomas.

Recent studies have shown that Conventional three panel markers ER/Vimentin/CEA panel is sufficient, appropriate and useful. Ancillary PR and P16 INK 4a add no value to the performance of the conventional three marker ER/Vimentin/CEA panel.

Key words: Uterine corpus malignancies, Endometrial carcinoma, Immunohistochemistry ER, P16,

INTRODUCTION:

The uterine corpus malignancies represent the third most common site of malignancy of the female genital system, following cervix and ovary. This neoplasm includes epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and trophoblastic tumours[3].

Endometrial carcinoma is the most common malignancy in developed countries and is frequently associated with obesity. Two major types were distinguished. Type I and Type II. Type I is estrogen dependent tumours, which follows hyperplasia-carcinoma sequence. These accounts for about 90% cases[4]. Type II is non – estrogen dependent tumours which occurs in old age and is more aggressive.

In developing countries Gestational trophoblastic disease is more common. Risk factors include a history of prior gestational trophoblastic disease, blood group A women married to group O men and a diet low in vitamin A[3].

Carcinosarcoma is a mixed epithelial and mesenchymal tumour, its prognosis is worse than that of other members of the epithelial category.

Lower uterine segment carcinoma mainly adenocarcinoma endometrium versus endocervix is difficult to distinguish since there is substantial morphologic overlap between them. The treatment modality varies for both entities. Endometrial adenocarcinoma is treated with simple hysterectomy and bilateral salphingo-oopherectomy while endocervical adenocarcinoma is treated with radical hysterectomy, pelvic lymphadenectomy and primary chemo-radiotherapy. Hence the difference in the therapeutic approaches necessitate attempts to distinguish these two tumors is paramount.

Application of immunohistochemical markers made its way. Several studies have attempted using a panel of IHC markers and found relatively good result in distinguishing between these adenocarcinomas. The most common panel includes antibody against Estrogen receptor (ER), progesterone receptor (PR), vimentin , carcinoembryonic antigen (CEA), and P16[8,9,11,12.]

They were used in different combinations in different studies to minimize the differences.

CEA and P16 positivity were more common in cervical adenocarcinomas about 62 % and 94% each respectively, Vimentin, ER, PR, were more common in endometrial adenocarcinomas, showing 70%, 90%, 96% positivity each[37]

Our study is directed towards the histopathological analysis of uterine corpus malignancies and its histologic subtypes correlated with age, the presentation, grade and staging of the tumor. The other part of the study is to analyse the role of Immunohistochemical markers ER and P16 to distinguish between endometrial adenocarcinoma vs. endocervical adenocarcinoma in biopsy/ curettage specimens.

The results have been compared with other journals and literature.

AIM OF THE STUDY:

1. To study the proportion of uterine corpus malignancies reported in the department of pathology, Thanjavur medical college from the period of January 2012 till 2015 June.

2. To analyse the various histopathological types of uterine corpus malignancies.

3. To classify and grade the endometrial carcinoma in order to predict the prognosis.

4. Lower uterine segment adenocarcinoma is a diagnostic difficulty, hence with help of two IHC markers endometrial adenocarcinomas can be distinguished from endocervical adenocarcinomas using ER and p16 IHC markers.

MATERIALS & METHODS*:*

STUDY PERIOD: January 2012 till June 2015

This study was conducted for, a period of three and half years in Thanjavur medical college and hospital. It is both a retrospective and a prospective study.

Totally we have received 7910 gynaecological specimens for histopathological examination. out of which 761 cases were reported as uterine corpus neoplasms including both benign and malignant tumors which excludes cervical, ovarian and adnexal neoplasms. out of which all cases of uterine corpus malignancy were recorded which counts about 60 in number and are taken for histopathological analysis .

The second objective is to analyse the role of immunohistochemical markers ER and P16 to distinguish the low grade endometrial adenocarcinoma versus endocervical adenocarcinoma. For Immunohistochemistry analysis, 10 cases of low grade endometrial adenocarcinoma and 10 cases of endocervical adenocarcinoma small biopsy specimen were taken for IHC study with ER and P16 markers.

INCLUSION CRITERIA:

1. All uterine corpus carcinomas

2. All uterine corpus sarcoma

3. Mixed malignant tumors

4. Malignant gestational trophoblastic disease

5. other malignant tumors

EXCLUSION CRITERIA:

1. Benign uterine corpus neoplasms

2.Endometrial hyperplasia with atypia

3. Endometrial intraepithelial neoplasia

4. cervical neoplasms

5. ovarian neoplasms

6. metastatic neoplasms.

HISTOPATHOLOGICAL EXAMINATION:

Endometrial curetting/biopsy specimen were fixed in 10% neutral buffered formalin in Toto, and also tissue bits were taken from selective areas of the hysterectomy specimens fixed in 10% neutral buffer formalin followed by routine processing. Sections of 3-4 micron thickness was made, stained with haematoxylin and eosin and subjected to histopathological examination.

IMMUNOHISTOCHEMICAL EVALUATION:

For IHC study, 10 cases of endometrial adenocarcinoma and 10 cases of endocervical adenocarcinoma diagnosed in small biopsies were taken and subjected to ER and P16 antibody markers study. The slides were then analysed and correlated with HPE report.

Immuohistochemical analysis were done in paraffin embedded tissue samples using the Next Generation Micro-Polymer HRP system based on non-biotin polymeric technology provided by Thermo Scientific Ultra vision Quanto detection system for Immunohistochemistry. 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 monoclonal antibody and then detected by the addition of secondary antibody conjugated with horse radish peroxidase-polymer and diaminobenzidine substrate.

Immunohistochemistry procedure:

Slide Preparation:

1. Sections with a thickness of 4 µ were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.
2. The slides were incubated for overnight at 58ºC.
3. The sections were deparaffinised in xylene for 15 minutes x 2changes.
4. The sections were dehydrated with absolute alcohol for 5 minutes for 2 changes.
5. The sections were then washed in tap water for 10 minutes.
6. The slides were then immersed in distilled water for 5 minutes.

Antigen Retrieval:

1. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 minutes. This step unmasks the antigenic determinants of fixed tissue sections.
2. The slides were then cooled to room temperature for 20 minutes and washed in running tap water for 5 minutes.
3. The slides were then rinsed in distilled water for 5 minutes.
4. They were washed with appropriate wash buffer (citrate buffer) for 5 minutes x 2 changes.
5. Peroxidase block was applied over the sections for 10 minutes.
6. The slides were washed in citrate buffer for 5 minutes x 2 changes.
7. Sections were covered with peroxidase block for 5 minutes.

Antibody application:

1. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 30 minutes.
2. The slides were washed in citrate buffer for 5 minutes x 2 changes.
3. The slides were covered with Primary antibody amplifier for 10 minutes.
4. The slides were washed in citrate buffer for 5 minutes x 2 changes.
5. The slides were covered with HRP micropolymer Quanto for 10 minutes.
6. The slides were washed in citrate buffer for 5 minutes x 2 changes.

Chromogen application:

1. DAB substrate was prepared by diluting 1 drop of DAB Quanto chromogen to 1 ml of DAB Quanto buffer.
2. DAB substrate solution was applied on the sections for 5 minutes.

3. The slides were washed in distilled water for 2 minutes.
4. The sections were counterstained with Hematoxylin for 2 seconds.
5. The slides were washed in running tap water for 5 minutes.
6. The slides were air dried, mounted with DPX.

Alternate methods of antigen retrieval

- Pressure cooker antigen retrieval
- Microwave and trypsin antigen retrieval

IMMUNOHISTOCHEMISTRY SCORING SYSTEM

Estrogen receptor scoring was done using Allred scoring system

Allred scoring system:[39]

The score was given based on the percentage of proportion of cells taken the stain and the intensity of the stain

Proportion of tumor cells taken nuclear stain	**Score**
No cells taken	0
<1%	1
1-10%	2
11-33%	3
34-66%	4
67-100%	5

Intensity of the stain – ER	**SCORE**
No staining	0
Weak	1
Intermediate	2
Strong	3

Allred score =proportion of cells taken nuclear stain + in score and intensity score

maximum score =8

minimum score = 0

Results ≤ 2 = negative

3-8 = positive

P16- SCORING: [17]

Tumor was given a score according to the intensity of nuclear staining.

and extent of stained cells.

Intensity of nuclear staining	Score
No staining	0
Weak staining	1
Moderate staining	2
Strong staining	3

Extent of stained cells	Score
No staining	0
1-10% of cells	1
11-50%	2
51-80%	3
81-100%	4

P16 SCORE= Intensity of the stain X Extent of positivity

maximum score = 12

minimum score = 0

RESULT: ≤ 4 : negative

≥ 4 : positive

REVIEW OF LITERATURE

UTERINE CORPUS MALIGNANCIES

WHO HISTOLOGICAL CLASSIFICATION OF TUMORS OF UTERINE CORPUS[3]

ENDOMETRIAL TUMORS AND RELATED LESIONS

Endometrial carcinoma

- Endometriod adenocarcinoma
- Mucinous adenocarcinoma
- Serous adenocarcinoma
- Clear cell adenocarcinoma
- Mixed cell adenocarcinoma
- Squamous cell carcinoma
- Transitional cell carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Others

Endometrial hyperplasia

Nonatypical hyperplasia

- Simple
- Complex

Atypical hyperplasia

- Simple
- Complex

Endometrial polyp

Tamoxifen related lesions

MESENCHYMAL TUMORS:

Endometrial stromal and related tumors

- Endometrial stromal sarcoma
- Endometrial stromal nodule
- Undifferentiated endometrial sarcoma

Smooth muscle tumors:

Leiomyosarcoma

- Epitheloid variant
- Myxoid variant

Smooth muscle tumor of uncertain malignant potential

Leiomyoma not otherwise specified

Histologic variants

- Mitotically active variant
- Cellular variant
- Hemorrhagic cellular variant
- Epitheloid variant

- Myxoid variant
- Atypical variant
- Lipoleiomyoma variant

Growth pattern variants:

- Diffuse leiomyomatosis
- Dissecting leiomyoma
- Intravenous leiomyomatosis
- Metastasizing leiomyoma

Miscellaneous mesenchymal tumors:

- Mixed endometrial stromal and smooth muscle tumor
- Perivascular epitheloid cell tumor
- Adenomatoid tumor

Other malignant mesenchymal tumor

Other benign mesenchymal tumors

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

- Carcinosarcoma (MMMT)
- Adenosarcoma
- Carcinofibroma
- Adenofibroma
- Adenomyoma

GESTATIONAL TROPHOBLASTIC DISEASE:

Trophoblastic neoplasms

- Choriocarcinoma
- Placental site trophoblastic tumor
- Epitheloid trophoblastic tumor

Molar pregnancies

- Hydatiform mole
    - Complete
    - Partial
- Invasive
- Metastatic

Non-neoplastic, non molar trophoblastic lesions

- Placental nodule and plaque
- Exaggerated placental site.

Miscellaneous tumors:

Sex cord like tumors

Neuroectodermal tumors

Melanotic paraganglioma

Tumors of germ cell type

lymphoid and Hematopoetic tumors

Malignant lymphoma

Leukemia

SECONDARY TUMORS

ENDOMETRIAL ADENOCARCINOMA

It is the primary malignant epithelial tumour arising in the endometrium .

Types :Type I and Type II

Type I endometrial adenocarcinoma

Constitutes about 80- 85 % of cases. It is estrogen dependent tumor follows the endometrial hyperplasia – carcinoma sequence. It includes the well and moderately differentiated tumor, predominantly of endometriod type.

: Risk factors : prolonged oestrogen exposure as in nulliparity, late menopause, anovulatory cycles with polycystic ovarian syndrome where there is unopposed hyperestrogen secretion happening stimulating the follicles, exogenous hormone replacement therapy, obesity which is an independent risk factor for carcinoma. It is by the action of peripheral conversion of fats into estrogen by aromatase enzyme.

ESSENTIAL DIAGNOSTIC CRITERIA OF ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (EIN)[73]

EIN CRITERIA	COMMENTS
1. Architecture	Gland area exceeds that of stroma, usually in a localized region
2. Cytological alterations	Cytologically differs between architecturally crowded focus and background
3. Size >1mm	Maximum linear dimension should exceed 1 mm. smaller lesions have unknown natural history.
Exclude benign mimics and cancer	

Type II endometrial adenocarcinoma:

This is non estrogen dependent carcinoma which occurs in old post-menopausal women.

These are high grade tumors with high grade nuclear features such as serous adenocarcinoma and clear cell adenocarcinoma. They have an aggressive behavior.

CHARECTERISTICS OF TYPE I & TYPE II ENDOMETRIAL CARCINOMA[6]

CHARACTERISTICS	TYPE I	TYPE II
Age	55-65 yrs	65-75 yrs
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometriod	Serous Clear cell Mixed mullerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
Mutated genes/genetic abnormalities	PTEN ARID1A PIK3CA KRAS MSICTNNB1	TP53 Aneuploidy PIK3CA CHD4 PPP2R1A

	TP53	
Behaviour	Indolent Spreads via lymphatics	Aggressive intraperitoneal and lymphatic spread

Clinical features:

Post menopausal bleeding

Abnormal uterine bleeding earlier in life.

In endometiod adenocarcinoma may be manifested by obesity, infertility and late menopause.

Endometriod adenocarcinoma:

This is the most common type, The tumor resembles that of normal endometrium. It is characterized by glandular or villoglandular pattern lined by simple to pseudostratified columnar cells that have their long axis perpendicular to the basement membrane with rounding or elongated nuclei polarized in the same direction.

Spectrum of histologic differentiation from very well differentiated carcinoma to undifferentiated carcinoma as the glandular differentiation decreases and is replaced by solid nests and sheets of cells.

with four different variants documented namely:

- Endometriod adenocarcinoma with squamoid differentiation
- Villoglandular variant
- Secretory variant

- Ciliated cell variant.

Variant with squamoid differentiations criteria for diagnosis:

1. Keratinization demonstrated with standard staining techniques
2. Intercellular bridge and/or
3. Three or more of the following four criteria
    a. Sheet like growth without gland formation or palisading
    b. Sharp margins
    c. Eosinophilic and thick glassy cytoplasm
    d. A decreased nuclear to cytoplasmic ratio as compared with foci elsewhere in the same tumor

Villoglandular variant

Next most common variant. Here the tumor cells are arranged in numerous villous fronds with a delicate central core. The cells are arranged in perpendicular to the basement membrane in contrast to the more complex papillary architecture and high grade nuclear features.This is usually seen involving part of a low grade endometriod carcinoma .

Secretary variant:

The glands are lined by epithelium with voluminous glycogen vacuoles in the sub nuclear location reminiscent of early secretary endometrium but can be identified by the confluent ,cribriform or villoglandular pattern .

Ciliated cell variant:

It is a very rare variant. The glands are lined by ciliated cells which resembles tubal epithelium with malignant features. ciliated cells may be seen in endometriod adenocarcinoma but to define as this variant it should be present in majority of glands.

MUCINOUS ADENOCARCINOMA

These are grade I tumors with favourable prognosis. The tumor cells contain intracytoplasmic mucin unlike endometriod and clear cell adenocarcinoma which has intraluminal mucin.

Incidence - 9% of endometrial carcinoma [3]

Variants of mucinous adenocarcinoma:

Microglandular adenocarcinoma

Intestinal type with goblet cells.

TNM AND FIGO STAGING OF NON- TROPHOBLASTIC TUMOURSNOF THE UTERINE CORPUS

TX		Primary tumor cannot be assed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	1 A B C	CONFINED TO CORPUS UTERI Limited to endometrium <1/2 of myometrial invasion >1/2 of myometrial invasion
T2	II	TUMOR INVADES CERVIX

	A B	Endocervical gland involvement Cervical stroma invasion
T3	III A B C/ N1	LOCAL AND REGIONAL SPREAD Direct extension or metastasis to serosa and/or adnexa Ascitic fluid or peritoneal washing + for tumor cells Vaginal involvement Metastasis to pelvic or paraaortic node
T4	IV A B/M1	 Bladder mucosa and/or bowel mucosa Distant metastasis

N	REGIONAL LYMPHNODES
X	Cannot be assessed
0	No node metastasis
1	Regional node metastasis
M	DISTANT METASTASIS
0	No distant metastasis
1	Distant metastasis

Grading of type 1(endometriod and mucinous) endometrial adenocarcinoma by FIGO grading system[38]

It is based on the degree of differentiation as defined by percentage of glandular and solid components (areas of squamous differentiation are not considered regions of solid growth)[59]

Grade1: <5% solid areas (non squamous,non-morular) growth pattern

Grade2: 6-50%

Grade3: >50%

Nuclear pleomorphism inappropriate for the tumor architecture increase the tumor grade by 1 degree.

SEROUS ADENOCARCINOMA:

It is an aggressive high grade tumor with high recurrence rate, classified as type II endometrial carcinoma. It is not associated with exogenous or endogenous estrogen stimulation. Usually arises from atrophic endometrium. It has a tendency for deep myometrial invasion and extensive lymphatic invasion.The precursor lesion is serous endometrial intraepithelial carcinoma also called as endometrial carcinoma in situ and surface serous carcinoma. But it carries the same prognosis since dissemination outside the uterus in the absence of invasion has also been noted.

Histopathology:

The neoplastic cells are arranged in complex papillary pattern having broad fibrovascular core with highly pleomorphic cytological changes.

The cells and nuclei are rounded and lack a perpendicular orientation to the basement membrane. The nuclei are poorly differentiated apically situated and have a large brightly eosinophilic macronucleoli.

There are often atypical mitosis , bizarre multinucleated cells are commonly present.

Psamoma bodies are found in 30 % cases. Prominent sloughing of cells are present.

CLEAR CELL ADENOCARCINOMA:

These are the other type II adenocarcinoma, less common than serous type. Incidence-1-5% occurs in old age group of people[3] .Adenocarcinoma exhibiting clear cells and hobnail appearance. There are three types of pattern arrangement noted such as, Solid, tubulocystic or papillary patterns or a combination of these three. They have a relatively better prognosis than serous adenocarcinoma.

Histopathology:

These cells typically have clear , glycogen filled cytoplasm and hob nail cells that project in to the lumens. Nuclei are highly pleomorphic, bizarre and multi nucleated.

Occasionally the cytoplasm is eosinophilic and granular like concocts.

MIXED ADENOCARCINOMA:

Tumors exhibiting both type I and type II endometrial carcinoma, the minor type should comprise atleast 10 % of total volume of tumor. More than 25 % of type II tumors carries a poor prognosis.

SQUAMOUS CELL CARCINOMA:

This is an uncommon tumor. So far only 70 cases have been documented in literature[3].The tumor cells composed of squamous cells with varying degree of differentiation. Its includes a rare verrucous variant.

Usually occurs in postmenopausal women and is often associated with cervical stenosis and pyometra.

It should be differentiated from SCC arising from Ca cervix extending to endometrium and endometriod adenocarcinoma with squamous differentiation.

It carries a poor prognosis although verrucous variant may be more favourable.

TRANSITIONAL CELL CARCINOMA:

The tumor cells resembles urothelial transitional cells, which should constitute about 90% of tumor cell volume.

They are grade 2- grade 3 tumors presenting as polypoid or papillary mass

It should be differentiated from urothelial carcinoma from bladder and ovary.

HPV type 16 is associated with this tumor.

SMALL CELL CARCINOMA:

This tumor comprises less than 1 % incidence. Uncommon tumor in endometrium. The histology is similar to that of small cell carcinoma in other organs. The prognosis is far better in stage I disease with a 5 year survival of about 60 % unlike in other sites.

UNDIFFERENTIATED CARCINOMA:

These tumors lack any kind of differentiation.

GENETICS OF ENDOMETRIAL CARCINOMA [3,6]

Inactivation of PTEN tumor suppressor pathway- endometrial type 1 adenocarcinoma

PTEN checks cell division and enables apoptosis via AKT- growth regulatory pathway. When PTEN function is lost, PI3K/AKT pathway becomes overactive and enhances the ability of oestrogen receptors to turn on the expression of

its target genes, leading to overgrowth of cell types that depend on estrogen for trophic signals such as endometrium and mammary epithelial cells

Normally PTEN is expressed only during estrogen driven proliferative phase of the endometrium.

TP53 tumor suppressor pathways mutation – endometrial type II adenocarcinoma.

Mutant protein accumulates in nuclei which can be demonstrated by IHC in most serous (type II adenocarcinoma).

Its expression is associated with poor clinical outcome

MOLECULAR DELINEATION OF PREMALIGNANT DISEASE:

- The earliest molecular change: loss of PTEN – are detectable at a stage before glands have undergone any change in the morphology
- Followed by accumulation of genetic damage MSI , KRAS mutation →emergence of histologically evident monoclonal lesions.

GENETIC SUSCEPTIBILITY:

Majority of cases are sporadic but rarely present as a manifestation of multicancer familial syndromes, examples include:

HNPCC- hereditary non polyposis colon cancer- caused by DNA mismatch repair genes that produce constitutive microsatellite instability.

Cowden syndrome: germ line PTEN inactivation.

MESENCHYMAL TUMORS:

Uterine mesenchymal tumors are derived from mesenchyme of the corpus consisting of endometrial stroma, smooth muscle and blood vessels or admixtures of these.

The most common mesenchymal malignant tumor of the uterine corpus are

1. Leiomyosarcoma
2. Endometrial stromal tumors

Clinical features:

Uterine enlargement, abnormal uterine bleeding, or pelvic pain.

ENDOMETRIAL STROMAL TUMOR:

2014 classification.

- Endometrial stromal sarcoma
  - low grade
  - High grade
- Undifferentiated endometrial sarcoma
- Endometrial stromal nodule

The average age of presentation is 45 years, usually presents with vaginal bleeding.

Microscopically these tumor cells resembles that of proliferative endometrial stromal cells. The individual cells are uniform and predominantly oval in shape. Individual cells are enveloped by reticulin fibers They are divided in to benign and malignant groups based on the type of margin of the lesion.

Endometrial stromal nodule have pushing margins which is a benign tumor

Endometrial stromal sarcoma have infiltrative margins which is a malignant tumor.

ENDOMETRIAL STROMAL SARCOMA LOW GRADE:

It's a rare tumor of the uterus comprising for only 0.2 % of all genital tract malignancy

GROSS:

Solitary well delineated predominantly intramural mass but invasion of the myometrium is more common

C/S: yellow to tan , soft, cystic and myxoid degeneration as well as necrosis and haemorrhage are seen occasionally.

Localization: metastasis is rare

extrauterine extension is present in one third of cases , which is seen as worm like plugs of tumor within the vessel of broad ligament and adnexa.

Histopathology: Low grade endometrial stromal sarcoma

Densely cellular tumor

composed of uniform oval to spindled cells of endometrial stromal type.

significant atypia and pleomorphism are absent.

Rich network of delicate small arterioles resembling the spiral arterioles of late secretory endometrium that supports the proliferating cells.

High mitotic index does not itself alter the diagnosis.

Other cellular changes noted are:

1. Cells with foamy cytoplasm, foamy histiocytes
2. Endometrial type glands seen in 10-11% of tumors [3]
3. Sex cord like structures
4. Myxoid and fibrous change
5. Perivascular hyalinization and stellate pattern of hyalinization
6. Necrosis is typically absent
7. Special stain: reticulin stain : dense network of fibrils surrounding individual cells or small group of cells
8. Smooth muscle differentiation (spindle or epitheloid) may develop but limited to <30% of the tumor
9. If smooth muscle component is > 30% - it is called as MIXED ENDOMETRIAL STROMAL AND SMOOTH MUSCLE TUMOR

Differential diagnosis:

1. stromal nodule

2. Intravenous leiomyomatosis

3. Adenomyosis with sparse glands

4. Adenosarcoma

In biopsy material it is highly impossible to distinguish low grade ESS from a stromal nodule or leiomyoma or a non neoplastic stromal proliferation.

Treatment

Resection, radiation therapy, progestin therapy or a combination.

Prognosis:

Indolent and late recurrences

5 year survival rate from 67% to 100%

Pulmonary metastasis occur in 10% of stage I tumors.

UNDIFFERENTIATED ENDOMETRIAL SARCOMA:

It is otherwise called as undifferentiated uterine sarcoma

Macroscopy:

One or more polypoid , grey to yellow fleshy endometrial masses with prominent haemorrhage and necrosis.

Histopathology :

Marked atypia and abundant mitotic activity. They lack the typical growth pattern and vascularisation of low grade endometrial stromal sarcoma. They resemble the sarcomatous component of carcinosarcoma.

These sarcomas are negative for estrogen and progesterone receptors.

Prognosis:

Aggressive and death occurs from tumor dissemination within 3 yrs after hysterectomy.

MALIGNANT SMOOTH MUSCLE TUMORS:

- Leiomyosarcoma
- Smooth muscle tumor of uncertain malignant potential

LEIOMYOSARCOMA

It's the most common malignant uterine sarcoma comprising about 1% of all uterine malignancies.

Median age of presentation is 50-55 years

Clinical features:

Leiomyosarcoma localized to the uterus and leiomyoma produce similar symptoms.

Rapid increase in size of the uterus after menopause

Spread: locally or by haematogenous dissemination most often to the lungs

Macroscopy:

Characteristically solitary , intramural mass , not associated with leiomyomas.

Average size 8 cm diameter and fleshy with poorly defined margins

C/S: grey-yellow or pink sectioned , zones of haemorrhage and necrosis are seen

Histopathology:

Cellular tumor composed of fascicles of spindled shaped cells that possess abundant eosinophili cytoplasm.

The nuclei are fusiform , have rounded ends, hyperchromatic with coarse chromatin and prominent nucleoli.

Tumor cell necrosis is typically prominent but need not be present.

DIAGNOSTIC CRITERIA FOR LEIOMYOSARCOMA

	Standard smooth muscle differentiation	Epitheloid differentiation	Myxoid differentiation
Histology	Fascicles of cigar shaped spindles cells with scanty to abundant eosinophilic cytoplasm	Rounded cells with central nuclei and clear to eosinophilic cytoplasm	Spindle-shaped cells set within an abundant myxoid matrix Low cellularity
Criteria for leiomyosarcoma	Any coagulative tumor cell necrosis (CTCN) <u>In the absence of</u> <u>CTCN</u> the diagnosis requires Diffuse, moderate to severe cytologic atypia and Mitotic index of >10 mf/10hpf If mf <10mf – this group is labelled as **"atypical leiomyoma with low risk of recurrence."**	CTCN+ <u>If CTCN (–)</u> Diffuse, moderate to severe cytologic atypia Mitotic index of >5mf/10hpf	CTCN (+) <u>If CTCN (–)</u> Diffuse, moderate to severe cytologic atypia Mitotic index of >5mf/10hpf

Comments	CTCN (-) Significant atypia (-) Mitotic index(+) >15mf/10hpf- " **mitotically active leiomyoma with limited experience"**	Focal epitheloid differentiation may be mimicked by cross-sectioned fascicles	Perinodular hydropic degeneration should not be included in this group.

CTCN: Abrupt transition from viable tumor to necrotic tumor, ghost outlines of cells usual , haemorrhage and inflammation uncommon.

MISCELLANEOUS MESENCHYMAL TUMORS:

These are the mesenchymal tumors that do not show smooth muscle or stromal differentiation.

- PERIVASCULAR EPITHELOID CELL TUMOR- uncertain malignant potential

MIXED EPITHELIAL AND MESENCHYMAL TUMORS:

The tumors composed of both epithelial and mesenchymal component.

- Carcinosarcoma
- Adenosarcoma
- Carcinofibroma

The benign tumors are Adenofibroma, Adenomyoma, Atypical polypoid variant.

	Benign epithelium	Malignant epithelium
Benign mesenchyme	Adenofibroma Adenomyoma (including atypical)	Carcinofibroma
Malignant mesenchyme	Adenosarcoma	Carcinosarcoma

CARCINOSARCOMA/ MALIGNANT MULLERIAN MIXED TUMOR/ METAPLASTIC CARCINOMA

This malignant neoplasm composed of admixture of malignant epithelial and mesenchymal components.

This is the most common malignancy of this group.

Usually occur in elderly postmenopausal women with median age of 65 years, occasional cases occur in younger women.

Possible risk factors:

Prior pelvic irradiation

Long term tamoxifen therapy [3]

Clinical features:

Vaginal bleeding is most frequent.

Abdominal mass and pelvic pain

Polypoid mass may prolapse through cervix

Most of them can be diagnosed by uterine curettage and is most diagnostic method, some need hysterectomy for diagnosis [3]

GROSS:

Polypoid , bulky, necrotic , hemorrhagic tumor that fill the endometrial cavity and deeply invade the myometrium.

Cartilage or bone tissue are found in many cases and gives a hard consistency.

Microscopy:

Malignant epithelial element-

Glandular- endometriod, serous, or clear cell type

Non-glandular – squamous or undifferentiated type

Malignant mesenchymal / sarcomatous element:

Composed of either homologous or heterologous elements

Homologous elements –

undifferentiated sarcoma

leiomyosarcoma

endometrial stromal sarcoma

Heterologous elements -

Malignant cartilage

Malignant skeletal muscle /rhabdomyoblast

Liposarcoma

Osteosarcoma

GESTATIONAL TROPHOBLASTIC DISEASE

Disorders of placental developement

Hydatidiform mole

Complete and Partial mole

Neoplasms of Trophoblast

Choriocarcinoma,

Placental site trophoblastic tumor

Epitheloid trophoblastic tumor

A common feature of all these lesions is that they produce human chorionic gonodotrophin and it serves as a marker for persistent disease.

CHORIOCARCINOMA

Gestational choriocarcinoma can occur following any type of pregnancy

Risk factor

Complete hydatidiform mole - major predisposing factor

Following abortion

Following term pregnancy

The tumor arises from the trophoblastic tissue.

Presenting features: Abnormal vaginal bleeding in the postpartum period,

Elevated serum hcG

Microscopy:

Absence of chorionic villi,

presence of dimorphic population of trophoblastic cells. The syncytiotrophoblastic cells alternating with nest or sheets of mononucleate cytotrophoblast or intermediate trophoblast giving a plexiform pattern, invading the normal tissues.

Hemorrhage and Necrosis are prominent.

syncytiotrophoblast have eosinophilic to amphophilic cytoplasm with small vacuoles or large lacunae that often contain RBCs. and have multiple nuclei ranging from 3-20 per cell

cytotrophoblast are small and uniform. They have a single nucleus and a prominent nucleoli.

Intermediate Trophoblast: large cells, polygonal in shape, one or two large hyperchromatic nuclei occur in choriocarcinoma.

IHC markers:

ST: hCG +

Inhibin- alpha+

PLACENTAL SITE TROPHOBLASTIC TUMOR:

these tumors are usually benign, despite destructive growth in the myometrium

About 15% of reported tumors have shown aggressive malignant behavior with disseminated metastasis.

EPITHELOID TROPHOBLASTIC TUMOR:

It is a rare tumor, recently recognized. They resemble the somatic carcinomas

IMMUNOHISTOCHEMISTRY ON UTERINE CORPUS MALIGNANCY [8]

no single marker is diagnostic to differentiate between endocervical and endometrial adenocarcinoma

	Endometrial adenocarcinoma UEC	Endocervical adenocarcinoma ECA
CEA	Up to 50% Cytoplasmic,luminal, Intensity - strong	100% Luminal Intensity - week
Vimentin	+++	-
ER	Nuclear positivity	
PR	Nuclear positivity	
P16	Diffuse Both nuclear and cytoplasmic	Patchy

international federation of gynecological and obstetrics FIGO grades 1 and 2 uterine endometrial carcinomas tumors express ER ,PR and vimentin

whereas most ECAs express CEA and P16 diffusely.

IMMUNOHISTOCHEMISTRY:

Albert Coons et al in 1941 first labelled antibodies directly with fluorescent isocyanate. Nakane and Pierce et al in 1966, introduced the indirect labelling technique in which the unlabelled antibody is followed by second antibody or substrate. Various stages of development of Immunohistochemistry include peroxidase – antiperoxidase method (1970), alkaline phosphatase labelling (1971), avidin biotin method

(1977) and two layer dextrin polymer technique (1993)[40].

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[41]. 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.[40]

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[42].

PITFALLS OF HEAT PRETREATMENT:

Drying of sections at any stage after heat pre-treatment 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 labelled 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[40].

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[43].

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.

USES OF IMMUNOHISTOCHEMISTRY IN LOWER UTERINE SEGMENT ADENOCARCINOMA:

Distinction between endocervical adenocarcinoma of endometrioid type from endometrial adenocarcinoma of endometrioid type can be done using a panel of conventional immunohistochemical markers ER, PR, CEA,and VIMENTIN.

other IHC markers found to be useful are P16, HPV ISH,ProExc.[34]

The pre-operative distinction between an uterine adenocarcinoma and an endocervical adenocarcinoma is very important because the treatment for an endometrial cancer is commonly a simple hysterectomy (sometimes if the cervical involvement is identified before surgery , the treatment is modified radical hysterectomy) , while for an endocervical adenocarcinoma primary chemotherapy is given with radical hysterectomy.

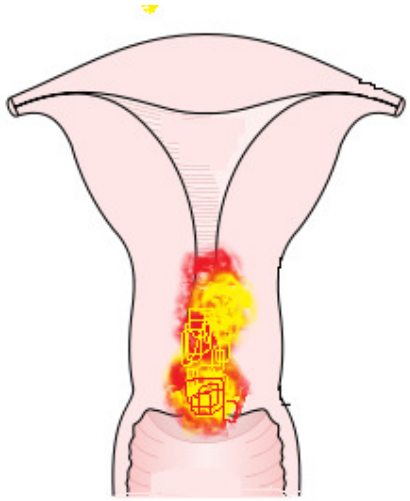


Figure 1. Tumour involving lower uterine segment and cervix arouse the suspicion of its primary

Estrogenic Receptor ER:[64]

ER, is an Estrogenic Receptor, which is a protein of 67 kDa molecular weight, this derives its name from the alpha estrogenic receptor. This estrogenic receptor gene composed of 140 kDa of DNA which is further divided into 8 exons,a C- terminus epitope, a SP1 clone and nuclear marker[52].

Estrogen and progesterone receptors belong to super family proteins. These nuclear transcription factors are involved in breast development, growth and tumorigenesis.[53] There are two forms of Estrogen receptors – Estrogen receptor α and Estrogen receptor β encoded by 6p25.1 and 14q genes respectively.[53]

Estrogen receptor α is found in endometrium, breast, ovarian stroma and hypothalamus. Estrogen receptor β is seen in kidney, brain, bone, heart and lungs. Estrogen receptors regulate the expression of progesterone and bcl2.[54]

Walker D et al in 1999 proposed that estrogen receptors are cytoplasmic in unliganded state. During activation, estrogen receptor diffuses into the cytoplasm and migrates to nucleus. After dimerisation of the receptor, it binds to Hormone

Responsive Elements in DNA and activate MAPK/P13K pathway to induce cell proliferation.

ER immunoexpression in the paraffin blocks need a boiling pretreatment in 10mMl citrate tampon, for a period of 20 minutes in a pH of 6.0 , and in the next 20 minutes it is allowed to cool at room temperature . Then the primary antibody is incubated into the tissues for next half an hour[52]

A study showed, 93% of adenocarcinomas arising from endometrium with strong estrogen receptor (ER) positivity, while only 38% of endocervical adenocarcinomas showing weak and focal ER positivity[55].

Progesterone Receptor PR:

PR is a Progesteronic Receptor, which is a regulating protein of the progesteronic receptor[55].

It was observed that PR positivity was noted in 81 % of endometrial adenocarcinomas, while focal PR positivity noted in endocervical adenocarcinomas[35.]

Along with ER expression , the PR expression appreciates not just the hormonal status of the tumour but it also the effect of the treatment of patients using hormones[52].

PR expression is considered as a parameter depicting the prognosis. It has epitope 412-566aa, clone SP2, and nuclear marker.

PR immunoexpression in the paraffin blocks need a boiling pretreatment in 10mMl citrate tampon, for a period of 20 minutes in a pH of 6.0 , and in the next 20

minutes it is allowed to cool at room temperature . Then the primary antibody is incubated into the tissues for next half an hour[52].

ER and PR immunoreactivity take positive staining reaction in endometrial adenocarcinoma and usually take negative staining in endocervical adenocarcinoma. Hence they are done commonly to exclude tumours having endocervical origin [53]

Carcinoembryonic antigen (CEA):

CEA is a glycoprotein of heterogeneous composition , with the molecular weight of 200000. It is found in the glycocalyx of epithelial cells of the fetus, especially in the epithelial lining of glands secreting mucin[44.].It is identifiable in very small quantities in certain benign tumors , and in normal cells of adults but in gastrointestinal adenocarcinoma , pancreatic adenocarcinoma, it is detected in large amounts and also found in lung and in medullary carcinoma of thyroid.

Because of the fact that it is primarily expressed by fetal tissues

and malignant tumors, it is referred to as an oncofetal antigen. Monoclonal antibodies are more specific than the conventional antisera[45]. According to the epitopes recognized by them, they have been divided into five major groups[46].

It was found that the earliest identified immunophenotypic difference between cervical and endometrial adenocarcinoma was the increased frequency and intensity of staining of CEA immunoreactivity in cervical adenocarcinomas[47], this observation is confirmed in multiple studies[49].

VIMENTIN:

Vimentin is the most important intermediate filament protein of the tissues of mesenchymal origin . Vimentin is one of the five major types of cytoplasmic intermediate filament (MW 57000). It is characteristic of the cells of mesenchymal nature, such as , fibroblasts , endothelial cells, and vascular smooth muscle cells.[48] Though it is characteristic of mesenchymal nature , it is not restricted to cells of mesodermal origin alone, but it is expressed in tumours of epithelial or neural nature also, not infrequently in conjunction with keratin and GFAP, respectively.[50] In the case of weakly differentiated neoplasms, this monoclonal antibody is used for the differential diagnosis.

Actually, vimentin is so ubiquitous that it used as a control of the immunohistochemical reaction , in the sense of questioning its reliability if there is no staining for vimentin in the tissue.

Vimentin is usually positive in endometrial carcinomas (80%), and is positive in about 30% of ovarian endometrioid adenocarcinomas. In contrast, vimentin is negative or only focally positive in adenocarcinomas arising from the colon or endocervix[51].

P16INK4a

p16INK4a gene is situated in the 9p21 chromosome which codes for a protein called a CDK4 and 6 which functions as a cell cycle inhibitor. It acts like a negative regulatory protein.

In a normal quiescent cell, retinoblastoma protein is in a hypophosphorylated active state by binding it to a transcription factor E2F. It inhibits the action of the transcription factor thereby prevents the progression of cell cycle. Hence Rb is a negative regulator of P16.

In high risk HPV infected cell, the viral transcription factors gets bind to Rb protein and make it inactive, so Rb protein cannot be able to inhibit the transcription of P16 tumor suppressor protein. Thus P16 is over expressed in dysplastic cells but not in normal cells.

identification of biomarker P16 by IHC in dysplastic cells in cervical cancer is an ongoing study all over the world[14] .

IMMUNOHISTOCHEMISTRY SCORING SYSTEM [39] :

Estrogen receptor staining are scored using 3 scoring system namely

1. ALLRED SCORING SYSTEM
2. H- SCORE
3. ASCOP/CAP SCORE

Allred scoring system:

Allred scoring system stratifies the carcinoma in to the cancers that are likely to respond to hormone therapy .

The score was given based on the percentage of proportion of cells taken the stain and the intensity of the stain

Proportion of tumor cells taken nuclear stain	**Score**
No cells taken	0
<1%	1
1-10%	2
11-33%	3
34-66%	4
67-100%	5

Intensity of the stain – ER	**SCORE**
No staining	0
Weak	1
Intermediate	2
Strong	3

ALLRED SCOREING FOR ER INTERPRETATION :

It's the sum of proportion score and intensity score

0-2 = negative

3-8 = positive

ALLRED SCORING BENEFITS IN BREAST CANCER

SCORE	Chance of benefit with hormone therapy.
0-1	No benefit
2-3	Small (20%)
4-6	Moderate (50%)
7-8	Good (75%)

H-SCORE:

IT assess the extent of nuclear immunoreactivity applicable to steroid receptors

The score is obtained by the formula

3 x % of strongly staining nuclei + 2 x % moderately staining nuclei + % of weakly staining nuclei.

Range = 0-300

ASCOP/CAP:

American society of cancer oncology/ college of American pathologist guidelines:

Tumors with 1-10% of the ER staining would be classified as ER positive.

In terms of prognostic value , ASCOP/CAP Scoring system is better compared to Allred scoring

P16- SCORING:

Tumor was given a score according to the intensity of nuclear or cytoplasmic staining and extent of stained cells.

Intensity of nuclear staining	Score
No staining	0
Weak staining	1
Moderate staining	2
Strong staining	3

Extent of stained cells	Score
No staining	0
1-10% of cells	1
11-50%	2
51-80%	3
81-100%	4

The final score was determined by multiplying the intensity and extent of positivity score of stained cells

Score = Intensity X Extent

Minimum score = 0

Maximum score = 12

Optimal cut off value of 4

4 or more - positive

0 - 3 - negative

IHC based on independent nuclear staining can sufficiently distinguish between endometrial and endocervical adenocarcinoma

MASTER CHART								
S.NO	**HPE-NO**	**IP-NO**	**AGE**	**PROVISIONAL DIAGNOSIS**	**Sp**	**GROSS**	**FINAL DIAGNOSIS**	**VA**
1.	G189/12	238975	55	CA ENDOMETRIUM	1		ENDOMETRIAL AC	ENI
2.	G276/12	195325	61	CA ENDOMETRIUM	1		ENDOMETRIAL AC	ENI
3.	G1200/12	204428	62	CA ENDOMETRIUM	3	Ragged, PE	ENDOMETRIAL AC	ENI
4.	G1806/12	4198	42	FIBROID UTERUS	3	Ragged PE	ENDOMETRIAL AC	ENI
5.	1960/12	private	55	PYOMETRA	2	Cystic, PE	ENOMETRIAL SCC	SAF
6.	G2769/12	JAYAM GH	55	ADENOMYOSIS UTERUS	3	Ragged, PE	ENDOMETRIAL AC	ENI
7.	G2809/12	219187	47	?CA ENDOMETRIUM	1		ENDOMETRIAL AC	ENI
8.	G3333/12	224779	47	CA ENDOMETRIUM	4	Ragged, PE	ENDOMERIAL AC	ENI
9.	G3502/12	225057	40	ENDOCERVICAL POYP	1	Polypoid	ENDOMETRIAL STROMAL SARCOMA	
10.	G4056/12	232013	52	CA ENDOMETRIUM	2	Ragged, PE	ENDOMETRIAL AC	ENI
11.	G4297/12	234133	62	ENDOMETRIAL CA	1		ENDOMETRIAL AC	SER (UP
12.	G4677/12	238975	47	ENDOMETRIAL CA	1		ENDOMETRIAL CA	ENI vill
13.	G82/13	247407	60	ENDOMETRIAL CA	2	Ragged, PE	ENDOMETRIAL AC	ENI
14.	G84/13	247407	44	ENDOMETRIAL CA	3	Ragged, PE	ENDOMETRIAL AC	ENI NO
15.	G268/	private	68		3	Ragged, PE	ENDOMETRIAL AC	SER

OBSERVATION AND RESULTS

The current study was carried out from January 2012 till June 2015 for a period of three and half years.

Totally we have received 7910 gynaecological specimens for histopathological examination. Out of which 761 cases are reported as uterine corpus neoplasm's including benign and malignant neoplasms. This constitutes for 9.6 % of cases excluding Cervical, ovarian, and adnexal neoplasms.

Table 1. Illustration of the total no of Uterine Corpus Neoplasms and its incidence year wise data.

	Total no of Specimens received	Benign neoplasm	Malignant neoplasm	No of uterine corpus neoplasms	Incidence per year
2012 Jan- Dec	5091	358	12	370	7.2%
2013 Jan-Dec	1199	153	19	172	14.3%
2014 Jan- Dec	1155	132	19	151	13.07%
Till June 2015	465	58	10	68	12.47%
	7910	701	60	761 (7910/761=9.6)	9.6% in 3.5 yrs

CHART NO: 1A

TOTAL NO OF GYNECOLOGICAL SPECIMENS RECEIVED IN THREE AND HALF YEARS PERIOD

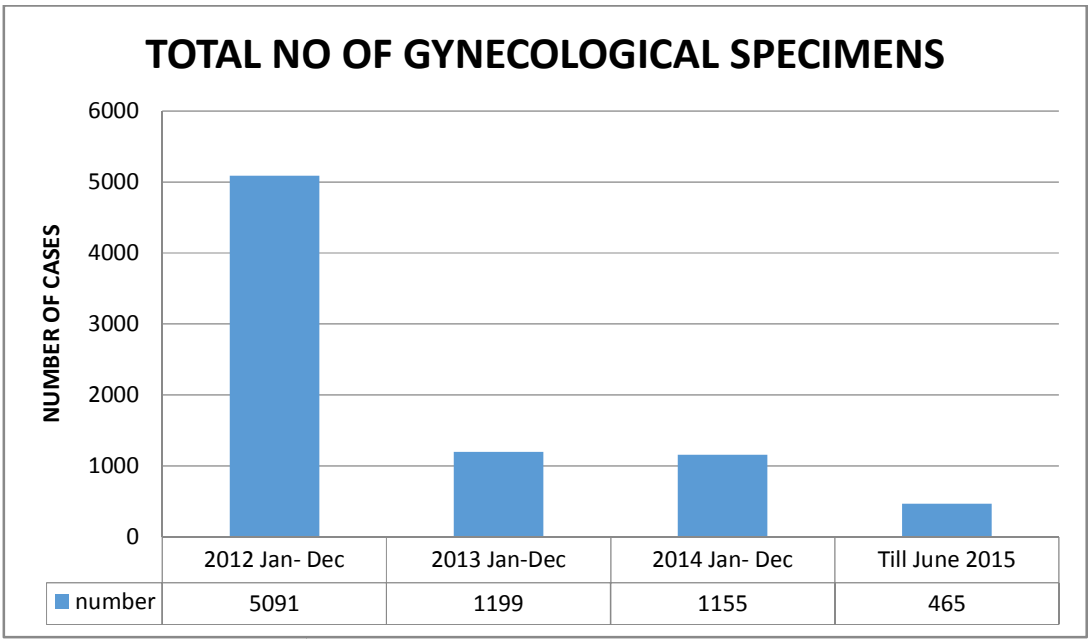
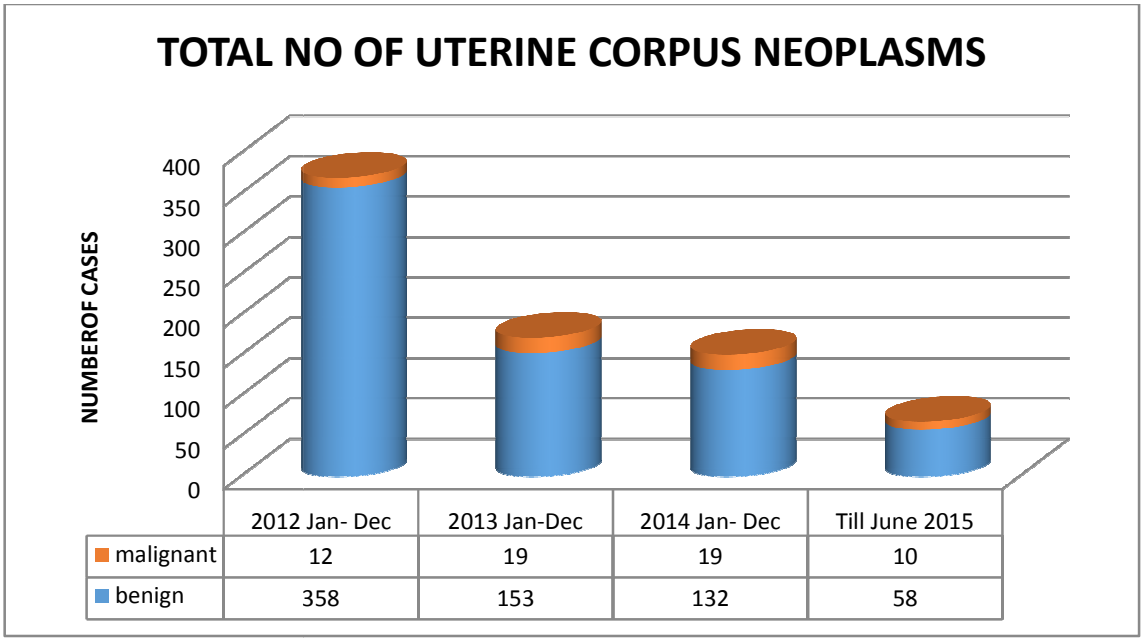


CHART NO: 1B - TOTAL NO OF UTERINE CORPUS NEOPLASMS



From this 761 uterine corpus neoplasms recorded in total of three and half years period, 60 cases were reported as malignant tumors, hence the overall incidence of uterine corpus malignancies in this given period is 7.8%.The malignant neoplasms documented within this period from our institution are

- Endometrial carcinomas,
- Endometrial stromal sarcomas,
- Leiomyosarcoma,
- Choriocarcinoma
- Carcinosarcoma.
- Germ cell neoplasm.

Table.2 & chart -2 Distribution of uterine corpus malignancies based on the histological type.

UTERINE CORPUS MALIGNANCIES YEAR WISE DATA						
Malignant cases reported in TMC	**2012**	**2013**	**2014**	**2015**	**Total**	**%**
Endometrial ca	11	13	17	8	49	81.6%
Endometrial stromal sarcoma	1	-	-	-	1	1.6%
Leiomyosarcoma	-	1	2	1	4	6.6%
Choriocarcinoma	0	3	-	1	4	6.6%
Germ cell tumors	-	1	-	-	1	1.6%
Carcinosarcoma	-	1	-	-	1	1.6%
Total	12	19	19	10	60/761=7.8%	
The incidence of uterine corpus malignancies in the given period is 7.8%						

Out of 60 cases of uterine corpus malignancies , 49 cases of endometrial carcinomas, 4 cases of choriocarcinoma, 4 cases of leiomyosarcoma and single case of endometrial stromal tumor, carcinosarcoma, germ cell neoplasm- yolk sac tumor each received.

It has been observed that predominant of the cases are arising from endometrial surface epithelial cells, i.e. endometrial carcinomas which constitutes for 81.6% of the total uterine corpus malignancy, followed by leiomyosarcoma 6.6% and choriocarcinomas of about 6.6% of cases. Other tumors such as endometrial stromal sarcoma, carcinosarcoma, germ cell neoplasm, yolk sac tumor carry the same incidence of about 1.66%.

Observation and analysis of individual uterine corpus malignancies:

Endometrial carcinomas:

This is the most common malignancy observed in our study. Out of 60 cases 49 cases are of Endometrial carcinoma which constitutes about 81.6% of cases.

Based on World health organization (WHO) classification of endometrial adenocarcinoma, there are about nine different differentiation of adenocarcinomas known to arise from endometrium. In our study five types of adenocarcinoma is noted.

Different histologic types and numbers of endometrial carcinoma has been documented as shown in Table no 3 , 42 cases of endometriod adenocarcinoma, 3 cases of uterine papillary serous adenocarcinoma, 2 case of poorly or undifferentiated carcinoma and single case of clear cell adenocarcinoma and squamous cell carcinoma each have been recorded.

CHART NO:2A

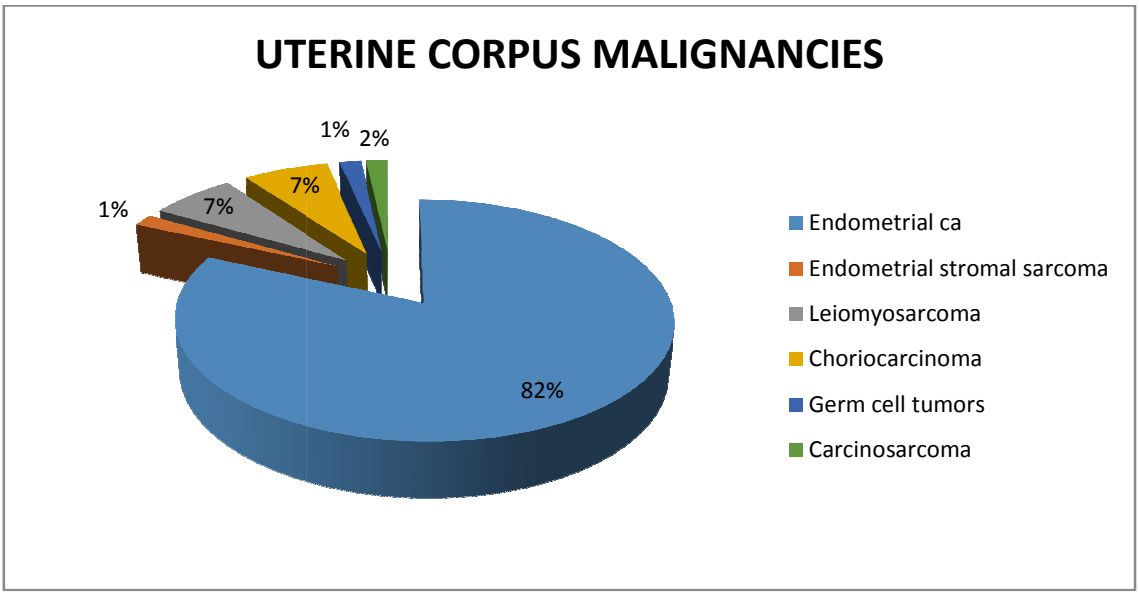


CHART NO: 2B DISTRIBUTION OF ENDOMETRIAL CARCINOMAS

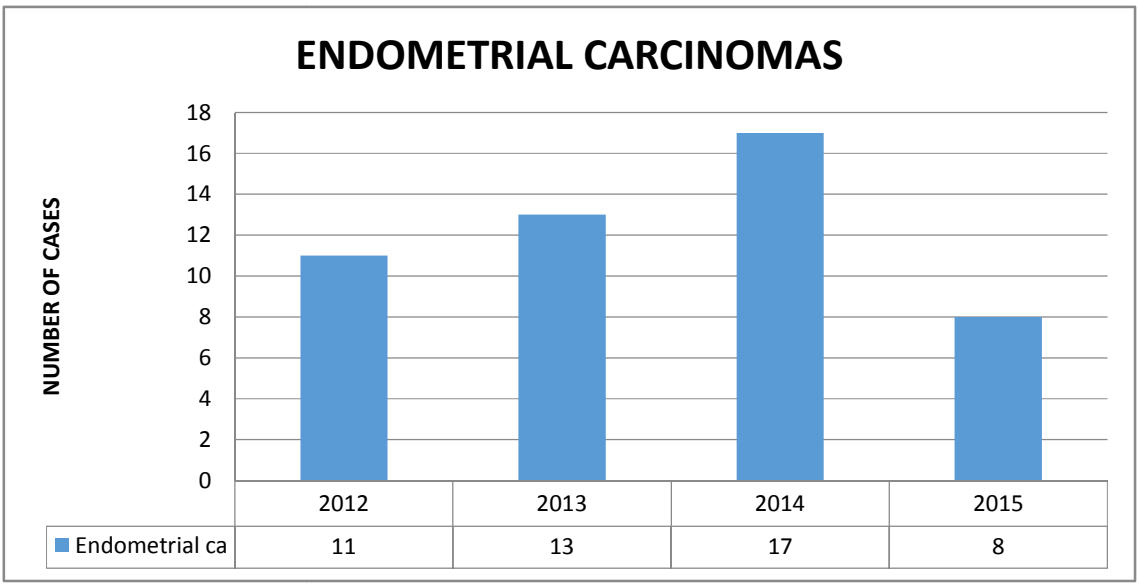


TABLE NO: 3 & CHART : 3 - DIFFERENT HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMAS

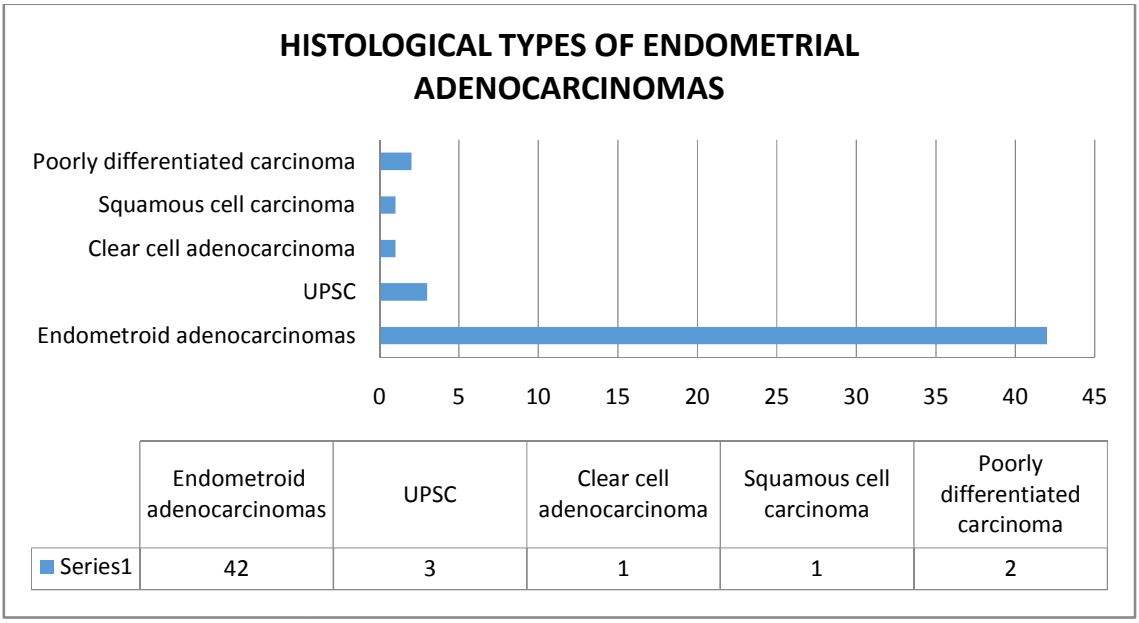
HISTOLOGICAL TYPES OF ENDOMETRIAL ADENOCARCINOMAS IN 49/60 CASES		
Endometroid adenocarcinomas	42	85.7%
UPSC		6.1%
Clear cell adenocarcinoma	1	2.04%
Squamous cell carcinoma	1	2.04%
Poorly differentiated carcinoma	2	4.08%

Among all the type, endometroid endometrial adenocarcinoma being the most common pattern noted which constitutes about 85% of cases , followed by uterine papillary serous adenocarcinoma of about 6% , undifferentiated or poorly differentiated tumor of 4.08% and 2.04% of clear cell adenocarcinoma and squamous cell carcinoma each

Different patterns of endometrial adenocarcinoma

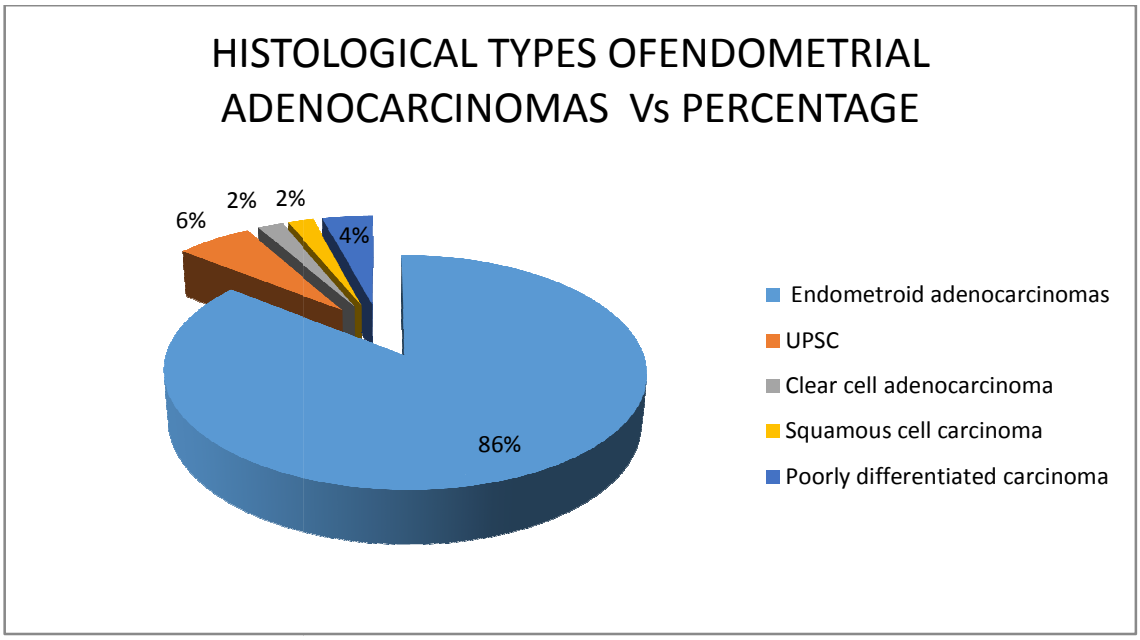
There are about 33 number of cases exhibiting endometriod NOS type pattern, 5 cases exhibiting endometriod carcinoma with squamous metaplasia, and four cases with villoglandular pattern in out of total 42 cases of endometriod endometrial adenocarcinoma

. CHART: 3A



	Endometroid adenocarcinomas	UPSC	Clear cell adenocarcinoma	Squamous cell carcinoma	Poorly differentiated carcinoma
Series1	42	3	1	1	2

CHART:3B



The most common pattern observed from the received specimens are endometriod not otherwise specified type which constitutes about 76.7%.

Followed by adenocarcinoma with squamous metaplasia 11% and villoglandular pattern 9.3%.

Table 4 & chart : 4- Illustrations of different patterns of endometrial adenocarcinoma

Endometriod endometrial adenocarcinoma variants: 42/60 cases		
Endometriod NOS	33	76.7%
Villoglandular type	4	9.30%
Endometriod with squamous metaplasia	5	11.6%

GRADING OF ENDOMETRIAL ADENOCARCINOMAS.

In our study the tumors are graded in to I, II, III, for endometriod adenocarcinomas. Others tumors such as uterine serous papillary adenocarcinoma, clear cell carcinoma and squamous cell carcinomas are graded as high grade tumors which carries the same poor prognosis as the grade III carcinomas as per WHO.

Based on the data collected within this three and half years period 37 cases fall under grade I tumors, 3 cases are of gradeII, four cases of Grade III and we have received 3 cases of uterine serous papillary adenocarcinoma, 1 case of clear cell adenocarcinoma, and one case of squamous cell carcinoma which all grouped in high grade tumors. Hence a total of 5 case of high grade malignant neoplasms documented here.

This corresponds to 75.5% of grade 1 tumors, 6.1 % of grade II tumors, 8.16 % of grade III tumors and 10.2% of high grade tumors as shown in table 5 & Chart 5.

Table -5 & chart-5 : Grading of endometrial adenocarcinoma

	Grading		
Endometrial carcinoma Total 49 cases	Grade I	37	75.5%
	Grade II	3	6.1%
	Grade III	4	04 %
	HIGH GRADE (UPSC & clear cell , squamous cell carcinoma)	5	10.2%

STAGING OF ENDOMETRIAL ADENOCARCINOMAS:

Table -6 & chart-6 : staging of endometrial carcinoma

Staging by AJCC in Hysterectomy specimen with Endometrial carcinoma cases	Total no of cases (25)	Percentage	
PT1aN0M0/ stage IA	13	52%	Stage I 80%
PT1bN0M0/ stage IB	7	28%	
PT2NoM0/ stage II	3	12%	Stage II 12%
PT3aN0M0/ stage IIIA	1	4%	Stage III 8%
PT3bN1M0/ stage IIIC1	1	4%	

Out of 49 cases of endometrial carcinomas , 25 cases are hysterectomy specimens, the rest all are small biopsy/curettage specimen. From the 25 hysterectomy specimen with endometrial carcinomas staging was done based on FIGO's classification.

CHART: 4

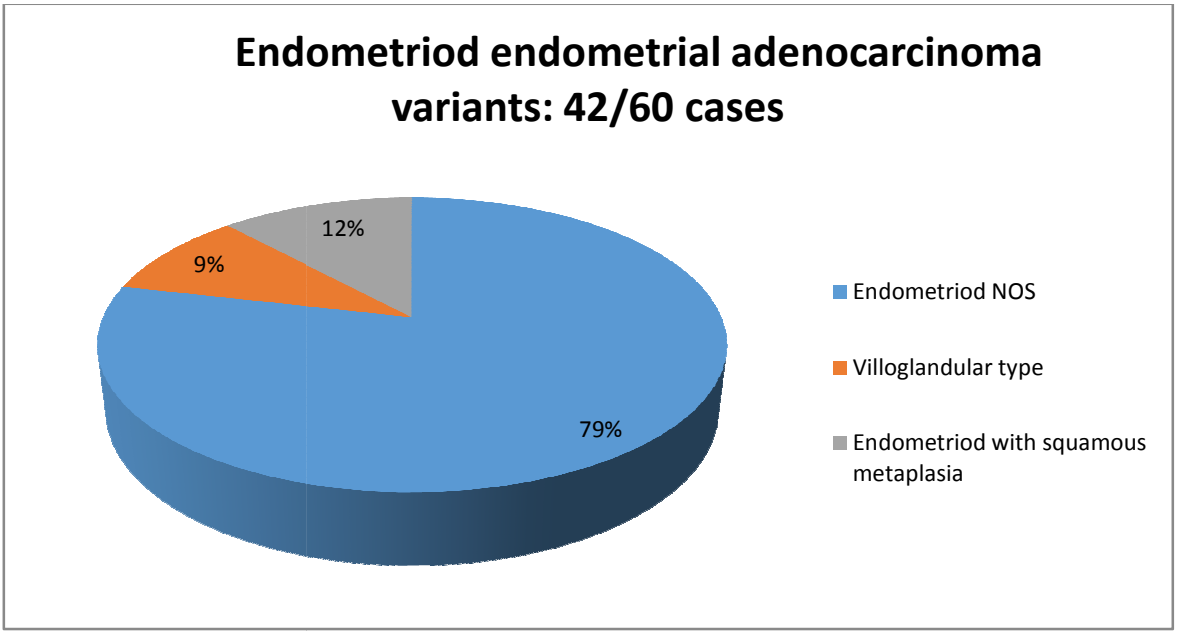


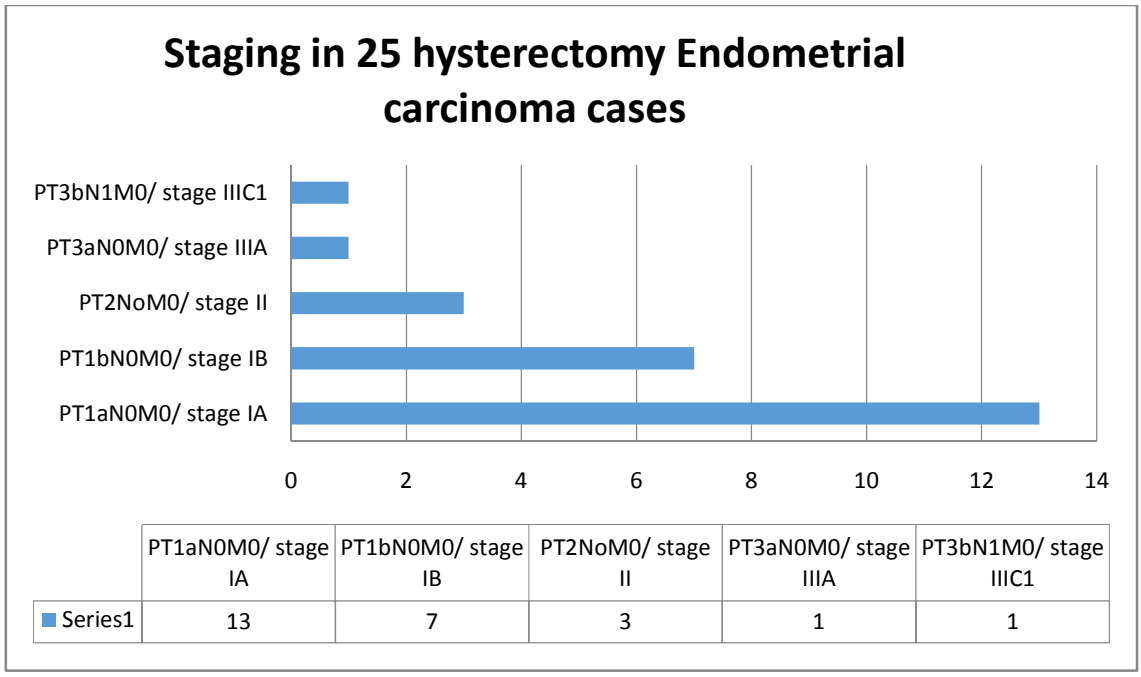
CHART 5

According to that 13 cases are in stage IA , 7 cases are IB, 3 cases fall in stage II, 1 case of stage III a and C1, which corresponds to 52% of stage IA, 28% of stage IB, 12% of Stage II cases and 4 % each of stage IIIA and stage III C1. To summarize stage I cases constitutes about 80%, stages II cases of 12%, stage III of 8 %.

GROSS PRESENTATION OF ENDOMETRIAL ADENOCARCINOMA

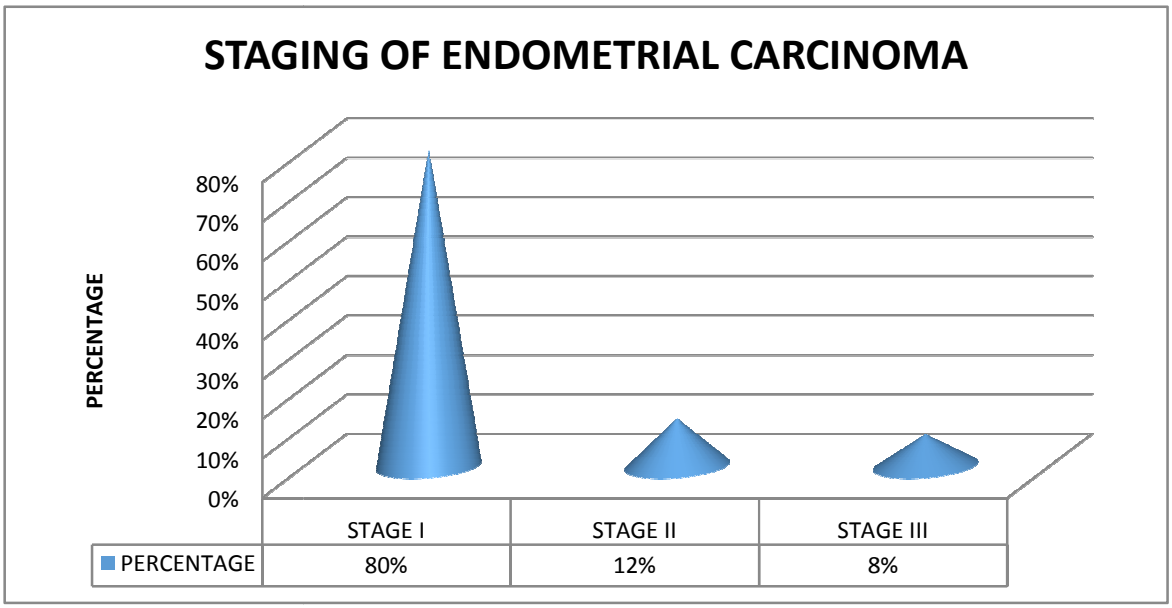
Majority of the cases presented as irregular ragged ,papillary growth filling the endometrial cavity and three cases presented as polypoid growth yet infiltrating in to the myometrium.

CHART: 6A



	PT1aN0M0/ stage IA	PT1bN0M0/ stage IB	PT2NoM0/ stage II	PT3aN0M0/ stage IIIA	PT3bN1M0/ stage IIIC1
Series1	13	7	3	1	1

CHART: 6B



	STAGE I	STAGE II	STAGE III
PERCENTAGE	80%	12%	8%

One case of squamous cell carcinoma of endometrium classically presented with cytic lesion with prior history of pyometra in an elderly women.

here 84% of endometrial adenocarcinoma cases presented as irregular, ragged , friable papillary growth, 12% of cases as polypoid and 4% as cystic as shown in table no-7

Table no :7 & chart no:7- illustration of gross presentation of endometrial carcinoma

ENDOMETRIAL CARCINOMA - GROSS **25 HYSTERECTOMY SPECIMENS**		
Irregular, ragged endometrium	21	84%
Polypoid	03	12%
Cystic	1	4%

Age distribution of endometrial adenocarcinomas:

CHART : 7

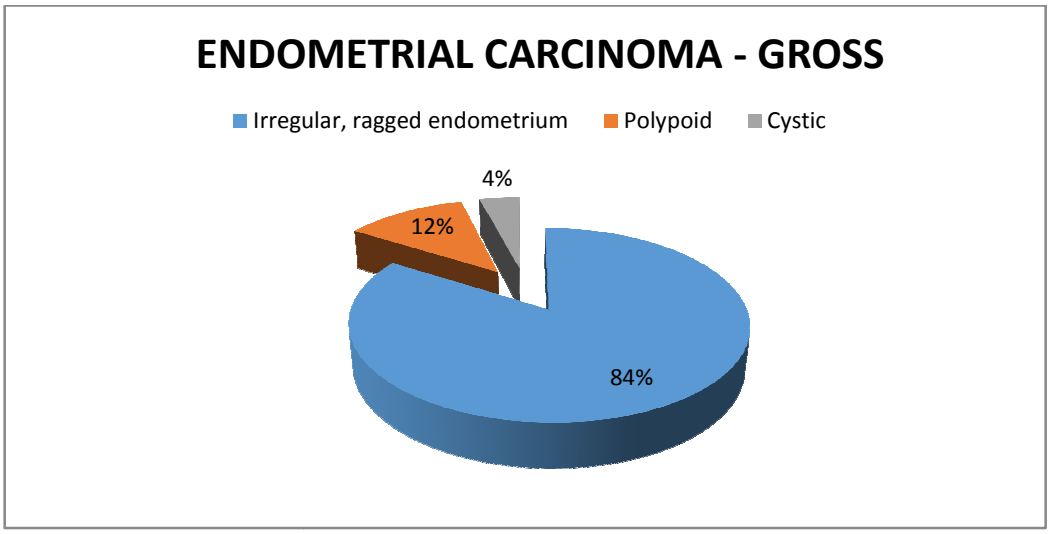

ENDOMETRIAL CARCINOMA - GROSS
Irregular, ragged endometrium
Polypoid
Cystic
4%
12%
84%

Table no: 8 & chart 8

AGE	GRADE I	GRADE II	GRADE III	HIGH GRADE		
20 – 29	--	--	-	--	0	0%
30 – 39	01	01	--	--	02	4.08%
40 – 49	11	01	01	--	13	26.5%
50 – 59	19	--	03	01	23	46.9%
60 – 69	05	--	--	03	08	16.3%
70 – 80	01	01	--	01	03	6.1%
Total : 49	37	03	04	05	49	100%
percentage	75.5%	6.12%	8.16%	10.2%		

TABLE 9 & CHART 9 : AGE DISTRIBUTION IN ENDOMETRIOD ADENOCARCINOMA

ENDOMETRIOD TYPE ENDOMETRIAL ADENOCARCINOMAS IN 42 CASES					
AGE	GRADE I	GRADE II	GRADE III		
20 – 29	--	--	-	0	0%
30 – 39	01	01	--	02	4.7%
40 – 49	11	01	00	12	28.5%
50 – 59	19	--	02	21	50%
60 – 69	05	--	--	05	11.9%
70 – 80	01	01	--	02	4.7%

From the data analysed for the age parameter from the master chart overall endometrial adenocarcinoma seems to appear more between in the 4th to 6th decade

CHART NO: 8A

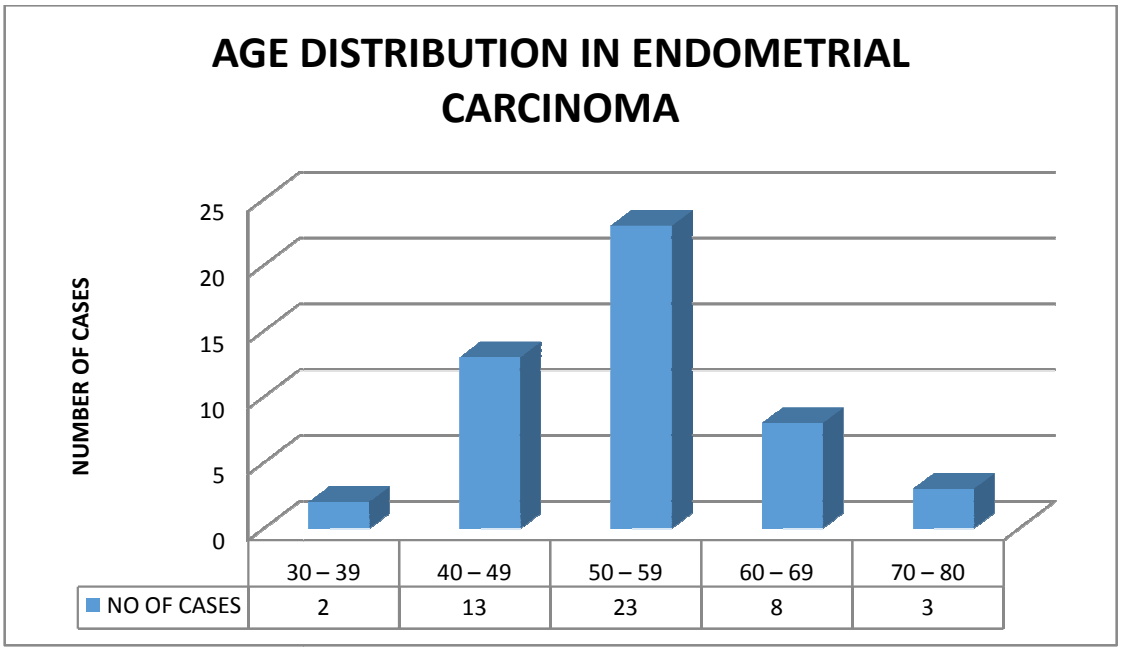
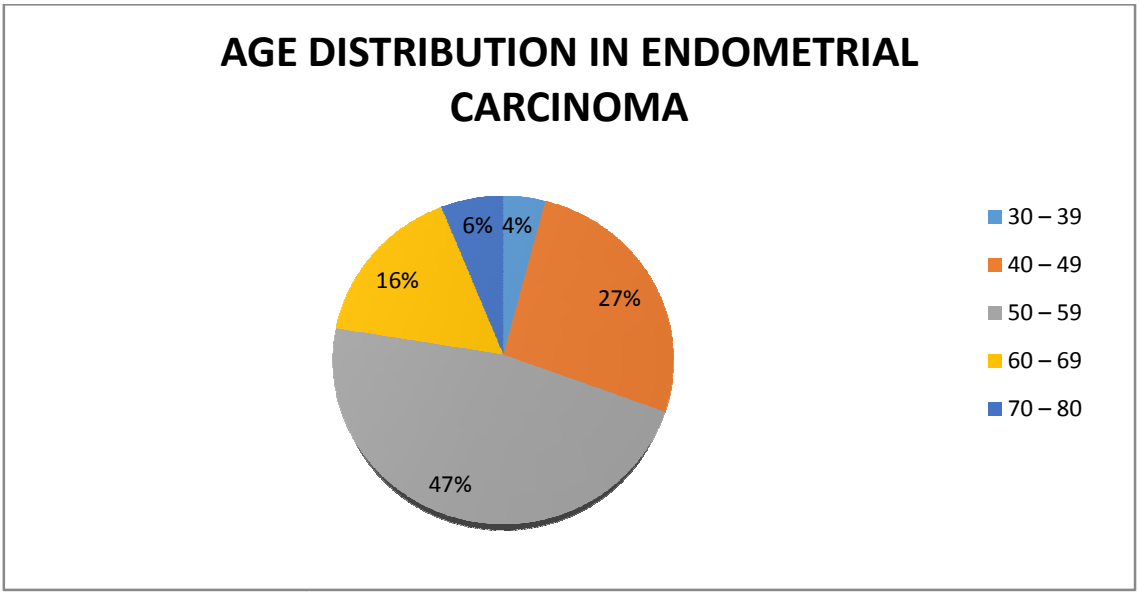


CHART NO: 8B



and well differentiated grade I adenocarcinoma is prevailing high in between 50 -60 years

LEIOMYOSARCOMA DATA ANALYSIS

LEIOMYOSARCOMA	AGE	GROSS	SIZE	GRADE
G1157/13	38	IM, Fairly circumscribed mass	13 cm	Low grade
G946/14	32	IM, fairly circumscribed	6X6 cm	Low grade
G788/14	55	Intra mural mass	10x7	High grade
G378/15	40	Intramural mass	9x9 cm	Low grade.

All the cases of leiomyosarcoma reported in our institution presented as fairly circumscribed intramural mass with an average size of 9.5 cm. The median age group of presentation is 39 years. 75 % tumors are in lowgrade with epitheloid differentiation. The incidence being 6.6% in our study.

CHORIOCARCINOMA

This is the next common malignant tumor observed following endometrial adenocarcinoma and leiomyosarcoma. totally 4 cases have been documented in this given period all fall within the age group between 2nd and 3rd decade. it carries the same incidence of 6.6% as that of leiomyosarcoma.

ENDOMETRIAL STROMAL SARCOMA

one case of endometrial stromal sarcoma has been reported in our study in a 40 years old lady presenting as a polyp. It constitutes 1.65% of uterine malignant neoplasm in this current study.

CARCINOSARCOMA

one case of carcinosarcoma has been reported in a 44 years old lady presenting as an intramural mass with homologous differentiation. It also carries a 1.6% incidence in our study.

GERM CELL NEOPLASM:

a rare case of yolk sac tumor in the endometrium is noted. This germ cell neoplasm was diagnosed in a 19 year old girl presenting like a sarcoma uterus.
Histopathological examination revealed a classic schiller dual bodies and the pattern. Its incidence is 1.6% in our study in the given period of time.

USE OF IMMUNOHISTOCHEMISTRY TO DISTINGUISH ENDOMETRIAL ADENOCARCINOMA VERSUS ENDOCERVICAL ADENOCARCINOMA.

We applied IHC markers ER and P16 antibody on 20 biopsy specimen which includes 10 cases, reported as endometrial adenocarcinoma and 10 cases reported as endocervical adenocarcinomas in our institution.

We Analysed the intensity and proportion of staining to give a positive or negative staining report and correlated with the HPE report.

IMMUNOHISTOCHEMISTRY INTERPRETATION

Estrogen receptor scoring was done using **ALLRED SCORING SYSTEM**

Allred scoring system:

The score was given based on the percentage of proportion of cells taken the stain and the intensity of the stain

Proportion of tumor cells taken nuclear stain	**Score**
No cells taken	0
<1%	1
1-10%	2
11-33%	3
34-66%	4
67-100%	5

Intensity of the stain – ER	**SCORE**
No staining	0
Weak	1
Intermediate	2
Strong	3

Allred score =

proportion of cells taken nuclear stain + in score and intensity score

maximum score =8

minimum score = 0

Results ≤ 2 = negative

3-8 = positive

P16- SCORING:

Tumor was given a score according to the intensity of nuclear sating

and extent of stained cells.

Intensity of nuclear sating	Score
No staining	0
Weak sating	1
Moderate staining	2
Strong staining	3

Extent of stained cells	Score
No staining	0
1-10% of cells	1
11-50%	2
51-80%	3
81-100%	4

P16 SCORE= Intensity of the stain X Extent of positivity

maximum score = 12

minimum score = 0

RESULT:

≤ 4 : negative≥ 4 : positive

S.NO	HPE no	HPE REPORT	Estrogens receptor - ER (ALLRED SCORE)					P16			
			INTENSITY	EXTENT	R= I + E 0-2 = NEG 2-8 = POS			INTENSITY (I)	EXTENT (E)	$Total$ R=IxE <4- neg >4 – POS	
Cases reported as endocervical adenocarcinoma											
1.	P823/15	EC AC	0	0	0	NEG		3	4	12	POS
2.	P645/15	EC AC	0	0	0	NEG		3	4	12	POS
3.	P522/15	EC AC	2	3	5	**POS**		3	4	12	POS
4.	P697/15	EC AC	0	0	0	NEG		1	4	3	**NEG**
5.	P3090/14	EC AC	0	0	0	NEG		3	4	12	POS
6.	P598/14	EC AC	1	3	4	**POS**		3	4	12	POS
7.	P2915/13	EC AC	0	0	0	NEG		3	4	12	POS
8.	P2697/13	EC AC	0	0	0	NEG		3	3	9	POS
9.	P2429/13	EC AC	1	3	4	**POS**		3	4	12	POS
10.	P625/13	EC AC	0	0	0	NEG		3	4	12	POS
Cases reported as endometrial adenocarcinoma											
1.	P78/14	EM AC	0	0	0	NEG		2	3	6	POS
2.	G1091A/13	EM AC	3	5	8	POS		2	1	2	NEG
3.	P1300/14	EM AC	3	5	8	POS		1	2	2	NEG
4.	P2438/14	EM AC	3	5	8	POS		2	1	4	NEG
5.	P152A/15	EM AC	3	5	8	POS		2	1	2	NEG
6.	P256/15	EM AC	3	5	8	POS		2	1	2	NEG
7.	P377/15	EM AC	3	5	8	POS		1	3	3	NEG
8.	P550/15	EM AC	0	0	0	NEG		3	4	12	POS
9	G11C/14	EM AC	0	0	0	NEG		2	3	6	POS
10.	p554/14	EM AC	0	0	0	NEG		3	4	12	POS

IP NO	AGE	GRADE	DIAGNOSIS	ER	P16
P823/15	37	WD	EC AC	NEG	POS
P645/15	35	WD -VG	EC AC	NEG	POS
P522/15	47	WD	EC AC	**POS**	POS
P697/15	60	WD	EC AC	NEG	**NEG**
P3090/14	52	WD	EC AC	NEG	POS
P598/14	41	WD-VG	EC AC	**POS**	POS
P2915/13	45	WD	EC AC	NEG	POS
P2697/13	57	WD	EC AC	NEG	POS
P2429/13	75	WD	EC AC	**POS**	POS
P625/13	62	WD-VG	EC AC	NEG	POS

ENDOCERVICAL ADENOCARCINOMA ER % P16 %

EMAC: Endometrial adenocarcinoma

IP NO	AGE	Diagnosis	Grading	ER	P16
P78/14	50	EM AC	Grade-1	NEG	POS
G1091A/13	57	EM AC	Grade-1	POS	NEG
P1300/14	54	EM AC	Grad-1	POS	NEG
P2438/14	65	EM AC	Grade-1	POS	NEG
P152A/15	50	EM AC	Grade-1	POS	NEG
P256/15	75	EM AC	Grade-2	POS	NEG
P377/15	38	EM AC	Grade-2	POS	NEG
P550/15	47	EM AC	Grade-1	NEG	POS
G11C/14	70	EM AC	Grade-3	NEG	POS
p554/14	50	EM AC	Grade-1	NEG	POS

ECAC: Endocervical adenocarcinoma

INFERENCE

POSITIVE	3/10	30 %	9/10	90%
NEGATIVE	7/10	70 %	1/10	10%
BOTH POSITIVE	3			
BOTH NEGATIVE	1			

In our study, out of 10 cases of endometrial adenocarcinoma, 6 cases showed positivity for ER which constitutes 60% positivity and out of 10 cases of

ENDOMETRIAL ADENOCARCINOMA	ER	%	P16	%
POSITIVE	6/10	60 %	4/10	40%
NEGATIVE	4/10	40%	6/10	60%
BOTH POSITIVE	0			
BOTH NEGATIVE	0			

endocervical adenocarcinoma 3 cases showed positivity i.e. about 30% of cases.

out of 10 endocervical adenocarcinomas 90% cases showed P16 positivity and in 10 cases of endometrial adenocarcinoma 40 % cases showed positivity.

out of 20 cases three cases showed both marker positivity 24.3% and one case was negative for both markers i.e. 5 % showed negativity for both markers

ASSOCIATION OF TUMOR GRADE WITH ER EXPRESSION

GRADE	ER POSITIVE	ER NEGATIVE

Grade I	4	3
Grade II	2	0
Grade III	1	0

.

Total the chi square statistics is 2.857,the P value is 0.23965 the result is not significant as it is more than 0.05.

DISCUSSION

Gynaecological cancers have increased in India and are estimated to be around 30 % of total cancer by 2020 among women in india[1]

uterine corpus malignancies constitutes the third most common site of cancer in female genital tract following cervix and ovarian neoplasm in our country and other developing countries, where as in developed countries endometrial carcinoma is the most common gynaecological malignancy reported.

This study was conducted with the objective of assessing the incidence and histopathological analysis of uterine corpus malignancies in Thanjavur medical college in a given period of three and half years from January 2012 till June 2015. The second objective is to distinguish endometrial adenocarcinoma from endocervical adenocarcinoma in a biopsy/curetting specimen using immunohistochemical marker ER and P16 .

In the given study period we have received 7910 cases out of which 761 cases are uterine corpus neoplasms comprising both 701 cases of benign and 60 cases of malignant neoplasm. This constitutes for 9.6% of cases of uterine corpus neoplasm.

Histopathologic analysis of uterine corpus malignancies was done on all 60 cases in total and compared with other literatures and journals in relation to incidence, age, presentation, grading, and staging of tumors .

The most common malignant tumor observed in our study is Endometrial carcinoma which constitutes about 82 %, followed by choriocarcinoma and leiomyosarcoma carrying the same percentage of 7% each. Other malignant tumor observed within this period are Endometrial stromal sarcoma, Carcinosarcoma and Germ cell neoplasm 2% each. Giving a incidence of uterine corpus malignancies in the given period about 7.8%

TABLE: 1 PERCENTAGE OF ADENOCARCINOMA OF UTERINE CORPUS IN OTHER STUDIES

Endometrial adenocarcinoma	Percentage
Kathryn m.greven et al[33]	85%
Paola A.Gehrig et al[11]	80%
Carol L Kosary [20] SEER statistics.	90.6%
F.Gholipour et al [21]	70.5%
Current study	82%

In comparison with other studies among uterine corpus malignancies, Endometrial adenocarcinoma is the most common malignant neoplasm observed in all studies with overall percentage above 80% as shown in the table no:1.this is in concordance with the present study.

In a large study conducted by carol L kosary[20] out of 48600 cases, 44059 cases are of endometrial adenocarcinoma that constitues about 90.6%.

Study conducted by kathryn m greven et al[33] and Pavlo et al[11] study shows a closer percentage of endometrial adenocarcinoma as in our current study .

According to the SEER fact sheet[20] the estimated new cases of endometrial carcinoma in 2015 is 54870, the percentage of all new endometrial cancer cases is

CHART:1 PERCENTAGE OF ADENOCARCINOMA OF UTERINE CORPUS.

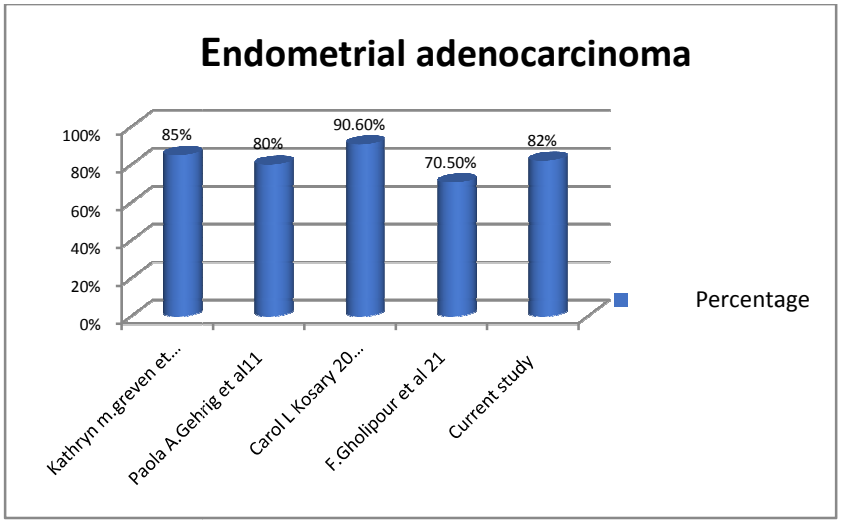
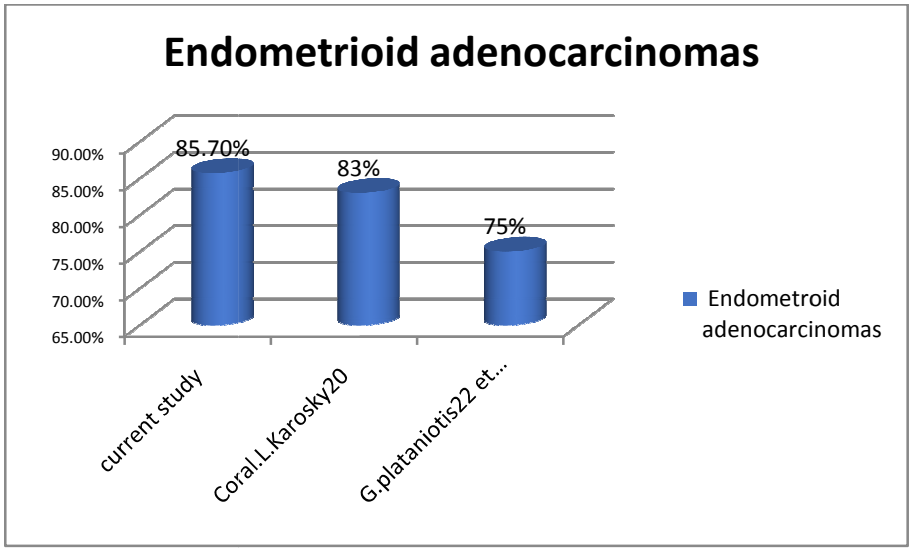


CHART 1B: PERCENTAGE OF ENDOMETRIOID ADENOCARCINOMAS



3.3% and the estimated death in 2015 is 10170. percentage of all cancer deaths is 1.7%. percent age of people affected surviving in 5 years is 81.7%

ADENOCARCINOMA OF UTERINE CORPUS : DISTRIBUTION BY HISTOLOGY

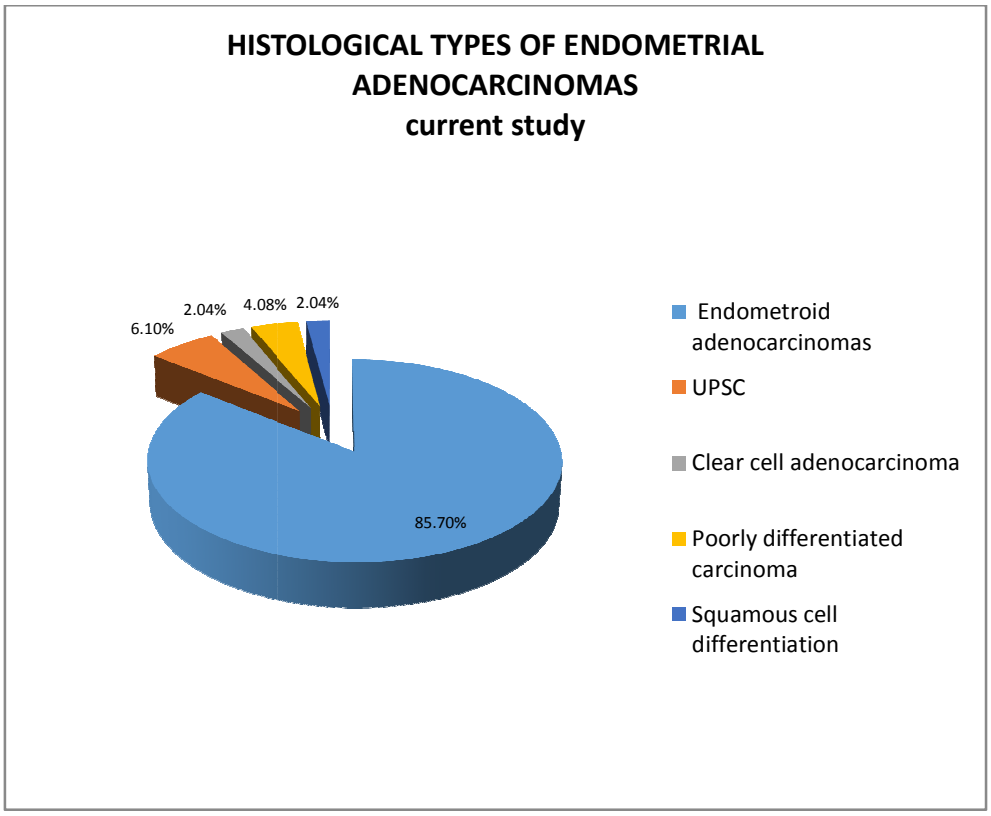
TABLE:2 COMPARISON OF HISTOLOGICAL TYPES

HISTOLOGICAL TYPES OF ENDOMETRIAL ADENOCARCINOMAS	current study	Coral.L.Karosky[20]	G.plataniotis[22] et al
Endometroid adenocarcinomas	85.7%	83%	75%
UPSC	6.1%	5.8%	5%
Clear cell adenocarcinoma	2.04%	1.6%	2%
Poorly differentiated carcinoma	4.08%	-	-
Squamous cell differentiation	2.04%	1.9%	1%

In comparison with other studies done by Carol.L.karosky[20] and G.plataniotis[22] Endometriod adenocarcinomas is the most common type with a mean percentage of 81% followed by next highest adenocarcinoma being uterine papillary serous adenocarcinoma with a mean of 5.6% and clear cell carcinoma with a mean incidence of 1.8%.

The other histologic type mentioned in other studies are not compared in our discussion.

CHART: 2 COMPARISION OF HISTOLOGICAL TYPES



DIFFERENT PATTERNS OF ENDOMETRIAL ADENOCARCINOMA:

77 % of endometrial adenocarcinoma exhibited endometrioid NOS type followed by villoglandular pattern 10% and endometrioid with squamous metaplasia of 12%.

TABLE NO : 3 : GRADING OF ENDOMETRIAL ADENOCARCINOMAS

Grading	Current study	Behiye etal[23]	Geisher Jp et al[25]	Paola et al[11]
Grade I	75.5%	40.9%	38%	23.6%
Grade II	6.1%	45.4%	47.6%	43.6%
Grade III	04 %	13.7%	13.8%	32.8%

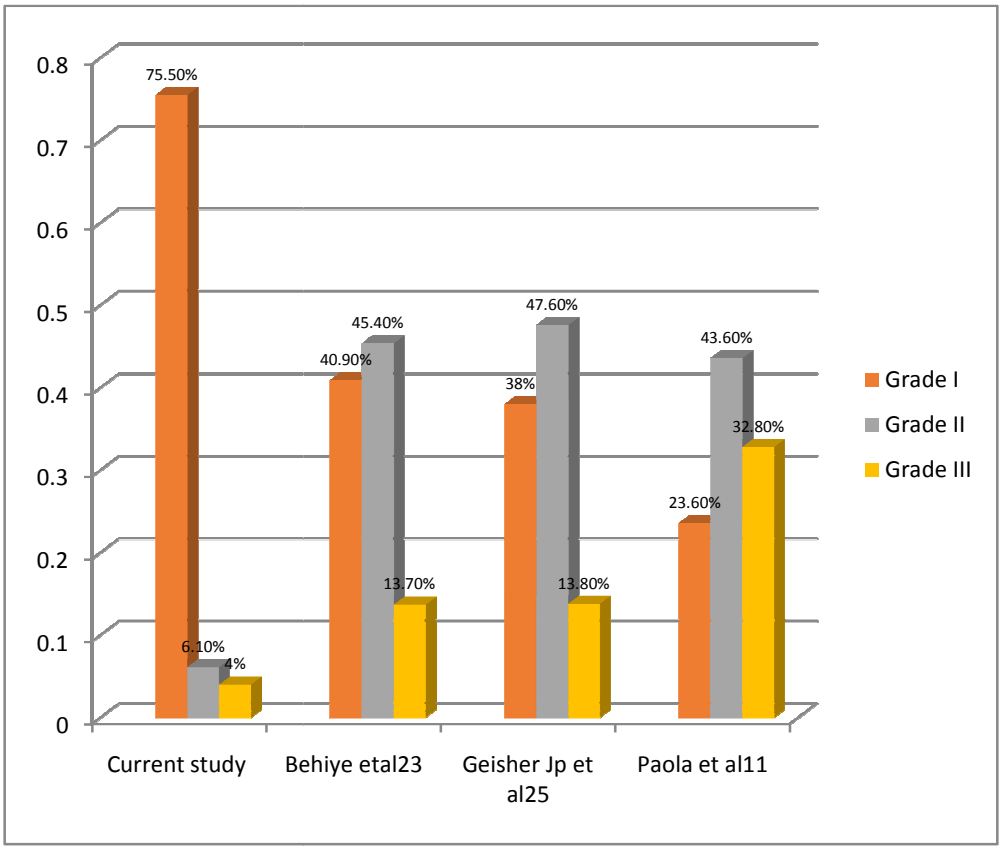
Grade II tumors are more common in endometrial adenocarcinomas , as shown in the table no:3 which is not in concordance with our study where Grade I tumors are more common.

from the study conducted by Behiye etal[23], in a total of 335 patients ,152 cases were of grade 2 (45.4%) and 40.9% & 13.7% of them had grade 1 and grade 3 disease

paola et al[11] out of 55 cases evaluated 13 had grade I (23.6%), 24 had grade 2(43.6%), 18 had grade 3 tumors (32.8%)

The study conducted by Geisher JP et al [25], showed that none of the grade I tumors had lymphnode metastasis , which is also observed in our study. The

CHART NO: 3 GRADING OF ENDOMETRIAL ADENOCARCINOMAS



former study concludes that pelvic and paraaortic node dissection is not required for grade I tumors. It should be reserved for grade 2 tumors and above.

TABLE : 4; UTERINE CANCER INCIDENCE BY STAGE:

STAGING	Percentage current study		Uterine Cancer Statistics Uk 2012	SEER statistics	Behiye et al[23]	Paola et al
PT1aN0M0/ stage IA	52%	Stage I 80%	57%	75.3%	80.2%	65.5%
PT1bN0M0/ stage IB	28%					
PT2NoM0/ stage II	12%	Stage II 12%	5.1 %	7.9%	6%	14.5%
PT3aN0M0/ stage IIIA	4%	Stage III 8%	7.8%	6%	9%	11%
PT3bN1M0/ stage IIIC1	4%					
STAGE IV	0%	STAGE IV	4%	7.5%	4.8%	
STAGE NOT KNOWN	0%	STAGE NOT KNOWN	24.5%	3.3%	-	

In our study 80 % of patients presented in stage I disease which is in close range with SEER statistics showing 75 % of patients presenting in stage I disease. where as in

UK cancer statistics data shows 57 % patient presenting in stage I disease and 66% in Paola et al[11] studies,

Most of the cases of endometrial carcinoma are diagnosed earlier because of the symptom of abnormal vaginal bleeding, the patient will seek medical consult and diagnosed earlier.

Only less percentage of cases reach stage IV as more common with the case of uterine serous papillary carcinoma of endometrial because of the tumor arising from atrophic endometrium and does not follow endometrial hyperplasia sequence hence they develop symptoms late present in advanced stages.

ADENOCARCINOMA AGE AND STAGE COMPARISON

When age and stage variables are compared 70 % of cases were diagnosed within the age range from 50- 69 years of age. This almost goes similar with the study conducted by carol L kosary[20].

Across all age groups 70 % or more of all cancers were diagnosed in stage I.

which goes in concordance with the literature that endometrial adenocarcinoma usually diagnosed earlier and hence the prognosis is better.

TABLE NO:5

	Age in years					
AJCC stage	Carol L	Current study	Carol L	Current study	Caro L	Current study
	20-49 yrs		**50-69 yrs**		**70+ yrs**	
Stage I	77.1	100 %	78.2 %	73.6 %	70.2%	-
Stage II	8.1%	-	7.0%	10.5%	6.8%	-
Stage III	5.9%	-	5.5%	15.7%	9.2%	-
Stage IV	5.5%	-	2.4%	-	4.8%	-
Unknown /unstaged	3.0%	-		-		-

In our current study majority of the uterine corpus neoplasms presented in grade I disease. with the median age of presentation of 51 years and with a mean age of 52.5 years.

inference of uterine cancer incidence by age:

INCIDENCE OF UTERINE SARCOMAS

In our study out of 60 cases of corpus uterine malignant neoplasms, uterine sarcomas constitutes about 9.8 %; which includes 66% of leiomyosarcoma, 16% of Endometrial stromal sarcoma and 16% of carcinosarcoma.

In the study conducted by carol l kosary[20], the incidence of uterine sarcoma is 7.7% which comprised of 34% of mullerian, 25 % of leiomyosarcoma ,19% of carcinosarcoma, and 16 % of carcinosarcoma. when compared to our study. the sarcoma incidence is 9.8%

TABLE NO: 6

Uterine Sarcoma incidence	**Current study**	**Carol L.kosary.**
Total	9.8%	7.7%
Leiomyosarcoma	66%	25%
Endometrial stromal sarcoma	16%	34%
Carcinosarcoma	16%	16%

In our study leiomyosarcoma carries higher incidence than endometrial stromal sarcoma as compared with carol L Kosary study

EVALUATION OF IMMUNOHISTOCHEMICAL MARKERS ER AND P16 EXPRESSION IN ENDOMETRIAL ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA CASES IN BIOPSY/CURETTINGS SPECIMEN.

TABLE NO-7A:COMPARISON OF ER EXPRESSION IN WELL DIFFRENTIATED ENDOMETRIAL (GRADE I) ADENOCARCINOMA :

STUDIES	**ER POSITIVE**
McCluggage et al[12]	93%
Staebler et al [27]	75%
Paola A.Gehrig et al [11]	87.3%
Sophia Kounelis et al [16]	54%
Current study	**60%**

Mccluggage et al evaluated 30 endometrial adenocarcinoma and 26 endocervical adenocarcinomas, in their study 93% were strongly positive forER.

staebler et al studied 24 endometrial and 24 endocervical adenocarcinomas found that 75% expressed ER.

Paola et al studied out of 55 endometrial adenocarcinoma 48 tumors were ER positive(87.3%)

sophia Kounelis study ,out of 61 endometrial adenocarcinoma cases 33 were positive for ER (54%)

in our current study out of 10 endometrial adenocarcinoma cases 6 cases showed positivity (60%)

CHART NO: 6 INCIDENCE OF UTERINE SARCOMAS

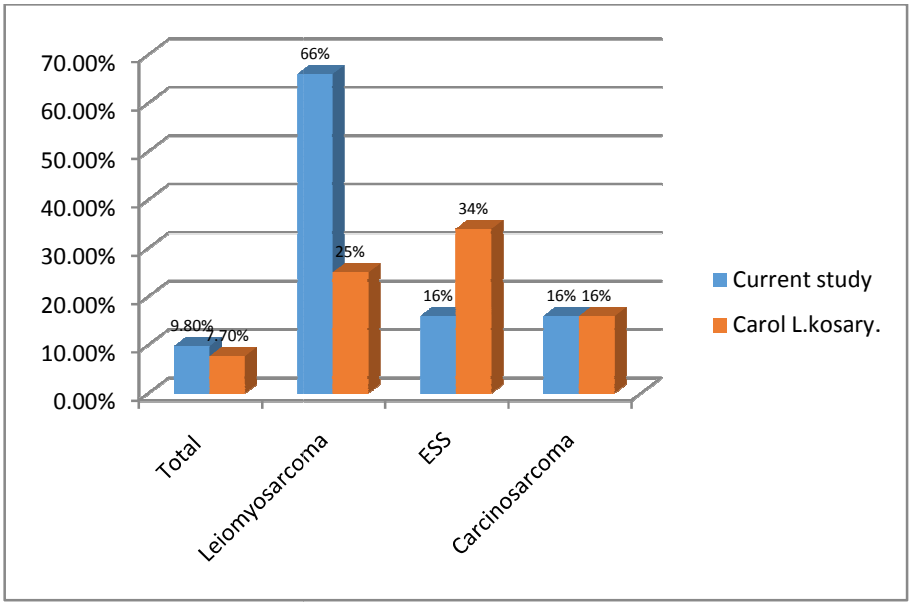


TABLE NO-7B: COMPARISION OF ER EXPRESSION IN ENDOCERVICAL ADENOCARCINOMA :

STUDIES	ER POSITIVE
Fujiwara et al [26]	20 %
Staebler et al [27]	4.2 %
A.Alkushi et al[28]	11 %
McCluggage et al [12]	38% (focal and weak)
Current study	**30 %**

Mccluggage et al evaluated 30 endometrial adenocarcinoma and 26 endocervical adenocarcinomas, in their study 38% showed focal weak positivity for ER.

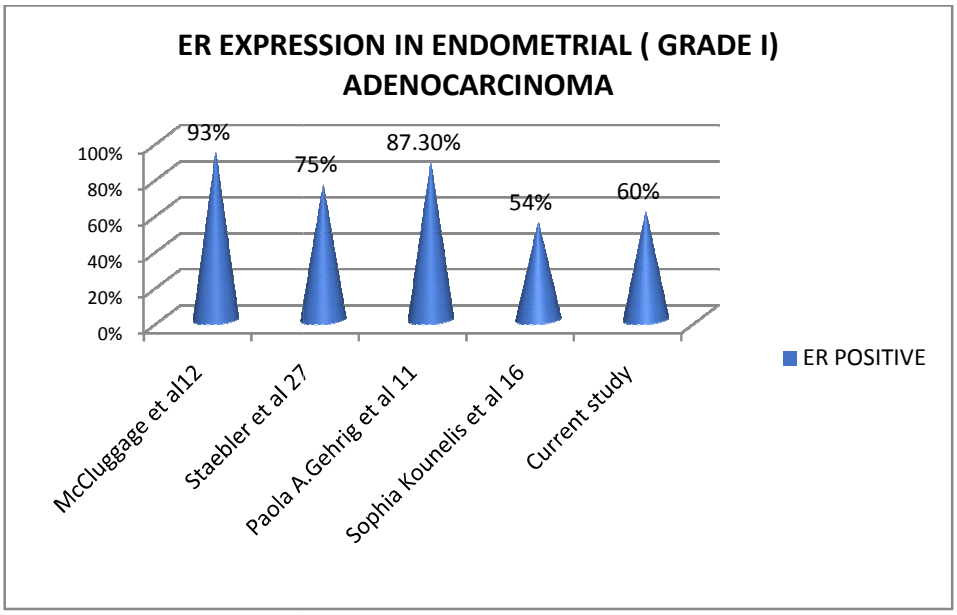
staebler et al studied 24 endometrial and 24 endocervical adenocarcinomas found that only 1 of 24 (4.2%) endocervical expressed ER.

A.Alkushi et al evaluated 84 endocervical adenocarcinoma , of which 9 cases were positive for ER.

Fujiwara et al study showed 17 out of 84 cases of endocervical adenocarcinoma was positive for ER.

in our study 3 out of 10 cases showed positivity for ER in Endocervical adenocarcinoma biopsies.

CHART NO: 7A &B: COMPARISION OF ER EXPRESSION IN WELL DIFFRENTIATED ENDOMETRIAL GRADE I ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA



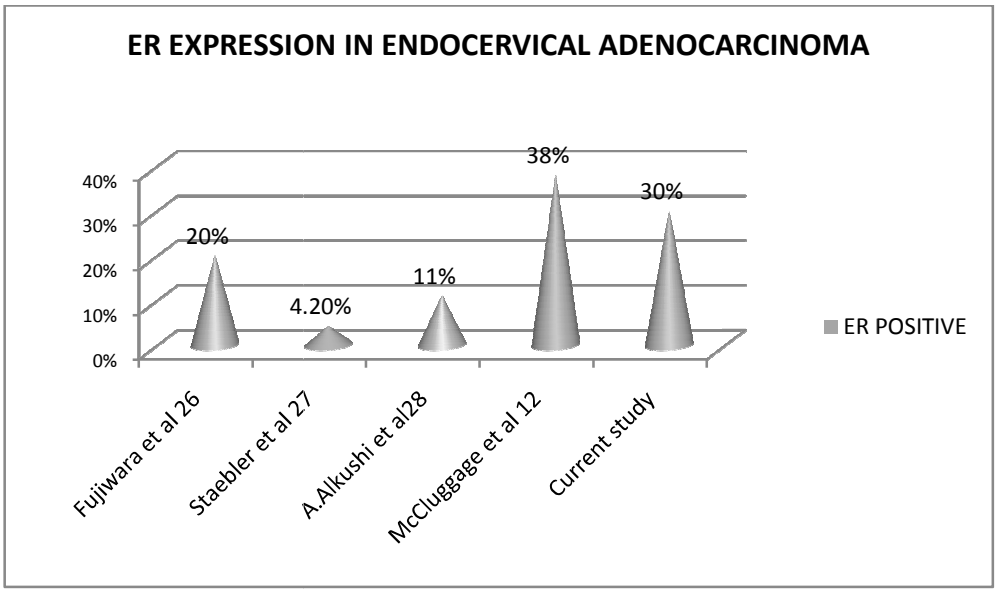

ER EXPRESSION IN ENDOCERVICAL ADENOCARCINOMA
40%
30%
20%
10%
0%
20%
4.20%
11%
38%
30%
ER POSITIVE
Fujiwara et al 26
Staebler et al 27
A.Alkushi et al28
McCluggage et al 12
Current study

CHART NO: 8A &B: COMPARISION OF P16 EXPRESSION IN WELL

TABLE NO-8A: COMPARISION OF P16 EXPRESSION IN WELL DIFFRENTIATED ENDOMETRIAL (GRADE I) ADENOCARCINOMA :

STUDIES	**P16 EXPRESSION**
Ansari-Lari et al [31]	35%
Chih-ping Han et al[17]	33%
McCluggage et al [32]	41%
Current study	**40%**

Ansari et al ,in his study 35 % of cases out of 24 endometrial adenocarcinomas showed patchy and weaker positivity.

Ching-Ping Han et al study showed 7 out of 21 endometrial adenocarcinoma cases stained positive for P16.

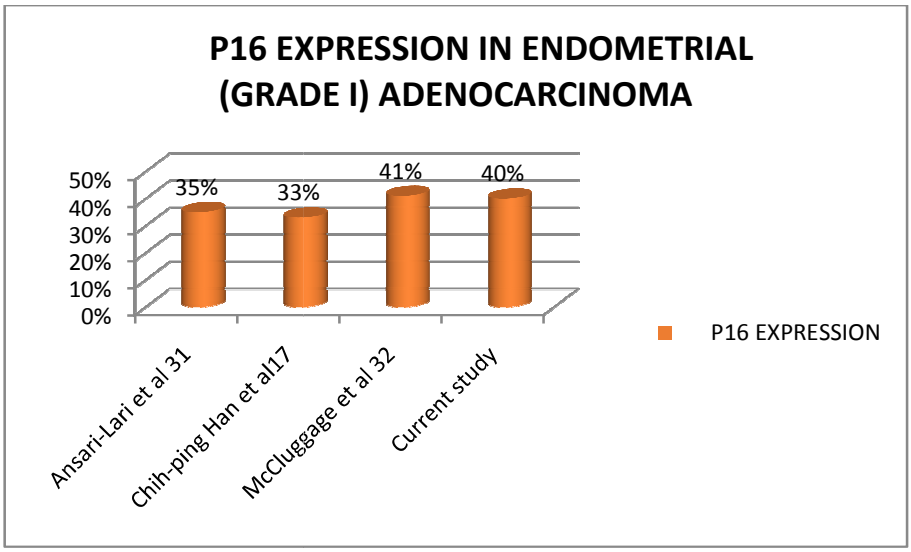
McCluggage, jenkin et al, in his study on 29 endometrial adenocarcinoma 40% cases expressed weak and patchy p16

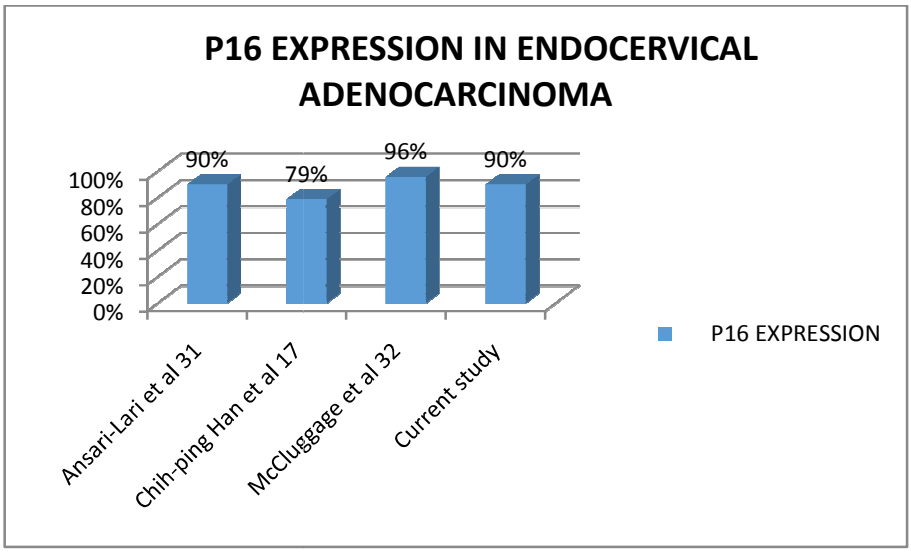
in our study 4 out of 10 cases showed P16 positivity that gives a percentage of 40%

TABLE NO-8B: COMPARISION OF P16 EXPRESSION IN ENDOCERVICAL ADENOCARCINOMA

STUDIES	P16 EXPRESSION
Ansari-Lari et al [31]	**90%**
Chih-ping Han et al [17]	**79%**
McCluggage et al [32]	**96%**
Current study	**90%**

CHART NO: 8A &B: COMPARISION OF P16 EXPRESSION IN WELL DIFFRENTIATED ENDOMETRIAL GRADE I ADENOCARCINOMA AND ENDOCERVICAL ADENOCARCINOMA





Ansari et al, in his study 18 out of 19 endocervical adenocarcinoma cases showed strong and diffuse positivity for P16

Ching-Ping Han et al study showed 11 out of 14 (79%) endocervical adenocarcinoma cases stained positive for P16.

McCluggage, jenkin et al, in his study on 23(96 %) endocervical adenocarcinoma cases 22 cases expressed diffuse positivity for P16

In our study 9 out of 10 (90%) cases showed strong and diffuse P16 positivity

STUDIES ON PANEL OF MARKERS:

McCluggage et al used 4 marker panel : ER, CEA, VIMENTIN , 34 βE12

Kong cs ,Beck et al[34] used 3 marker panel: vimentin , ER or PR , and HPV marker (P16, proExc, HPV ISH . this three panel marker is optimal for determining the site of origin for usual endometrial and endocervical adenocarcinoma however these panel do not perform well with special variants.

Steebler et al [35] studied the use of Hormone receptor immunohistochemistry and HPV in situ hybridization are useful.

Lai-Fong Kok et al[36] study on Reappraisal of three markers (ER/vimentin/CEA), four marker (ER/vimentin/CEA/PR) and five marker (ER/vimentin/CEA/PR/P16INK4A) panel in the diagnostic distinction between primary endocervical and endometrial adenocarcinoma in a tissue micro array study recommends the conventional three marker ER/Vimentin/CEA panel is sufficient, appropriate and useful. Ancillary PR and P16 INK 4a add no value to the performance of the conventional three marker ER/Vimentin/CEA panel

INFERENCE :

No single markers are diagnostic to differentiate between endocervical and endometrial adenocarcinomas.

p16 is predominantly strong diffuse positive in endocervical carcinomas[31,32]

ER Marker is predominantly positive in endometrial adenocarcinomas [12,12,16,26,27,28]

Application of panel of immunohistochemical markers will be able to distinguish endometrial adenocarcinoma from endocervical adenocarcinomas

Conventional three panel markers ER/Vimentin/CEA panel is sufficient, appropriate and useful. Ancillary PR and P16 INK 4a add no value to the performance of the conventional three marker ER/Vimentin/CEA panel.

CONCLUSION

1. Uterine corpus malignancies is the third most common malignancies in the female genital tract following cervix and ovary in developing countries like India

2. It is the first most common female genital tract malignancy in developed countries

3.. The overall incidence of cases of uterine corpus malignancy in the given period of three and half years is 9.6% in Thanjavur medical college and hospital.

4. The uterine carcinoma carries the percentage of 82% predominantly of adenocarcinoma type.

5. Endometrial adenocarcinoma is the most common malignancy recorded

6.The other Histological types received in our study are uterine papillary serous carcinoma, clear cell adenocarcinoma , poorly or undifferentiated carcinoma and a case of squamous cell carcinoma

6.. In our current study majority of the uterine corpus neoplasms presented in grade I disease. with the median age of presentation of 51 years and with a mean age of 52.5 years.

7. Endometriod Nos type is most common histological type of endometrial adenocarcinoma observed in our study.

8. Grade I tumors of endometrial adenocarcinoma is commonly noted in our study than Grade 2 tumors which is mostly common in other literatures.

9. In our study 80 % of patients presented in stage I disease because of earlier presentation due to abnormal vaginal bleeding and hence the earlier diagnosis.

10**.** The percentage of uterine sarcomas documented within this period is 9.8% which includes the cases of Leiomyosarcoma, Endometrial stromal sarcoma, carcinosarcoma

Immunohistochemical marker evaluation for ER and P16 on Endometrial adenocarcinoma and Endocervical adenocarcinoma.

1. ER nuclear immuno-histo stain is predominantly positive in endometrial adenocarcinomas [12,12,16,26,27,28] in 60% of cases

2..p16 Immuno-histostaining showed predominantly strong and diffuse positivity in endocervical adenocarcinomas[31,32] in 90% of cases in our study

3. Both ER and P16 are positive in 30% of cases

4. High grade endometrial adenocarcinomas poorly express ER

5.No single markers is diagnostic to differentiate between endocervical and endometrial adenocarcinomas.

4. Panel of immunohistochemical markers will help to distinguish endometrial adenocarcinoma from endocervical adenocarcinomas

5.Conventional three panel markers ER/Vimentin/CEA panel is sufficient, appropriate and useful. Ancillary PR and P16 INK 4a add no value to the performance of the conventional three marker ER/Vimentin/CEA panel

ANNEXURE I

WHO Histological Classification of Tumors of the Uterine Corpus

Epithelial Tumors and Related Lesions

Endometrial carcinoma
Endometrioid adenocarcinoma
Variant with squamous differentiation
Villoglandular variant
Secretory variant
Ciliated cell variant
Mucinous adenocarcinoma
Serous adenocarcinoma
Clear cell adenocarcinoma
Mixed cell adenocarcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Others
Endometrial hyperplasia
  Nonatypical hyperplasia
    Simple
    Complex
  Atypical hyperplasia
    Simple
    Complex
Endometrial polyp
Tamoxifen-related lesions

Mesenchymal Tumors

Endometrial stromal and related tumors
  Endometrial stromal nodule
  Endometrial stromal sarcoma, low grade
  Undifferentiated endometrial sarcoma
Smooth muscle tumors
  Leiomyosarcoma
    Epithelioid variant
    Myxoid variant
  Smooth muscle tumors of uncertain malignant potential
  Leiomyoma, not otherwise specified
    Histological variants
      Mitotically active variant
      Cellular variant
      Hemorrhagic cellular variant
      Epithelioid variant
      Myxoid variant

Atypical variant
Lipoleiomyoma variant
Growth pattern variants
Diffuse leiomyomatosis
Dissecting leiomyoma
Intravenous leiomyomatosis
Metastasizing leiomyomatosis
Miscellaneous mesenchymal tumors
Mixed endometrial stromal and smooth muscle tumors
Perivascular epithelioid cell tumor
Adenomatoid tumor
Other malignant mesenchymal tumors
Other benign mesenchymal tumors

Mixed Epithelial and Mesenchymal Tumors

Carcinosarcoma (malignant mixed Müllerian tumor)
Adenosarcoma
Carcinofibroma
Adenofibroma
Adenomyoma
Atypical polypoid variant

Gestational Trophoblastic Disease

Trophoblastic neoplasms
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor
Molar pregnancies
Hydatidiform mole
Complete
Partial
Invasive
Metastatic
Nonneoplastic, nonmolar trophoblastic lesions
Placental site nodule and plaque
Exaggerated placental site

Miscellaneous Tumors

Sex cord-like tumors
Neuroectodermal tumors
Melanotic paraganglioma
Tumors of germ cell type
Others

Lymphoid and Hematopoietic Tumors
Malignant lymphoma
Leukemia

ANNEXURE II

Tumor, Node, Metastasis (TNM) Staging Scheme and FIGO of Nontrophoblastic Tumors of the Uterine Corpus

PRIMARY TUMOR (T)		
TNM categories	**FIGO Stages**	
TX		Primary tumor cannot be assessed
TO		No evidence of primary tumor
Tis	0	Carcinoma in situ (preinvasive carcinoma)
TI	I*	Tumor confined to corpus uteri
TIa	IA	Tumor limited to endometrium
TIb	IB	Tumor invades less than one half of myometrium
TIc	1C	Tumor invades one half or more of myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Endocervical glandular involvement only
T2b	IIB	Cervical stromal invasion
T3 and/or N1	III	Local and/or regional spread as specified in T3a, b, N1, and FIGO IIIA, B, C below
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
T3c	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa
M1	IVB	Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa)

REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

ANNEXURE III

(1) Leiomyosarcoma	
Stage	Definition
I	Tumor limited to uterus
IA	<5 cm
IB	>5 cm
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	>One site
IV	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(2) Endometrial stromal sarcomas (ESS) and adenosarcoma[a]	

Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, Adenosarcomas, and carcinosarcomas)

Stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	>One site
IV	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

ANNEXURE IV[73]

Differential microscopic criteria between endometrial hyperplasia and adenocarcinoma

MICROSCOPIC CRITERIA	ADENOMATOUS HYPERPLASIA	ATYPICAL HYPERPLASIA	ADENOCARCINOMA
Nuclei			
Profiles	Smooth and oval	Irregular	Irregular
Size	Uniform	Large, variable	Large, variable
Nucleoli	Small, round	Large, irregular	Large, irregular, spiculated
Mitoses	Numerous in stroma and glands	Numerous	Variable
Cytoplasm	Abundant, amphophilic	Sometimes scant; may be very abundant, with dense eosinophilia	Scant, pale, amphophilic
Glands			
Lining epithelium	Tall columnar, single layered	Stratification, loss of polarity	Loss of polarity
Profiles	Dilated, irregular, with outpouching and infoldings	Irregular, with intraglandular tufting *but no bridging*	Irregular, with cribriform pattern and intraglandular bridging
Size	Variable	Variable	Variable
Stroma	Usually abundant, cellular	Scant, with crowding	Scant

ANNEXURE V

Criteria and diagnostic terms for uterine smooth muscle tumors (freely adapted from the work of Richard Kempson and his co-workers)

COAGULATIVE NECROSIS	MITOTIC COUNT PER 10 HPF	ATYPIA		DIAGNOSIS
Present	Greater than 10	Moderate to severe (focal or diffuse)		Leiomyosarcoma
		None to mild		Leiomyosarcoma
	Equal to or less than 10	Moderate to severe (focal or diffuse)		Leiomyosarcoma
		None to mild		STUMPa
Absent	Greater than 10	Moderate to severe	Diffuse	Leiomyosarcoma
			Focal	STUMPb
		None to mild		Mitotically active leiomyoma (up to 15 mitoses/10 HPF are allowed)
	Equal to or less than 10	Moderate to severe	Diffuse	STUMPc
			Focal	Leiomyomad
		None to mild		Leiomyoma

[a] Of the three tumors here placed in the STUMP category, this is the one most likely to behave in a malignant fashion. Actually, it is regarded as a probable leiomyosarcoma in Kempson's scheme. The alternative possibility of an infarction in a leiomyoma due to torsion or other factors should be considered.

[b] In Kempson's scheme, this is designated as STUMP if the mitotic activity is higher than 15.

[c] This is referred to as ‘atypical leiomyoma with low risk of recurrence’ in Kempson's scheme.

[d] This is designated as ‘leiomyoma with limited experience’ in Kempson's scheme

BIBILIOGRAPHY

1.Richard r. Barakat maurie markman. epidemiology of gynecological cancers ,fith edition , Epidemiology of gynecological cancers.

2.Theonia boyd, bradleyj.quade and christopher P.crum. female genital tract developement.pg13-17

3.World health organization classification ot tumours: tumors of the breast and female genital organs pg 217- pg257

4.Crum.Nucci.Lee ; Diagnostic gynecologic and obstetrics pathology ;2nd edition

5. Robert j.kurman,M.D; Diagnosis of endometrial biopsies and

curettings;, 2nd edition Pg: 208-250

6.. Robbins & cotran pathologic basis of disease ; kumar.Abbas.Aster 19th edition: pg no 991-1043

7. Niamhconlon, MB, Mario M.leitao,et al; grading uterine endometrial carcinoma. A proposal that binary is best.

8 Khush Mittal, M.d; robert soslow,M.D; W.G. McCluggage, FRCpath: application of immunohistochemistry to Gynecologic pathology.

9.Rodney T.Miller, M.D.,Director of Immunohistochemistry ; endocervical vs endometrial adenocarcinoma , update on useful immunohistochemical markers

10.Castrillon DH, Lee KR, Nucci MR. Distinction between endometrial and endocervical adenocarcinoma: an immunohistochemical study. Int. J. Gynecol. Pathol. 2002; 21; 4–10.

11. Paola A.Gehrig et al : Estrogen receptor status, determined by immunohistochemistry , as a predictor of recurrence of stage 1 endometrial carcinoma

12. .McCluggage WG, Sumathi VP, McBride HA, Patterson A. A panel of immunohistochemical stains, including carcinoembryonic antigen,

vimentin, and estrogen receptor, aids the distinction between primary endometrial and endocervical adenocarcinomas. Int. J. Gynecol. Pathol. 2002; 21; 11–15.7.

13 .Ansari-lari MA, Staebler, Ronnett BM: distinction of endocervical and endometrial adenocarcinomas : P16 expression corelated with Human papilloma virus 180A ,2003

14. McCluggage WG, Jenkins D. p16 immunoreactivity may assist in the distinction between endometrial and endocervical adenocarcinoma. Int. J. Gynecol. Pathol. 2003; 22; 231–235.

15. Dabbs DJ, Geisinger KR, Norris HT. Intermediate filaments in endometrial and endocervical carcinomas. The diagnostic utility of vimentin patterns. Am. J. Surg. Pathol. 1986; 10;568–576.8.

16. Sophia Kounelis, Nikiforos, Efi kouri, Domenico Coppola: immunohistochemical profile of endometrial adenocarcinoma: A study of 61 cases and review of literature

17. Chih-Ping Han , Lai-Fong Kok et al : scoring of P16 ink 4a immunohistochemistry based on independent nuclear staing alone can sufficiently distinguish between endocervical adenocarcinoma and

endometrial adenocarcinomas in a tissue microarray study.

18.HalperinR, zehavi S, Habler L, Hadas E : comparitive immunohistochemical study of endometrioid and serous papillary carcinoma of endometrium.

19. Ioachin E.Immunohistochemical tumour markers in endometrial carcinoma

20. Carol L kosary ; tumors of corpus uteri ; chapter 15 pg no: 123-132

21.F Gholipour , MKadivar , ASKazzazi et al; Indian journal of cancer Vol 46 no:3 september 2009; Assesment of gynecological malignancies : A multicentric study in Tehran 1995-2005.

22. G.Platanioitis.M castiglione ESMO guidelines working group; Annals of oncology; endometriod cancer; ESMO clinical practice guidelines for dignosis treatment and follow up.

23. Behiye pinar cilesiz; comparison of preoperative endometrial biopsy grade and final pathologic diagnosis in patients with endometriod endometrial carcinoma

24. Marie-claude renaud: joint SOGC-GOC-SCC clinical practice guidelines; epidemiology and investigation for suspected endometrial

cancer.

25. Giesler JP,Wiemann Mc, Zhouz; using FIGO histologic grade to determine when to perform lymphadenectomies in endometriod adenocarcinoma of endometrium.

26. Hisaya Fujiwara, M.D., Ph.D. Guillermo Tortolero-Luna, M.D., Ph.D. ichele Follen Mitchell, M.D., M.S. (ER) and John P. Koulos, M.D. Thomas C. Wright, Jr., M.D. Adenocarcinoma of the Cervix.Expression and Clinical Significance of Estrogen and Progesterone Receptors. CANCER February 1, 1997 / Volume 79 / Number 3

27. Staebler A, Sherman ME et al (2002) Hormone receptor immunohistochemistry and human papillomavirus in situ hybridization are useful for distinguishing endocervical and endometrial adenocarcinomas. Am J Surg Pathol 26(8):998–1006

28. A. Alkushi , J. Irving .F. Hsu, B. Dupuis ,C. L. Liu,M. Rijn .C. B. Gilks Immunoprofile of cervical and endometrial adenocarcinomas using a tissue microarray .Virchows Arch (2003) 442:271–277

29. Chiung- Lingliao, Ming-yung lee et al:Progesterone receptor does

not improve the performance and test effectiveness of the conventional 3-marker panel, consisting of estrogen receptor, vimentin and carcinoembryonic antigen in distinguishing between primary endocervical and endometrial adenocarcinomas in a tissue microarray extension study

30. Kenta masuda et al. Carcinoma of the Lower Uterine Segment (LUS): Clinicopathological Characteristics and Association with Lynch Syndrome

31. Ansari-Lari MA, Staebler A, Zaino RJ, Shah KV,:Distinction of endocervical and endometrial adenocarcinomas: immunohistochemical p16 expression correlated with human papillomavirus (HPV) DNA detection.

32. McCluggage WG , Jenkins D : p16 immunoreactivity may assist in the distinction between endometrial and endocervical adenocarcinoma.

33. Kathryn M.Greven,M.D, Maurie Markman et al; Cancer Network of the journal oncology; Uterine corpus tumors.

34. Kong CS[1], Beck AH, Longacre TA; A panel of 3 markers including p16, ProExC, or HPV ISH is optimal for distinguishing between primary endometrial and endocervical adenocarcinomas.

35. Staebler A[1], Sherman ME, Zaino RJ, Ronnett BM :Hormone receptor immunohistochemistry and human papillomavirus in situ hybridization are useful for distinguishing endocervical and endometrial adenocarcinomas.

36. Lai-Fong Kok et al; A reappraisal of three-marker (ER/Vim/CEA), four-marker (ER/Vim/CEA/PR), and five-marker (ER/Vim/CEA/PR/p16INK4a) panels in the diagnostic distinction between primary endocervical and endometrial adenocarcinomas in a tissue microarray study.

37. Rodney T.Miller,M.D: The focus immunohistochemistry, Endocervical Vs endometrial adenocarcinom; update on useful immunohistochemical markers

38. Peter A.Humphery Louis P.Dehner The washington Manual of surgical Pathology pg 517-534

39. Wang Y[1], Ma XL, Xi CG, Lin J, Ren CX, Liu CR;Correlation between estrogen receptor status and clinicopathologic parameters in endometrial cancer: a comparative study by immunohistochemistry using different scoring systems

40. Bancroft JD, Marilyn Gamble (Ed), Theory and practice of histological techniques, Churchill Livingstone 2002. 391.

41. Huang S, Minnassian H, More J D et al. Application of immunofluorescent staining in paraffin sections improved by trypsin digestion, Laboratory Investigation 35:383-

42. Miller K, Auld J, Jessup E, Rhodes A, Antigen unmarking by pressure cooker method. A comparison with microwave oven heating and traditional methods, Advances of anatomical pathology,2:60-64.

43. Pluzek KY, Sweeney E, Miller KD, Isaacson P, A major advance for IHC Epos, J Pathol 169 (Suppl) abstract 220

44.Primus FJ, Clark CA, Goldenberg DM: Immunohistochemical detection of carcinoembryonic antigen. In: DeLellis RA, ed. Diagnostic immunohistochemistry, New York: Masson; 1981:263-276.

45. Jothy S, Brazinsky SA, Chin-A-Loy M, Haggarty A, Krantz MJ, Cheung M, Fuks A: Characterization of monoclonal antibodies to carcinoembryonic antigen with increased tumor specificity. Lab Invest 1986; 54:108-117.

46. Esteban JM, Paxton R, Mehta P, Battifora H, Shively JE: Sensitivity

and specificity of Gold types 1 to 5 anti-carcinoembryonic antigen monoclonal antibodies. Immunohistologic characterization in colorectal cancer and normal tissues. Hum Pathol 1993; 24:322-328.

47. Cohen C, Shulman G, Budgeon LR (1982) Endocervical and endometrial adenocarcinoma: an immunoperoxidase and histochemical study. Am J Surg Pathol 6:151–157

48. Leader M, Collins M, Patel J, Henry K: Vimentin. An evaluation of its role as a tumour marker. Histopathology 1987; 11:63-72.

49. A. Alkushi , J. Irving .F. Hsu, B. Dupuis ,C. L. Liu,M. Rijn .C. B. Gilks Immunoprofile of cervical and endometrial adenocarcinomas using a tissue microarray .Virchows Arch (2003) 442:271–277

50. Azumi N, Battifora H: The distribution of vimentin and keratin in epithelial and nonepithelial neoplasms. A comprehensive immunohistochemical study on formalin- and alcohol-fixed tumors. Am J Clin Pathol 1987; 88:286-296.

51. Rodney T. Miller, M.D. Director of Immunohistochemistry Immunohistochemistry in the Diagnosis of Metastatic Carcinoma of Unknown Primary Origin. ProPath Laboratory ,January 2011

52. Adriana Radu, Corina D. Frandes, O. Pop, Mircea Sferdian, L. D. Stretcu: The immunohistochemical study of endometrial and Endocervical carcinomas using anti-vimentin in coexpression with anti-ER. Studia universitatis "vasile goldiş", Vol. 20, issue 3, 2010, pp. 23-26

53. Li X, Huang J, Yip, Bambara RA, Single chain estrogen receptor reveal that the ER alpha/beta hetero dimer emulates functions of ER alpha dimer in genomic estrogen signaling pathways. Mol Cell Biol 2004; 24(17); 7681-94.

54. Suzanne AW, Fuqua Rachel Schiff, Disease of breast ed: The biology of ERs, 585-590

55. Zaino RJ (2002) The fruits of our labors: Distinguishing endometrial from endocervical adenocarcinoma. Int J Gynecol Pathol 21:1–3

56. Zaino RJ (2002) The fruits of our labors: Distinguishing endometrial from endocervical adenocarcinoma. Int J Gynecol Pathol 21:1–3

57.Agnieszka K. Witkiewicz . Thomas C. Wright . Alex Ferenczy . Brigitte M. Ronnett .Robert J. Kurman.Blausteins pathology of the female genital tract, 6 th edition,2011.

58.Yemelyanova A, Ji H et al (2009) Utility of p16 expression for distinction of uterine serous carcinomas from endometrial endometrioid and endocervical adenocarcinomas: immunohistochemical analysis of 201 cases. Am J Surg Pathol 33(10):1504–1514

59. Niamh conlon, MB et al : Grading Uterine Endometriod carcinoma A proposal that Binary is best american journal ;volume 38;number12 December 2014

60. Shannon N. Westin, Robin A. Lacour, Diana L. Urbauer, Rajyalakshmi Luthra, Diane C. Bodurka, Karen H. Lu and Russell R. Broaddus,;Carcinoma of the Lower Uterine Segment: A Newly Described Association With Lynch Syndrome; JCO December 20, 2008 vol. 26 no. 36 5965-5971

61.National cancer Institute at the National Institutes of Health,cervical cancer treatment, 11/21/2013

62. Cohen C, Shulman G, Budgeon LR (1982) Endocervical and endometrial adenocarcinoma: an immunoperoxidase and histochemical study. Am J Surg Pathol 6:151–157

63.Azumi N, Battifora H: The distribution of vimentin and keratin in epithelial and nonepithelial neoplasms. A comprehensive

immunohistochemical study on formalin- and alcohol-fixed tumors. Am J Clin Pathol 1987; 88:286-296

64. Klaus Bodner, Peter Laubichler, Oliver Kimberger,Klaus Czerwenka, Robert Zeillinger And Barbara Bodner-Adler. Oestrogen and Progesterone Receptor Expression in Patients with Adenocarcinoma of the Uterine Cervix and Correlation with Various Clinicopathological Parameters. ANTICANCER RESEARCH 30: 1341-1346 (2010)

65. Farveen Marican Abu Backer, Nik Raihan Nik Mustapha,and Nor Hayati Othman. Clinicopathological comparison of adenocarcinoma of cervix and e ndometrium using cell cycle markers: p16ink4a, p21waf1, and p27Kip1 on 132 Cancers. Infectious Diseases in Obstetrics and Gynecology Volume 2011, Article ID 857851,6pages

66. Hisaya Fujiwara, M.D., Ph.D. Guillermo Tortolero-Luna, M.D., Ph.D. ichele Follen Mitchell, M.D., M.S. (ER) and John P. Koulos, M.D. Thomas C. Wright, Jr., M.D. Adenocarcinoma of the Cervix.Expression and Clinical Significance of Estrogen and Progesterone Receptors. CANCER February 1, 1997 / Volume 79 / Number 3

67.Nora T. Kizer, MD, Feng Gao, MD, PhD,Saketh Guntupalli, MD,Premal H. Thaker, MD, Matthew A. Powell, MD, Paul J. Goodfellow, PhD, David G. Mutch, MD, and Israel Zighelboim, MD. Lower Uterine Segment Involvement is Associated with Poor Outcomes in Early-Stage Endometrioid Endometrial Carcinoma; Ann Surg Oncol. 2011 May; 18(5): 1419–1424.

68.Nicolae A, Goyenaga P, McCluggage WG, Preda O, Nogales FF. Endometrial intestinal metaplasia: a report of two cases, including one associated with cervical intestinal and pyloric metaplasia. Int. J. Gynecol. Pathol. 2011; 30; 492–496

69. Eswari et al;Endometrial carcinoma ovary and uterus - synchronus primary or metastasis ;A case report

70. Natalia Buza et al;Her2 Neu in endometrial carcinoma : A promising therapeutic Target.

71. Hannes G.Kasper ; the utility of Immunohistochemistry in differential diagnosis of Gynecological disorder.

72. McMacCluggage et al; Recent advances in Immunohistochemistry in gynecologic pathology Volume 40, Issue 4, pages 309–326

73.Tavassoli F, Kraus FT. Endometrial lesions in uteri resected for atypical endometrial hyperplasia. Am J Clin Pathol 1978, **70:** 770–779