Dissertation on

"AN IMMUNOHISTOCHEMICAL STUDY ON INTRATUMORAL AND PERITUMORAL LYMPHATIC VESSEL DENSITY AS A PROGNOSTIC PARAMETER IN ENDOMETRIAL CARCINOMA"

Submitted in partial fulfillment for the Degree of

M.D PATHOLOGY BRANCH – III

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

CHENNAI

INSTITUTE OF PATHOLOGY MADRAS MEDICAL COLLEGE

CHENNAI - 600003

MAY - 2019

CERTIFICATE

This is to certify that this dissertation entitled "**AN IMMUNOHISTOCHEMICAL STUDY ON INTRATUMORAL AND PERITUMORAL LYMPHATIC VESSEL DENSITY AS A PROGNOSTIC PARAMETER IN ENDOMETRIAL CARCINOMA**" is the original work of **Dr.PREETHA.S,** in partial fulfilment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R. Medical University to be held in May 2019.

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DECLARATION

I, **Dr.PREETHA.S,** solemnly declare that the dissertation titled "**AN IMMUNOHISTOCHEMICAL STUDY ON INTRATUMORAL AND PERITUMORAL LYMPHATIC VESSEL DENSITY AS A PROGNOSTIC PARAMETER IN ENDOMETRIAL CARCINOMA**" is the bonafide work done by me at the Institute of Obstetrics and gynaecology, Madras Medical College under the expert guidance and supervision of **Prof. Dr. M.P.KANCHANA, M.D.,** Professor of Pathology, Department of pathology, Institute of Obstetrics and Gynaecology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place: Chennai

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ACKNOWLEDGMENT

I express my sincere thanks to **Prof. Dr. Jayanthi**, Dean, Madras Medical College and Rajiv Gandhi Government General Hospital, for permitting me to utilize the facilities of the Institution.

I take the opportunity to express my gratitude to **Prof.Dr.Bharathi vidhya jayanthi**, M.D., Director and Professor, Institute of Pathology, Madras Medical College, Chennai for her keen interest, constant encouragement and valuable suggestions throughout the study.

I am extremely thankful to Prof. **Dr.M.P. KANCHANA, M.D.,** Professor of Pathology, Department of pathology, Institute of obstetrics and gynecology and **Dr.Rajesh Natraj, M.D.,** Assistant professor of Pathology, Institute Of Pathology, Madras Medical College, for their valuable suggestions, constant support, advice and encouragements throughout the study.

I am truly thankful to **Prof.Dr.Sudha Venkatesh M.D., Prof.Dr.Padmavathi M.D., Prof.Dr.Ramamoorthi M.D., Prof.Dr.Rama M.D., Prof.Dr.Geetha Devadas M.D., Prof. Dr.S.Pappathi M.D., Prof. Dr.Rajavelu Indira M.D., Prof.Dr.Selvambigai M.D.,** for their valuable suggestions and encouragement throughout the study.

I express my heartfelt sincere thanks to **Dr. Revathy M.D.,** Assistant Professor of Pathology, Institute of Obstetrics and Gynaecology and all my Assistant Professors for their help and suggestions during the study.

I also would like to thank the Institutional Ethics Committee for approving my study.

I am thankful to the statistician for the help in statistical analysis.

I am thankful to my colleagues, friends, technicians and staff in the Department of Pathology, Institute of obstetrics and gynecology, and in the Institute of Pathology, Madras Medical College, Chennai for all their help and support they extended for the successful completion of this dissertation. My sincere thanks also go to all the patients and their families who were co-operative during the course of this study.

Last but not the least, I am grateful to my family members and friends for their constant support and belief in me.

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Dear Dr. PREETHA.S,

The Institutional Ethics Committee has considered your request and approved your study titled **"AN IMMUNOHISTOCHEMICAL STUDY ON INTRATUMORAL AND PERITUMORAL LYMPHATIC VESSEL DENSITY AS A PROGNOSTIC PARAMETER IN ENDOMETRIAL CARCINOMA" - NO.19122017.**

The following members of Ethics Committee were present in the meeting hold on **05.12.2017** conducted at Madras Medical College, Chennai 3

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

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

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ABBREVIATIONS

DM	:	Diabetes mellitus
HT	:	Hypertension
LVD	:	Lymphatic Vessel Density
I-LVD	:	Intratumoral lymphatic vessel density
P-LVD	:	Peritumoral lymphatic vessel density
TDF	:	Testis determining Factor
LMP	:	Last menstrual period
WHO	:	World Health Organisation
EIN	:	Endometrial intraepithelial neoplasia
AH	:	Atypical Hyperplasia
MMMT	:	Malignant Mixed Mullerian Tumour
HNPCC	:	Hereditary nonpolyposis colorectal cancer
MELF	:	Microcystic, elongated and Fragmented
EMA	:	Epithelial membrane antigen
FIGO	:	International Federation of Gynaecology and Obstetrics
CEA	:	Carcinoembryonic antigen
PAS	:	Periodic acid Schiff

SEIC	:	Serous endometrial intraepithelial carcinoma
ER	:	Estrogen receptor
PR	:	Progesterone receptor
SCNEC	:	Small cell neuroendocrine carcinoma
LCNEC	:	Large cell neuroendocrine carcinoma
GCT	:	Germ cell tumour
IGCNU	:	Intratubular Germ cell neoplasia, unclassified
CK	:	Cytokeratin
HRP	:	Horse radish peroxidase
HPF	:	High power field
H & E	:	Hematoxylin & Eosin
DAB	:	Diamino benzidine

CONTENTS

INTRODUCTION

INTRODUCTION

Among women, Endometrial carcinoma is the sixth most commonly occurring cancer[1] following cervix and ovary. Incidence rates are low in India[2]

The incidence of endometrial carcinoma is rising as life expectancy increases in postmenopausal women and mostly associated with high estrogen exposure, DM and HT. The peak incidence is in the age group of 55- to 65-years with a median age of 63.[3,4] In women below 40 years, incidence of endometrial cancer is 2 to 14%.[5] The most common symptom is abnormal vaginal bleeding and postmenopausal bleeding.

Endometrial carcinoma is broadly classified into two types as type I and type II. Type I carcinomas are strongly associated with estrogen stimulation and common in both premenopausal and postmenopausal women. Whereas type II occurs mostly in postmenopausal women and not estrogen dependent.[6] Type I tumours are of low grade with good prognosis usually and type II are high grade with aggressive behaviour.

Prognosis of endometrial adenocarcinoma mainly depends on the type, stage and grade.

Lymphatic invasion and nodal metastasis plays an important role in the spread and prognosis of endometrial adenocarcinoma.[7] Tumor angiogenesis which is the formation of new blood vessels associated with a neoplasm is required for tumor growth and metastases and is regarded as one of the most important events occurring in the neoplastic process.

Lymphatic spread occurs through cancer cell permeation of tumor lymphatics, thus involving the regional lymph nodes. However, it is not clear whether lymphatic dissemination occurs as a result of cancer cell infiltration of new lymphatic vessels or preexisting ones.[8] Recently, D2-40 has been studied to recognize tumor-associated lymphatic vessels in many tumors.

D2-40, an IgG2a monoclonal antibody, was generated against an oncofetal membrane antigen M2A. D2-40 has been reported to be a specific marker for lymphatic endothelium in normal and also in neoplastic tissue. D2-40 has shown to stain endothelium of lymphatic vessels and lymphangiomas but negative in hemangiomas[9].

Studies have demonstrated that endometrial cancers with high peritumoral and intratumoral lymph-angiogenesis are significantly more associated with lymphovascular invasion and lymph node metastases[10]

Therefore, assessing LVD with D2-40 in the endometrial carcinoma might be a valuable parameter for predicting patients having an increased risk of developing of metastasis.

In addition, D2-40 aids in increasing the frequency of detection of lymphatic invasion compared to routine hematoxylin and eosin stain.[10]

This study aims to detect the tumor lymph-angiogenesis, by D2-40, which is a predictive marker for the risk of lymph node metastasis and its relation to other prognostic parameters in Endometrial Carcinoma and might help to select endometrial cancer patients who will benefit from lymphadenectomy.[11]

AIMS AND OBJECTIVES

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1. To study the tumor lymph-angiogenesis, detected by D2-40, as a predictive marker for the risk of lymph node metastasis and its relation to other prognostic parameters in Endometrial Carcinoma.
2. Also, patients who underwent Total Abdominal Hysterectomy without Lymph node dissection can be kept under surveillance for lymph node metastasis.
3. To compare the efficacy of Pipelle sampling and Endometrial curettage in detecting endometrial carcinoma and to compare the concordance of FIGO grade of endometrial adenocarcinomas in pre-operative biopsy and hysterectomy specimens

REVIEW OF LITERATURE

REVIEW OF LITERATURE

EMBRYOLOGY

The reproductive system is functionally immature until puberty. In females, due to the lack of Y chromosome and consequent absence of TDF (testis determining factor), the gonad differentiates into an ovary.

Around 5th week of gestation, germ cells migrate through the dorsal mesentery of the gut into the intermediate mesoderm, later the germ cells appear within the genital ridge for differentiation into gonads[14]. Upto 7th week, the development of both the female and male embryos are morphologically sexually indifferent [12]

There are two ductal systems for the formation of internal genitalia. The paramesonephric (Müllerian) ducts form female structures and the mesonephric (Wolffian) ducts form male structures. Both male and female embryos develop both ducts initially. Later paramesonephric ducts persist in the female with regression of mesonephric duct but vestigial structures such as the Gartner's duct, epoophoron and the paraoophoron may persist.[13]

Descent of ovary occurs by the third month into the ovarian fossa in pelvis. The ovaries contain 6–7 million primordial follicles by 5 -6months of gestation[15]

Summary of key phases of fetal genital tract development

Phase of genital development	Time (weeks of gestation)
Indifferent gonadal phase	4–6
Gonadal differentiation	7
Ductal differentiation	9–11
External genitalia differentiation	10–12

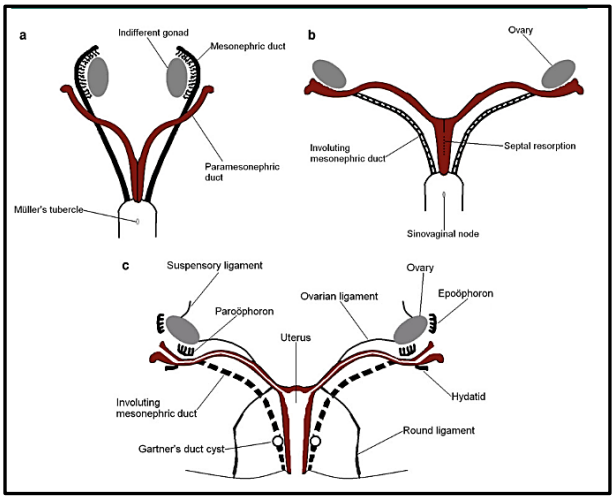


Figure 1: Development of female genital tract

The cranial end of the paramesonephric fused ducts forms the future uterus. The unfused cranial ends remain open as the fimbrial portions of the fallopian tubes. The caudal end of the fused ducts will form the upper two-thirds of the vagina. The lower most fused paramesonephric ducts fuse with the ascending endoderm of the sinovaginal bulb forming the lower third of the vagina. The hymen is a membrane separating the vagina from the urogenital sinus develops and is perforated at birth.[16]

ANATOMY

The uterus is a thick-walled, pear shaped muscular organ situated in the pelvis between the urinary bladder and rectum. It lies posterior to the bladder and uterovesical space, and anterior to the rectum and recto-uterine pouch. Adult nulliparous uterus measures 7 to 8cm X 5cm X 2.5cm and weighs 40 to 80 g.

The uterus is divided into the muscular upper two-third body of the uterus (corpus uteri) and fibrous cervix (cervix uteri) forms the lower third.

The uterine tubes enter the uterus on both sides at the uterine cornua. The round and ovarian ligaments are inferoanterior and inferoposterior, respectively, to each cornu. The dome-like fundus is covered by peritoneum. On the lateral sides of the body, the peritoneum is reflected laterally to form the broad ligament as a flat sheet to the pelvic wall. Uterus is supported by the cardinal ligament, uterosacral ligaments and inferiorly by the pelvic diaphragm, urogenital diaphragm, and perineal body.

The adult non-pregnant cervix is narrower and cylindrical than the uterine body and is 2.5 cm long. The uterus most commonly lies in an anteflexed and anteverted position in 50% of women. The uterus is comprised of three tissue layers which include the following:

- Endometrium: the inner lining and consists of the functional (superficial) and basal endometrium.
- Myometrium: the muscle layer and is composed of smooth muscle cells.
- Serosa/Perimetrium: the thin outer layer composed of epithelial cells[17]

BLOOD SUPPLY

Uterine artery, a branch of the anterior division of the internal iliac artery supplies the uterus. These enter the uterine wall, divide and run circumferentially as groups of anterior and posterior arcuate arteries. From the arcuate arteries, many helical arteriolar rami pass into the endometrium. Uterine veins drain into the internal iliac veins[18]

LYMPHATICS

Uterine lymphatics exist in the superficial (sub peritoneal) and deep parts of the uterine wall. Collecting vessels from the body of the uterus and cervix pass in the parametrium laterally to three main groups of lymph nodes: the external iliac, internal iliac and the obturator nodes

The external and internal iliac nodes present around their corresponding arteries. Lymph vessels from the fundus of the uterus and the uterine tubes accompany the lymphatic drainage of the ovaries to para-aortic nodes. The region surrounding the isthmus of the uterine tube may drain along the round ligament to the superficial inguinal nodes[18].

MICROSTRUCTURE

The uterus is composed of three main layers. From lumen outwards, these are the endometrium (mucosa), myometrium (smooth muscle layer) and serosa (or adventitia)

ENDOMETRIUM

The endometrium is formed by a layer of connective tissue, a single-layered columnar epithelium which is supported by the endometrial stroma. Before puberty, the epithelium is ciliated and cuboidal. It has glands composed of columnar cells secreting glycoproteins and glycogen. After puberty, the structure of the endometrium varies with the phase of the menstrual cycle. The glands are tubular which are perpendicular to the luminal surface penetrating up to the

myometrial layer. The stroma consists of a highly cellular connective tissue, blood and lymphatic vessels between the endometrial glands.

MYOMETRIUM

The myometrium is composed of smooth muscle and loose connective tissue, contains blood vessels, lymphatic vessels and nerves. It is dense and thick at the uterine midlevel and fundus but thin at the tubal orifices. The body of the uterus has four muscular layers. The submucosal (innermost) layer is composed of longitudinal and some oblique smooth muscle fibres. Where the lumen of the uterine tube passes through the uterine wall, this layer forms a circular muscle coat. The vascular layer is external to the submucosal layer and is rich in blood vessels, as well as longitudinal muscle; it is succeeded by a layer of predominantly circular muscle, the supravascular layer. The outer, thin, longitudinal muscle layer, the subserosal layer, lies adjacent to the serosa.

SEROSA

The uterine body is covered by peritoneal serosa, which continues downwards posteriorly to cover the supravaginal cervix. The anterior cervix and the lateral surfaces of the uterine body and cervix are not covered by peritoneum.

DATING OF ENDOMETRIUM/MENSTRUAL CYCLE

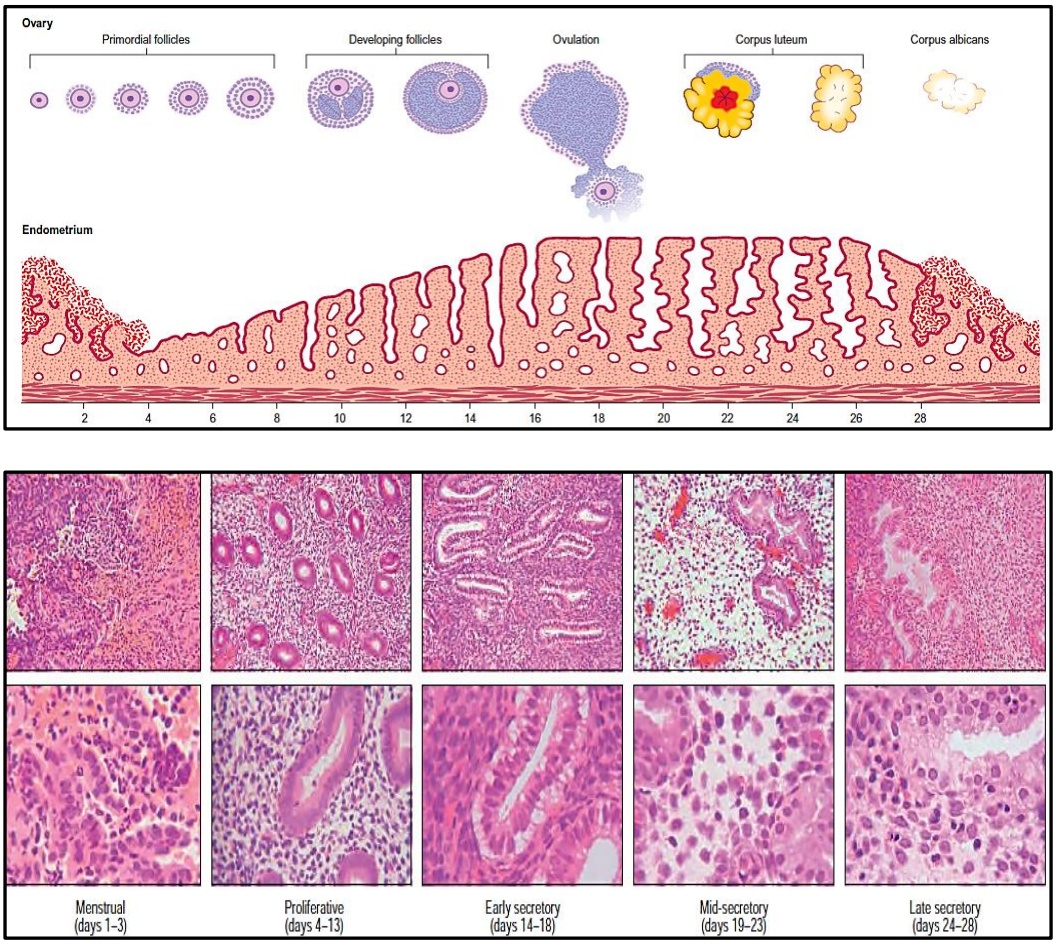


Figure 2: Dating of endometrium/ Menstrual cycle

Menstrual Phase

It is the phase of endometrial shedding which occurs if there is failure of fertilisation and/or implantation of the ovum. Spasmodic constriction in the spiral arterioles of the endometrial stratum functionalis occurs which is manifested by degeneration of the superficial layers of the endometrium and leakage of blood into the stroma. The endometrial glands are serrated and collapsed and the stroma is condensed, collapsed, and aggregate into tightly packed balls called as stromal blue balls separating from glands.

Other features indicative of this phase are the presence of necrotic debris, neutrophil infiltration, interstitial hemorrhage, and fibrin deposition. Apoptotic bodies are identified within both the glands and the stroma.[18,6]

Proliferative Phase

Endometrial stroma proliferates and becomes thicker and richly vascularised. The simple tubular glands elongate to form more numerous long coiled glands that begin secretion with ovulation. The proliferative phase is initiated and maintained until ovulation by the increasing production of oestrogens from developing ovarian follicles.

The endometrial glands lined by pseudostratified cuboidal or low columnar cells with moderate amount of basophilic cytoplasm, nuclei are oval or rounded and may contain small nucleoli; they remain orientated to the basement membrane, and on cross section they appear are tubular. Occasional mildly dilated gland is a normal feature and of no significance. Mitotic figures are easily identified within the glands.

In the late-proliferative phase, the glands become progressively more convoluted and tortuous and appear more variable in size and shape.

The endometrial stroma is densely cellular, and the stromal cells are small and oval with hyperchromatic nuclei and indistinct cytoplasm and cell borders. Mitotic figures are present within the stroma, scant thin walled blood vessels present. Estrogenic activity during the proliferative phase often results in focal ciliation of the surface epithelial cells[19,6]

Secretory Phase

After ovulation, release of progesterone from the corpus luteum results in the production of a copious thick glycogen-rich secretion by the endometrial glands. In this phase, endometrium reaches its maximum thickness.

The secretory phase is divided into three stages, namely the early secretory phase (from the 2nd to 4th postovulatory day), the mid-secretory phase (from the 5th to 9th postovulatory day), and the late-secretory phase (from the 10^{th} to 14^{th} postovulatory day)

In early secretory phase, the endometrial glands have tubular appearance and mitotic activity may be identified. The initial morphological feature of ovulation is the appearance within the glandular epithelium of subnuclear vacuoles which typically appear on the 16th day. There is a progressive increase in the number of and distribution of subnuclear vacuoles until they involve almost all cells within most glands in the functionalis.

Ovulation has said to be occurred when there are subnuclear vacuoles in at least 50% of the cells in at least 50% of the glands; stroma is the same as in late proliferative endometrium.

In mid-secretory phase, glandular secretion increases. Supranuclear vacuoles present and secretions are seen within glandular lumina. Glands are angular with no mitotic activity.

Stromal edema increases being most prominent in the mid-zone, more conspicuous eosinophilic cytoplasm; these cells are referred to as predecidual cells.

In the late-secretory phase, there is secretory exhaustion and glands are serrated. Predecidual sromal change increases forming the stratum compactum. Endometrial stromal granulocytes are present in this phase.

Postmenopausal Endometrium

The cyclical production of oestrogen and progesterone from the ovaries stops after menopause, resulting in atrophy of the whole genital tract.

The glands are lined by cuboidal to low columnar cells with no mitosis or secretory activity. Cystically dilated glands are seen. Stroma is less cellular without mitosis. Stromal disintegration may be present.

The myometrium also becomes atrophic after menopause and the uterus shrinks to about half its former size.

ENDOMETRIAL SAMPLING

Indication

Endometrial sampling is done for histological examination for abnormal uterine bleeding in women suspected to have endometrial hyperplasia or endometrial carcinoma[21]

Types

1. Dilatation & curettage:

   It is considered as the "gold standard" procedure for endometrial sampling, which requires cervical dilatation to allow insertion of a curette into the endometrial cavity. It requires anesthesia for cervical dilatation. The curette is drawn across the anterior and posterior endometrial surfaces, scraping the tissue.[22.] Complications include hemorrhage, infection, or perforation.

2. Endometrial biopsy:

   It is a relatively painless office procedure not requiring anaesthesia. These samples are taken either with a small sharp curette, such as the Novak or Randall curette, or with a device that uses suction to aspirate the tissue, such as the Pipelle endometrial aspirator.

3. Pipelle:

   Pipelle and related devices are widely used nowadays because they are simple to use, cost effective, and reliable for giving adequate tissue sample. The Pipelle-type device uses a hand-held piston to generate negative pressure and aspirate tissue through a narrow cannula inserted into the endometrial cavity.[22]

   In Pipelle sampling, stromal architecture is better preserved and it takes shorter time compared to dilatation and curettage and has fewer complications. Hence, it can be used as an initial screening procedure.[23]

4. Aspiration:

The Vabra curette is a stainless steel cannula which is 24 cm in length and 3 mm in diameter with a chamber for collection of the specimen at one end.[24]

It is reliable in obtaining endometrial tissue and detects 95% of malignant intrauterine pathology.[25] But it not as effective as the Pipelle device and offers high cost.[26]

5. Cytology:

Liquid-based cytology is found to be a more effective method for processing of the endometrial specimen[27]. It can be done using several devices like TAO brush[28] It has a covering sheath which protects the brush from collecting any contaminating tissue from cervix. A sound mark is provided on the brush to indicate depth of 6.5 cm. Once the brush is in place, the sheath is removed. It is then rotated 4–5 times by a simple watch-winding motion to collect tissue from the entire endometrium. The sheath is then replaced, ensuring that the endometrial tissue is retained on the brush. The brush is removed and placed directly in the fixative solution. The entire procedure takes approximately 30s. The Tao Brush is considered a better tolerated invasive device for collection of endometrial tissue. There is less chance of sample contamination from the endocervix.[29]

6. Hysteroscopic biopsy:

Office hysteroscopy is performed preferably in the first phase of the menstrual cycle in premenopausal women and at any time after menopause, without anaesthesia. It has the advantage of direct endoscopic visualization of the endometrial cavity.

The accuracy of diagnosis using hysteroscopy is high for endometrial cancer, but only moderate for endometrial disease.[30]

Adequacy

There is no specific criteria for adequacy. Usually postmenopausal biopsy will mostly yield only scant tissue. An endometrial biopsy containing such scant tissue which cannot be typed, are considered "unassessable" rather than "inadequate" or "insufficient.

In majority of cases, the presence of only scant tissue is not a reason for repeat biopsy, providing the endometrial cavity has been entered and at least some endometrial tissue is present in the biopsy specimen to confirm this.[31]

Prerequisites

Ideally, the biopsy should be taken between the 7th and 11th postovulatory days in the mid-secretory phase. Age, adequate history, details of the menopausal status, the date of onset of the last menstrual period (LMP) and the length of the menstrual cycle in premenopausal women should be collected.

Any History of exogenous hormones, especially progestins, before biopsy to control the bleeding in perimenopausal women should be collected which is usually not conveyed to the pathologist[6]

WHO CLASSIFICATION OF TUMOURS OF THE UTERINE CORPUS: (2014)[32] – (ANNEXURE -1)

Earlier by WHO since 1994, Precursor lesions had been divided into four groups of hyperplasia, according to the degree of architectural crowding (simple/complex), and nuclear alterations (atypical/non-atypical)[33].

In the recent 2014 edition, a two-group system of "hyperplasia without atypia" and "atypical hyperplasia"[34] replaces the four-tier system. Also, excessively proliferating glandular lesions divided into two groups, hyperplasia and endometrial intraepithelial neoplasia (EIN) has been proposed, based on studies of clonality, morphometry and cancer risk[37].

The criteria for the diagnosis of EIN is the same as for atypical hyperplasia and the reproducibility and risk of progression to endometrioid carcinoma are also similar[35].

Patient management is currently based on a two-tier system[36] and consequently, there was general agreement that a two-tier system would be preferable, either using the terms "hyperplasia without atypia" and "atypical hyperplasia/endometrioid intraepithelial neoplasia." The original term "endometrial intraepithelial neoplasia" has been changed to "endometrioid intraepithelial neoplasia" to indicate that the latter is a precursor of endometrioid carcinoma and not of serous carcinoma.

PRECURSORS LESIONS OF ENDOMETRIAL CARCINOMA

(i) Hyperplasia Without Atypia

It is defined as an exaggerated proliferation of glands of irregular sizes and shapes, with an increase in the gland to stroma ratio compared to the proliferative endometrium, but without significant cytological atypia.

Incidence: Rates of endometrial hyperplasia without atypia are many-fold higher than for carcinoma[38,39]

Histogenesis: Unopposed oestrogenic stimulation is the cause of Hyperplasia without atypia.

Risk factors: Obesity, polycystic ovarian syndrome and diabetes[40]

Clinical features: Occurs in perimenopausal age group with abnormal noncyclical vaginal bleeding being the most common symptom.

Gross: The endometrium varies in thickness from the uniform 5 mm, tan appearance of late proliferative phase to highly thickened, sometimes as polypoidal or spongy with cysts.

Microscopy: Glands vary in shape and size, separated by varying amounts of stroma resulting in back-to-back crowding with little stroma. Irregular distribution of Glands occur, while some glands may have normal coiled architecture, cystically dilated or branched.

The endometrium is lined by stratified columnar cells, with frequent mitotic figures. Focal haemorrhage and stromal breakdown are common.

"Disordered proliferative phase"- Proliferation of glands without cytological atypia that exceeds that of normal proliferative endometrium but less than that of

the crowding seen in hyperplasia. Normal gland to stroma ratio is usually maintained but there may be focal mild glandular crowding and branching.[6] The risk of endometrial cancer in such patients is estimated to be less than 2%[41]

Prognosis and predictive factors: Women who are exposed to unopposed oestrogen have a 3–4 times increased risk of endometrial carcinoma, rising to 10-fold after a duration of a decade[42]. Progression to well-differentiated endometrial carcinoma occurs in 1–3% of women[43]

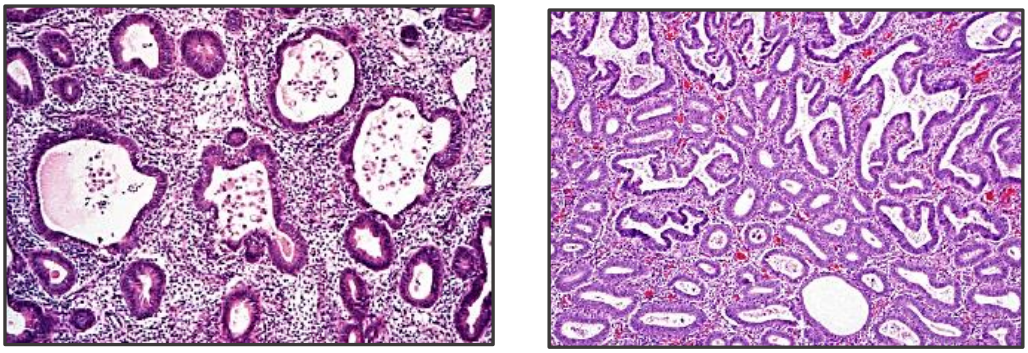


Figure 3A & 3B : Hyperplasia without atypia

(ii) Atypical Hyperplasia / Endometrioid Intraepithelial Neoplasia

Presence of Cytological atypia superimposed on endometrial hyperplasia defines atypical hyperplasia (AH)/endometrioid intraepithelial neoplasia (EIN).

Synonyms: Complex atypical endometrial hyperplasia; simple atypical endometrial hyperplasia; endometrial intraepithelial neoplasia.

Incidence: The average age at presentation is 53 years[44,45]

Histogenesis: Continuous unopposed oestrogenic stimulation leads to progression of hyperplasia without atypia to AH/ EIN. Risk factor being Endogenous or exogenous hyperoestrinism [46].

Clinical features: Postmenopausal bleeding or abnormal vaginal bleeding in perimenopausal women. AH/ EIN shows concurrent carcinoma in approximately 25–40% of women[48,50]

Gross: The endometrium appears to be diffusely thickened up to 1 cm and may present as a visible polyp. Many have no distinguishing macroscopic features[51]

Microscopy: AH/ EIN is composed of aggregates of crowded cytologically altered tubular or branching glands. Within the lesion, gland to stroma ratio is increased.

The distinction between endometrial hyperplasia without atypia and those with atypia/ EIN is based on nuclear atypia which include enlargement, pleomorphism, rounding, loss of polarity and nucleoli[52,43]

AH/ EIN is usually accompanied by metaplastic changes which have no bearing on clinical outcome, but the nuclear rounding and enlargement may add to the diagnostic difficulty.

Genetics: AH/ EIN contains similar genetic changes seen in endometrioid endometrial carcinoma[53]. These include microsatellite instability[54], PAX2 inactivation[56], PTEN, KRAS, and CTNNB1 (BETA-catenin) mutation[55,57].

Risk factors: Unopposed estrogens, Tamoxifen,[62] Obesity[58], Cowden syndrome[59] and Lynch syndrome (hereditary non-polyposis colon cancer) [60]

Prognosis: One-third of women with a preoperative biopsy diagnosis of AH/ EIN will be diagnosed with cancer at immediate hysterectomy or during the first year of follow-up[47,43,49]

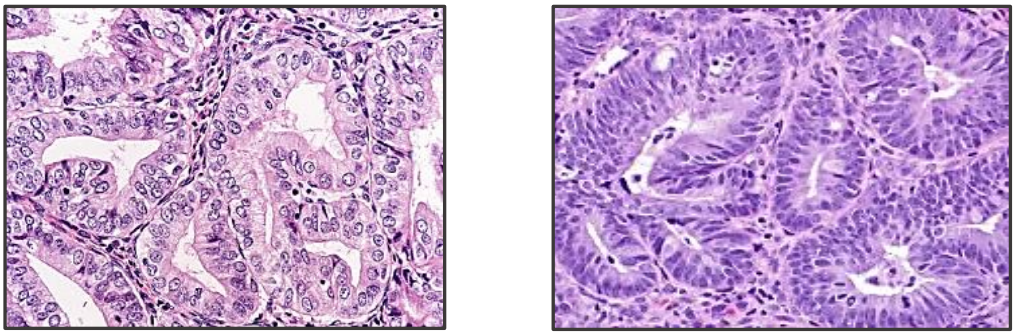


Figure 4A & 4B : Atypical hyperplasia / EIN

Differential Diagnosis: Reactive Changes, Persistent Estrogen Effect, Mid to Late Secretory Endometrium, Endometrial Polyps, Endometrial Breakdown, Endometrioid adenocarcinoma.

To differentiate from carcinoma:

Endometrial stromal invasion: It is the stromal and epithelial alterations associated with invasive carcinoma. It is identified by,

(1) An irregular infiltration of glands associated with an altered fibroblastic stroma (desmoplastic response);

(2) A confluent glandular pattern in which individual glands, uninterrupted by stroma merge, forming a cribriform pattern; or

(3) An extensive papillary pattern.

Occasionally, complex hyperplasias can display a papillary architecture, including the presence of fibrovascular cores, but these are characterized by bland cytology, absence of epithelial stratification, and a low level of mitotic activity[61]

(4) Myoinvasion: unfortunately, myometrium is rarely available for evaluation in a biopsy or curettage specimen.

ENDOMETRIAL CARCINOMA

Endometrial carcinoma is the fifth most common cancer in women worldwide[63,42]

Based on clinicopathologic and molecular genetic features, endometrial carcinoma is broadly classified into two major categories, referred to as type I and type II. Most common form of endometrial carcinoma is the endometrioid subtype, the prototype of type I carcinoma [64]

Some types of endometrial carcinoma are not related to hormonal factors and hyperplasia[65]. Under this category, Serous carcinoma is the most common form of endometrial carcinoma and represents type II carcinoma.

FEATURE	TYPE I	TYPE II
Unopposed estrogen	Present	Absent
Menopausal status	Pre- and perimenopausal	Postmenopausal
Precursor lesion	Atypical hyperplasia	Endometrial Intraepithelial carcinoma
Tumor grade	Low	High
Myometrial invasion	Variable, often Minimal	Variable, often deep
Histologic subtypes	Endometrioid	Serous and clear cell
Behavior	Indolent	Aggressive
Genetic alterations	PTEN mutation Microsatellite instability K-ras mutation	P53 mutation

Malignant Mesodermal (Mullerian) mixed tumors (MMMTs, carcinosarcomas) are classified as mixed epithelial and nonepithelial tumors in the WHO classification of uterine tumors but as epithelial tumors in the ovarian tumor

classification. This inconsistency is because of the confusion regarding the histogenesis and classification of carcinosarcomas in different anatomic sites.

Recent molecular genetic data support that both components in these biphasic tumors are clonally derived from a transformed epithelial cell. Hence, many investigators now consider these tumours as poorly differentiated carcinomas that exhibits sarcomatous differentiation.

ETIOLOGY:

1) **Hormonal**

- Unopposed estrogen therapy[66]
- Endogenous elevated levels of unopposed estrogen which varies with menopausal status[67]

2) **Constitutional**

- Obesity[68]- due to the increased availability of peripheral estrogens as a result of aromatization of androgens to estrogens in the adipose tissue and lower concentrations of sex hormone-binding globulins in obese women [69]
- Diabetes
- Nulliparity[70]

ENDOMETRIOID CARCINOMA

Definition

Endometrioid carcinoma of the usual type is a glandular neoplasm which displays an acinar, papillary or solid configuration, but lacks the nuclear features of endometrial serous carcinoma.

These are referred to as endometrioid because they resemble proliferative-phase endometrium. They do not contain areas showing more than 10% of serous, mucinous, or clear cell differentiation.

Epidemiology

Worldwide in 2008, there were 2,88,000 newly diagnosed uterine corpus cancers of which about 70–80% were of the endometrioid type.[71-74]

Endometrioid carcinoma occurs in the age group from the second to the eighth decade. Only 1–8% of endometrial carcinomas occur in women under 40 years[75]

Risk factors

Among type I carcinomas (low-grade endometrioid adenocarcinoma and its variants) are similar.

Postmenopausal women, polycystic ovary syndrome or oestrogen-producing ovarian tumours[76,77], Earlier age at menarche, Later age at menopause, Nulliparity or Obesity.[78] A positive family history of endometrial carcinoma[80], Lynch syndrome[79] (hereditary nonpolyposis colorectal cancer, HNPCC) or Cowden syndrome[81]

Protective factors

Later age at first birth and last birth [82,83] Continuous combined hormone replacement therapy, Oral contraceptives (high progestin potency)[84], Injectable progestins, Intrauterine devices, smoking[85] and tubal ligation[86].

Clinical Features

The average age at diagnosis is about 63 years[87]. 90% of patients have vaginal discharge, usually in the form of bleeding. Women with advanced disease may have abdominal pain, distension, or pelvic pressure.

Gross

Endometrium appears shaggy, glistening and tan composed of one or more discrete nodules or separate polypoid masses. It may also be diffuse and exophytic. Necrosis and haemorrhage are variable.

Myometrial invasion usually seen as well-demarcated, firm, gray-white tissue with linear extensions beneath an exophytic mass or as multiple, white nodules with necrotic areas within the uterine wall.

Microscopy

As already mentioned, it displays a glandular or villoglandular architecture lined by stratified columnar epithelium having crowded, complex, branching architecture with a smoothly contoured glandular lumen. Tumour cells have eosinophilic granular cytoplasm showing mild to moderate nuclear atypia with inconspicuous nucleoli except in poorly differentiated carcinomas. The mitotic index is highly variable.

FIGO Grading

It is based on the architectural pattern and nuclear features.[89]

Architectural grading of endometrial carcinoma[90]	
Grade I	No more than 5% of the tumor is composed of solid masses
Grade II	6–50% of the tumor is composed of solid masses
Grade III	More than 50% of the tumor is composed of solid masses

In endometrioid carcinomas with squamous differentiation, it is essential to exclude masses of squamous epithelium in determining the amount of solid growth.

The nuclear grade is determined by the variation in nuclear size and shape, chromatin distribution, and size of the nucleoli.

Grade 1	Nuclei are oval, mildly enlarged, and have evenly dispersed chromatin
Grade 2	Nuclei have features intermediate to grades 1and 3
Grade 3	Nuclei are markedly enlarged and pleomorphic, with irregular coarse chromatin, and prominent eosinophilic nucleoli

The presence of grade 3 nuclei in more than 50% of the tumour is associated with more aggressive behaviour and therefore upgrades the tumour by one grade[91].

Mitotic activity is an independent histologic variable, but it is usually increased with increasing nuclear grade, like abnormal mitotic figures.

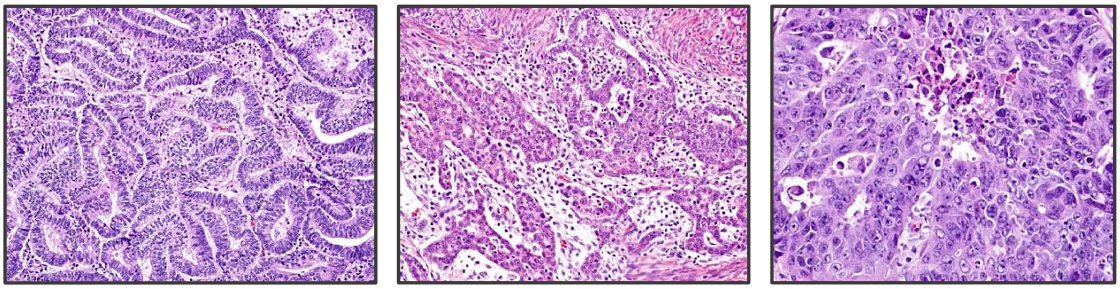


Fig 5A, 5B & 5C: Endometrioid adenocarcinoma Grade I, Grade II and Grade III

When there is marked discordance between nuclear and architectural grade which is uncommon in endometrioid type, it should raise suspicion of serous carcinoma.

The discordance between the curettage and hysterectomy specimens is observed in 15–25% of cases[92]

Depth Of Myometrial Invasion

Endometrial carcinoma may manifest various forms of myometrial invasion.[88] It can invade as a broad pushing front or it can infiltrate the myometrium diffusely as masses, cords, or clusters of cells, and individual glands. In case of diffuse pattern of infiltration, the neoplastic glands elicit a reactive stromal response characterized by loose fibrous tissue accompanied by a chronic inflammatory infiltrate surrounding the glands.

An unusual form of myoinvasion which consists of outpouching of neoplastic glands that become detached and lined by flattened epithelium appearing as microcysts associated with a fibromyxoid stromal reaction – MELF (microcystic, elongated, and fragmented)

In a multivariate analysis, MELF invasion was associated with lymphovascular invasion, but not with poor prognosis.[93]

Myoinvasion is measured from the endomyometrial junction to the deepest point of invasion.

Figo Staging

Revised 2009 FIGO Staging System For Carcinoma Of Endometrium - (Annexure 2)

Immunohistochemistry

Pan-cytokeratins, epithelial membrane antigen (EMA), CA125, Ber EP4, and B72.3. There is strong staining for Vimentin. Expression of ER and PR is seen in majority of FIGO grades 1 and 2 endometrioid carcinomas and in approximately one half of FIGO grade 3 endometrioid carcinomas without serous, clear cell or undifferentiated features[95]

Diffuse expression of carcinoembryonic antigen (CEA) is seen in tumors showing extensive mucinous differentiation. Also express CDX2,[96] Cytokeratin 7 positive and negative for Cytokeratin 20[97] Prominent p53 staining is seen in serous, clear cell, or undifferentiated tumors.[98]

Distinction between an endocervical and a well differentiated endometrial carcinoma is at times difficult without IHC. Expression of ER and PR favour endometrial origin, while the absence of these hormone receptors along with diffuse reactivity for p16 or positive in situ hybridization for HPV is favours endocervical origin[105,94].

Spread

Occurs by lymphatic and vascular dissemination, direct extension to contiguous organs, and transperitoneal and transtubal seeding. Most common is Lymphatic metastasis. Endometrial carcinoma tends to spread to the pelvic lymph nodes before involving paraaortic lymph nodes.

Lung Involvement without metastasis to mediastinal lymph nodes suggests hematogenous spread.

Treatment

Hysterectomy and bilateral salpingo-oophorectomy is the standard treatment for endometrial carcinoma. The current approach is to treat by hysterectomy supplemented by surgical staging and to administer postoperative radiation to patients who have poor prognostic factors which put them at higher risk of recurrence.

Variants Of Endometrioid Carcinoma

1) Endometrioid carcinoma with squamous differentiation

Between 10 and 25% of endometrioid carcinomas exhibit foci of squamous differentiation[99] It is recognized by keratin pearl formation, intercellular bridges or solid masses of cells which are polygonal with abundant dense eosinophilic cytoplasm and distinct cell membranes. Squamous differentiation observed at the stromal interface or as morules (nests of cells with a prominent oval to spindle cell appearance) bridging adjacent glands. It is not included in the estimation of solid growth for grading endometrioid adenocarcinoma.

At least 10% of a tumor should have squamous element to qualify as an adenocarcinoma with squamous differentiation.

2) Endometrioid carcinoma with secretory differentiation

The age range is from 35 to 79 years, with a mean age of 55–58.[100] Less than 2% of typical endometrioid adenocarcinomas are composed of columnar cells having single, large, sub or supranuclear glycogen vacuoles rather than eosinophilic cytoplasm[101]. They resemble endometrial glands of the secretory phase. Classic endometrioid carcinomas with secretory differentiation are well differentiated.

3) Villoglandular variant

The median age is 61 years. Villoglandular carcinoma displays a papillary architecture with thin delicate papillary fronds and central fibrovascular core. Papillae are lined by stratified columnar cells having oval nuclei exhibiting mild to moderate atypia.[102] Myometrial invasion usually is superficial.[103]

4) Ciliated Carcinoma

It is a rare form of differentiation seen in low grade endometrioid carcinoma[104] In normal endometrium, Estrogen induces cilia formation. Microscopically, ciliated carcinoma is always well differentiated, displays a cribriform pattern. Cells lining the gland lumens in the cribriform areas have prominent eosinophilic cytoplasm and cilia. The cells have irregular nuclear membrane with coarse chromatin and prominent nucleoli.

5) Mucinous differentiation

Those endometrioid carcinomas with less than 50% of mucinous component are designated as endometrioid carcinomas with mucinous differentiation.

Other variants include sertoliform and microglandular types.

Genetics

Most commonly, it is the mutation or inactivation of PTEN (> 50%)[106] followed by mutations in PIK3CA (30%)[107], PIK3R1 (20–43%) [108], ARID1A (40% of low-grade carcinomas) [109], KRAS (20–26%)[110] and TP53 (30% of grade 3 endometrioid carcinomas)[110] About 35% of tumours display microsatellite instability.[111] Microsatellite instability due to hypermethylation of the MLH1 gene promoter is seen in sporadic endometrioid carcinomas [112].

Susceptibility

Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) is due to germline transmission of defective DNA mismatch repair genes (MSH2, MLH1, MSH6 and PMS2). It is the most common cause of familial endometrial carcinoma affecting the lower uterine segment more frequently.[114] The lifetime risk for carcinoma is 25–60%[113]

Cowden syndrome is an autosomal dominant disorder caused by a germline mutation of PTEN. It has a lifetime risk of 28% for developing endometrial carcinoma. The median age of diagnosis is in the fourth decade.

Prognosis and Predictive Factors

Age, histological grade, depth of myometrial invasion, lymphovascular invasion and FIGO staging are the most important predictors of lymph node involvement and outcome applicable to all endometrioid adenocarcinomas and its variants [99,113].

The risk of nodal spread and recurrence is related to depth of myometrial invasion. Significant low survival is associated with tumours showing myometrial invasion involving the outer half.

MUCINOUS CARCINOMA

It is an uncommon endometrial carcinoma with > 50% of the neoplasm composed of mucinous cells containing periodic acid–Schiff- (PAS-) positive, diastase-resistant intracytoplasmic mucin. Accounting for 1–9% of endometrial carcinomas[115]. Seen in the age group of 47 to 89 years and typically present with vaginal bleeding, exogenous estrogen is a risk factor[116]

Macroscopy:

Mucinous carcinomas can be suspected by their gelatinous or mucoid texture.

Microscopy:

Glandular or villoglandular architecture lined by uniform, mucinous columnar cells with minimal stratification. The mucin is identified as basophilic globules or slightly pale, granular cytoplasm which is positive for mucicarmine and CEA. Typically it presents as Cystically dilated glands filled with mucin and papillary fronds surrounded by extracellular lakes of mucin containing

neutrophils. Squamous differentiation is usually present. Mild to moderate Nuclear atypia with low mitotic activity. Myometrial invasion is usually limited to the inner-half[116]

Genetics:

High prevalence of somatic KRAS mutations is seen in mucinous carcinomas and in papillary mucinous metaplasia[117]

Differential Diagnosis:

Endocervical adenocarcinoma - Immunohistochemistry can be helpful to differentiate.

Prognosis and predictive factors:

Mucinous carcinomas have a good prognosis as they are almost always well differentiated[118]

SEROUS CARCINOMA

It is an endometrial carcinoma characterized by a complex papillary and/or glandular architecture with diffuse, marked nuclear pleomorphism. This is the prototypical type II tumour with an high aggressive behaviour [119]

Women with serous carcinomas are more often multiparous, post tubal ligation, current smokers, have a history of breast carcinoma and/or tamoxifen use and are less commonly obese than women with endometrioid carcinomas[120]

Clinical features:

Postmenopausal, occurring in sixth decade and presents with vaginal bleeding.

Gross:

Usually the uterus is small but may be enlarged by tumour. It can be exophytic having papillary appearance. The uterine cavity may be distended by a tumour mass but the tumour can arise on the surface of an endometrial polyp.

Microscopy:

When the lesion is confined to the epithelium, it is Serous endometrial intraepithelial carcinoma (SEIC). It develops directly on a polyp or in atrophic endometrium.

Serous carcinomas have complex papillary architecture (pure form), solid and glandular pattern. Papillae vary from short, branching and hyalinized to long thin and delicate with central fibrovascular core. Papillae are lined by epithelial cells with large atypical nuclei, prominent nucleoli and scant cytoplasm. The luminal surface appears scalloped or frayed. Mitotic figures are numerous. Myoinvasion shows gaping glands.

Differential Diagnosis:

High grade endometrioid with ambiguous features [121]

Aberrant p53 expression (intense and diffuse staining of at least 75% of the tumour cells or complete absence of p53 immunoreactivity) supports the diagnosis of serous carcinoma. In contrast, a p53 stain show variable intensity in less than 75% of the neoplastic cells correlates with a high-grade endometrioid carcinoma.

A very high Ki-67 index is also more typical of serous carcinoma but does not exclude a high-grade endometrioid carcinoma.

Histogenesis:

SEIC replaces the surface epithelium and/or glands of the endometrium without invading the stroma and is almost always associated with atrophic endometrium or an endometrial polyp[122].

It is often impossible to differentiate SEIC from early stromal invasion, hence it is recommended that these lesions in biopsies be termed “minimal uterine serous carcinoma”[123]

Genetic profile:

The most common somatic mutations include TP53 (80–90%), PIK3CA (24–40%), FBXW7 (20–30%), and PPP2R1A (18–28%) [124]

Susceptibility:

Germline BRCA1/2 mutations is associated with the development of serous carcinoma[125]

Prognosis and predictive factors:

A unique feature of SEIC is that, it is frequently associated with disseminated pelvic serous carcinoma, though it does not invade the endometrium.[126] Serous carcinoma confined to the endometrium has an overall excellent prognosis [127]

CLEAR CELL CARCINOMA

Clear cell carcinoma is composed of polygonal or hobnail cells having clear or eosinophilic cytoplasm arranged in papillary, tubulocystic or solid patterns, with at least focal high-grade nuclear atypia.

These are uncommon endometrial carcinomas accounting for 2% and are considered one of the type II endometrial carcinomas. The mean age at diagnosis is in the late sixties.[129]

Risk factors include Multiparity and cigarette smoking. But diabetes mellitus and obesity are less frequent than in women with endometrioid carcinoma[128]

Histopathology:

Papillary, tubulocystic or solid pattern. The papillae are short and branching, with hyalinized stroma[130] Exhibits prominent nuclear atypia with marked nuclear pleomorphism and variably sized nucleoli. Mitotic figures are usually numerous. Also contain densely eosinophilic extracellular globules or hyaline bodies in two-third cases.

Differential diagnosis:

Secretory or squamous variants of endometrioid carcinoma

Serous carcinoma

Immunohistochemistry:

Clear cell carcinoma is usually ER and PR negative and rarely overexpresses p53[132]. The Ki-67 labelling index is at least 25–30%.

Low-grade endometrioid carcinoma is strongly positive for ER and PR and negative for p53, whereas serous carcinoma is negative or weakly positive for ER and PR and diffusely positive for p53 [133].

Histogenesis:

Usually arise in a background of atrophic endometrium or polyp.

Genetic profile:

Somatic mutations in PTEN and TP53 (30–40%),[134] mutations in PIK3CA (20%), with a lower frequency of KRAS mutations and microsatellite instability in about 10–15% [135] Loss of expression of BAF250a (ARID1A) occurs in 26% of clear cell carcinomas, without mutations in ARID1A.[136]

Prognosis:

These tumours tend to be deeply invasive, high grade, and are associated with deep myometrial invasion, high nuclear grade, lymphovascular space invasion, and pelvic lymph node metastasis.[131] Most studies reported a 5-year survival of less than 50% regardless of stage.[137]

NEUROENDOCRINE TUMOURS

This is a diverse group of neoplasms that share a morphological neuroendocrine phenotype. It is rare, representing < 1% of endometrial cancers with no specific risk factors.

Classified as:

Low-grade neuroendocrine tumour

Carcinoid tumour

High-grade neuroendocrine carcinoma

Small cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma

Incidence:

Affects postmenopausal patients, with an average age 60 years at diagnosis for small cell neuroendocrine carcinoma (SCNEC)[138] and 55 years for large cell neuroendocrine carcinoma (LCNEC) [139]

Macroscopy:

SCNEC usually produces bulky, exophytic, polypoid intraluminal masses with variable myometrial invasion.

Microscopy:

SCNEC:

It resembles the small cell carcinoma of the lung,[140] The growth pattern may be diffuse, trabecular, nested or have rosette-like structures, with tumour composed of poorly cohesive ovoid cells with scant cytoplasm and condensed chromatin. There is frequent nuclear moulding, numerous mitotic figures, necrosis and apoptotic bodies.

LCNEC:

They are identified by their arrangement in well demarcated nests, trabeculae or cords with peripheral palisading. Tumour cells are polygonal, large, with vesicular or hyperchromatic nuclei and a prominent nucleolus. There is extensive geographic necrosis and high mitotic activity.[141]

Immunohistochemistry:

SCNEC stain for chromogranin A, synaptophysin, C D56, vimentin and cytokeratins (dot-like pattern).

To diagnose a LCNEC, a neuroendocrine growth pattern should be present in at least part of the tumour, with expression of one or more of the neuroendocrine markers like chromogranin, CD56, synaptophysin, in more than 10% of the neoplastic cells.

Prognosis and predictive factors:

Prognosis for SCNEC and LCNEC is poor, but there is one report that shows favourable prognosis when the tumour was confined to an endometrial polyp [142].

MIXED CARCINOMAS

It is an endometrial carcinoma is composed of two or more different histological types, one of them is of the type II category. The most common combination is endometrioid and serous carcinoma. The minimum percentage of the second component has arbitrarily been set at 5%.

The highest grade component determines the behaviour of these tumours. Presence of even 5% of a serous component in a mixed carcinoma adversely influences outcome.[143]

UNDIFFERENTIATED AND DEDIFFERENTIATED CARCINOMAS

Undifferentiated carcinoma of the endometrium is a malignant epithelial neoplasm without any differentiation. Dedifferentiated carcinoma is a combination of undifferentiated carcinoma and a second component of either FIGO grade 1 or 2 endometrioid carcinoma.

Incidence:

Undifferentiated carcinomas are uncommon. It is associated with Lynch syndrome.[145] The median age is 55 years.[144]

Macroscopy:

Most undifferentiated carcinomas form large, polypoid presenting as intraluminal masses. Necrosis is common.

Microscopy:

- Monomorphic undifferentiated carcinoma:

  It is composed of small to intermediate-sized dyscohesive cells of relatively uniform size which are arranged in sheets without any obvious nested or trabecular architecture resembling plasmacytoma, lymphoma, "high-grade endometrial stromal sarcoma" or small cell carcinoma.[146] There is no gland formation. Cells have condensed nuclear chromatin and > 25 mitotic figures per 10 HPF. Tumour-infiltrating lymphocytes are often numerous.[144]

- Dedifferentiated carcinoma:

  In 40% of monomorphic undifferentiated carcinomas, there is a second component of either FIGO grade 1 or 2 endometrioid carcinoma. Here, the differentiated endometrioid component lines the endometrial cavity, while the undifferentiated component grows beneath it.

Immunohistochemistry:

Occasional tumour cells exhibit intense staining for EMA [146] and CK18[144] in the absence of staining with pan-cytokeratins. Tumour cells express vimentin but not ER, PR or E-cadherin.

Prognosis and predictive factors:

These are highly aggressive, with recurrence or death from tumour occurring in about 55–95% of women[146]

MIXED EPITHELIAL AND MESENCHYMAL TUMOURS

CARCINOSARCOMA/ MALIGNANT MIXED MÜLLERIAN TUMOUR

It is a biphasic tumour composed of high grade carcinomatous and sarcomatous elements, accounting for < 5% of all uterine malignancies.[147] There is an association with tamoxifen therapy[148] or long-term unopposed estrogen usage. It can occur as a long-term complication of pelvic radiotherapy. In such cases, the mean time-interval from irradiation to the development of tumour is between 10 and 20 years[149]

Risk factors and Clinical features are similar to endometrioid carcinoma.

Macroscopy:

The tumour is characteristically polypoid and large almost filling the entire uterine cavity and protruding through the cervical os. It is soft, with areas of

necrosis, haemorrhage and cystic degeneration. There is myoinvasion and sometimes cervical involvement.

Microscopy:

Has two components of high-grade epithelium and mesenchyme which are usually distinct and sharply demarcated. The epithelium is usually of endometrioid or serous types but other Müllerian cell types may also be seen. The mesenchymal component is a high-grade, non-specific sarcoma, but heterologous elements including chondrosarcoma, rhabdomyosarcoma and rarely osteosarcoma are seen in 50% of cases[149]

Neuroectodermal differentiation may rarely occur[150]. These tumours commonly exhibit deep myometrial and lymphovascular invasion.

Histogenesis:

These tumours are thought to be a derivative of epithelial origin, exemplifying the epithelial-mesenchymal transition[151,152]

Genetic profile:

TP53 mutation is the most common molecular alteration[153]

Prognosis and predictive factors:

These tumours have a poor outcome and the pattern of spread similar to high-grade endometrial carcinoma [154,155] Metastatic spread is typically to pelvic and para-aortic lymph nodes and distant haematogenous metastases to brain, lung and bone[156]

Serous and clear cell carcinomatous elements are associated with an increased frequency of other adverse prognostic features. And presence of heterologous elements is also considered a poor prognostic factor in stage I patients.[157] with a rhabdomyosarcomatous component having the worst prognosis.

PROGNOSTIC FACTORS FOR ENDOMETRIAL CARCINOMA

The risk factors for the recurrence of endometrial carcinoma can be divided into uterine and extrauterine factors[158]

(i) Uterine factors

(1) histologic type,

(2) grade,

(3) depth of myometrial invasion,

(4) cervical involvement,

(5) vascular invasion,

(6) presence of atypical endometrial hyperplasia,

(7) hormone receptor status, and

(8) DNA ploidy and S-phase fraction.

(ii) Extrauterine factors

(1) adnexal involvement,

(2) intraperitoneal metastasis,

(3) positive peritoneal cytology, and

(4) pelvic and paraaortic lymph node metastasis.

LOW RISK GROUP

Patients without evidence of extrauterine disease, no cervical involvement, and no evidence of vascular invasion are at a low overall risk of recurrence. In such patients, the grade and depth of invasion are important prognostic factors.

HIGH RISK GROUP

Women with evidence of extrauterine disease, cervical involvement, or vascular invasion constitute a high-risk group. If anyone of the three factors is positive, the frequency of recurrence is 20%, increasing to 43% for two positive factors, and 63% for three factors[159]

(iii)Clinical Factors

Age, race, and socioeconomic status are prognostic factors in endometrial cancer. Age is considered an important independent risk factor[160] Women aged 45 or less have a better prognosis than women more than 45years because of a significantly higher proportion of early-stage disease and less myometrial invasion[161]

It is also observed that there is decreased survival for women over age 50 unrelated to surgical stage or grade of carcinoma.[162]

Histologic Grade

5-year overall survival rates for women with surgical stage I endometrial carcinoma has been found to be dropped from 92.1% (grade 1) to 87.5% (grade 2) to 74.5% (grade 3)[163]

Histologic grade is highly correlated with other prognostic factors such as age, stage, and depth of myometrial invasion.

Surgical–Pathological Staging (FIGO Staging)

The new FIGO staging system adopted in 2009 with input from the International Society of Gynecological Pathologists[164], representing a refinement to the system last revised in 1988.

Major changes from the staging system of 1988 include:

- The inclusion of tumors without myometrial invasion and those with inner half myometrial invasion in stage IA,
- Elimination of cervical gland involvement from stage II,
- Elimination of positive peritoneal fluid cytology from stage IIIA, and
- Separation of pelvic from paraaortic lymph node metastases within stage IIIC.

Multiple studies have confirmed the prognostic utility of surgical–pathologic stage[165,166]

Myometrial Invasion

In 2009, FIGO staging of endometrial carcinoma,

Stage IA - The combination of tumors that lack any myoinvasion from those with inner half myometrial invasion is based on two observations:

- There is low reproducibility and diagnostic difficulty in distinguishing true superficial myometrial invasion from those tumors involving the basal endometrium as it interdigitates normally with the myometrium[167]
- There is almost no difference in the survival rate between patients with carcinoma confined to the endometrium and those with superficial myometrial invasion (91% versus 90%) [163]

Myometrial invasion, independent of grade of the tumour, is an important predictor of prognosis[168]

It is recommended to measure the maximum depth of invasion in millimeters and expressing it as a percentage of the myometrial thickness. The distance of the tumor from the serosa also has prognostic significance[169]

Cervical Involvement

According to the new FIGO staging system, stage II – includes tumours with cervical stromal involvement which is characterized by carcinoma that is not confined to preexisting endocervical glands or the surface epithelium and typically elicits a stromal reaction.[170]

In the absence of extrauterine disease, Cervical involvement is associated with an elevated risk of recurrence with an overall relapse rate of 16%.

Peritoneal Cytology

Previously, stage III A – included a positive peritoneal cytology, however, it is no longer used in the staging of endometrial adenocarcinoma.

Positive peritoneal cytology has been associated with other risk factors for recurrence like deep myometrial invasion, high grade, or extrauterine spread[171]

Vascular Invasion And Lymph Node Metastases

The presence of neoplastic cells within endothelial-lined channels is defined as Venous or lymphatic invasion. Vascular invasion can be assessed reliably in the myometrium peripheral to the bulk of the tumor mass.

An useful marker of vascular invasion is the presence of perivascular lymphocytic infiltrates in the myometrium but not lymphocytic infiltrate at the tumor–myometrial junction [172]

Frequency of vascular invasion increases with aggressive cell types, decreasing histologic differentiation and deeper myometrial invasion[173]

It has been observed that metastasis to pelvic lymph nodes occur in about 10% of women with endometrioid endometrial adenocarcinoma [174] The presence of positive paraaortic lymph nodes is most important prognostic indicator[159].

Endometrial Hyperplasia And Metaplasia

Among nontumor risk factors, the presence of atypical endometrial hyperplasia and various metaplasias, especially ciliated cell and eosinophilic change has a favorable prognosis as it correlates with low tumor grade and lack of myometrial invasion [175]

In contrast, atrophic endometrium correlates with high-grade tumors[176]

Ploidy

Ploidy has almost always remained a strong predictor of outcome.[177] Hence, DNA content can be considered a prognostic indicator of endometrial adenocarcinoma.

Hormonal Receptor Status

Several studies have reported variable results regarding the correlation of hormone receptor expression and prognosis. In two studies, PR persisted as a significant prognosticator of survival assessed using multivariate analyses.[178] Also, Loss of BCL-2 expression was significantly related to the probability of tumor recurrence or lymph node metastasis[179]

IMMUNOHISTOCHEMISTRY

In 1941, Albert Coons et al first labelled antibodies directly with fluorescent isocyanate. Nakane and Pierce et al introduced the indirect labelling technique in which the unlabelled antibody is followed by second antibody or substrate in 1966, Various immunohistochemical methods include peroxidase-anti peroxidase method (1970), alkaline phosphatase labelling (1971), avidin biotin method (1977) and two layer dextrin polymer technique (1993).

ANTIGEN RETRIEVAL

To unmask the antigenic determinants in fixed tissue sections, following methods are used:

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 introduced this technique in 1976, and it depends on the breakdown of formalin cross linkages. The most commonly used enzymes include proteinase and trypsin. Over digestion, under digestion and antigen destruction are the disadvantages.

Microwave antigen retrieval

This technique allows rapid and uniform heating of the paraffin sections. Hence it is widely used.

Pressure cooker antigen retrieval

In 1995, Miller et al 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[180]

Pitfalls Of Heat Pretreatment

Sections get dried at any stage after heat treatment destroys antigenicity. Fibrofatty tend to detach from slides while heating. In poorly fixed tissues, nuclear details are damaged. Not always, all the antigens are retrieved by heat pretreatment and some of them show altered staining pattern.

Detection Systems

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

In the direct method, primary antibody is directly conjugated with the label. Most commonly used labels are horse radish peroxidase, fluoro-chrome and alkaline phosphatase. Indirect method is a two step method, labelled secondary antibody reacts with primary antibody bound to specific antigen. The sensitivity of immunohistochemical stains are increased by the use of peroxidase enzyme complex or avidin biotin complex.

Pluzek et al introduced enhanced polymer one step staining in 1993, which uses large numbers of primary antibody and peroxidase enzymes are attached to dextran polymer back bone. This is the rapid and sensitive method[181].

Dextran polymer conjugate two step visualization system has greater sensitivity and is less time consuming.

ROLE OF LYMPHATIC VESSEL MARKER IN ENDOMETRIAL CARCINOMA - D2-40 (PODOPLANIN)

The antibody D2-40 detects podoplanin which is a oncofetal transmembrane glycoprotein encoded by a gene on the short arm of chromosome 1 (1p36.21) being expressed in various tissues. Breiteneder-Geleff and colleagues initially described this expression in glomerular podocytes of the rat, lymphatic endothelium, mesothelium, various epithelia, follicular dendritic cells, and germ cells in several species, including humans. Tumors showing differentiation toward these lineages may be podoplanin-positive, such as mesothelioma, seminoma, follicular dendritic cell sarcoma, and tumors of skin adnexa.

Podoplanin is mainly expressed during the vertebrate development in lymphatic endothelial cells and so it is thought to be a selective marker for lymphatic channels. Podoplanin Overexpression significantly increases the endothelial cell adhesion, migration, and vascular lumen formation.

D2-40 shows high sensitivity and specificity for normal lymphatic channels in a variety of tissues[182] . It stains the lymphatic endothelium intensely and crisply whereas it does not stain the normal vascular endothelium. D2-40 is highly sensitive and specific in identifying lymphatic space invasion[183].

Recent studies reveal D2-40 as a highly sensitive and specific marker (up to 100%) for malignant mesothelioma[184] However, D2-40 expression has also

been reported in approximately 50% of ovarian carcinomas, 30% of lung carcinomas, and 30% of breast carcinomas.

Though D2-40 (podoplanin) is widely used to identify the lymphovascular endothelial cells and mesothelioma; showing diffuse strong positive cytoplasmic and membrane staining in dysgerminoma, this marker is still not generally used in the primary panel for their diagnosis.

Also, D2-40 shows excellent sensitivity for IGCNU and seminoma, including a diffuse staining in metastatic/extratesticular sites. But D2-40 has a lower sensitivity for nonseminomatous GCT and nontesticular neoplasms of lymphatic and vascular endothelial origin and epithelioid mesothelioma[185]

Expression is seen in a subset of angiosarcomas, kaposiform hemangioendothelioma, and Kaposi sarcoma. This reflects the lymphatic differentiation within these tumors. But it has limited utility because of lack of specificity.

MATERIALS AND METHODS

MATERIALS AND METHODS

We conducted a two year retrospective and prospective study from May 2016 to May 2018 in the Department of pathology, Institute of obstetrics and gynaecology, Madras Medical College/ Rajiv Gandhi Govt. General Hospital, Chennai.

There were about 57 cases of endometrial carcinoma diagnosed in hysterectomy specimens. All of these cases were reviewed. Among them, due to the unavailability of blocks for 3 cases, the remaining 54 cases were subjected to immunohistochemical analysis. We also included non neoplastic (5 cases) and premalignant lesions (3cases) of endometrium. Out of the 5 non neoplastic lesions, 1 case was simple hyperplasia and the rest 4 were benign endometrial polyp. Out of the 3 cases of premalignant lesions, 2 were endometrial intraepithelial neoplasia and 1 was atypical endometrial hyperplasia.

Inclusion Criteria

All patients who underwent total hysterectomy, bilateral salpingo-oophorectomy with/ without pelvic and para-aortic lymph node dissection for endometrial carcinoma were included in the study.

Exclusion Criteria

- Benign and malignant Mesenchymal tumours of uterus.
- Non specific inflammatory conditions.
- Lack of paraffin blocks with representative tumor tissue was excluded from the study population.

Control

Non Neoplastic lesions of endometrium and Pre-Malignant lesions detected in hysterectomy specimens.

METHOD OF DATA COLLECTION

All relevant details of the cases regarding age, parity, menstrual status, presenting complaints, type of pre-operative biopsy with diagnosis were obtained for all 62 cases reported during the study period from patient records.

For endometrial carcinoma, specimens were grossed as per protocol and all representative sections were submitted for routine histopathological examination. The following parameters were evaluated:

Tumor site, size, configuration, histologic type, FIGO grade, depth of myometrial invasion, lymphovascular invasion, cervical, parametrial or adnexal involvement, pelvic and paraaortic lymphnode status, omental deposits, peritoneal wash cytology and FIGO staging.

One paraffin block containing the maximum bulk of the tumour with maximum depth of invasion is chosen for immunohistochemical study.

IMMUNOHISTOCHEMICAL EVALUATION (ANNEXURE -3)

Immunohistochemical analysis of D2-40 (Podoplanin) was performed in paraffin embedded tissue blocks using super sensitive polymer HRP system based on non-biotin polymeric technology.

Four micron sections from formalin fixed paraffin embedded tissue blocks were transferred onto positively charged slides and deparaffinised in xylene and rehydrated in a descending grades of alcohol. Heat induced antigen retrieval was

done. The antigen was bound with mouse monoclonal antibody (Pathnsitu) against D2-40 in a ready to use dilution and then detected by adding secondary antibody conjugated with horse radish peroxidase-polymer and diaminobenzidine substrate. Slides will be counterstained with hematoxylin, cleared in alcohol and xylene and mounted.

Lymphatic vessels in the deeper part of the myometrium are used as positive internal controls.

Interpretation

The antibody treated slides were analysed for the presence or absence of reaction in lymphatic vessels, localization, intensity of the stain and counting of lymphatic vessels.

Staining

Cytoplasmic and membranous staining of lymphatic endothelial cells. Negative in blood vessels.

Counting Of Lymphatic Vessel And Scoring Of Lymphatic Vessel Density

First, the sections were examined at low magnification (x100) for identifying areas of hot spots i.e. areas with more intense staining[10]. Three areas of hot spots were selected and examined under higher magnification (x400) without the knowledge of the patient status. Three or more randomly selected areas were counted in case of no apparent hotspots. Immunostained vessels without a muscle layer or red blood cells in the lumen are considered lymphatic vessels. Lymphatic vessels showing complete immunostained endothelial lining were counted in both Intratumoral and peritumoral areas. Intratumoral lymphatic

vessels are those that are present within the main tumour mass surrounded by tumour cells. Peritumoral lymphatic vessels are those which are one high power field (HPF) away from the invasive tumour front. Highest number in both intratumoral and peritumoral areas were recorded for data analysis.

Lymphatic vessel density (LVD) was classified as Low (< 10 vessels / HPF), moderate (10-15vessels/HPF) and high (>15 vessels / HPF). This classification of lymphatic vessel density was based on the study by Maghraby et al[10]

Statistical Analysis

The statistical evaluation was performed with IBM-SPSS statistical package for the social sciences version 20. An initial analysis of collected variables were performed. Lymphatic vessel count and the density were correlated with various prognostic parameters like age, histologic type of tumour, FIGO grade, depth of myometrial invasion, lymphovascular invasion, lymphnode status, peritoneal wash and stage of endometrial carcinoma. Also lymphatic vessel count of carcinoma was compared with that of nonneoplastic and premalignant endometrial lesions. Pearson Chi square test was used for this analysis. In the present study, the P value below 0.05 is considered significant.

OBSERVATIONS

AND

RESULTS

OBSERVATION AND RESULTS

Period of study from May 2016 to May 2018. Total of 57 cases reported as endometrial carcinoma, 5 as nonneoplastic and 3 cases of premalignant endometrial lesions in hysterectomy specimens in the department of pathology, Institute of obstetrics and Gynaecology.

Out of 57 cases of endometrial carcinoma, 3 were not included due to lack of representative tumour tissue. Hence, our study population included 54 cases of endometrial carcinoma.

CHART 1: NUMBER OF CASES STUDIED

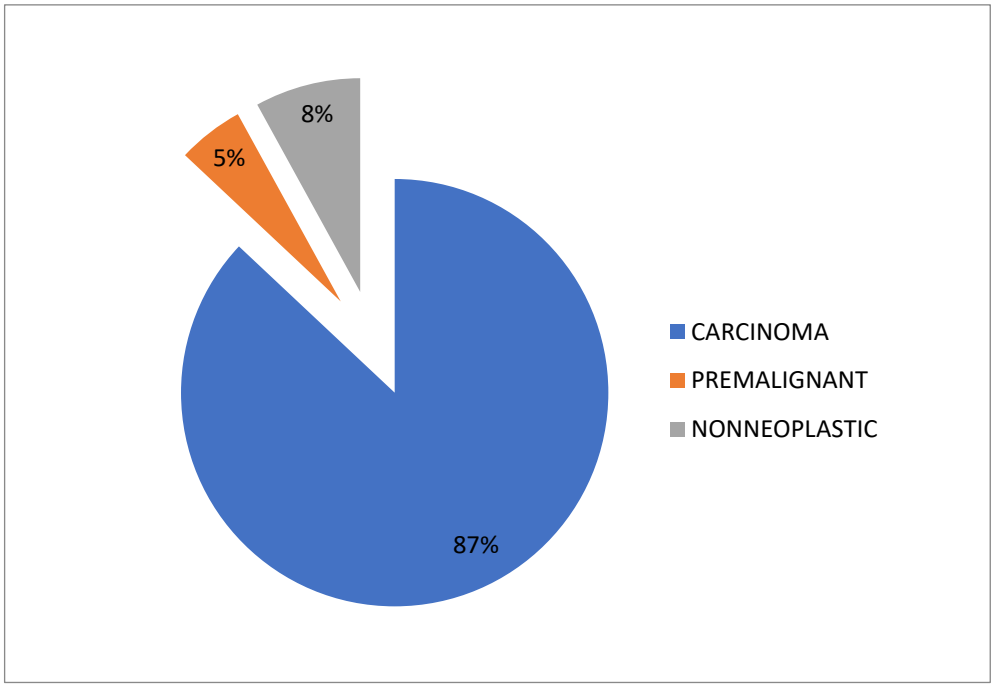
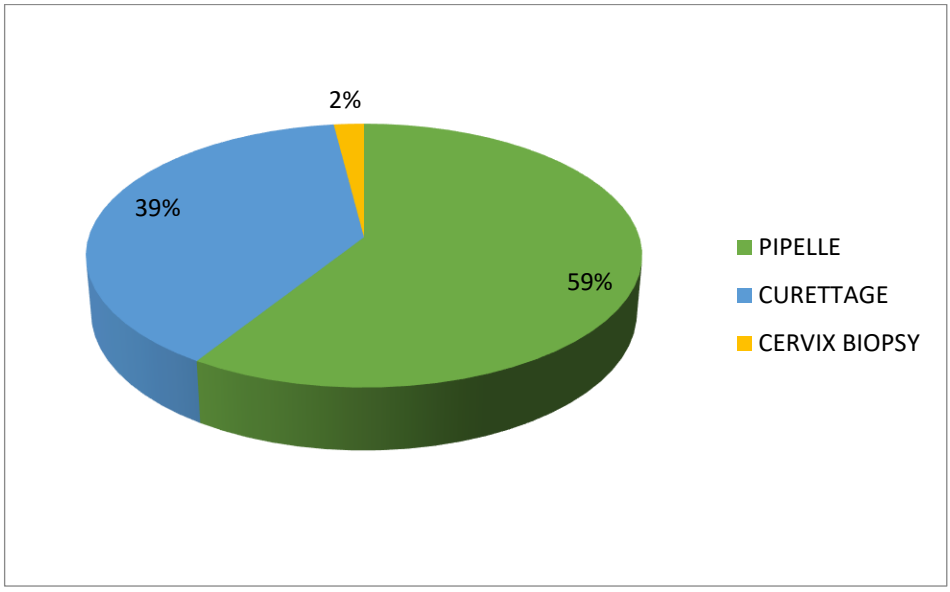
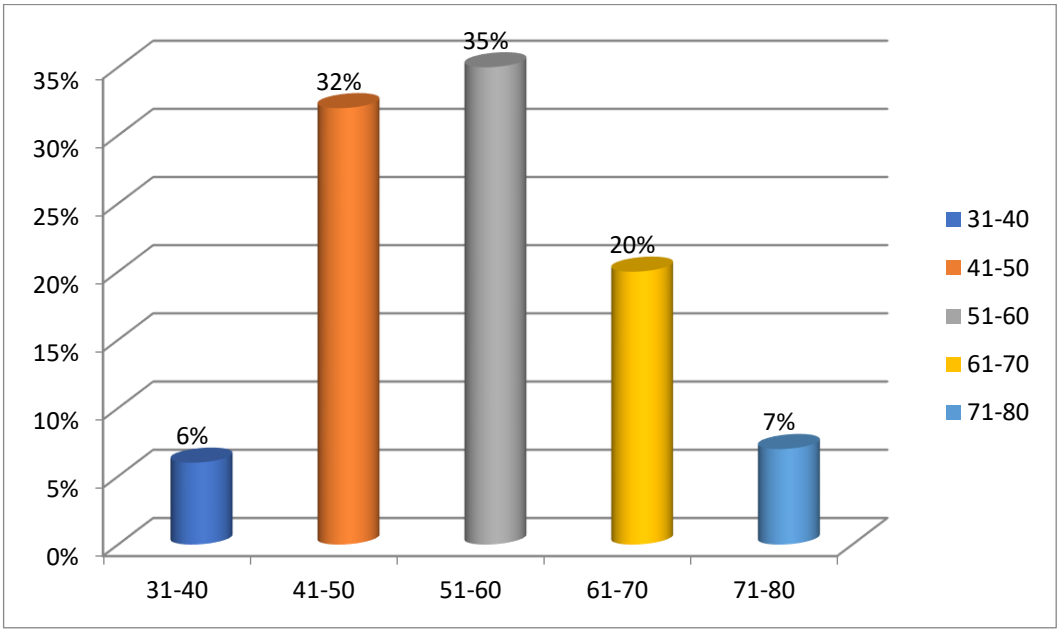


CHART 2: TYPE OF ENDOMETRIAL SAMPLING



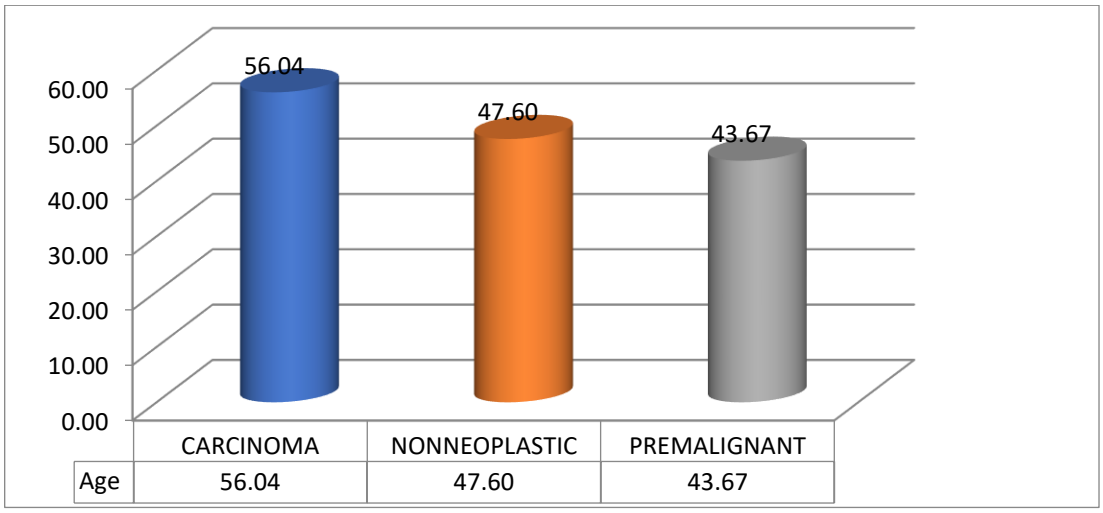
Out of the 54 cases of endometrial carcinoma, 41 of them underwent endometrial sampling preoperatively. Of which, pipelle was done in 24 cases (59%), curettage in 16 cases (39%) and one case of cervix biopsy (2%).

CHART 3 : AGE DISTRIBUTION OF ENDOMETRIAL CARCINOMA



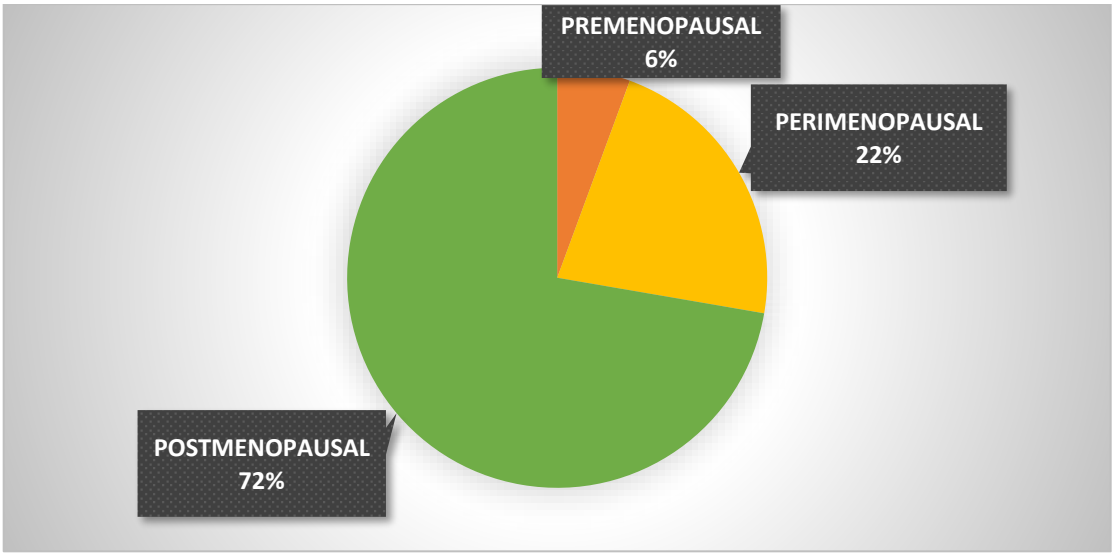
Among 54 cases of endometrial carcinoma, 19 (35%) belong to the sixth decade and 17 cases (32%) belong to 5th decade. Mean age at diagnosis was 56years. Majority were in the postmenopausal age.

CHART 4: MEAN AGE OF PRESENTATION OF CARCINOMA, PREMALIGNANT AND NONNEOPLASTIC LESIONS



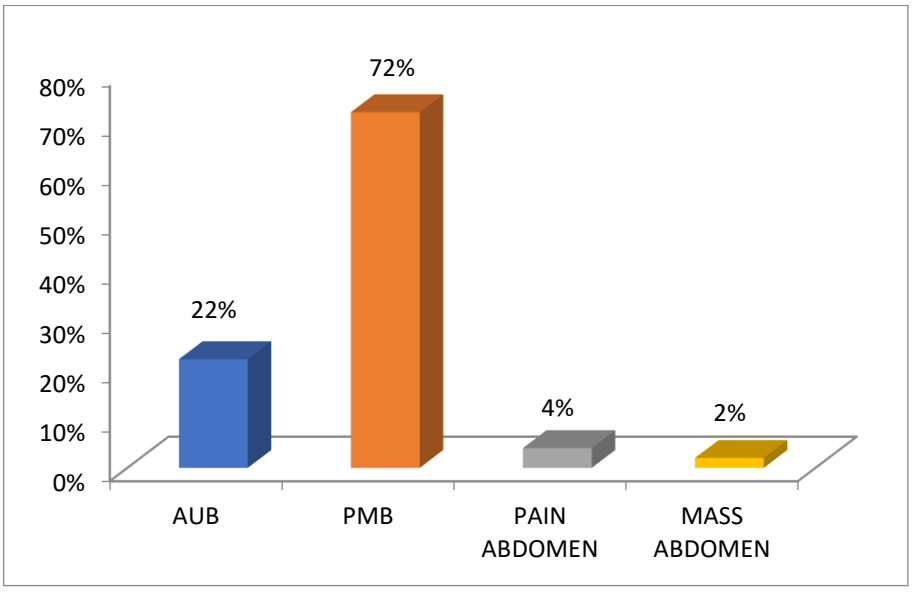
Mean age of presentation for nonneoplastic and premalignant lesions was in the perimenopausal age group whereas the mean age for carcinoma was found to be in postmenopausal age group.

CHART 5: MENSTRUAL STATUS WITH CARCINOMA



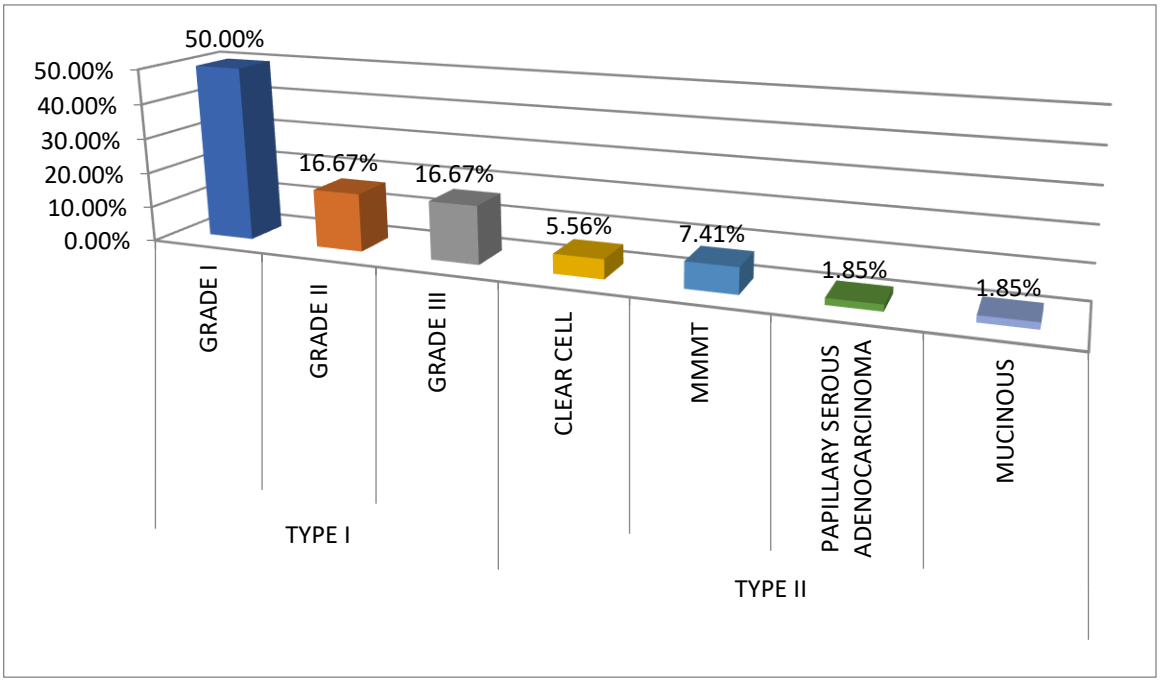
In our study, 72.2% cases were postmenopausal. Among the postmenopausal women, 6 (15.4%) of them were nulliparpous. 22% were in perimenopausal age.

CHART 6: PRESENTING COMPLAINT IN ENDOMETRIAL CARCINOMA



Most common presentation of endometrial carcinoma was found to be bleeding per vaginum constituting 51 cases (94%).

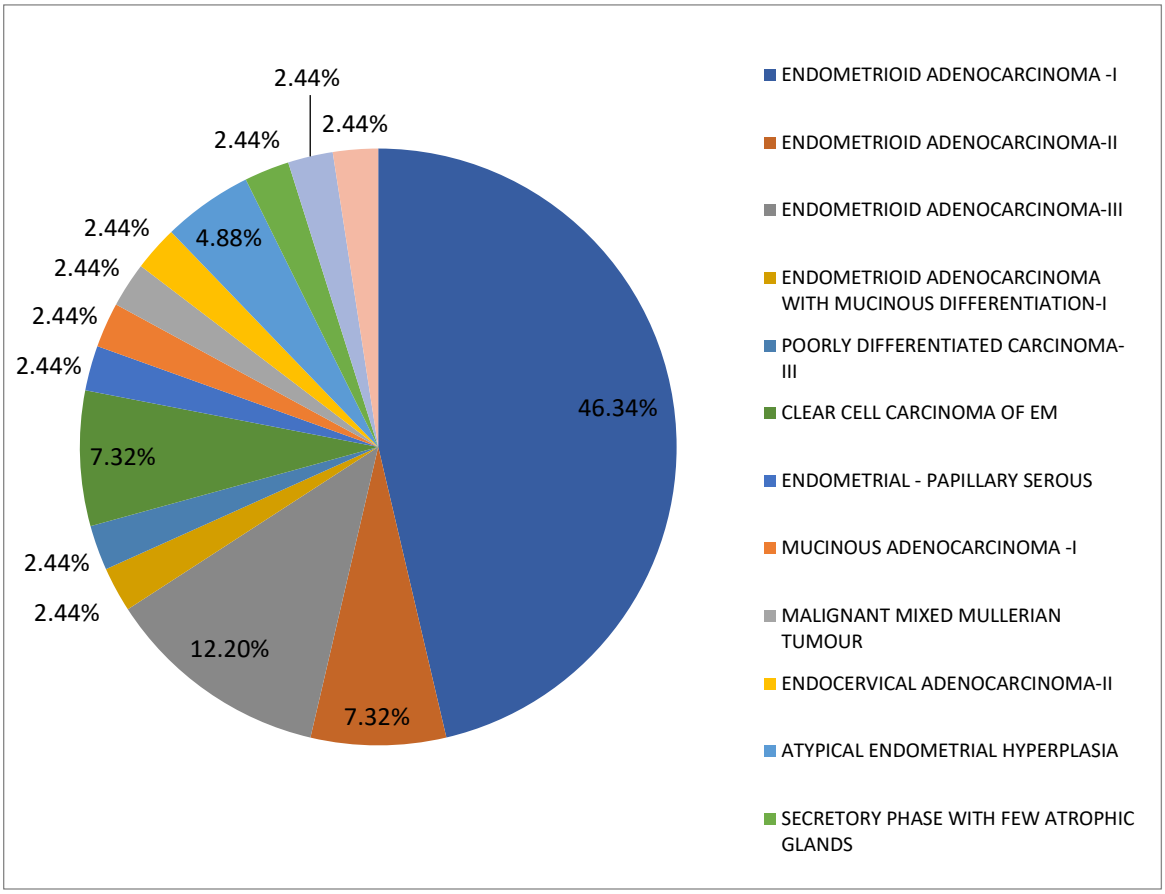
CHART 7: DISTRIBUTION OF HISTOLOGIC TYPES OF CARCINOMA IN HYSTERECTOMY



Most common histologic type was Endometrioid adenocarcinoma constituting 83.3% (45 out of 54 cases). Remaining were 4 cases (7.4%) of malignant mixed Mullerian tumour, 3 cases (5.6%) of clear cell carcinoma of endometrium and 1 case (1.8%) of papillary serous carcinoma and mucinous adenocarcinoma each.

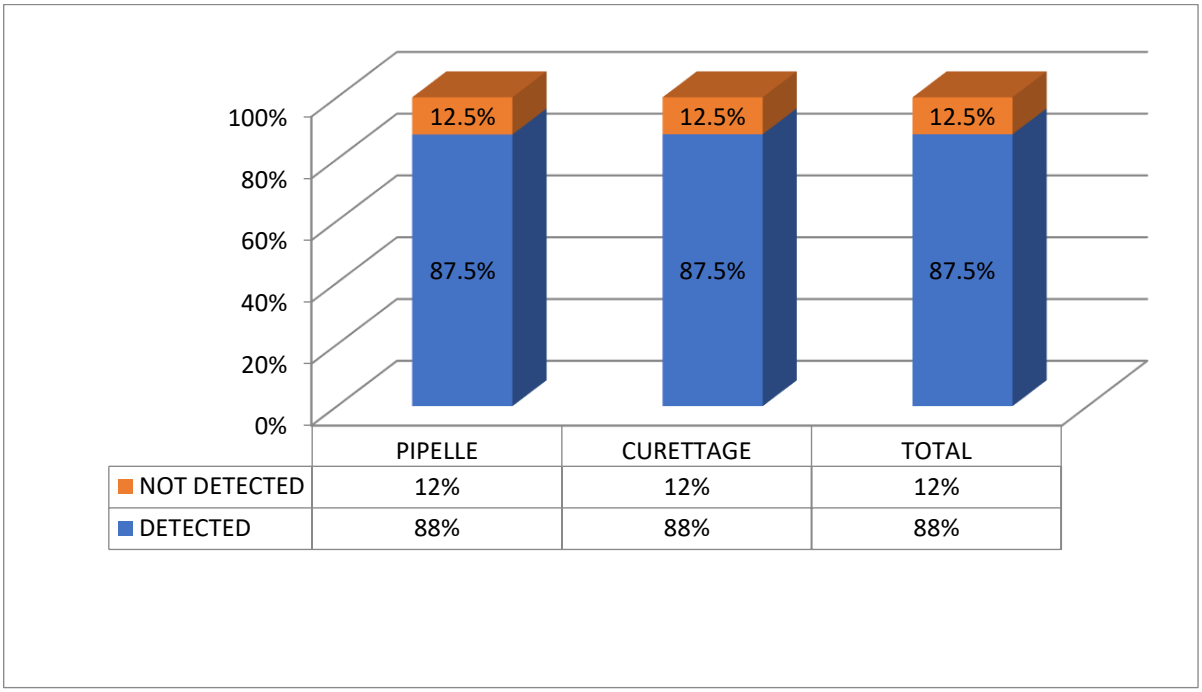
Among the endometrioid adenocarcinoma, FIGO grade was distributed as 27cases (50%) with grade I, 9 cases (16.7%) with grade II and another 9 cases (16.7%) of grade III. FIGO Grade I being the most common at the time of diagnosis.

CHART 8: PREOPERATIVE HISTOPATHOLOGICAL DIAGNOSIS IN THE STUDY POPULATION



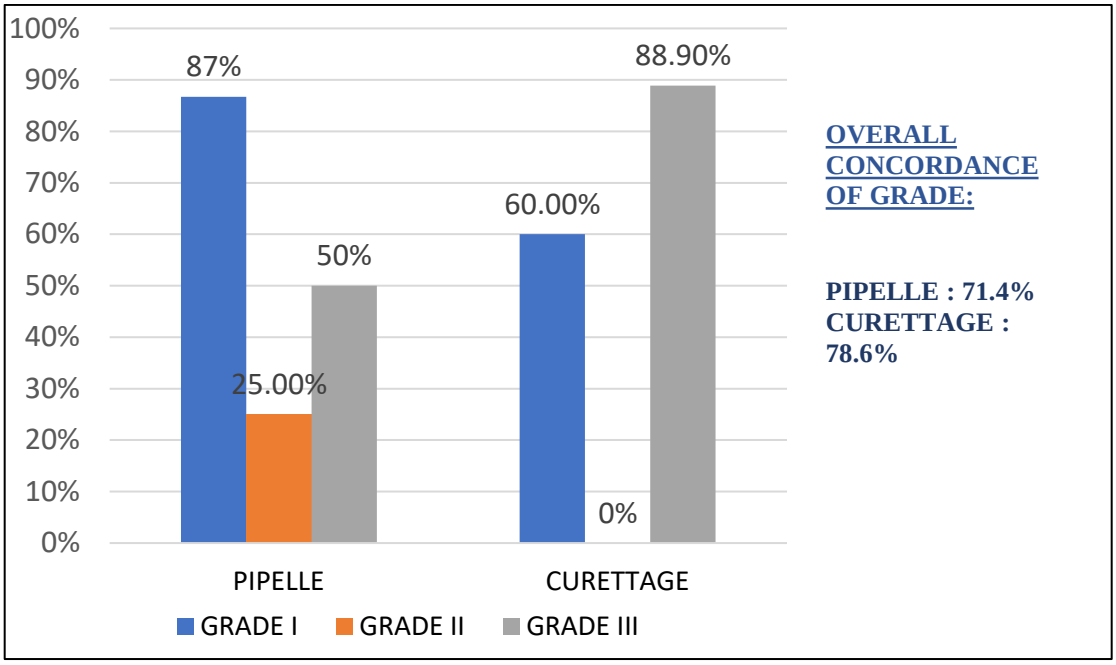
Out of the 54 cases of endometrial carcinoma, 41 of them underwent endometrial sampling preoperatively. Out of 41, 27 cases (65.85%) were diagnosed as Endometrioid adenocarcinoma, of which grade I constituted 19 cases (46.34%), 3 cases (7.32%) of grade II, 5 cases (12.2%) of Grade III, followed by 3Cases (7.32%) of clear cell type of endometrial carcinoma. Rest of them were single cases. Among 40 cases of pipelle and curettage samples, 3 cases were not contributory and 2 were diagnosed as atypical endometrial hyperplasia.

CHART 9: DETECTION OF CARCINOMA IN PREOPERATIVE BIOPSY



The efficacy in detecting carcinoma with pipelle and curettage was found to be 87.5% for both the methods. Remaining 5 cases (12.5%) were atypical endometrial hyperplasia, secretory endometrium and inconclusive because of lack of endometrial glands in the sample received.

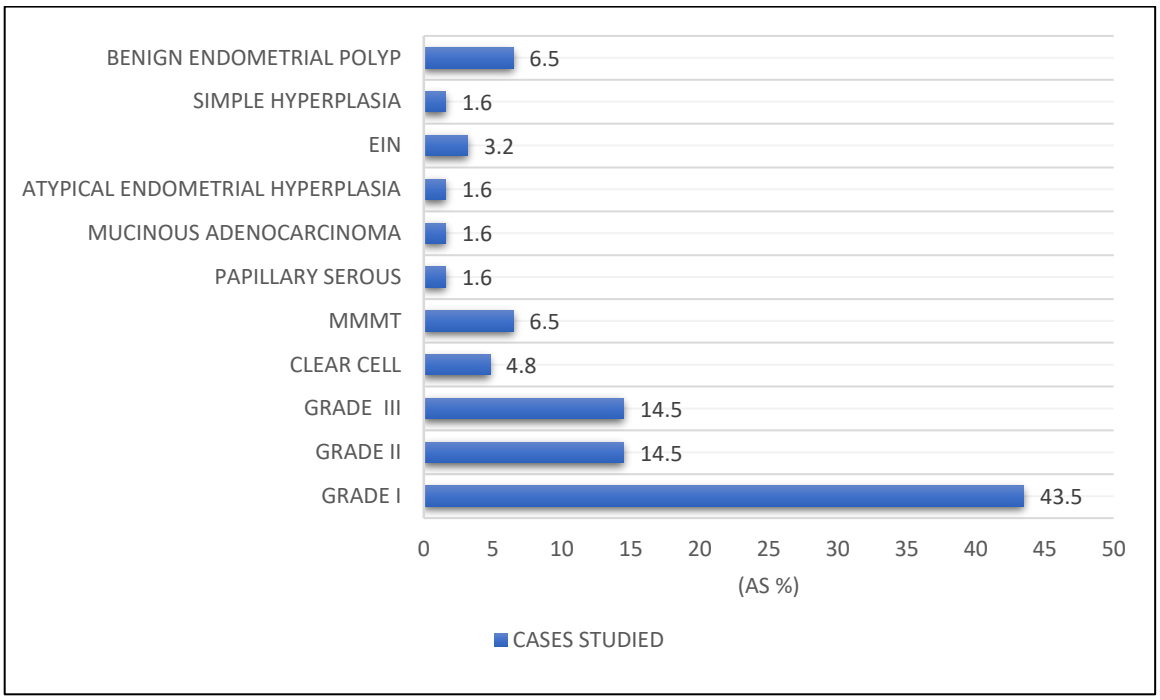
CHART 10 : CONCORDANCE OF FIGO GRADE OF PRE-OPERATIVE BIOPSY WITH HYSTERECTOMY



The concordance of grade with hysterectomy was found to 71.4% with pipelle and 78.6% with curettage. A statistical analysis was performed between method and grade (P value <0.001) which was statistically significant.

CHARTS: 9 & 10 Implies either of the two methods of endometrial sampling are equally effective in detection of carcinoma and concordance of Figo grade postoperatively. Hence, either of the method can be used based on the convenience.

CHART 11: DISTRIBUTION OF CASES FOR IMMUNOHISTOCHEMICAL STUDY



We did immunohistochemical study on 54 cases of endometrial carcinoma, 5 nonneoplastic lesions and 3 premalignant conditions of endometrium diagnosed in hysterectomy specimens.

Of which, 45 cases were of endometrioid adenocarcinoma distributed as 27 cases (43.5%) of Grade I, 9 cases (14.5%) of Grade II and 9 cases (14.5%) of Grade III. 3 cases of clear cell carcinoma of endometrium, 4 cases of Malignant Mixed Mullerian Tumour, one case of papillary serous carcinoma and mucinous adenocarcinoma. Among the 3 premalignant lesions, 2 were atypical endometrial hyperplasia and 1 was endometrial intraepithelial neoplasia (EIN). Out of 5 nonneoplastic lesions, 4 were benign endometrial polyp and 1 was simple hyperplasia.

CORRELATION OF INTRATUMORAL AND PERITUMORAL LV SCORING WITH PROGNOSTIC PARAMETERS:

(LV SCORING - LV COUNT and LV DENSITY)

The following statistical analysis is performed in two ways with LV scoring:

1) Between the various prognostic parameters of endometrial carcinoma and lymphatic vessel count (LV count)* in the Intra and Peritumoral region.

2) Between the various prognostic parameters of endometrial carcinoma and lymphatic vessel Density (LVD)** in the Intra and Peritumoral region.

*LV count is taken as the mean lymphatic vessel count for that particular group.

**LVD is classified as LOW (<10 lymphatic vessels /HPF), MODERATE (10-15 lymphatic Vessels/ HPF) and HIGH (>15 lymphatic vessels / HPF). In our study, we had cases with only LOW and MODERATE LVD.

TABLE 1 (A): AGE WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

		LV Count Intratumoral				LV Count Peritumoral		
		N	Mean	Standard Deviation	P value	Mean	Standard deviation	P value
Age Range	31-40	3	2.67	2.08	0.06	7.33	3.21	0.455
	41-50	17	4.47	3.62		6.41	2.76	
	51-60	19	2.63	1.95		6.89	3.48	
	61-70	11	1.64	1.29		5.27	2.05	
	71-80	4	2.5	1.29		8.25	3.86	

This table shows the association between Age with Intratumoral and Peritumoral LV count. It was found to be statistically insignificant (P value >0.05) in both regions.

TABLE 1(B): AGE WITH LVD (INTRATUMORAL AND PERITUMORAL)

Age Range	LVD Intratumoral				LVD Peritumoral			
	Low	Moderate			Low	Moderate		
	Count	Count	Chi square value	P value	Count	Count	Chi square	P value
31-40	3	0	6.913	0.141	2	1	5.653	0.227
41-50	14	3			14	3		
51-60	19	0			15	4		
61-70	11	0			11	0		
71-80	4	0			2	2		

This table shows the association between Age with Intratumoral and Peritumoral LV density. It was found to be statistically insignificant. (P value >0.05) in both regions.

TABLE 1(C): MEAN AGE WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

	Age	N	Mean	Std. Deviation	P value
Intratumoral LV count	≥ 55.00	32	2.3438	1.75259	**0.026**
	< 55.00	22	3.9545	3.38733	
Peritumoral LV count	≥ 55.00	32	6.6875	3.21727	0.662
	< 55.00	22	6.3182	2.74966	

This table shows the association between Mean Age with Intratumoral and Peritumoral LV count. It was found to be **statistically significant (P value < 0.05) with Intratumoral LV count** and not significant with peritumoral LV count.

Hence, we found that when mean age is taken into consideration, it is statistically significant with Intratumoral LV count.

TABLE 2(A): HISTOLOGIC TYPE WITH LV COUNT

(INTRATUMORAL AND PERITUMORAL)

	LV Count Intratumoral				**LV Count Peritumoral**		
	N	Mean	Standard Deviation	P value	MEAN	Standard Deviation	P value
Endometrioid Adenocarcinoma	45	3.09	2.53	**0.023**	6.53	2.9	0.581
Clear Cell	3	0.33	0.58		4.33	1.53	
MMMT	4	2.75	2.06		7.75	5.19	
Papillary Serous	1	10			6		
Mucinous Adenocarcinoma	1	1			9		

This table shows the association between histologic type with Intratumoral and Peritumoral LV count. It is inferred that **histologic type is statistically significant with Intratumoral LV count** (P- value of < 0.05) and not significant with peritumoral LV count.

TABLE 2(B): HISTOLOGIC TYPE WITH LVD (INTRATUMORAL AND PERITUMORAL)

	LVD Intratumoral				**LVD Peritumoral**			
	Low	Moderate			Low	Moderate		
	count	count	chi square value	P value	count	count	chi square value	P value
Endometrioid adenocarcinoma	43	2	17.578*	**0.001**	36	9	1.313	0.859
Clear cell	3	0			3	0		
MMMT	4	0			3	1		
Papillary serous	0	1			1	0		
Mucinous adenocarcinoma	1	0			1	0		

This table shows the association between histologic type with Intratumoral and Peritumoral LV Density. It is found to be **statistically significant with Intratumoral LVD (P- value of < 0.05)** and not with peritumoral LVD.

Hence, we conclude that histologic type of endometrial carcinoma correlates with Intratumoral LV count and LVD.

TABLE 3(A): FIGO GRADE WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

		LV Count Intratumoral				LV Count Peritumoral		
		Count	Mean	Standard Deviation	P value	Mean	Standard Deviation	P value
FIGO grade	I	27	3.67	2.96	0.118	6.22	3.02	0.704
	II	9	1.89	1.69		7.22	2.99	
	III	9	2.56	.88		6.78	2.59	
	Non Endometrioid	9	2.56	3.28		6.56	3.75	

This table shows the association between FIGO grade with Intratumoral and Peritumoral LV count.

Both were found to be statistically insignificant.

TABLE 3(B): FIGO GRADE WITH LVD (INTRATUMORAL AND PERITUMORAL)

		LVD intratumoral				LVD peritumoral			
		Low	Moderate			Low	Moderate		
		Count	Count	Chi square value	P value	Count	Count	Chi square value	P value
Figo grade	I	25	2	1.765	0.623	22	5	1.964	0.58
	II	9	0			6	3		
	III	9	0			8	1		
	Non Endometrioid	8	1			8	1		

This table shows the association between FIGO grade with Intratumoral and Peritumoral LVD. Both were found to be statistically insignificant.

We conclude that there is no association between FIGO grade and intratumoral and peritumoral LVCount / Density.

TABLE 4(A): DEPTH OF MYOMETRIAL INVASION WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

		LV count Intratumoral				LV count Peritumoral		
		N	Mean	Standard deviation	P value	Mean	Standard deviation	P value
Depth of myometrial invasion	<50%	11	3.91	3.62	0.204	5.36	1.63	0.052
	>50%	43	2.77	2.33		6.84	3.22	

This table shows the association between Depth of myometrial invasion with intratumoral and peritumoral LV count. It is found to be statistically insignificant in both regions.

TABLE 4(B): DEPTH OF MYOMETRIAL INVASION WITH LVD (INTRATUMORAL AND PERITUMORAL)

	LVD Intratumoral					LVD Peritumoral			
	Low		Moderate			Low	Moderate		
	Count		Count	Chi square value	P value	Count	Count	Chi square value	P value
Depth of myometrial invasion	<50%	9	2	4.197*	**0.04**	11	0	3.14	0.076
	>50%	42	1			33	10		

This table shows the association between Depth of myometrial invasion in endometrial carcinoma with intratumoral and peritumoral LVD. It is inferred **that association with Intratumoral LVD is statistically significant (p value <0.05)** and not with peritumoral LVD.

Thereby, we conclude that the Depth of myometrial invasion in endometrial carcinomas correlates with Intratumoral LVD.

TABLE 5(A): LYMPHOVASCULAR INVASION WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

		LV count Intratumoral				LV count Peritumoral		
		N	mean	standard deviation	P value	mean	standard deviation	P value
Lympho vascular invasion	Present	8	4	3.89	0.25	7.75	4.27	0.221
	Absent	46	2.83	2.38		6.33	2.75	

This table shows the association between lymphovascular Invasion(LVI) with intratumoral and peritumoral LV count. It is found to be statistically insignificant in both regions.

TABLE 5(B): LYMPHOVASCULAR INVASION WITH LVD

(INTRATUMORAL AND PERITUMORAL)

Lympho vascular invasion	**LVD Intratumoral**				**LVD Peritumoral**			
	Low	Moderate			Low	Moderate		
	Count	Count	Chi square value	P value	Count	Count	Chi square value	P value
Present	7	1	0.863	0.353	5	3	2.242	0.134
Absent	44	2			39	7		

This table shows the association between lymphovascular Invasion(LVI) with intratumoral and peritumoral LV density. It is found to be statistically insignificant in both regions.

Hence, we conclude that LVI does not correlate with Intratumoral and peritumoral LV count/density.

TABLE 6(A): LYMPHNODE STATUS WITH LV COUNT

(INTRATUMORAL AND PERITUMORAL)

		LV count Intratumoral				**LV count Peritumoral**		
		N	Mean	Standard deviation	P value	Mean	Standard deviation	P value
Lymph node status	Positive	6	2.83	1.6	0.415	8.67	4.59	0.159
	Negative	31	2.65	2.48		6.45	2.81	

This table shows the association between lymphnode status with intratumoral and peritumoral LV count. It is found to be statistically insignificant in both regions.

TABLE 6(B): LYMPHNODE STATUS WITH LVD (INTRATUMORAL AND PERITUMORAL)

Lymphnode status	LVD Intratumoral				LVD Peritumoral			
	Low	Moderate			Low	Moderate		
	Count	Count	Chi square value	P value	Count	Count	Chi square value	P value
Positive	6	0	0.199	0.656	3	3	3.403	0.065
Negative	30	1			26	5		

This table shows the association between lymphnode status with intratumoral and peritumoral LV density. It is found to be statistically insignificant in both regions.

Hence, we conclude that lymphnode status does not correlate with intratumoral and peritumoral LV count/ Density.

TABLE 7(A): PERITONEAL WASH WITH LV COUNT

(INTRATUMORAL AND PERITUMORAL)

		LV count Intratumoral				**LV count Peritumoral**		
		N	Mean	Standard deviation	P value	Mean	Standard deviation	P value
Peritoneal wash	Positive	5	3.6	5.27	0.247	5.4	2.79	0.68
	Negative	32	2.5	1.48		6.69	2.75	

This table shows the association between peritoneal wash status with intratumoral and peritumoral LV count. It is found to be statistically insignificant in both regions.

TABLE 7(B): PERITONEAL WASH WITH LVD (INTRATUMORAL AND PERITUMORAL)

	LVD Intratumoral				**LVD Peritumoral**			
	Low	Moderate			Low	Moderate		
Peritoneal wash	Count	Count	Chi square value	P value	Count	Count	Chi square value	P value
Positive	4	1	6.578*	**0.01**	4	1	0.027	0.869
Negative	32	0			27	5		

This table shows the association between peritoneal wash status with intratumoral and peritumoral LV density. It is found that there **is significant statistical association (p value <0.05) between peritoneal wash and intratumoral LVD** and not with peritumoral LVD.

Hence, it is concluded that peritoneal wash status correlates with Intratumoral LVD.

TABLE 8(A): FIGO STAGE WITH LV COUNT (INTRATUMORAL AND PERITUMORAL)

		LV Count Intratumoral				LV Count Peritumoral		
		N	Mean	Standard Deviation	P value	Mean	Standard Deviation	p value
Stage	IA	11	3.91	3.62	0.069	5.36	1.63	0.277
	IB	29	2.62	1.82		6.9	3.11	
	II	2	3	1.41		7	0	
	IIIA	2	8	7.07		7	1.41	
	IIIB	1	0			4		
	IIIC	5	2.8	1.79		8.8	5.12	
	IVB	4	1.75	0.96		4.5	1.73	

This table shows the association between FIGO stage of endometrial carcinoma with intratumoral and peritumoral LV count. It is found to be statistically insignificant in both regions.

TABLE 8(B): FIGO STAGE WITH LVD (INTRATUMORAL AND PERITUMORAL):

		LVD intratumoral				LVD peritumoral			
		Low	Moderate			Low	Moderate		
		Count	Count	Chi square value	P value	Count	Count	Chi square value	P value
Stage	IA	9	2	13.283*	**0.039**	11	0	10.854	0.093
	IB	29	0			22	7		
	II	2	0			2	0		
	IIIA	1	1			2	0		
	IIIB	1	0			1	0		
	IIIC	5	0			2	3		
	IVB	4	0			4	0		

This table shows the association between FIGO stage of endometrial carcinoma with intratumoral and peritumoral LV density. It is found there is **significant association with intratumoral LVD with a P value of <0.05** and no association with peritumoral LVD.

Hence we conclude that FIGO stage of endometrial carcinoma correlates with intratumoral LVD.

TABLE 9: CORRELATION OF LV COUNT IN CARCINOMA WITH PREMALIGNANT AND NONEOPLASTIC LESIONS

	Group	N	Mean	Std. Deviation	P value
LV count Intratumoral	Nonneoplastic & premalignant	8	6.6250	2.92465	**0.001**
	Carcinoma	54	3.0000	2.64218	
LV count Peritumoral	Nonneoplastic & premalignant	8	6.6250	2.92465	0.939
	Carcinoma	54	6.5370	3.01389	

CHART 12: CORRELATION OF LV COUNT IN CARCINOMA WITH PREMALIGNANT AND NONEOPLASTIC LESIONS

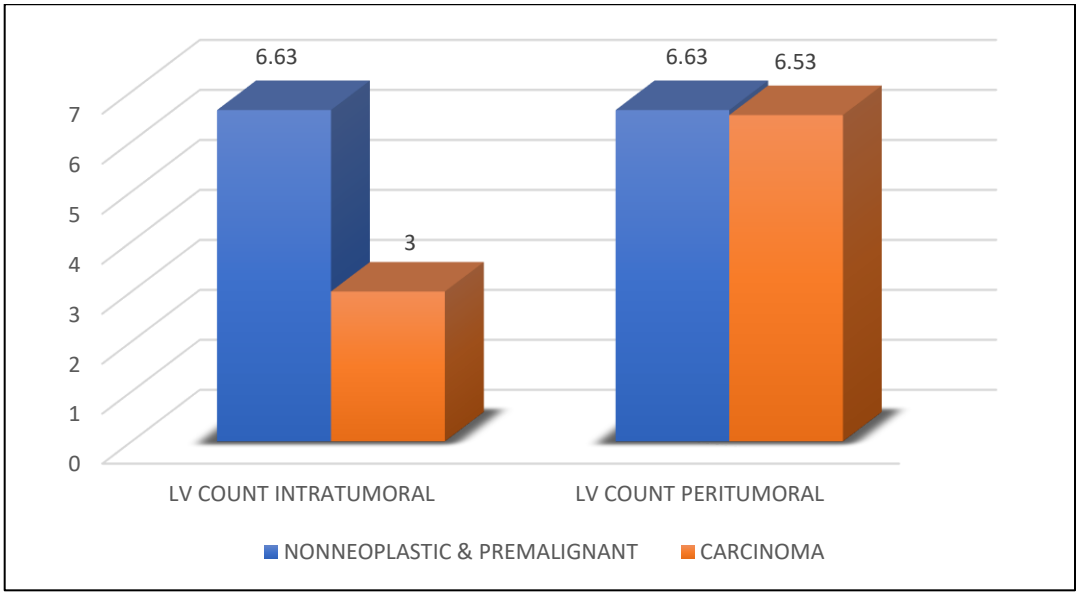


TABLE 9 & CHART 13 shows that the number of lymphatic vessels observed in nonneoplastic and premalignant lesions were found to be **significantly lower** than those observed in intratumoral region of endometrial adenocarcinoma **(p value < 0.05)**

TABLE 10: INTRATUMORAL VS PERITUMORAL LV COUNT:

	N	Mean	Std. Deviation	P value
Intratumoral count	54	3.0000	2.64218	**0.01**
Peritumoral count	54	6.5370	3.01389	

CHART 13: INTRATUMORAL VS PERITUMORAL LV COUNT

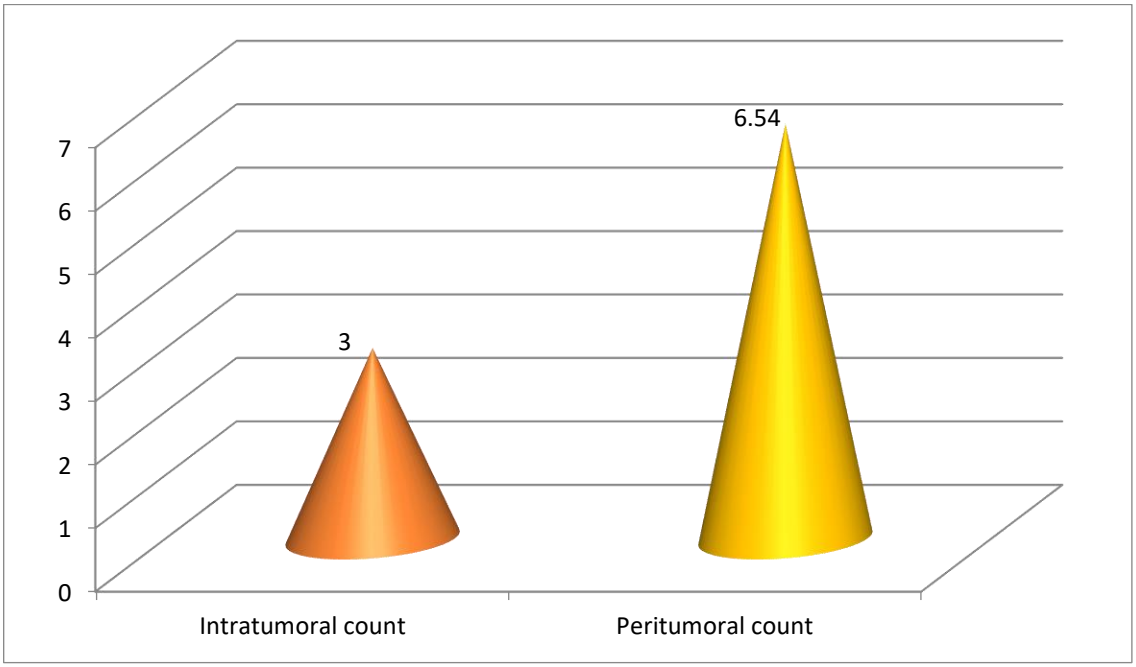


TABLE 10 & CHART 14 shows that there **is significant correlation between intratumoral and peritumoral lymphatic vessel count (p value <0.05)** in all the endometrial carcinomas studied. i.e. the intratumoral lymphatic vessel count was found to be 3.0 ± 2.64 and peritumoral lymphatic vessel count was 6.53 ± 3.01

COLOUR PLATES

HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMA IN OUR STUDY

Fig 1: H&E (400x) Endometrioid Adenocarcinoma – GRADE I

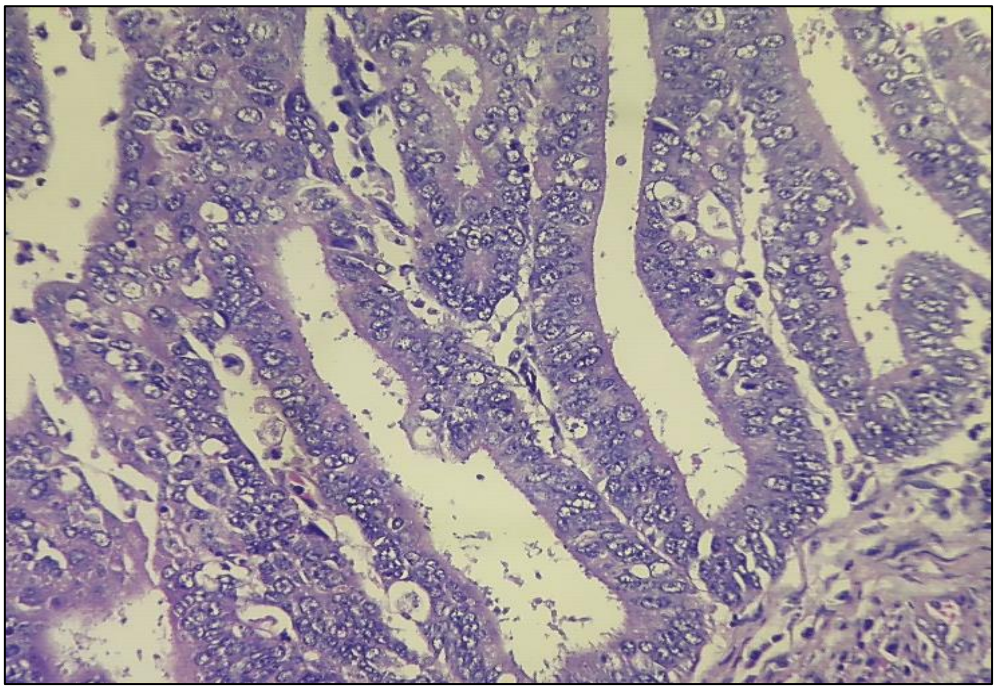


Fig 2: H&E – (400x) Endometrioid Adenocarcinoma – GRADE II

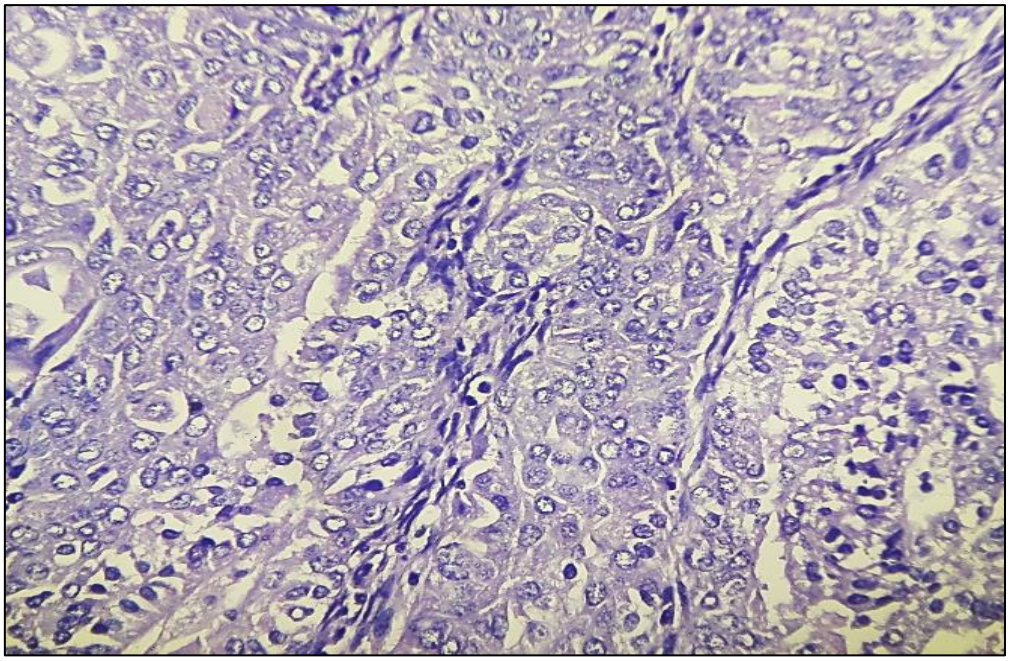


Fig 3: H & E - (400x) Endometrioid Adenocarcinoma – GRADE III

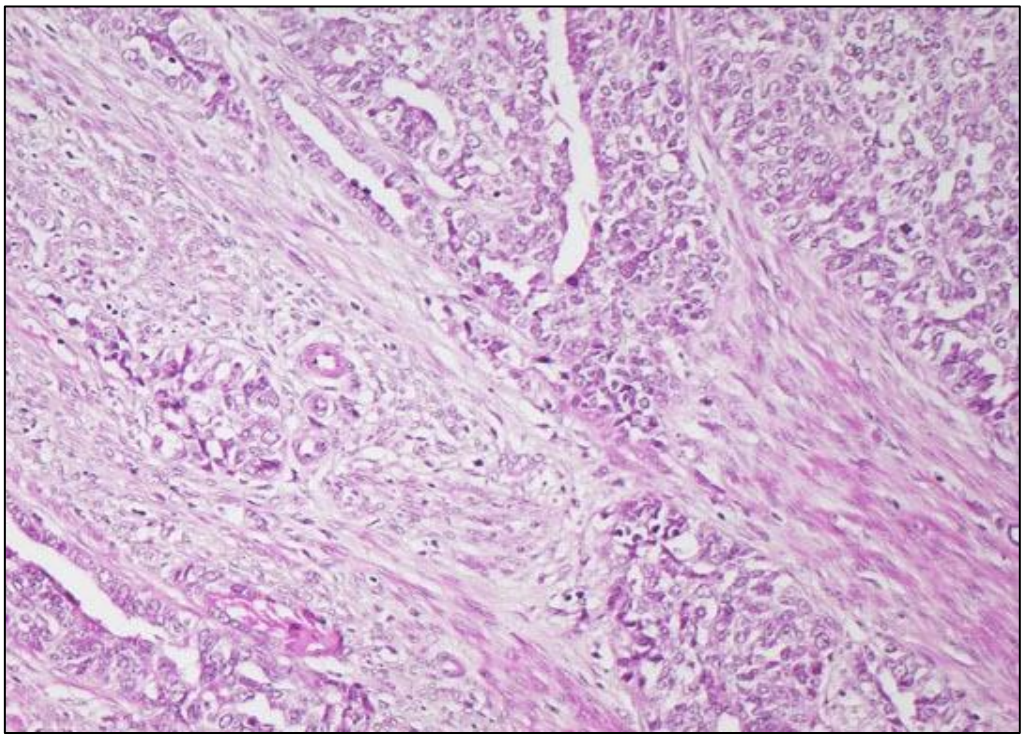


Fig 4: (400x) H & E - Clear Cell Adenocarcinoma

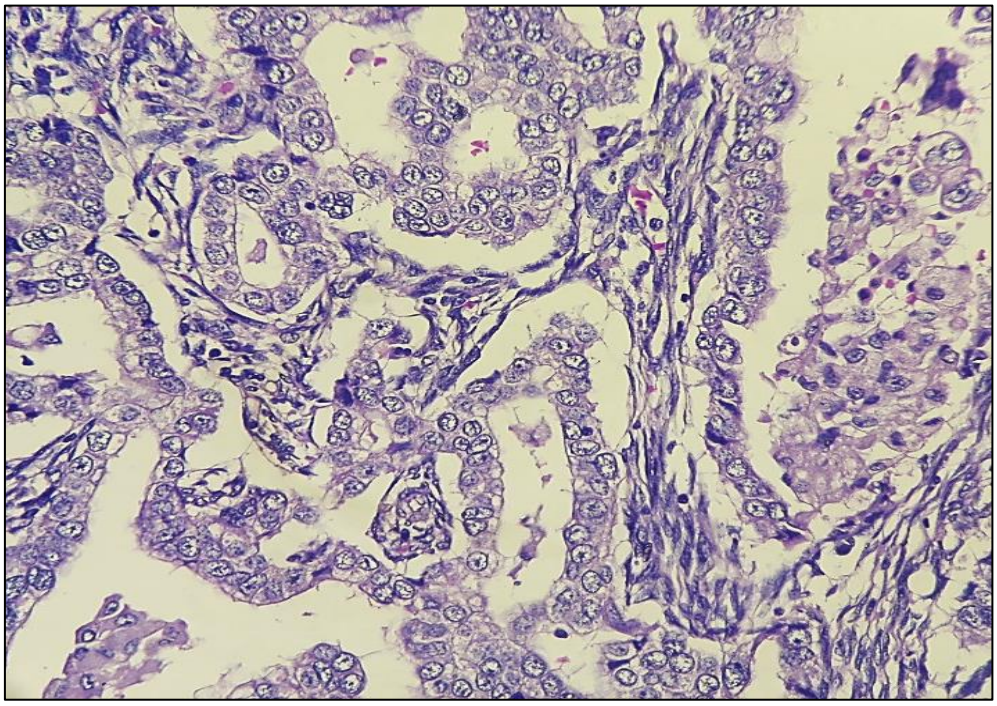


Fig 5: H & E (100x) - Uterine Papillary Serous Carcinoma

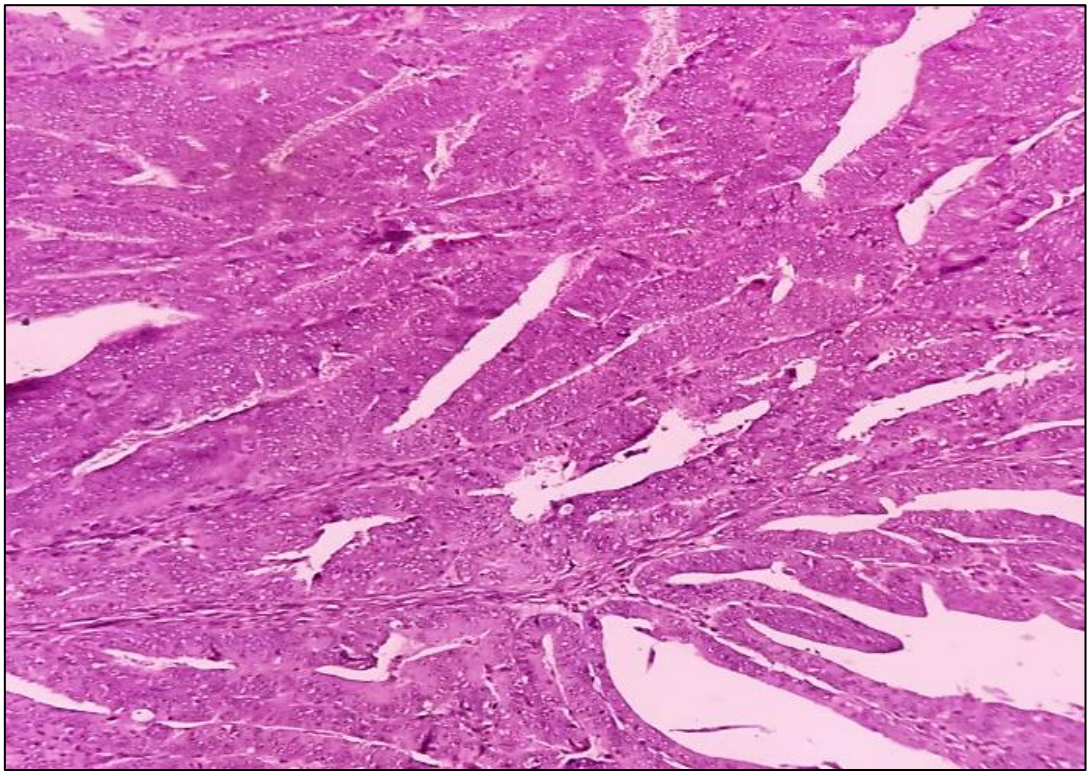


Fig 6: H&E -Mucinous Adenocarcinoma (400x)

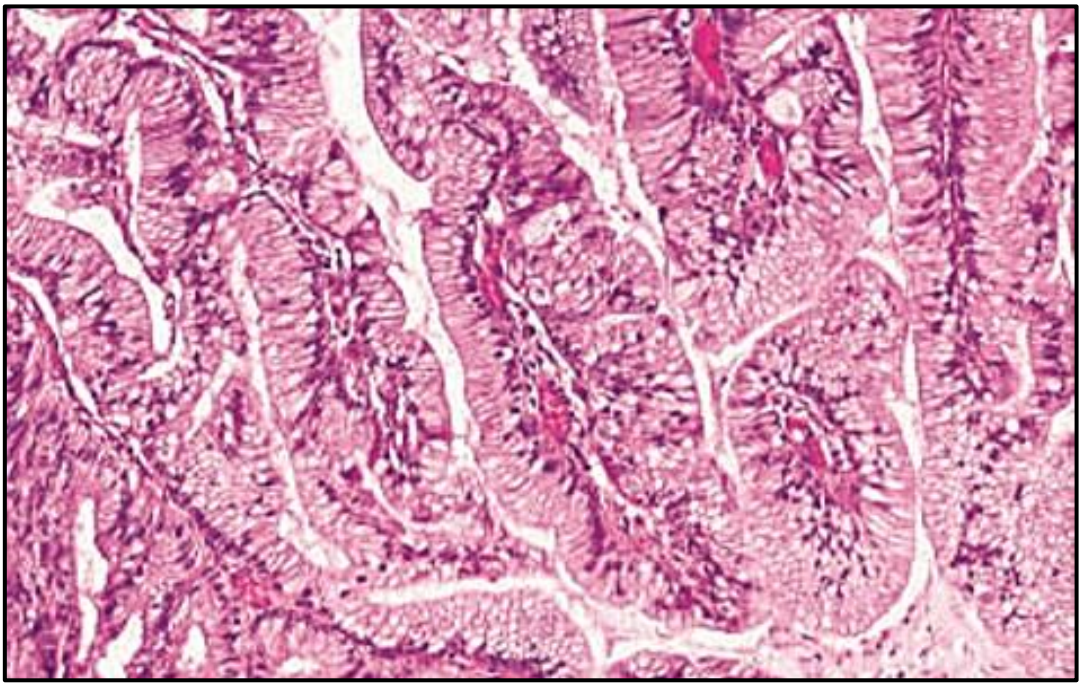
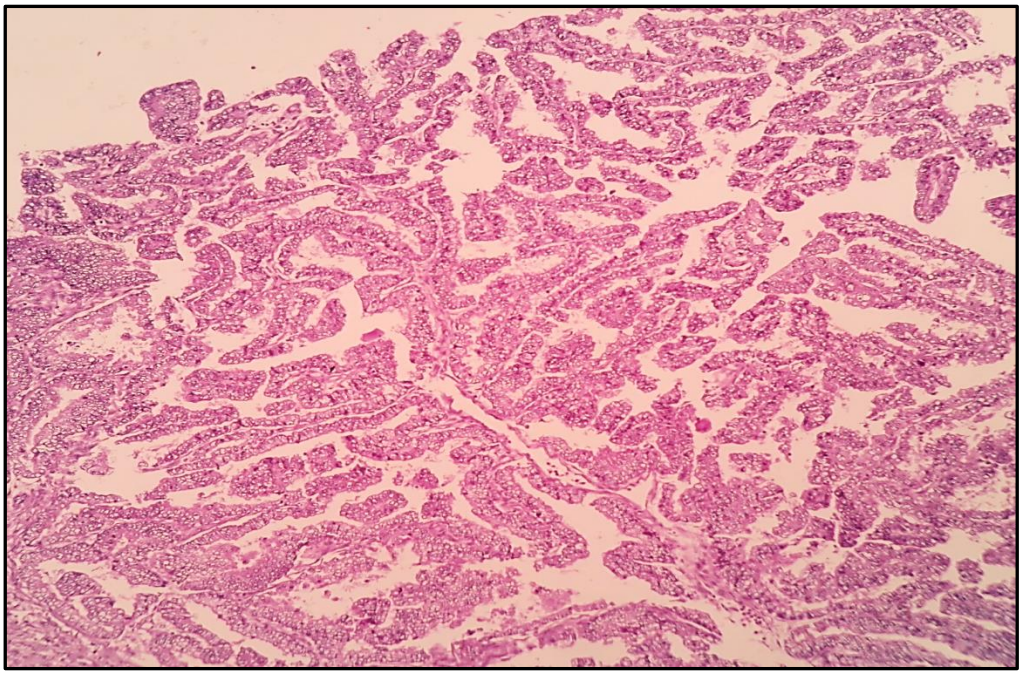
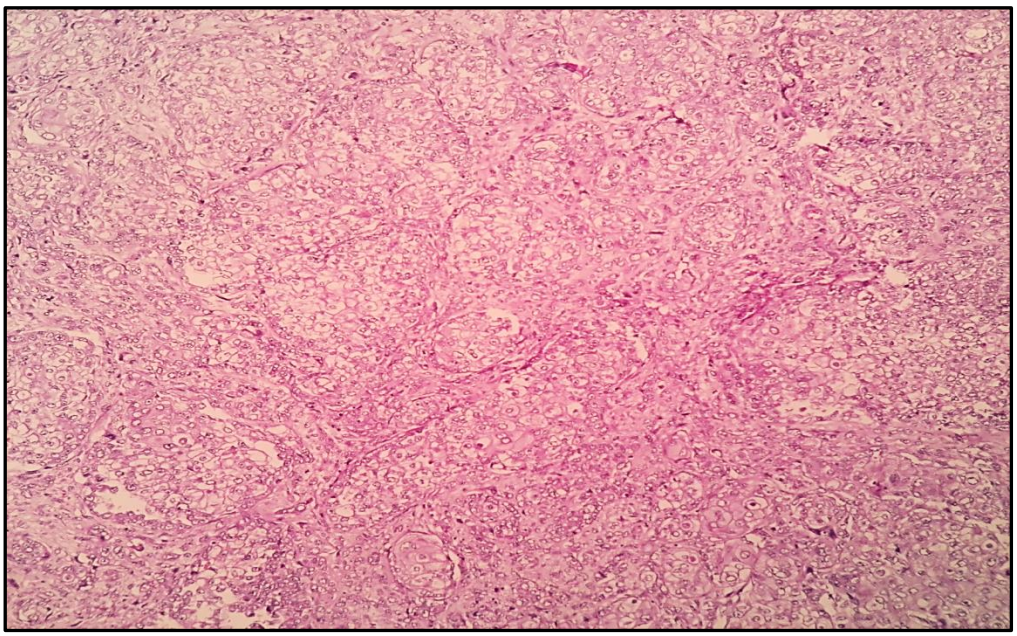


Fig 7 : H & E - (100x) Malignant Mixed Mullerian Tumour (MMMT) - Epithelial and mesenchymal component





IMMUNOHISTOCHEMISTRY WITH D2-40 IN OUR STUDY

Fig 8: IHC D2-40 – (400x) Shows Myometrium With D2-40

Positive Lymphatic Vessels (Internal Control)

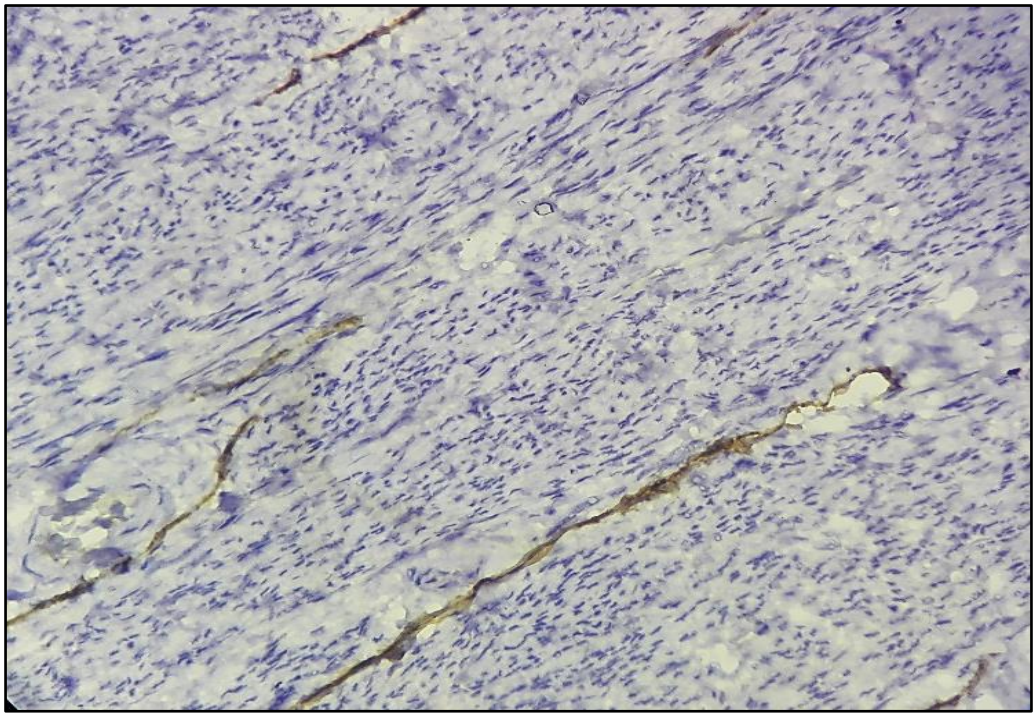


Fig 9: IHC D2-40 -(400x) Shows Small And Collapsed Lymphatic Vessels In The Intratumoral Region

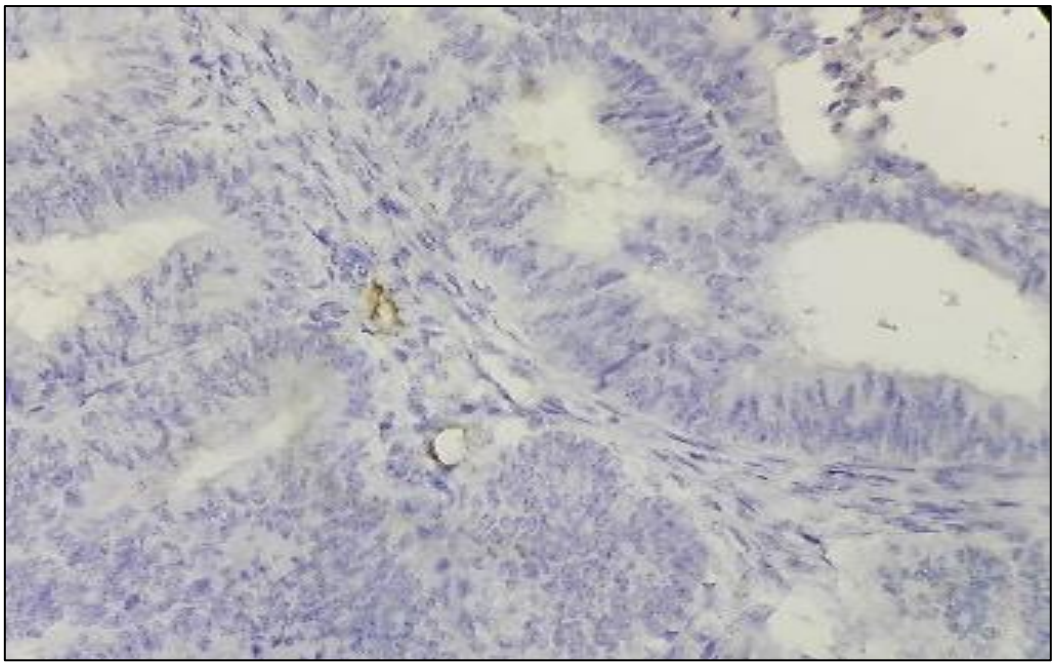
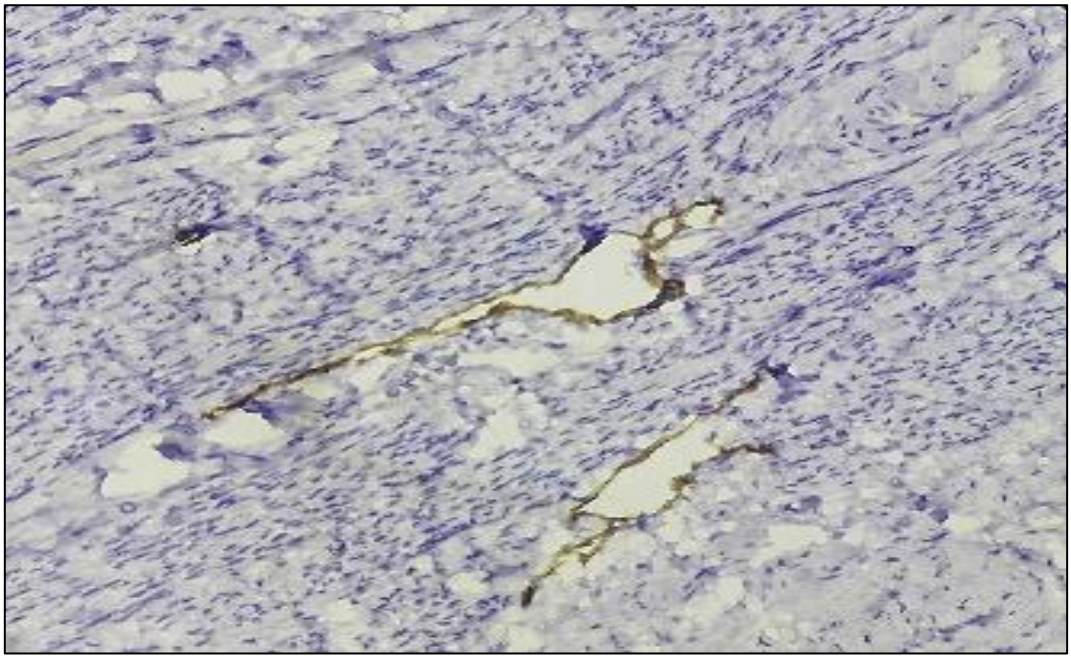


Fig 10: IHC D2-40 -(400x) Shows Dilated And Enlarged Lymphatic Vessels In The Peritumoral Region



IHC D2-40 IN NON NEOPLASTIC AND PREMALIGNANT LESIONS OF ENDOMETRIUM

Fig 11: H&E - (100x) Benign Endometrial Polyp

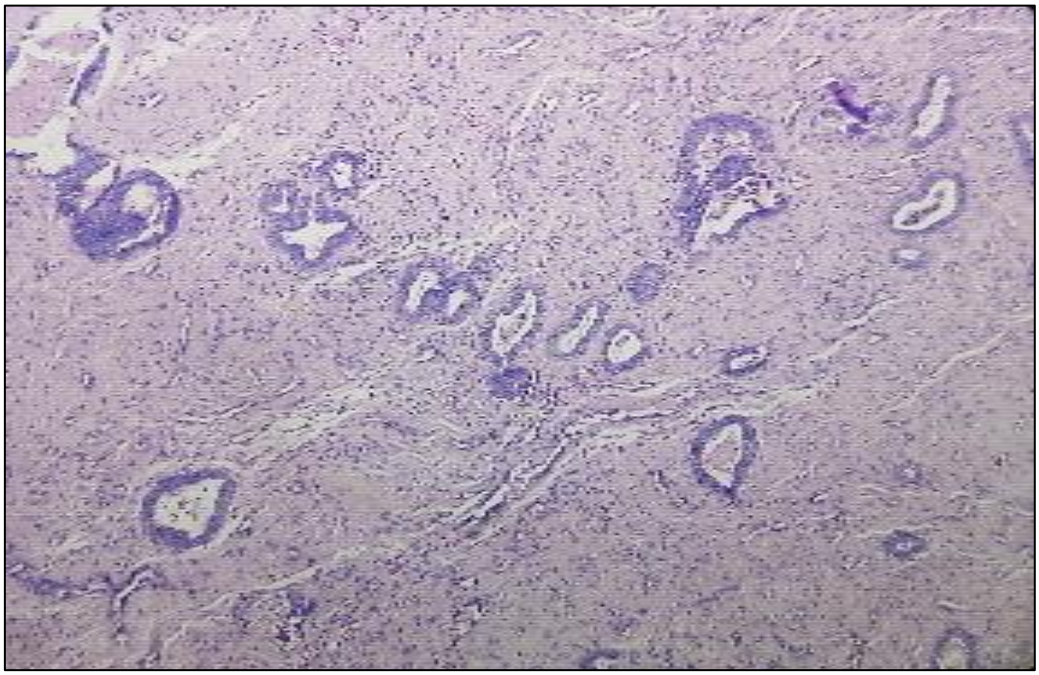


Fig 12: IHC D2-40 (400X) In Benign Endometrial Polyp

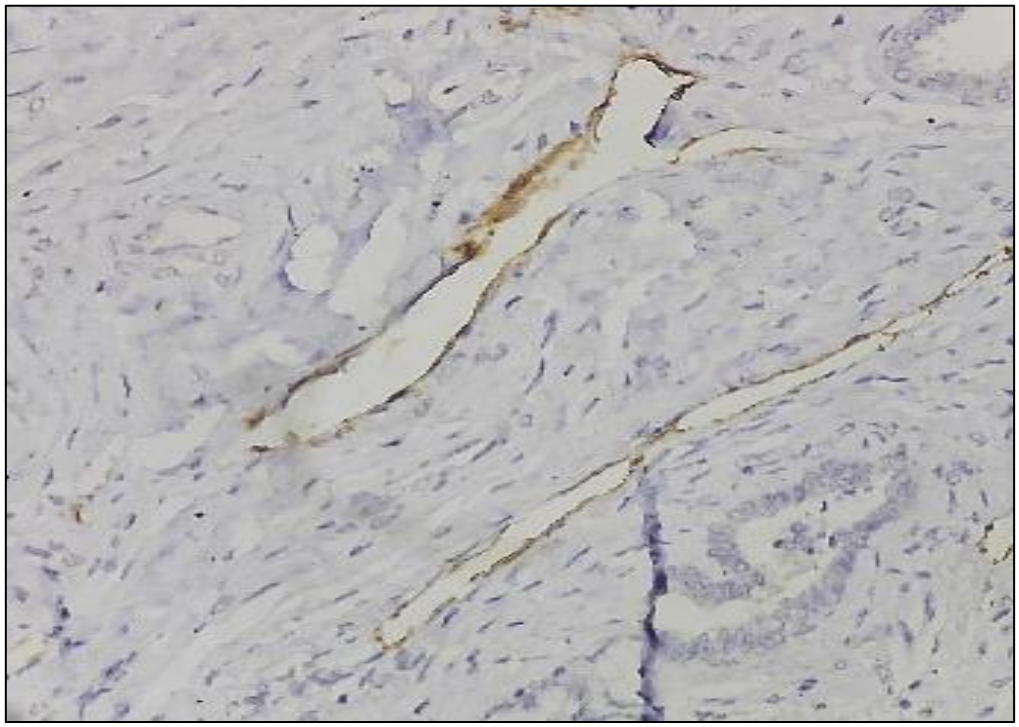


Fig 13: H&E – (100x) Simple Hyperplasia

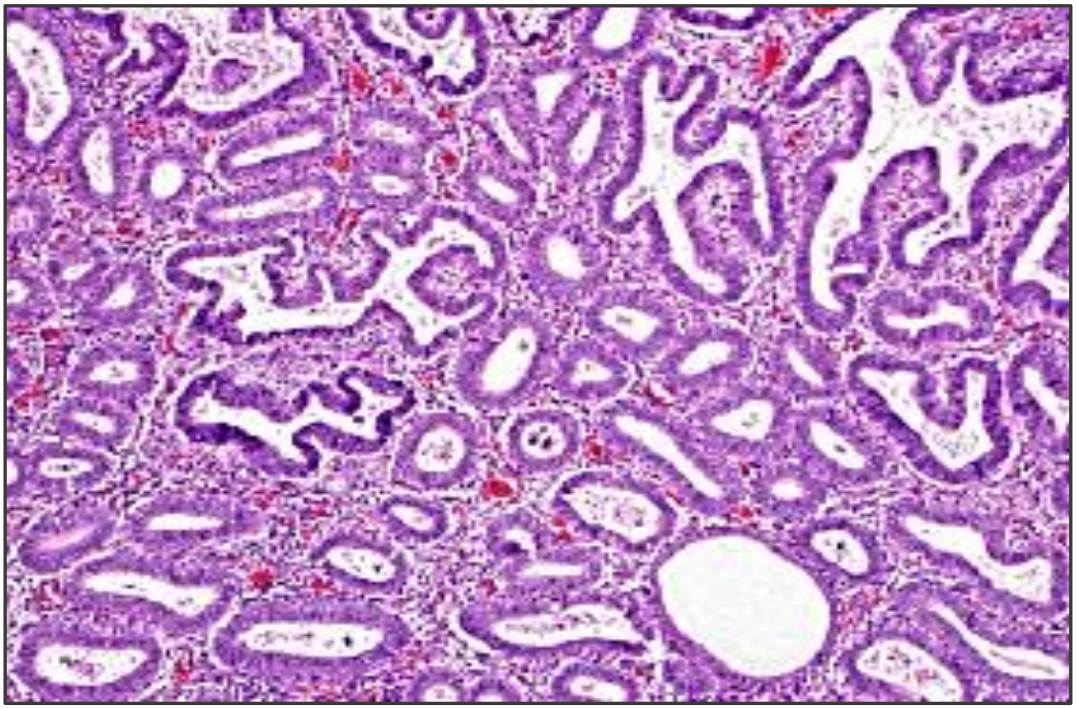


Fig14 : IHC D2-40 (400x) In Simple Hyperplasia

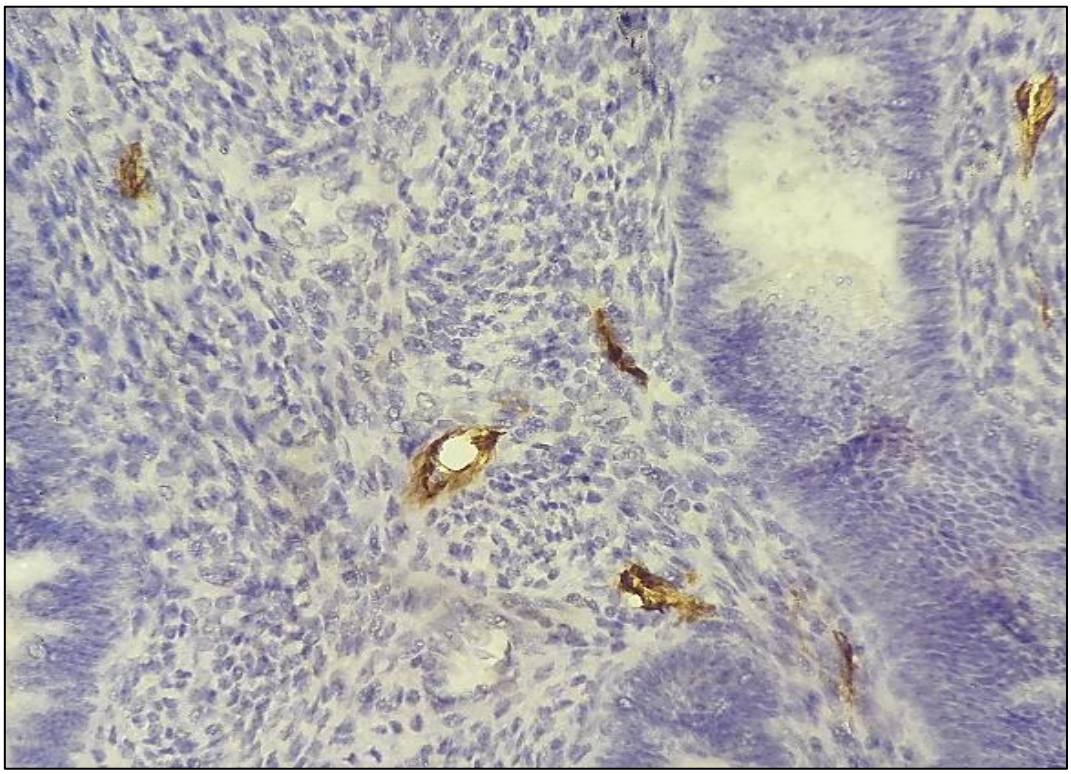


Fig 15: H&E - (400x) Atypical Endometrial Hyperplasia

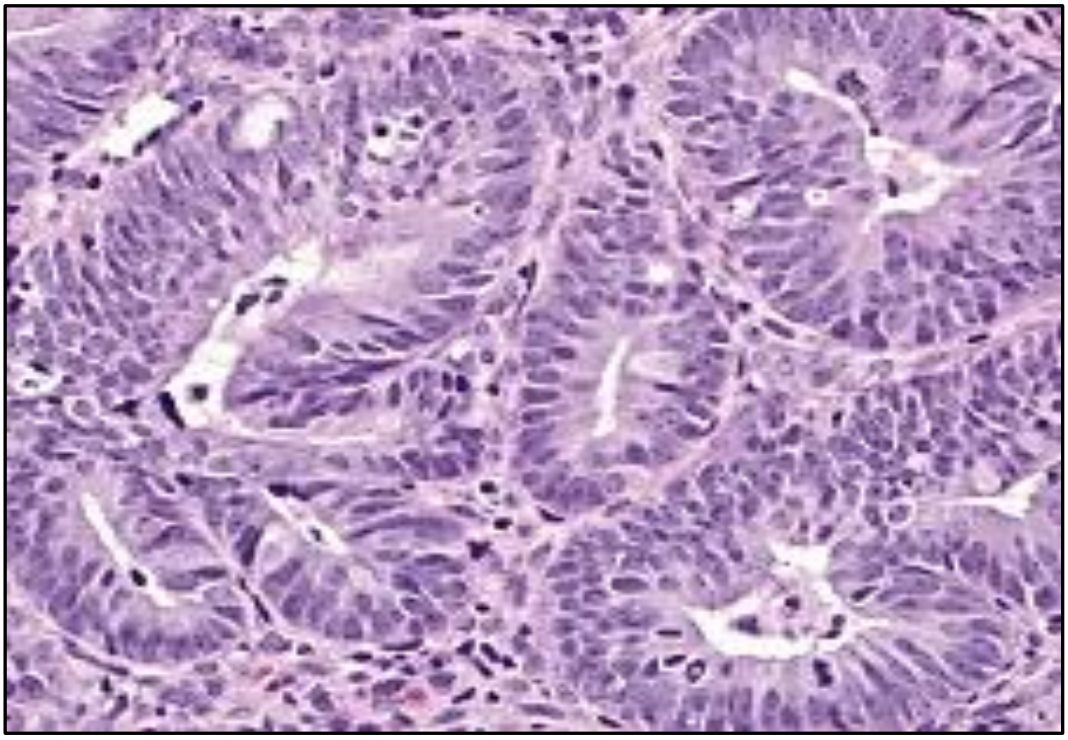


Fig16 : IHC D2-40 (400x) In Atypical Endometrial Hyperplasia

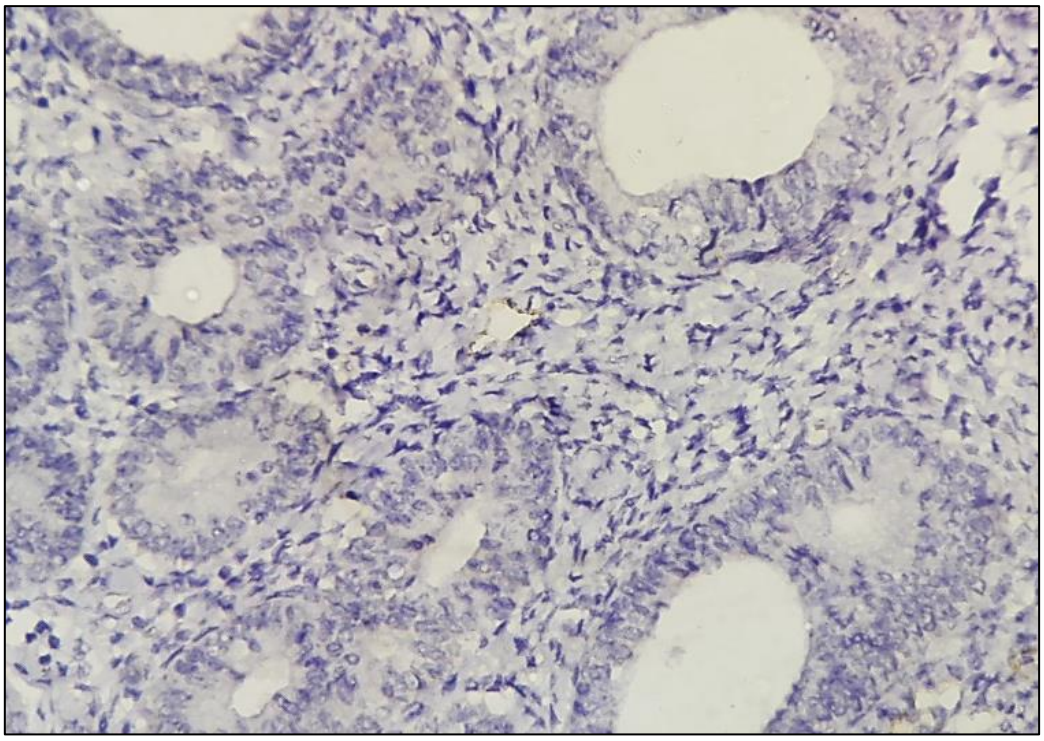


Fig 17: H&E- (400x) Endometrial Intraepithelial Neoplasia (EIN)

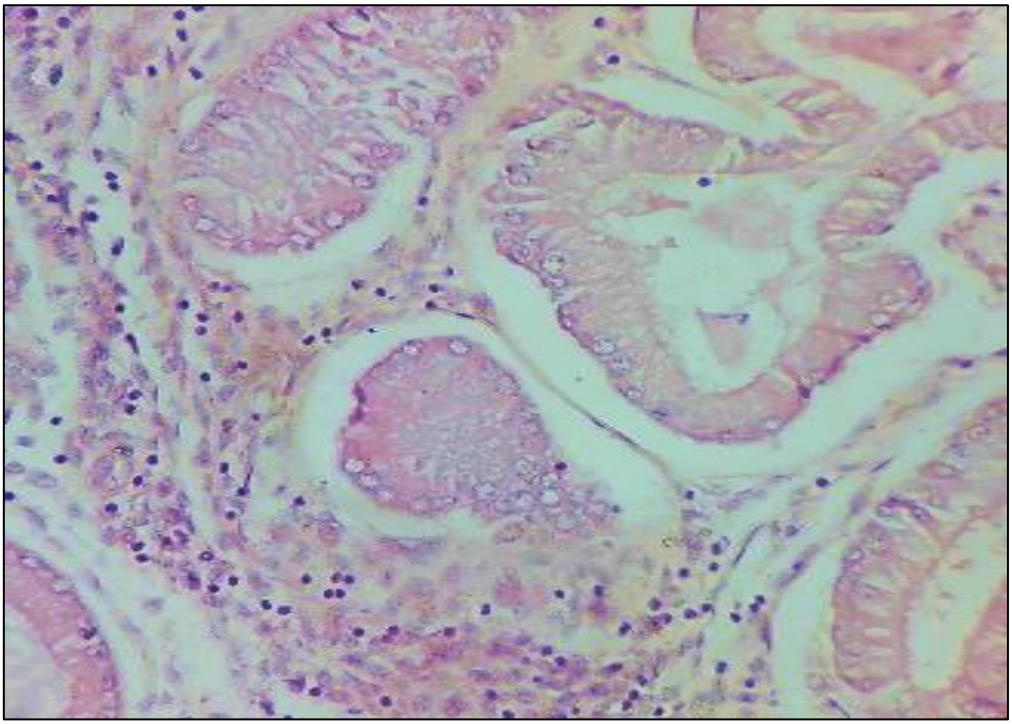
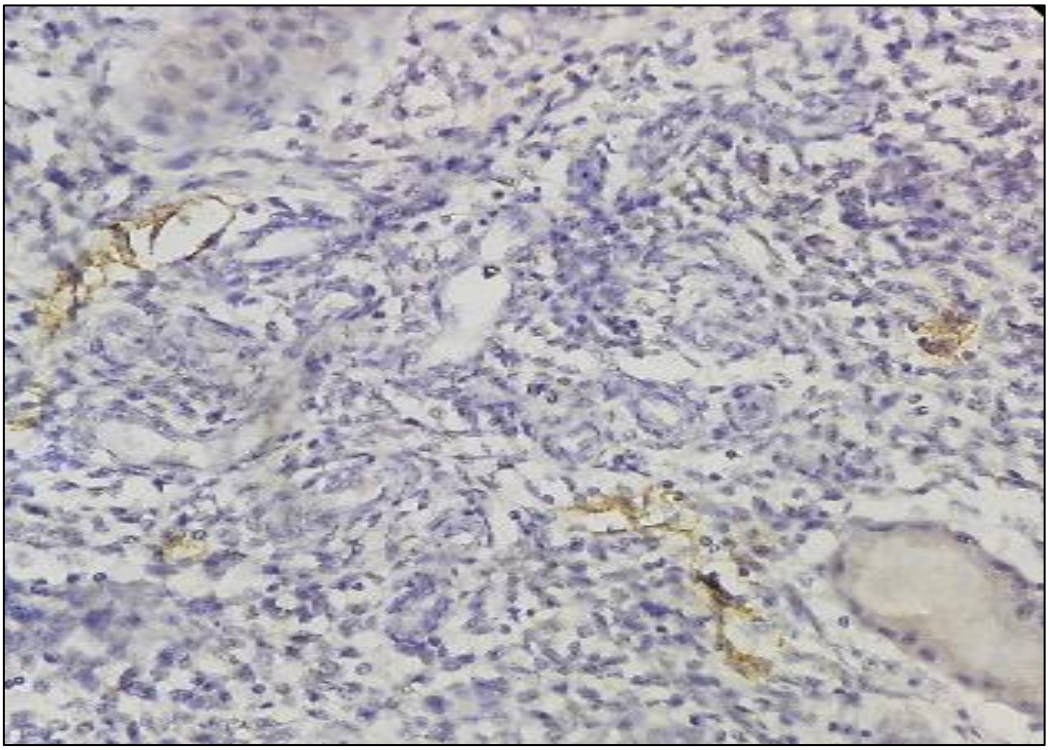


Fig 18: IHC D2-40 (400x) In Endometrial Intraepithelial Neoplasia (EIN)



DISCUSSION

DISCUSSION

Endometrial carcinoma is the sixth most commonly occurring cancer among women.[1] Incidence rates are low in India[2]

The outcome of patient with endometrial carcinoma is influenced by various prognostic parameters. These parameters also varies according to the risk groups.

In patients under low risk group i.e. those without evidence of extra-uterine disease, cervical involvement and vascular invasion, the risk of recurrence is considered to be low. In such patients, the prognosis depends mainly on the histologic type, FIGO Grade and depth of myometrial invasion.

Whereas in patients under high risk group i.e. those with evidence of extra-uterine disease, cervical involvement or vascular invasion, the risk of recurrence is high. In such patients, lymphovascular invasion, lymphnode status, positive peritoneal cytology and stage of the disease.

It has been observed that metastasis to pelvic lymph nodes occur in about 10% of women with endometrioid endometrial adenocarcinomas.[174] Also, the presence of para aortic lymph nodes is considered an important prognostic parameter.[159]

In this study, we evaluated the immunohistochemical expression of D2-40 (podoplanin) in the lymphatic endothelial cells both in intratumoral and peritumoral regions of endometrial carcinoma and correlated their expression with various clinicopathological variables like age, histologic type, FIGO grade, depth

of myometrial invasion, lymphovascular invasion, lymphnode status, peritoneal wash status and stage of the disease.

In this study, we also compared the efficacy of pre-operative biopsy in the detection of carcinoma and the concordance of FIGO grade with hysterectomy specimens.

In this study we also found that D2-40 could be useful in identifying lymphatic invasion as it outlines the lymphatic vessel which is generally difficult on routine histological sections.

In our study, we included nonneoplastic lesions and premalignant lesions of endometrium diagnosed in hysterectomy specimens to look for the intra-lesional immunohistochemical expression of D2-40 in comparison with its expression in endometrial carcinomas.

Our study was done on 62 cases. Of which, 54 cases were endometrial carcinoma, 3 cases premalignant lesions and 5 cases of nonneoplastic lesions, diagnosed in hysterectomy specimens.

Age group and presentation:

In this study, most commonly affected age group was the fifth and sixth decade with a age range of 34 to 75years. Mean age at diagnosis was 56years. Incidence of endometrial carcinoma in women below 40 years was found to be 5.6%. This is similar to the incidence observed by Chakalova et al[188] Duska et al[4] and Ota et al[186]

Mean age of presentation for nonneoplastic and premalignant lesions was in the perimenopausal age group whereas the mean age for carcinoma was found to be in postmenopausal age group. This is similar to the study by Soliman et al[190]

Most common presentation of endometrial carcinoma was found to be bleeding per vaginum (94%) which is similar in other studies by Chakalova et al and as per ESMO guidelines 2013[189]

Histologic type of endometrial carcinoma:

In our study, the most common histologic type was Endometrioid adenocarcinoma constituting 83.3% (45 out of 54 cases). Remaining were non endometrioid constituting 4 cases (7.4%) of malignant mixed Mullerian tumour, 3 cases (5.6%) of clear cell carcinoma of endometrium and 1 case (1.8%) of papillary serous carcinoma and mucinous adenocarcinoma each. The occurrence of endometrioid adenocarcinoma was similar to observations in the literature[191]

The non endometrioid carcinomas in our study constituted 16.7%, compared with other studies which showed 18% by Fowler JM, Ramirez N, Cohn D et al and 14% by Lambropoulou M, Alexiadis G, Limberis V et al[192]

Among the endometrioid adenocarcinoma, FIGO grade I was found to be the most common at the time of diagnosis in our study (50%), 9 cases (16.7%) with grade II and another 9 cases (16.7%) of grade III. This is similar to the literature stated by Garg et al[114]

Among the non endometrioid, clear cell carcinoma was found to be in 5.6% cases which is similar to the study done by Joyce Varughese et al[193] where the incidence observed is between 1% to 6%.

Preoperative biopsy versus hysterectomy:

Among the 54 cases of endometrial carcinoma, 41 of them underwent pre-operative endometrial sampling either with Pipelle or Endometrial curettage. Pipelle was done in 24 cases (59%), curettage in 16 cases (39%) and one case underwent cervix biopsy (2%). The preoperative histopathological diagnosis revealed endometrioid adenocarcinoma being the most common in our study accounting for 65.8% of cases. The efficacy of preoperative biopsy in detecting carcinoma was found to be 87.5% for both pipelle and curettage in our study. In comparison to a meta-analysis assessing the accuracy of endometrial sampling devices in detection of carcinoma showed the efficacy of pipelle[194,195]

STOVALL ET AL	40 cases	98%
ZORLU ET AL	26 cases	92%
GULDO ET AL	65 cases	86%
IN THIS STUDY	24 cases	87.5%

In this study, the concordance of FIGO grade with hysterectomy was found to be 71.4% for pipelle and 78.6% for curettage. Two other studies by Kang et al[196] and Leitao et al[197] showed concordance of about 85%.

IMMUNOHISTOCHEMICAL EXPRESSION OF D2-40 (PODOPLANIN):

The immunohistochemical expression of D2-40 (podoplanin) in the lymphatic endothelial cells both in intratumoral and peritumoral regions of endometrial carcinoma and correlated their expression with various clinicopathological variables like age, histologic type, FIGO grade, depth of myometrial invasion, lymphovascular invasion, lymphnode status, peritoneal wash status and stage of the disease.

The intra-lesional immunohistochemical expression of D2-40 in nonneoplastic lesions and premalignant lesions of endometrium diagnosed in hysterectomy specimens was compared with its expression in endometrial carcinomas.

In our study, we identified the presence of intratumoral lymphatics in 92% of cases and peritumoral lymphatics in 100% of cases. We found that most of the intratumoral lymphatics were small and collapsed whereas the peritumoral lymphatics were dilated and enlarged. This is similar to other studies by Saad et al[198] and Van Trappen et al[199]

In majority of cases in our study, we found that Intratumoral lymphatic vessel count was significantly lower than the peritumoral LV count except 4 cases wherein the intratumoral LV count was higher than peritumoral lymphatic vessels. It was observed in two cases of endometrioid adenocarcinoma of grade I, one case of grade II and other was papillary serous carcinoma. This is similar to studies conducted by Maghraby et al[10] and Gao et al[187] wherein it is said that with the

growth of the tumour, the lymphatics inside the tumour are either destroyed or compressed.

Based on studies by Maghraby et al, which showed presence of D2-40 positive lymphatic vessels in nonneoplastic conditions, we also observed D2-40 positive lymphatic vessels in both nonneoplastic and premalignant lesions of endometrium in our study. But they were significantly lower than observed in endometrial carcinomas.

CORRELATION OF LV COUNT/ DENSITY WITH PROGNOSTIC PARAMETERS:

The statistical analysis was done in two ways with LV count and with LV density.

Correlation with age:

Using age range, the cases distributed as 31-40, 41- 50, 51- 60, 61-70 and 71-80.

It is observed that the intratumoral LV count ranges from 1.6 to 4.5 with majority in the range of 2.6 to 4.5, similarly the LV count in peritumoral region ranges from 5.3 to 8.3 with majority in the range of 5.3 to 6.9. There is no association between age range and mean LV count in both regions.

When comparing the LV density grouped as low and moderate, it was observed that 3 cases had higher(moderate) intratumoral density in the age group of 41-50 years and 10 cases had higher (moderate) peritumoral density in 41-60 years age group. However, it was not statistically significant.

But when mean age of 55 years was taken into consideration, there was significant association with the intratumoral LV count with a P value of <0.05. This was in contrast to the study done by Gao et al in 102 patients, wherein there was no association observed between mean age and LV count in both regions.

Correlation with Histologic type:

We had 45 cases of endometrioid adenocarcinoma, 3 cases of clear cell carcinoma, 4 cases of Malignant mixed Mullerian tumour, one case of papillary serous carcinoma and mucinous adenocarcinoma.

In correlation with intratumoral LV count/ intratumoral LV density and histologic type, it was found to be statistically significant with a p value < 0.05. This is in contrast to the study by Gao et al, wherein there was no association observed between histologic type and LV count in both intratumoral and peritumoral regions.

Correlation with FIGO grade:

In our study, 27 cases were Grade I, 9 cases were Grade II and 9 cases were Grade III. Since the majority of cases had similar LV count/ LV density without much difference between the grades, there was no significant association observed between the FIGO grade and LV count/density in our study. This is similar to the study by Gao et al but in contrast to another study done by Maghraby et al which showed significant association with peritumoral LVD.

Correlation with Depth of myometrial invasion:

The depth of myometrial invasion observed in our study were grouped based on FIGO staging as < 50% and ≥ 50%. In our study, 11 cases had less than 50% invasion and 43 cases had more than myometrial invasion. We observed that the Intratumoral LV density significantly associated with the depth of myometrial invasion with a p value of < 0.05. This was in contrast to the study by Gao et al, which did not show any association.

Correlation with Lymphovascular invasion and lymphnode status:

In our study, lymphovascular invasion was found to be positive in 8 cases and negative in 46 cases. It was found to be statistically insignificant in both regions using both LV count and LV density. This was in contrast to the study done by Gao et al and Maghraby et al wherein there was significant association of LV invasion with peritumoral lymphatic count and density.

Out of 54 cases, only 37 cases had undergone staging laparotomy. Hence, lymphnode status was assessed only for these cases. Of which 6 cases showed positive lymphnodes and 31 cases were negative. However in our study, there was no significant association observed between lymphnode status and LV count/Density in both intratumoral and peritumoral regions. Studies by Gao et al and Maghraby et al, showed significant correlation with peritumoral LV count/ density.

Correlation with peritoneal wash status:

Out of 54 cases, only 37 cases had undergone staging laparotomy. Hence, peritoneal wash was sent for cytology in these cases. Of which, 5 cases showed positive peritoneal cytology and 32cases were negative. Analysis revealed significant association between peritoneal wash status and intratumoral LV density with a p value of <0.05. However this was in contrast to the study by Maghraby et al in which there was no association observed with peritoneal wash in both regions.

Correlation with FIGO stage:

In our study, there were 11 cases in stage IA, 29 cases in stage IB, 2 cases in stage II, 2 cases in stage IIIA, 1 case in stage IIIB, 5 cases in stage IIIC and 4 cases in stage IVB. There was significant association observed between the stage of disease and Intratumoral LVD with a p value <0.05. Study by Gao et al showed significant association but with peritumoral LV count.

FOLLOW UP OF PATIENTS

Among the 54 cases, 24 patients who were diagnosed with stage I disease were under clinical follow up and 11 cases belonging to stage II, III and IV were given chemotherapy/ radiotherapy and followed up clinically. Remaining patients were lost to follow up.

SUMMARY

SUMMARY

- During the study period from May 2016 to May 2018 in the Department of pathology, Institute of Obstetrics and Gynaecology, Egmore, 57 cases were reported as endometrial carcinoma.
- Among them, 54 cases were subjected to immunohistochemical analysis with D2-40, remaining 3 cases were excluded due to lack of representative section of tumour. We also included 5 cases of nonneoplastic lesions and 3 cases of premalignant lesions of endometrium.
- The mean age of endometrial carcinoma was 56 years, postmenopausal with bleeding per vaginum being the most common clinical presentation.
- Incidence of endometrial carcinoma in women below 40 years was found to be 5.6%.
- Most common histologic type was Endometrioid adenocarcinoma constituting 83.3% with 50% constituting Grade I, 16.7 % of grade II and Grade III each.
- Non endometrioid cases were 7.4% of malignant mixed Mullerian tumour, 5.6% of clear cell carcinoma of endometrium and 1.8% of papillary serous carcinoma and mucinous adenocarcinoma each.
- Out of the 54 cases of endometrial carcinoma, 41 of them underwent endometrial sampling preoperatively of which 65.9% were of endometrioid adenocarcinoma.

- The efficacy in the detection of endometrial carcinoma by pre-operative biopsy was found to be 87.5% with both pipelle and curettage.
- The concordance of FIGO grade of preoperative biopsy with hysterectomy specimen was to be 71.4% for pipelle and 78.6% for curettage.

- 74% of cases presented to the hospital with stage I disease.
- Immunohistochemical expression of D2-40 (Podoplanin) showed a significant statistical correlation between Intratumoral LV density with mean age, histologic type of endometrial carcinoma, depth of myometrial invasion, peritoneal wash status and stage of the disease and no such correlation was observed with FIGO grade, Lymphovascular invasion and lymphnode status which needs further evaluation.
- Immunohistochemical expression of D2-40 in non neoplastic and premalignant lesions of endometrium showed significant lower LV count when compared to carcinoma.
- Immunohistochemical expression of D2-40 in endometrial carcinomas revealed that the intratumoral LV count was significantly lower than the peritumoral LV count. The lymphatic vessels in the intratumoral region were found to be small and collapsed whereas those found in peritumoral region were dilated and enlarged.

CONCLUSION

CONCLUSION

In our study the different types of endometrial carcinoma in the 2 years from May 2016 to May 2018 was studied.

In this study, there was significant correlation of D2-40 positive lymph vessels with mean age, histologic type, depth of myometrial invasion, peritoneal wash status and stage of endometrial carcinoma. But there was no significant association observed with FIGO grade, lymphovascular invasion and lymphnode status. Hence, this needs further evaluation for assessing the risk of lymphnode metastasis in endometrial carcinoma using D2-40.

This study concludes that both pipelle and curettage are equally effective in detecting endometrial carcinoma preoperatively and the Concordance of FIGO grade between preoperative biopsy and hysterectomy specimens was statistically significant with both methods.

Out of the 54 cases, follow up of 35 cases was available. All of them were under clinical follow up and the comment on prognosis can only be made on long term follow up.

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BIBLIOGRAPHY

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ANNEXURES

ANNEXURES

ANNEXURE – 1

WHO Classification of tumours of the uterine corpus[a,b]

Epithelial tumours and precursors	
Precursors	
Hyperplasia without atypia	
Atypical hyperplasia / Endometrioid intraepithelial neoplasia	8380/2*
Endometrial carcinomas	
Endometrioid carcinoma	8380/3
Squamous differentiation	8570/3
Villoglandular	8263/3
Secretory	8382/3
Mucinous carcinoma	8480/3
Serous endometrial intraepithelial carcinoma	8441/2*
Serous carcinoma	8441/3
Clear cell carcinoma	8310/3
Neuroendocrine tumours	
Low-grade neuroendocrine tumour	
Carcinoid tumour	8240/3
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed cell adenocarcinoma	8323/3
Undifferentiated carcinoma	8020/3
Dedifferentiated carcinoma	
Tumour-like lesions	
Polyp	
Metaplasias	
Arias-Stella reaction	
Lymphoma-like lesion	
Mesenchymal tumours	
Leiomyoma	8890/0
Cellular leiomyoma	8892/0
Leiomyoma with bizarre nuclei	8893/0
Mitotically active leiomyoma	8890/0
Hydropic leiomyoma	8890/0
Apoplectic leiomyoma	8890/0
Lipomatous leiomyoma (lipoleiomyoma)	8890/0
Epithelioid leiomyoma	8891/0
Myxoid leiomyoma	8896/0*
Dissecting (cotyledonoid) leiomyoma	8890/0
Diffuse leiomyomatosis	8890/1
Intravenous leiomyomatosis	8890/1
Metastasizing leiomyoma	8898/1
Smooth muscle tumour of uncertain malignant potential	8897/1
Leiomyosarcoma	8890/3
Epithelioid leiomyosarcoma	8891/3
Myxoid leiomyosarcoma	8896/3
Endometrial stromal and related tumours	
Endometrial stromal nodule	8930/0
Low-grade endometrial stromal sarcoma	8931/3
High-grade endometrial stromal sarcoma	8930/3
Undifferentiated uterine sarcoma	8805/3
Uterine tumour resembling ovarian sex cord tumour	8590/1*
Miscellaneous mesenchymal tumours	
Rhabdomyosarcoma	8900/3
Perivascular epithelioid cell tumour	
Benign	8714/0*
Malignant	8714/3*
Others	
Mixed epithelial and mesenchymal tumours	
Adenomyoma	8932/0
Atypical polypoid adenomyoma	8932/0
Adenofibroma	9013/0
Adenosarcoma	8933/3
Carcinosarcoma	8980/3
Miscellaneous tumours	
Adenomatoid tumour	9054/0
Neuroectodermal tumours	
Germ cell tumours	
Lymphoid and myeloid tumours	
Lymphomas	
Myeloid neoplasms	
Secondary tumours	

ANNEXURE - 2

Revised 2009 FIGO staging of carcinoma of endometrium

STAGE I[a]	Tumour confined to the corpus uteri	
	IA	No or less than half of the myometrium
	IB	Invasion equal to or more than half of myometrium
STAGE II	Tumour invades the cervical stroma but does not extend beyond the uterus[b]	
STAGE III	Local and/ or regional spread of tumour[c]	
	IIIA	Tumour invades serosa of the corpus uteri and/ or adnexas
	IIIB	Vaginal and/ or parametrial involvement
	IIIC	C1– positive pelvic nodes C2- positive paraaortic nodes with or without positive pelvic nodes
STAGE IV	Tumour invades bladder and /or bowel mucosa and / or distant metastases	
	IVA	Tumour invasion of bladder and /or bowel mucosa
	IVB	Distant metastases, including intra-abdominal metastases and/or inguinal nodes

[a] includes grades 1,2,3

[b] Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II

[c] Positive cytology has to be reported separately without changing the stage.

ANNEXURE - 3

IMMUNOHISTOCHEMISTRY PROCEDURE

1) 4 micron thick sections were cut from formalin fixed paraffin embedded tissue samples and transferred to positively charged slides.
2) The slides were incubated at 58oC for overnight.
3) The sections were deparaffinized in xylene for 15 minutes x 2 changes.
4) The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.
5) The sections were washed in tap water for 10 minutes.
6) The slides were then immersed in distilled water for 5 minutes.
7) Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.
8) The slides were then cooled to room temperature and washed in running tap water for 5 minutes.
9) The slides were then rinsed in distilled water for 5 minutes.
10) Wash with appropriate wash buffer for 5 minutes x 2 changes.
11) Apply peroxidase block over the sections for 10 minutes.
12) Wash the slides in buffer for 5 minutes x 2 changes.
13) Cover the sections with protein block for 15 minutes.
14) The sections were drained without washing and appropriate antibody was applied over the sections and incubated for one hour.
15) The slides were washed in wash buffer for 5 minutes x 2changes.

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

17) DAB substrate solution was applied on the sections for 2 minutes.

18) The slides were washed in distilled water for 5 minutes.

19) The sections were counterstained with Hematoxylin stain.

20) The slides were washed in running tap water for 3 minutes.

21) The slides were air dried and mounted with DPX.

INFORMATION SHEET

- We are conducting a study on endometrial carcinoma among patients attending Institute of Obstetrics and Gynecology, Government General Hospital, Chennai and for that your specimen may be valuable to us.

- The purpose of this study is to predict the risk of lymph node metastases in endometrial cancer patients and its prognostic significance.

- We are selecting certain cases and if your specimen is found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

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

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

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

Signature of investigator Signature of participant

Date

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு :

இம்முனோஹிஸ்டோ கெமிஸ்ட்ரி மூலம் கர்பப்பை புற்றுநோயில், புற்றுநோய் கட்டியின் உள்ளேயும் அதை சுற்றியும் உள்ள நிணநீர் நாளங்கள் பற்றிய முன் கணிப்பு அளவூரு ஆய்வு.

ஆய்வாளர் : மரு. செ. பிரீத்தா,
இரண்டாம் ஆண்டு,
நோய்குறியியல் துறை,
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 600003.

தங்களது கர்பப்பை புற்றுநோய் கட்டி (அறுவை சிகிச்சை செய்யப்பட்ட கட்டி) இங்கு பெற்றுக்கொள்ளப்பட்டது.

தாய் சேய் நல மருத்துவமனைக்கு வரும் கர்பப்பை புற்றுநோய் உள்ள நோயாளிகளில் கர்பப்பை புற்றுநோய் கட்டிகளை சில சிறப்புப் பரிசோதனைகளின் மூலம் எளிதில் கண்டுபிடித்து ஆராய முடியும் என்பதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்கள் எடுத்து சில சிறப்புப் பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்குள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த கர்பப்பை புற்றுநோய் திசு பரிசோதனை முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வை பற்றிய சந்தேகங்களுக்கு தொடர்பு கொள்ள வேண்டியவர் : மரு. செ. பிரீத்தா, செல் : 9843936539

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....

INFORMED CONSENT FORM

Title of the study : **"An Immunohistochemical study on intra tumoral and peri tumoral lymphatic vessel density as a prognostic parameter in endometrial carcinoma"**

Name of the Participant:
Name of the Principal (Co-Investigator) :
Name of the Institution : Institute of Pathology, Madras Medical College.
Name and address of the sponsor / agency (ies) (if any) :
Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in **"An Immunohistochemical study on intra tumoral and peri tumoral lymphatic vessel density as a prognostic parameter in endometrial carcinoma".**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study in which the endometrial tumor tissue will be subjected to histopathological examination and special tests.
4. I have been explained about my rights and responsibilities by the investigator. I have the right to withdraw from the study at any time.
5. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
6. I have understand that my identity will be kept confidential if my data are publicly presented
7. I have had my questions answered to my satisfaction.
8. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:
Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :

இம்முனோஹிஸ்டோ கெமிஸ்ட்ரி மூலம் கர்பப்பை புற்றுநோயில், புற்றுநோய் கட்டியின் உள்ளேயும் அதை சுற்றியும் உள்ள நிணநீர் நாளங்கள் பற்றிய முன் கணிப்பு அளவுரு ஆய்வு.

சென்னை மருத்துவக் கல்லூரி நோய்குறியியல் துறையில் மரு. செ. பிரீத்தா அவர்கள் மேற்கொள்ளும் இந்த ஆய்வில் பங்குகொள்ள ..... ஆகிய நான் முழு மனதுடன் சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் கர்பப்பை புற்றுநோயினை குறித்த இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....

MASTER CHART

S.NO.	BIOPSY NO.	AGE	AGE RANGE	PARITY	MENSTRUAL STATUS	PRESENTING COMPLAINT	PIPELLE/ CURETTAGE	small bx no.	SMALL BIOPSY DIAGNOSIS WITH FIGO GRADE	HISTOPATHOLOGICAL DIAGNOSIS	TYPE	FIGO GRADE	DEPTH OF MYOMETRIAL INVASION	LVI	LN STATUS	PERITONEAL WASH	STAGE	INTERPRETATION-D2-40 STAIN				FOLLOW UP
																		INTRA TUMORAL		PERI TUMORAL		
																		LV COUNT	LVD	LV COUNT	LVD	
1	1346/16	44	41-50	PARITY	PERIMENOPAUSAL	AUB	P	1267/16	ATYPICAL ENDOMETRIAL HYPERPLASIA	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	<50%	neg	NIL	NIL	IA	11	mod	6	LOW	YES
2	1407/16	48	41-50	PARITY	PERIMENOPAUSAL	AUB	P	1021/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	<50%	neg	NIL	NIL	IA	3	LOW	6	LOW	NA
3	1639/16	51	51-60	PARITY	POSTMENOPAUSAL	PMB	C	1509/16	ENDOMETRIAL - PAPILLARY SEROUS	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	>50%	neg	neg	NIL	IB	2	LOW	5	LOW	YES
4	1981/16	75	71-80	NP	POSTMENOPAUSAL	PMB	C	1598/16	ENDOMETRIOID ADENOCARCINOMA -I	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	>50%	neg	neg	+	IB	1	LOW	10	mod	NA
5	2142/16	55	51-60	PARITY	POSTMENOPAUSAL	PMB	C	1886/16	ENDOMETRIOID ADENOCARCINOMA-III	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	neg	NIL	neg	II	4	LOW	7	LOW	YES
6	2324/16	40	31-40	PARITY	PREMENOPAUSAL	AUB				ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	>50%	neg	neg	neg	IB	2	LOW	5	LOW	NA
7	2350/16	40	31-40	PARITY	PREMENOPAUSAL	AUB	CX BX	2134/16	ADENOCARCINOMA- I	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	>50%	+	+	neg	IIIC	1	LOW	11	mod	YES
8	2418/16	67	61-70	PARITY	POSTMENOPAUSAL	PMB	C	2039/16	ENDOMETRIOID ADENOCARCINOMA-III	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	+	+	neg	IIIA	3	LOW	8	LOW	YES
9	2443/16	50	41-50	NP	POSTMENOPAUSAL	PMB	C	2351/16	SECRETORY PHASE WITH FEW ATROPHIC GLANDS	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	+	NIL	+	IVB	2	LOW	4	LOW	YES
10	2985/16	66	61-70	PARITY	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IVB	3	LOW	7	LOW	NA
11	3152/16	45	41-50	PARITY	PERIMENOPAUSAL	PAIN ABDOMEN	P	2899/16	MO EM GLANDS	CLEAR CELL CARCINOMA OF ENDOMETRIUM	II		>50%	neg	neg	+	IVB	1	LOW	3	LOW	YES
12	3190/16	34	31-40	PARITY	PREMENOPAUSAL	AUB FOR 1 YR	P	3020/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	neg	IB	5	LOW	6	LOW	NA

13	3252/16	60	51-60	PARITY	POSTMENOPAUSAL	PMB	P	2934/16	ENDOMETRIOID ADENOCARCINOMA - II	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	>50%	neg	neg	neg	IB	0	LOW	10	mod	NA
14	3336/16	54	51-60	PARITY	POSTMENOPAUSAL	PMB	P	3123/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	NIL	IB	1	LOW	3	LOW	YES
15	3356/16	56	51-60	PARITY	POSTMENOPAUSAL	PMB	P	3253/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	<50%	neg	neg	neg	IA	2	LOW	9	LOW	YES
16	3518/16	55	51-60	PARITY	POSTMENOPAUSAL	PMB				MALIGNANT MIXED MULLERIAN TUMOUR	II		>50%	+	+	NIL	IIIC	5	LOW	15	mod	YES
17	3545/16	50	41-50	PARITY	POSTMENOPAUSAL	PMB	P	3374/17	ENDOCERVICAL ADENOCARCINOMA-II	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	neg	neg	+	IVB	1	LOW	4	LOW	NA
18	3814/16	75	71-80	PARITY	POSTMENOPAUSAL	PMB	P	3747/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	NIL	IB	4	LOW	12	mod	YES
19	3853/16	60	51-60	PARITY	POSTMENOPAUSAL	PMB	P	3371/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	4	LOW	6	LOW	YES
20	3856/16	48	41-50	PARITY	PERIMENOPAUSAL	AUB	P	3499/16	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	<50%	neg	neg	NIL	IA	6	LOW	4	LOW	NA
21	3871/16	60	51-60	NP	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	neg	IB	3	LOW	6	LOW	YES
22	364/17	60	51-60	NP	POSTMENOPAUSAL	PMB	P	113/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	NIL	IB	8	LOW	12	mod	NA
23	870/17	70	61-70	PARITY	POSTMENOPAUSAL	PMB	C	538/17	MALIGNANT MIXED MULLERIAN TUMOUR	MALIGNANT MIXED MULLERIAN TUMOUR	II		>50%	+	+	neg	IIIC	1	LOW	4	LOW	YES
24	1007/17	43	41-50	PARITY	PERIMENOPAUSAL	AUB	P	743/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	6	LOW	12	mod	NA
25	1179/17	60	51-60	PARITY	POSTMENOPAUSAL	PMB	P	992/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	3	LOW	4	LOW	NA
26	1316/17	57	51-60	PARITY	POSTMENOPAUSAL	PMB	C	1182/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	<50%	neg	NIL	NIL	IA	0	LOW	5	LOW	NA
27	1386/17	55	51-60	PARITY	POSTMENOPAUSAL	PMB	P	985/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	NIL	IB	1	LOW	4	LOW	YES

28	1638/17	45	41-50	PARITY	PERIMENOPAUSAL	AUB	P	1389/17	ENDOMETRIOID ADENOCARCINOMA-III	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	neg	IB	3	LOW	5	LOW	NA
29	1639/17	58	51-60	PARITY	POSTMENOPAUSAL	PMB	C	1461/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-MODERATELY DIFFERENTIATED	I	II	<50%	neg	neg	neg	IA	1	LOW	3	LOW	YES
30	1711/17	70	61-70	PARITY	POSTMENOPAUSAL	PMB	C	1435/17	ATYPICAL ENDOMETRIAL HYPERPLASIA	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	<50%	neg	NIL	NIL	IA	2	LOW	4	LOW	YES
31	1735/17	75	71-80	PARITY	POSTMENOPAUSAL	PMB	P	1375/17	ENDOMETRIOID ADENOCARCINOMA WITH MUCINOUS DIFFERENTIATION-I	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	+	+	neg	IIIC	3	LOW	3	LOW	NA
32	SP9/17	70	61-70	PARITY	POSTMENOPAUSAL	PMB	C	1363/17	CLEAR CELL CARCINOMA OF EM	CLEAR CELL CARCINOMA OF ENDOMETRIUM	II		>50%	neg	neg	neg	IIIB	0	LOW	4	LOW	YES
33	1946/17	61	61-70	PARITY	POSTMENOPAUSAL	PMB	P	1529/17	ENDOMETRIOID ADENOCARCINOMA-I	ENDOMETRIOID ADENOCARCINOMA-VILLOGLANDULAR	I	I	>50%	neg	neg	neg	IB	1	LOW	7	LOW	YES
34	2185/17	60	51-60	NP	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	II	III	<50%	neg	NIL	NIL	IA	2	LOW	4	LOW	YES
35	2473/17	72	71-80	PARITY	POSTMENOPAUSAL	PMB	P	2246/17	ENDOMETRIOID ADENOCARCINOMA-II	ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	2	LOW	8	LOW	YES
36	2493/17	45	41-50	PARITY	PERIMENOPAUSAL	AUB	P	2454/17	POORLY DIFFERENTIATED CARCINOMA- III	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	neg	NIL	NIL	IB	3	LOW	7	LOW	NA
37	2494/17	45	41-50	PARITY	PERIMENOPAUSAL	AUB				ENDOMETRIOID ADENOCARCINOMA-WELL DIFFERENTIATED	I	I	>50%	neg	NIL	NIL	IB	1	LOW	4	LOW	YES
38	2905/17	70	61-70	NP	POSTMENOPAUSAL	PMB	C	2717/17	CLEAR CELL CARCINOMA OF EM	CLEAR CELL CARCINOMA OF ENDOMETRIUM	II		>50%	neg	neg	neg	IB	0	LOW	6	LOW	YES
39	2976/17	62	61-70	PARITY	POSTMENOPAUSAL	PMB	C	2797/17	ENDOMETRIOID ADENOCARCINOMA-III	ENDOMETRIOID ADENOCARCINOMA-POORLY DIFFERENTIATED	I	III	>50%	neg	neg	neg	II	2	LOW	7	LOW	YES
40	3031/17	60	51-60	PARITY	POSTMENOPAUSAL	PMB	C	2686/17	CLEAR CELL CARCINOMA OF EM	MALIGNANT MIXED MULLERIAN TUMOUR	II		>50%	neg	neg	neg	IB	4	LOW	8	LOW	NA
41	3329/17	64	61-70	PARITY	postmenopausal	PMB	C	2875/17	Mucinous adenocarcinoma -I	ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED WITH MUCINOUS	I	I	<50%	neg	neg	neg	IA	4	LOW	6	LOW	YES
42	3410/17	42	41-50	PARITY	PERIMENOPAUSAL	MASS ABDOMEN	P	2528/17	ENDOMETRIOID ADENOCARCINOMA -I	ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	>50%	+	neg	+	IIIA	13	mod	6	LOW	YES

43	3497/17	50	41-50	PARITY	postmenopausal	PMB				ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	>50%	neg	neg	NIL	IB	4	LOW	11	mod	NA
44	3520/17	55	51-60	PARITY	postmenopausal	PMB	P	2917/17	ENDOMETRIOID ADENOCARCINOMA -I	ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	<50%	neg	neg	neg	IA	2	LOW	6	LOW	NA
45	3666/17	48	41-50	PARITY	PERIMENOPAUSAL	AUB	P	3105/17	ADENOCARCINOMA-II	ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	>50%	PRESENT	+	neg	IIIC	4	LOW	11	mod	YES
46	176/18	68	61-70	PARITY	POSTMENOPAUSAL	PMB				MALIGNANT MIXED MULLERIAN TUMOUR	II		>50%	neg	neg	NIL	IB	1	LOW	4	LOW	NA
47	177/18	56	51-60	PARITY	POSTMENOPAUSAL	PMB	C	3719/17	ENDOMETRIOID ADENOCARCINOMA -III	ENDOMETRIOID ADENOCARCINOMA - POORLY DIFFERENTIATED	I	III	>50%	neg	neg	neg	IB	3	LOW	12	mod	YES
48	195/18	50	41-50	PARITY	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA - VILLOGLANDULAR TYPE	I	I	>50%	neg	neg	neg	IB	3	LOW	4	LOW	NA
49	371/18	48	41-50	PARITY	PERIMENOPAUSAL	AUB	P	203/18	SECRETORY PHASE WITH SECRETORY EXHAUSTION	PAPILLARY SEROUS ADENOCARCINOMA	II		<50%	neg	NIL	NIL	IA	10	mod	6	LOW	NA
50	539/18	64	61-70	PARITY	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	1	LOW	1	LOW	NA
51	1217/18	48	41-50	PARITY	PERIMENOPAUSAL	PAIN ABDOMEN				ENDOMETRIOID ADENOCARCINOMA- POORLY DIFFERENTIATED	I	III	>50%	neg	neg	neg	IB	3	LOW	8	LOW	NA
52	1283/18	57	51-60	PARITY	POSTMENOPAUSAL	PMB	C	1008/18	Endometrial adenocarcinoma-I	ENDOMETRIOID ADENOCARCINOMA - WELL DIFFERENTIATED	I	I	>50%	neg	neg	neg	IB	4	LOW	3	LOW	YES
53	1456/18	50	41-50	PARITY	POSTMENOPAUSAL	PMB				ENDOMETRIOID ADENOCARCINOMA - MODERATELY DIFFERENTIATED	I	II	>50%	neg	neg	neg	IB	2	LOW	8	LOW	NA
54	2709/18	55	51-60	PARITY	POSTMENOPAUSAL	PMB				MUCINOUS ADENOCARCINOMA	II		>50%	neg	neg	neg	IB	1	LOW	9	LOW	NA

	NON NEOPLASTIC :																	INTRALESIONAL LV COUNT				
1	2109/16	50	41-50		POSTMENOPAUSAL	UV PROLAPSE				BENIGN ENDOMTRIAL POLYP								12				
2	2112/16	50	41-50		PERIMENOPAUSAL	FIBROID UTERUS				BENIGN ENDOMTRIAL POLYP								8				
3	3407/16	40	31-40		PREMENOPAUSAL	AUB				SIMPLE HYPERPLASIA								7				
4	273/17	58	51-60		POSTMENOPAUSAL	PMB	C		COMPLEX HYPERPLASIA WITHOUT ATYPIA	BENIGN ENDOMETRIAL POLYP								5				
5	988/17	40	31-40		PREMENOPAUSAL	AUB				BENIGN ENDOMTRIAL POLYP								8				
	PREMALIGNANT:																					
1	1614/16	36	31-40		PREMENOPAUSAL	AUB				ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA								6				
2	3745/16	56	51-60		POSTMENOPAUSAL	PMB				ATYPICAL ENDOMETRIAL HYPERPLASIA								2				
3	2033/17	39	31-40		PREMENOPAUSAL	AUB	P	2014/17	COMPLEX HYPERPLASIA WITHOUT ATYPIA	ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA								5				