HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS

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M.D. DEGREE

In

PATHOLOGY – BRANCH III

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DECLARATION

I hereby declare that the dissertation entitled **"HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS"** was done by me in the Department of Pathology, Coimbatore Medical College from October 2012 – July 2014 under the guidance and supervision of **Prof. Dr.A. ARJUNAN , M.D.,** Department of Pathology, Coimbatore Medical College.

This dissertation is submitted to the Tamilnadu Dr.MGR Medical University, Chennai towards the partial fulfillment of the requirement for the award of M.D. Degree in Pathology.

I have not submitted this dissertation on any previous occasion to any University for the award of any degree.

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This is to certify that the dissertation entitled **"HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS"** is a record of bonafide work done by **Dr.P.Priyanka** in the Department of Pathology, Coimbatore Medical College, Coimbatore under the supervision of **Dr. C. Lalitha M.D.,** Professor and Head, Department of Pathology Coimbatore Medical College and Hospital and under the guidance of Prof. **Dr.A. Arjunan M.D.,** Department of Pathology Coimbatore Medical College and Hospital and submitted in partial fulfillment of the requirements for the award of M.D. Degree in Pathology by The Tamilnadu Dr.MGR Medical University, Chennai. This work has not been previously done for the award of a degree or diploma.

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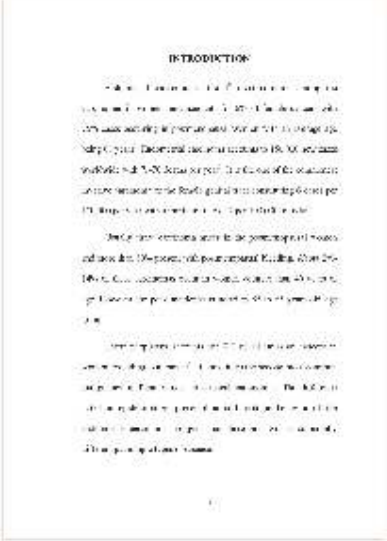

INTRODUCTION


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ABSTRACT

TITLE OF THE STUDY :

HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS

BACKGROUND:

Endometrial carcinoma is the 4th most common among the carcinomas in women, and accounts for 6% of female cancers with 75% cases occurring in postmenopausal women with the peak incidence noted in 55-65 years. Type l tumor occurs in the younger age, arise in the background of hyperplastic endometrium, are of low grade and has a favorable prognosis and show positivity for ER and PR. Whereas Type II carcinomas (serous papillary carcinomas and clear cell carcinomas) occurs in the older age, in the background of atrophic endometrium, show aggressive behaviour and has poor prognosis and are p53 positive.

However, some cases of morphologically type I endometrioid carcinomas may express p53 as that of type II carcinomas and this may have a role in the management of the patients.

OBJECTIVE:

To correlate the clinical features and histopathological features of endometrial carcinoma, to analyze the spectrum of histopathological features of endometrial carcinomas and to correlate the expression of ER, PR and p53 with the histopathological grade of endometrial carcinomas.

MATERIAL AND METHODS:

This is a cross sectional prospective study conducted during October 2012- July 2014 in the Department of Pathology, Coimbatore Medical College, Coimbatore. Thirty cases of endometrial carcinomas were examined histomorphologically and correlated immunohistochemically.

RESULTS:

Thirty cases of endometrial carcinomas were included in the study. The incidence of endometrial carcinomas in our hospital was found to be 1.73%. The expression of ER in type I carcinomas were 81.25% and in type II was 21.43%. It was found that there was a positive correlation between the expression of ER and type I tumor. The expression of PR in type I carcinomas were 75% and in type II 28.75% showed positivity. In the present study, there was a positive correlation between the expression of PR and type I tumor. The

expression of p53 in type I carcinomas were 43.75% and in type II 78.57% showed positivity. In the present study there was statistical correlation between the type II endometrial carcinomas and p53 expression.

CONCLUSION:

The immunohistochemical study of ER, PR and p53 and its significance on the prognosis are few in literature when compared to breast carcinoma. Our data will be definitely an important addition to the existing literature.

KEYWORDS:

Endometrial carcinoma, immunohistochemistry, ER, PR and p53.

INTRODUCTION

Endometrial carcinoma is the 4th most common among the carcinomas in women, and accounts for 6% of female cancers with 75% cases occurring in postmenopausal women with an average age being 61 years[1]. Endometrial carcinoma accounts to 150,000 new cases worldwide with 7,470 deaths per year[1]. It is the one of the commonest invasive carcinoma of the female genital tract constituting 6 cases per 100,000 per year with a mortality rate of 2 per 100,000 in India[1].

Usually these carcinoma arises in the postmenopausal women and more than 80% present with postmenopausal bleeding. About 2%-14% of these carcinomas occur in women younger than 40 years of age. However the peak incidence is noted in 55 to 65 years old age group.

These neoplasms accounts for 7% of all invasive cancers in women excluding skin cancer[2]. It constitutes the second most common malignancy in females next to cervical carcinomas. The difference noted in epidemiology, presentation and biologic behavior of the endometrial carcinomas suggest that there are two fundamentally different pathologic types of disease.

Endometrial carcinoma have two basic clinicopathologic forms, type I and type II.

Type I carcinomas occur in the younger age, in the background of hyperplastic endometrium. They account for 80-85% of all endometrial carcinomas and are generally low grade. They result from unopposed estrogenic stimulation and prognosis is generally good with a five year survival of 80%.

Type II carcinomas are high grade neoplasms which occur in the older age in the background of atrophic endometrium and are not related to sustained estrogen stimulation. They account for 15%-20% of all endometrial carcinomas and occurs in postmenopausal women. They are high grade tumours frequently with deeper myometrial invasion and increased lymphatic spread.

Endometrioid carcinoma like any other adenocarcinoma expresses pancytokeratins and glycoprotein associated markers CA125[4], Ber-EP4[5,6], B72.3[7]. Nearly all endometrioid carcinomas are CK 7 positive and CK20 negative[6,7]. Unlike other adenocarcinomas, endometrioid adenocarcinoma expresses vimentin. Endometrioid adenocarcinoma showing mucinous differentiation expresses CEA and COX2[6,7].

Type I carcinomas show expression of ER, PR, Bcl2, Beta catenin and PTEN whereas, type II carcinomas (uterine papillary serous, clear

cell carcinomas) show immunopositivity for p53, p16 and Ki67 and usually do not express ER and PR.

In Type l carcinomas, ER and PR will be positive and the treatment consisting of hysterectomy along with hormonal therapy will be sufficient, whereas Type II carcinomas (since the tumor is aggressive) are usually p53 positive and are aggressive and hence these patients along with hysterectomy, needs chemotherapy and radiotherapy and further follow up.

However some cases of morphologically type I endometrioid carcinomas may express p53 as that of type II carcinomas and this may have a role in the management of the patients.

In our study, the histomorphology of endometrial carcinomas are correlated with immunohistochemistry using the panel of markers constituting ER, PR and p53.

Aim and Objectives

AIM OF THE STUDY

The aim of this study is to study the spectrum of histomorphology of endometrial carcinomas with special reference to immunohistochemical findings including ER, PR and p53

OBJECTIVES

1. To correlate the clinical features and histopathological features of endometrial carcinoma.
2. To analyze the spectrum of histopathological features of endometrial carcinomas.
3. To correlate the expression of ER, PR and p53 with the histopathological types of endometrial carcinomas.

Review of Literature

REVIEW OF LITERATURE

Primary endometrial carcinomas constitute a range of morphologies including carcinomas closely resembling endometrial epithelium (endometrioid) , clear cell carcinomas, uterine papillary serous carcinomas, and carcinomas sharing one or more of these features, undifferentiated carcinomas and tumours with mixed epithelial - mesenchymal differentiation.

Anatomy of uterus

The uterine cavity is a hollow, pear shaped organ weighing 40-80 grams and measuring approximately 8X5X4 cms[8].

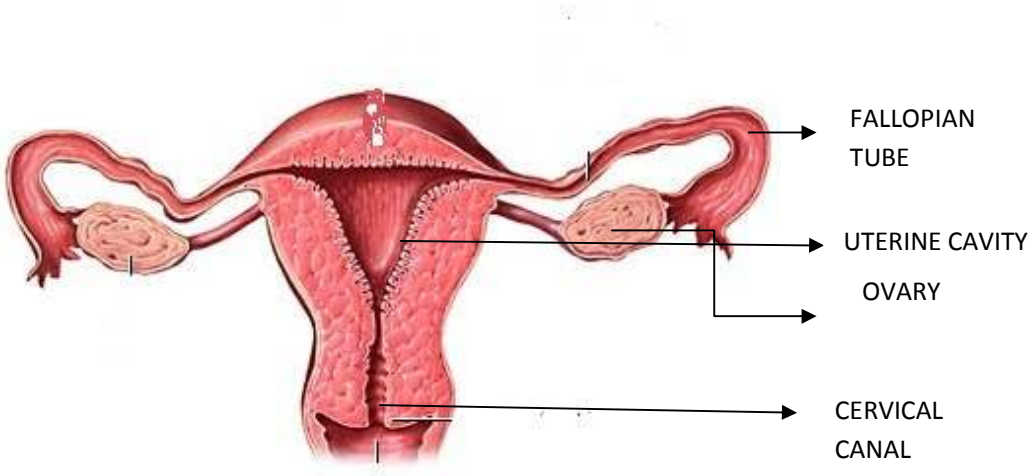


Figure.1: Anatomy of the uterus

The uterine cavity is lined by endometrial mucosa constituting the endometrium which is highly specialized active layer responding to cyclic ovarian hormones and is essential for menstrual and reproductive function.

The middle layer is the thick muscular layer, the myometrium which is formed primarily of smooth muscle cells and the serosal covering, enveloping the uterus[9].

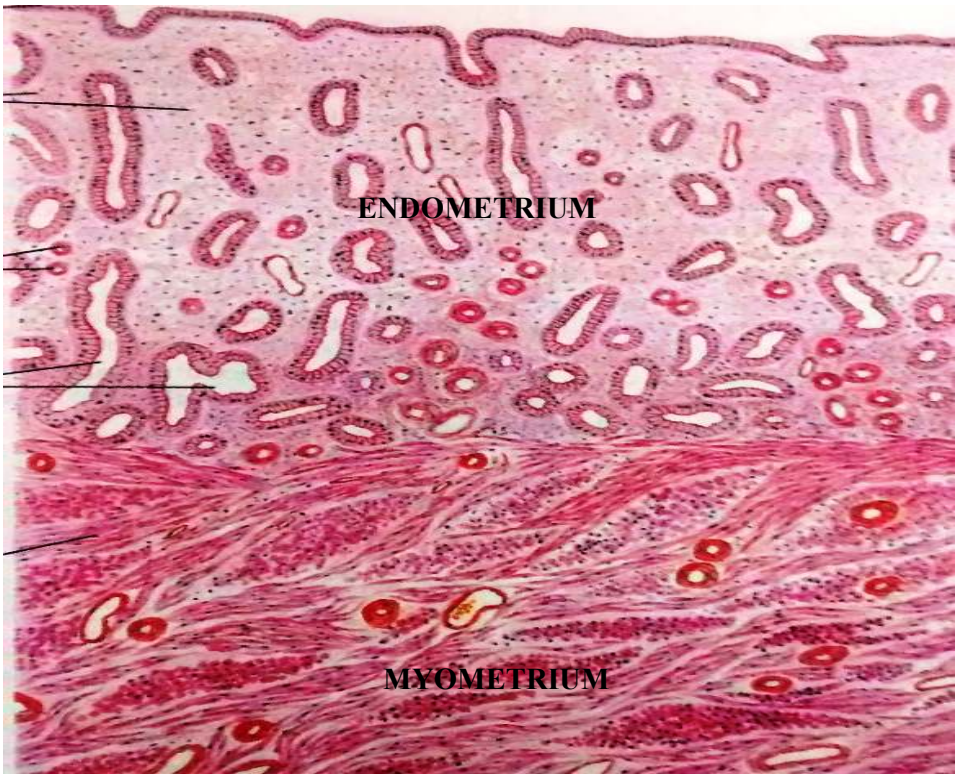


Figure 2 : Histology of uterus

Embryology of female genital tract:

The development of the uterus is complex. Approximately until the 8th week of the gestation, the primordial ie the mesonephric ducts and paramesonephric ducts exist simultaneously. The differentiation of the sex involves multiple steps in which hormonal signals, growth factors and specific genetic influences are required.

In the females, absence of Y chromosome and lack of testosterone exposure causes the fusion and canalization of the paramesonephric ducts in the midline and forms the female pelvic organs[10].

UTERINE CYCLE[11]

The uterine corpus is divided into the uterine cavity and the cervix. The uterus consists of an inner endometrial layer, outer muscular myometrium and a serosal covering. The lining of the epithelium is simple columnar forming glands, separated by stromal cells.

The endometrium is formed of two layers, the stratum functionalis and stratum basalis. The stratum functionalis is further divided into superficial stratum compactum and the deep stratum spongiosum. The stratum spongiosum has maximal secretory activity and unresponsive stroma while the stratum compactum responds remarkably to hormonal

stimulation with a prominent predecidual reaction and numerous granulocytes with less secretory activity. The basalis consists of tubular glands and compact stroma with no secretory or mitotic activity in these glands.

The junction between the endometrium and the endocervical epithelium consists of the isthmic endometrium. The glands in the isthmic endometrium are typically flattened and slit like, lined by an epithelium containing a mixture of columnar cells and ciliated cells with more fibrous stroma.

THE MENSTRUAL CYCLE[11]

The bleeding from the secretory endometrium is associated with ovulatory cycle, which, does not exceed a length of 5 days is defined as normal menstrual cycle[12].

The menstrual cycle has two main phases, the proliferative phase and the secretory phase.

The normal proliferative phase[13]

This phase lasts two weeks under physiological conditions, fluctuating between ten and twenty days. In the early phase the endometrium is thin with sparse non-budding, non branching glands and a loose stroma of spindle cells. At about 8-10 days, an increase in endometrial thickness as a result of stromal edema which peaks at day ten, is noted.

In the preovulatory period as the estrogen level decreases, the stromal edema comes down and is followed by the continuous growth of the glands which is seen to be lined by tall columnar cells with basophilic cytoplasm. The nuclei becomes pseudostratified and ovoid with coarse chromatin. The endometrial stroma is densely cellular with small and oval cells, with small dark staining nuclei and indistinct cytoplasm. Mitosis is frequent.

In the late proliferative phase the glands will have increased tortuosity and variability, with less mitotic activity. Subnuclear vacuoles and stromal edema starts to appear.

The secretory phase[14,15].

Around the 14th day of the cycle, ovulation occurs. In the first and second day of post ovulatory day, the endometrial glands becomes larger, less basophilic because of the interruption of the pseudostratified epithelium by vacuoles.

Early secretory phase:

This phase which lasts from day fifteen to nineteen is heralded by the appearance of the subnuclear vacuoles. The basal vacuoles will push the nuclei to the middle of the cell creating a piano key like appearance. At seventeenth day, there are uniform subnuclear vacuoles. The vacuoles move toward the lumen on eighteenth day and on the nineteenth day, the nuclei migrates to the base again. No mitotic activity is seen.

Mid secretory phase:

This phase lasts from day nineteen to day twenty five. There is secretory exhaustion seen in this phase. At day twenty, there is a peak in the intraluminal secretions. On day twenty one, there is increased stromal edema with prominent spiral arterioles. Stromal edema is at its peak on

day twenty two. By day twenty three, the edema decreases and the stromal predecidualisation commences.

On day twenty four, the predecidua extends to bridge the vascular elements.

Late secretory phase:

This phase is from day twenty six to twenty eight and shows extension of the predecidual change from the surface lining downward deep into the stratum compactum. On day twenty seven, numerous granulated lymphocytes appear. In the central spongy part of the endometrium the glands have a characteristic sawtooth appearance.

Menstrual phase[16]

If pregnancy has not occurred the late secretory phase leads to menstrual phase, starting fourteen days after ovulation. Histologically there will be crumbling of the stroma and glandular collapse and hemorrhage in the superficial stroma.

The stromal cells form tightly clustered ball and separate from the glands , which will have an unusually deep blue colour and overlying epithelial cells appear degenerative

POSTMENOPAUSAL ENDOMETRIUM[12]

After the ovary stops producing estrogen and progesterone the endometrium is no longer stimulated and hence undergoes atrophy. The postmenopausal endometrium is usually thin and inactive though there may be changes in the thickness.

The glands become small and scant and are lined by cuboidal or flattened cells and often are unevenly distributed throughout the tissue. The stroma becomes fibrous and the cells of the stroma lose their cytoplasm and appear acellular.

Another pattern of post menopausal endometrium is the cystic atrophy which consists of cystically dilated glands which are lined by flattened epithelium and the lumen contains partly non-specific secretions and partly transudate.

DISORDERED PROLIFERATIVE ENDOMETRIUM[12,15,17,18]:

Prolonged proliferation of endometrium due to anovulation gives rise to disordered proliferative endometrium. It is an intermediate between normal proliferative and benign hyperplastic endometrium. The patient usually presents with irregular uterine bleeding.

It is characterized by cystically dilated endometrial glands which are distributed irregularly with patchy stromal breakdown, resulting from focal thrombosis. Tubal metaplasia of endometrial glands is also common.

ENDOMETRIAL EPITHELIAL METAPLASIA[12,15]:

The change in cellular differentiation of one type of epithelium into another type of epithelium which is not present in the normal endometrium is defined a endometrial metaplasia. Some of the most common forms are squamous, mucinous or ciliated.

Squamous metaplasia

This occurs in benign reactive process and carcinoma. Few causes associated with benign changes are chronic endometritis, intrauterine device and trauma.

Two types of squamous metaplasia are seen.

A) Typical squamous metaplasia

B) Morular metaplasia.

Typical squamous metaplasia:

This occurs in scattered areas. The term icthyosis uterus is described as when whole of the endometrium is extensively replaced by squamous epithelium. It is associated with cervical obstruction and chronic inflammation.

Morular metaplasia:

Morular metaplasia is seen as cohesive small, round, granuloma like aggregates of squamous cells located in-between the glands. These morules may enlarge to form sheets with radially arranged glands around the periphery.

At times the morular metaplasia is seen associated with some degree of glandular crowding wherein endometrial intraepithelial neoplasia and nearby adenocarcinoma has to be ruled out.

Mucinous metaplasia:

Mucinous metaplasia is characterised by glands of the endometrium being lined by cuboidal or columnar epithelium with prominent intracytoplasmic mucin.

There are three types of mucinous metaplasia:

i. **Type A** – The glands in this type are lined by endocervical like cuboidal epithelium usually presenting in perimenopausal women.

ii. **Type B** – This type is characterized by architectural complexity and pseudopapillary pattern.

iii. **Type C** – In this type the glands of the mucinous epithelium are arranged in cribriform pattern or are seen to exhibit microglandular or villoglandular pattern. This is associated with significant risk of adenocarcinomas.

Ciliated or tubal metaplasia:

This type of epithelium is characterized by columnar epithelium which is lined by cilia with clear round cells seen in-between the cells and are normally found in proliferative phase.

Clear cell metaplasia:

In this type, the epithelial cells have abundant clear cytoplasm which is easily confused with clear cell carcinoma.

Features favoring clear cell metaplasia are:

a) The glands of the endometrium should have normal architecture and distribution.
b) Bland nuclear features.
c) Metaplasia in focal areas.
d) Grossly there should not be any visible tumor.
e) There should not be stromal invasion.
f) There should be strong positivity for Estrogen receptor.

Hobnail metaplasia:

This rare type is characterized by cells with rounded nuclear protrusion beyond the cytoplasmic borders. It is often associated with Arias stella reaction and is caused by degenerative changes associated with necrosis and exfoliative artifact.

Eosinophilic metaplasia:

In this type, the glands are lined by cells which have granular eosinophilic cytoplasm because of the presence of increased mitochondria.

Other non epithelial metaplasia

Some endometrial mesenchymal metaplasia includes cartilaginous and osseous metaplasia, smooth muscle metaplasia, glial metaplasia and extramedullary hematopoiesis.

ENDOMETRIAL POLYPS:

Endometrial polyps are defined as polypoidal structure with benign glands and stroma. It can be sessile or pedunculated. The polyps in the endometrium are one among the frequent causes of abnormal uterine bleeding and are commonly found in patients in women of the reproductive age group, postmenopausal women and in patients with hormonal replacement therapy and tamoxifen therapy.

Microscopically, there are abnormally dilated glands lined either by atrophic epithelium, or by poorly developed secretory epithelium or proliferative epithelium in a fibrous stroma. The stroma characteristically contains thick walled blood vessels and sometimes the ectatic vessels. The polyp are divided into

a) Hyperplastic polyp.
b) Atrophic polyp.
c) Functional polyp.

ENDOMETRIAL HYPERPLASIA

DEFINITION[19]

Endometrial hyperplasia is defined as a proliferating endometrium with glandular architectural abnormalities resulting in either cystically dilated glands (simple hyperplasia) or crowded glands (complex hyperplasia).

Endometrial hyperplasia occurs as a consequence of

a) High levels of estrogen for a long period.
b) Repeated anovulatory cycles.
c) Ovarian neoplasms secreting estrogen.
d) Increased levels of estrogen due to peripheral conversion of androgen.

The hyperplastic endometrium is white to tan tissue that may be seen as diffuse thickening or polyp like lesion.

Various classifications of endometrial hyperplasia:

Tavassoli and Krauss (1978)[20] classified endometrial hyperplasia as

a) Cystic hyperplasia,
b) Adenomatous hyperplasia,
c) Atypical hyperplasia.

Ronnett B.M and Robert J.Kurman (2004)[19] classified endometrial hyperplasia as

1. Hyperplasia without cytologic atypia (non atypical hyperplasia)

    a) Simple,

    b) Complex.

2. Hyperplasia with cytologic atypia (atypical hyperplasia)

    a) Simple,

    b) Complex.

According to **WHO classification**[17]

1. Hyperplasia without atypia

    a) Simple hyperplasia without atypia

    b) Complex hyperplasia without atypia

2. Atypical hyperplasia

    a) Simple atypical hyperplasia

    b) Complex atypical hyperplasia

HYPERPLASIA[14,17,18,19]

Simple hyperplasia without atypia:

This is characterized by mild increase in gland to stromal ratio. The glands are round and tubular, exhibiting marked variation in size and shape. The cells in the glands are pseudostratified. It has oval nuclei with dispersed chromatin and inconspicuous nucleoli. The stroma is cellular as in proliferative phase. Mitotic figures and apoptotic bodies are noted. There is 1% chances of these lesions progressing to adenocarcinoma.

Complex hyperplasia without atypia:

In this type the glands show over crowding and budding. The polarity and the pseudostratification of the cells are maintained. Mitotic activity is <5mitosis per 10 high power field. Apoptotic bodies may be frequently encountered. Approximately 3% of these lesions progresses to adenocarcinoma.

Atypical hyperplasia:

In atypical hyperplasia, the cells appear paler and are characterized, cytologically, by the presence of stratification of cells with round vesicular nuclei and slightly prominent nucleoli.

Simple hyperplasia with atypia:

It has similar architectural features as that of simple hyperplasia in addition they show stratification of cells with round vesicular nuclei and slightly prominent nucleoli. Approximately 8% of these lesions progresses to carcinoma.

Complex hyperplasia with atypia:

This type is similar to that of complex hyperplasia, in addition they show stratification of cells with round vesicular nuclei and slightly prominent nucleoli. There are about 25% chances for these lesions turning into carcinoma.

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA[12,15,17]

Endometrial intraepithelial neoplasia is described as monoclonal proliferation of endometrial glands which are altered cytologically and architecturally. The rate of transformation into type I endometrioid adenocarcinoma is 26-37% and intraepithelial carcinoma in type II carcinomas arise instantly without preceding hyperplasia or atypia as in type I carcinomas.

The features of EIN include:

a) The crowded glands are lined by columnar epithelial cells with rounded non-stratified nuclei or elongated pseudostratified nuclei with clumped smudged chromatin and prominent nucleoli.

b) Absence of stromal invasion.

c) The size of the intraepithelial lesion should be greater than 1mm.

ENDOMETRIAL ADENOCARCINOMA[12,15,17,21]

Endometrial adenocarcinomas usually arise in postmenopausal women and account for 80% of the postmenopausal bleeding. Carcinomas of the endometrium are broadly classified into following two types:

Estrogen dependent type I tumors and non estrogen dependent type II tumours.

Type I tumors are usually seen in premenopausal and perimenopausal women in patients with hyperplastic endometrium, and usually does not invade the myometrium at earlier stages.

Most of them are well to moderately differentiated and rarely presents with distant metastasis and hence usually have a better prognosis.

Whereas type II tumours are usually seen to occur in females little older than type I. Type II tumours, are usually of higher grade and presents with distant metastasis and are associated with poor prognosis.

RISK FACTORS FOR DEVELOPING ENDOMETRIAL CARCINOMA:

1. Estrogen
2. Tamoxifen therapy
3. Polycystic ovary syndrome
4. Obesity
5. Reproductive factors

Estrogen:

Both the exogenous and endogenous estrogen play a significant role in tumors genesis. The patients who are at risk of developing carcinoma from exogenous exposure to estrogen are:

a) Women taking oral contraceptive pills sequentially,

b) Postmenopausal women who are receiving estrogen replacement therapy,

c) Women with ovarian dysgenesis who had received estrogen therapy during puberty.

The patients on endogenous estrogen are:

a) Patients with granulosa cell tumour of the ovary or theca cell tumour of the ovary.,

b) Women with anovulatory cycles.,

c) Postmenopausal women who were obese.,

d) Women suffering from liver disease[22].

Tamoxifen:

Tamoxifen is used in the treatment of breast cancer has been associated with two to three times increase risk of endometrial carcinoma[24].

Obesity:

Obesity is one among the significant risk factor in endometrial cancer[25]. Body mass index of ~ 30kg/m^2 or higher has elevated risk of endometrial carcinoma.

Polycystic ovarian syndrome:

Also known as ovarian hyperandrogenism is generally associated with chronic anovulation and progesterone deficit.The risk of endometrial cancer in these patients is about 5%[26].

Reproductive and other factors:

Early menarche and late menopause exposes the individual to increased risk of carcinoma due to increase in duration of exposure to estrogen. Nulliparity and infertility are associated with anovulation and progesterone insufficiency.

Granulosa cell tumour, thecoma, polycystic ovary disease and hyperthecosis are associated with prolonged exposure of estrogen.

WHO HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE UTERINE CORPUS[27]

I. Epithelial carcinoma

i. Endometrioid adenocarcinoma

ii. Variant with squamous differentiation

iii. Villoglandular variant

iv. Secretory variant

v. Ciliated cell variant

vi. Mucinous adenocarcinoma

vii. Serous adenocarcinoma

viii. Clear cell adenocarcinoma

ix. Mixed cell adenocarcinoma

x. Squamous cell carcinoma

xi. Transitional cell carcinoma

xii. Small cell carcinoma

xiii. Undifferentiated carcinoma

xiv. Others.

ENDOMETRIOID ADENOCARCINOMA[19]:

GROSS FEATURES:

Grossly the size of the uterus may be normal , small atrophic or slightly enlarged. The cut surface may show diffuse thickening of the endometrium or it can also present as single mass or two – three separate masses. Usually the tumour has raised rough shaggy surface with ulceration, occupying atleast half of the surface area of the endometrium. The myometrial invasion may or may not be present depending upon the stage of the tumour.

MICROSCOPY:

The cellular features generally resembles proliferative endometrium with a complicated architecture including solid growth, villoglandular pattern, cribriform like growth or maze like interconnected lumen. The individual epithelial cells are large, with nuclear stratification, coarse clumped chromatin and prominent nucleoli. Tumours may be seen associated with focal differentiation to squamous, mucinous or tubal epithelium.

The endometrial adenocarcinoma usually spread centrifugally into the stroma. A diagnosis of myoinvasion is made when the malignant glands have transgressed the endo-myometrial junction into the underlying muscular uterine wall.

International Federation of Gynaecology and Obstetrics (FIGO) grading recommended by WHO:

ARCHITECTURAL GRADING:

Grade 1 – 5% or less of non squamous solid growth .

Grade 2 – 6-50% of non squamous solid growth.

Grade 3 – 50% or more of non squamous growth.

CYTOLOGICAL GRADING[19]

Grade 1 – oval nuclei ,with mild enlargement and evenly dispersed chromatin.

Grade 2 – intermediate between grade 1 and grade 3.

Grade 3 – markedly enlarged pleomorphic nuclei with irregular coarse chromatin and prominent eosinophilic nucleoli.

To note: Cytological features are used in formulating the final grade.

a) Tumours with low architectural grade but having higher cytological grade should be regarded as high grade tumour.
b) Nuclear grade takes primacy over the architecture in serous adenocarcinomas and clear cell adenocarcinomas.

Low grade carcinoma[19]:

Tumours in this grade consists of <5% of solid growth pattern characterized by irregular and larger malignant glands lined by columnar cells. There are many variants in this category which includes secretory variant, villoglandular variant, endometrioid adenocarcinoma with squamous, mucinous or tubal differentiation.

Intermediate grade carcinoma:

In this grade tumour constitutes 6-50% of solid growth pattern characterized cytologically by high degree of nuclear pleomorphism,(ie)three to four times the variation in nuclear size and more coarse clumped chromatin.

High grade carcinoma[19]:

This grade of tumour consists of solid growth exceeding 50%.These tumours include high grade type I endometrioid carcinomas,

serous carcinomas and clear cell carcinoma (type II), neuroendocrine carcinomas and undifferentiated carcinomas.

VARIANTS OF ENDOMETRIAL CARCINOMA[19]

Endometrial carcinoma with squamous differentiation[21]:

Numerous morphologic forms of endometrial adenocarcinoma have been described. Some, such as adenoacanthoma, adenosquamous carcinoma, secretory carcinoma, and ciliated carcinoma, are thought to represent variants of ordinary type I ('endometrioid') adenocarcinoma. Others, notably papillary serous carcinoma, clear cell carcinoma, and mucinous adenocarcinoma, are usually without squamous component regarded as being high grade type II , although a tumour can have mixed types.

Adenoacanthoma is the term traditionally given to the well-differentiated endometrioid adenocarcinoma containing similarly well-differentiated (benign-appearing) squamous elements derived from metaplasia of the tumor glands .

Adenosquamous (mixed) carcinoma refers to the endometrioid carcinoma containing malignant appearing squamous elements.Patients with adenosquamous carcinoma are said to have a worse prognosis than

those with adenocarcinoma or adenoacanthoma. However, several studies have shown that, stage by stage and grade by grade, there are no prognostic differences between pure adenocarcinoma, adenoacanthoma, and adenosquamous carcinoma.

In other words, once an endometrial adenocarcinoma is clinically staged and microscopically graded into well-differentiated, intermediate, and poorly differentiated categories, the presence and appearance of a focal squamous component would seem immaterial.

Morphologic studies have suggested – and immunocytochemical studies have supported – the notion that adenoacanthoma and adenosquamous carcinoma represent a spectrum of squamous metaplasia in a single tumor type rather than two independent entities.

Endometrial adenocarcinoma - villoglandular variant:

This variant is similar to villoglandular adenocarcinoma arising from the endocervix and is characterized by slender long delicate papillae lined by well differentiated tumour cells and this pattern can be seen in typical endometrial type (type I) or may be entirely papillary[29] and should

not be confused with type II serous papillary carcinoma. Cytologically they resemble grade I carcinoma.

Endometrial adenocarcinoma with ciliary cell differentiation[28,30]:

Ciliated cells are usually uncommon but can be encountered. A minimum of 75% of the cells should be ciliated to consider it as ciliated cell adenocarcinoma. They usually have a good prognosis.

Endometrial carcinoma with secretory differentiation:

This variant resembles glands of early or mid secretory endomerium[28].The changes in this variant are subnuclear and ssupranuclear vacuolation. It is associated with good prognosis.

MUCINOUS ADENOCARCINOMA:

Mucinous adenocarcinoma is a tumor subtype characterized by abundant mucin secretion. It is distinguished from mucinous metaplasia by virtue of its architectural and cytologic atypia. It should be noted that scattered foci of mucin positivity are often found in ordinary endometrial adenocarcinoma. The distinction between endometrial mucinous adenocarcinoma and primary endocervical adenocarcinoma cannot be made on the basis of morphologic or histochemical features.

Immunohistochemically, most uterine mucinous adenocarcinomas are reactive for CK7 but not for CK20 or CDX2.

Grossly it resembles endometrioid adenocarcinoma with secreted tenacious mucous. In microscopy the cells are tall with basal nuclei and prominent intracytoplasmic mucin which involves atleast half of the cells[35].

Periodic acid Schiff, alcian blue and mucicarmine are all useful stains to identify mucin.

SEROUS ENDOMETRIAL INTRAEPITHELIAL CARCINOMA:

The precursor of serous adenocarcinoma of endometrium is endometrial intraepithelial carcinoma[36,37]. It occurs in postmenopausal age group in a background of atrophic endometrium. The atrophic endometrium shows abrupt transition where highly pleomorphic cells with severe nuclear atypia and high mitotic activity without stromal invasion replacing the endometrial surface glands. The cells express strong p53 immunoreactivity and loss of ER and PR[37].

SEROUS ADENOCARCINOMA (Type II) :

This is an aggressive form of endometrial carcinoma constituting 1-10% of all endometrial cancers. It occurs in older age group ie 4-10

years older than women with endometrioid carcinoma (type I). These patients have history of having been received estrogen therapy and also lack hyperplasia or previous or concurrent endometrial intraepithelial neoplasia[38] of endometrioid type I cancer. 90% of the patients are parous, 10% are obese or have diabetes[39]. Grossly they appear as bulky necrotic masses[37].

On microscopy the tumour cells are arranged in branching papillae exhibiting nuclear stratification forming tufts which detaches freely. The papillae are often irregular and are lined by polygonal cells with large pleomorphic, hyperchromatic nuclei containing macronucleoli. These tumours show an increase in mitosis when compared to type I endometrial cancers.

In about one third of the cases psamomma bodies are seen[40]. The tumour invades the myometrium commonly with granulation tissue type of response at the invasion site.

In 80-90% of the serous carcinomas p53 mutation is encountered. Immunohistochemistry shows diffuse and intense nuclear staining involving almost all tumours cells[41,37]. ER and PR are absent or only weakly expressed in most tumors[42].

CLEAR CELL ADENOCARCINOMA[28]:

This tumour comprises of about 1-6% of all endometrial endocarcinoma and is a prototype of type II endometrial carcinoma. The mean age is 65-69 years. It is less associated with obesity, diabetes and hormone replacement therapy. There are various patterns that include papillary, tubulocystic and solid. Among the various patterns, the papillary pattern is common.

On microscopy the tumour cells arranged in small rounded papillae with hyalinised fibrovascular cores. The papillae and tubules are lined by hobnail cells with the nucleus, bulging into the lumen with prominent clear cytoplasm, because of the presence of glycogen or may display oxyphilic cytoplasm.

A frequent and characterisctic of this tumour is intracytoplasmic hyaline bodies. The lumen of the tubules and cysts may contain mucin. The tumour cells will have pleomorphic nuclei with prominent nucleoli and frequent mitotic figures.

Immunohistochemically, unlike the type I tumors they are negative for ER and PR and unlike type II tumors , they are p53 negative.

MIXED ADENOCARCINOMA[41]:

This adenocarcinoma consists of mixture of type I endometrioid adenocarcinoma or their variants and type II carcinoma. The minor component should constitute 10% of the neoplasm. The prognosis of the tumor depends on the quantity of the most aggressive component.

MALIGNANT MESODERMAL (MULLERIAN) MIXED TUMOUR(CARCINOSARCOMA):

These tumours constitute less than 5% of endometrial carcinoma. Factors which are associated with this type of tumour are body weight, exogenous estrogen, nulliparity, tamoxifen therapy and pelvic irradiation.

Grossly the tumour presents as polypoidal, necrotic, fleshy and hemorrhagic mass occupying the uterine cavity with extensive involvement of the myometrium.

On microscopy the tumour is composed of dual population of cells.The epithelial component can be endometrioid, squamous, mucinous, clear cell and undifferentiated. The mesenchymal component can be homologous such as fibrosarcoma, stromal sarcoma and leiomyosarcoma. The tumor has the worst prognosis.

UNDIFFERENTIATED CARCINOMA:

Undifferentiated carcinoma are those that lack any evidence of differentiation after extensive sampling. It constitutes less than 2% of endometrial tumours[35]. On microscopy the cells are pleomorphic with prominent nuclear atypia. The prognosis is poor. Few other types of endometrial carcinomas are transitional cell carcinoma, squamous cell carcinoma and small cell carcinoma.

METASTATIC CARCINOMA

Metastatic carcinoma of endometrium is to be suspected if one or more of the following features are present.

1. A tumour with an unusual macroscopic and histological pattern for primary.
2. Diffuse displacement of the endometrial stroma by the tumor cells.
3. Lack of premalignant changes in endometrial glands.

Most common tumors which metastasizes are breast carcinoma, stomach carcinoma followed by melanoma, lung, colon, pancreas and kidney[19].

STAGING OF ENDOMETRIAL CARCINOMA-

INTERNATIONAL FEDERATION OF GYNAECOLOGISTS AND OBSTETRICIANS[15]

Stage 1 - Tumour that is confined to uterus

1a: The tumour which does not invade the myometrium or invades less than half of the myometrium.

1b : The tumour which invades half and more than half of the myometrial wall.

Stage II - The tumour invading the stroma of the cervix but not extending beyond the uterus.

Stage III – Tumour extending outside the uterus

IIIa – Tumour involving the serosa and / or adnexa .

IIIb – Directly extending or metastasizing to the vagina and Parametrium.

IIIc1 – Positive Pelvic lymph node metastasis.

IIIc2 – Positive para aortic lymph nodes with or without positive pelvic lymph nodes.

Stage IV

IVa – Tumour invading into the mucosa of the bladder and or mucosa of the bowel.

IVb – Metastasis to distant sites including intraabdominal metastases and or inguinal lymph nodes..

MYOMETRIAL INVASION:

Myometrial invasion is in the form of jagged, irregular branching glands surrounded by granulation tissue.

VASCULAR AND LYMPHATIC INVASION:

Vascular invasion appears to be an independent prognostic factor. Its presence even in the early stage well differentiated endometrioid carcinoma (type I) appears to be associated with greater- risk of recurrence and poor prognosis[9].

Following are the pitfalls in identifying vascular / lymphatic invasion:

a) The presence of contaminants / floaters in vascular spaces.
b) The intraoperative use of uterine manipulator in cases of laparoscopically obtained hysterectomy leading to pseudovascular invasion.
c) The vascular / lymphatic invasion by histiocyte like cells.

Cervical involvement:

Tumours with extension into the cervical epithelium are considered as stage I with good prognosis and if there is invasion of the cervical stroma the prognosis is poor and is considered as stage II[43].

Peritoneal washing cytology in endometrial carcinoma:

Peritoneal washings are collected in saline at the time of surgery and processed immediately to avoid artefacts and degeneration of the cells. Positive peritoneal washings for endometrioid type (type I) of endometrial carcinoma constitutes single tumor cells and three dimensional clusters of tumor cells. Individual cells have enlarged nuclei, coarse chromatin and prominent nucleoli with scant to moderate amount of cytoplasm.

Yanoh et al found that endometrial carcinoma and positive peritoneal cytology exhibiting high cellularity, scalloped edges of cell clusters and isolated cells were associated with the presence of intra abdominal macroscopic metastatic lesion.

Papillary serous carcinomas and clear cell carcinomas (type II) are among the aggressive tumors and are characterized cytologically by marked nuclear pleomorphism, prominent nucleoli and abnormal mitoses.

It has been reported that upto 4.1% of cases with positive peritoneal cytology recurred[44].

PROGNOSTIC FACTORS:

a) The stage of the disease,
b) The histological architecture,
c) The cytological grade,
d) The invasion of the myometrium,
e) The involvement of the cervix,
f) The involvement of the adnexa,
g) The lymphovascular involvement,
h) The positive peritoneal cytology.

Other prognostic factors include DNA ploidy, diploidy being associated with higher disease free survival. Immunohistochemical staining for ER, PR, p53 and Ki67 has been suggested as important parameters in assessing the prognosis in endometrial carcinomas. Finally a number of molecular alterations have also been proposed as putative prognostic factors for endometrial carcinoma including assessment of microsatellite instability and alterations in PTEN and B- catenin.

IMMUNOHISTOCHEMISTRY

ESTROGEN AND PROGESTERONE RECEPTORS [45,46]

Estrogen receptor (ER) constitutes a group of receptors which gets activated by 17β-estradiol (estrogen). It is one among the nuclear hormone receptor. The family of ER has two groups of receptors, intracellular receptors (ER), and the estrogen G protein coupled receptor GPR30 (GPER). The main function of the ER is as a DNA binding transcriptional factor that regulates the expression of gene.

Along with additional functions which are independent of binding of the DNA[19.] Because there is alternative RNA splicing, there appears to be several nuclear isoforms of ER. At least three ER alpha and five ER beta isoforms have been identified. The ER beta isoforms receptor subtypes will transactivate transcription when there is a heterodimer along with the functional ERß1 receptor. The ERß3 receptor appears to occur at high levels in the testis. The other two ER alpha isoforms were 36 and 46kDa[47,48..]

Both these forms of ERs are expressed in various tissue types; but there appears to be some differences in their pattern of expression.In the breast cancer cells,stromal cells of the ovary,in the endometrium and in the hypothalamus ER alpha forms were found. The *ERβ* protein was seen to be expressed in the brain, heart, bone, kidney, intestinal mucosa, lungs,

endothelial cells and in the prostate[45,49] . The ERs were regarded as cytoplasmic receptors in the unliganded state, but visualization research observed a fraction of the ERs located in the nucleus[50]. Different ligands have varying affinity for the alpha and the beta isoforms of the ER.

- 17-beta-estradiol appears to bind to both the receptors,
- Estrone specifically binds to the alpha receptor,
- Estriol binds preferentially to the beta receptor,

The subtypes of selective estrogen modulators tends to bind to either the alpha or beta- subtype. Also, the combinations of different estrogen receptor might respond differently to the various ligands translating them to tissue selective agonistic and antagonistic effects. The ratio of alpha to the beta- subtype concentration appears to play certain role in some disease[51,52.]

The principle of the selective estrogen receptor modulators is based on its ability to promote the interactions of ER with various proteins like the transcriptional coactivator or co repressors. The ratio of coactivator to co repressor protein appears to be different in various tissues[53].

The result of which is, the same ligand may act as an agonist in some tissue (where there is predominance of coactivators) while antagonistic in the other tissue (where there is corepressors domination). For example, tamoxifen which is an antagonist in breast[54] and is used in treatment of breast carcinomas also acts as an ER agonist in bones preventing osteoporosis and also acts as partial agonist in the endometrium exposing to endometrial carcinomas.[55.]

The progesterone receptor (PR) also known as NR3C3 a nuclear receptor subfamily 3, group C, member 3, is an intracellular steroid receptor that preferentially binds to progesterone. There are two main forms, A and B differing in their molecular weights. PR-A and PR-B are simiilar in sequence, except that PR-A appears to lack 164 amino acids at the N-terminus, forming the shortest of the two proteins[46,56.]

Estrogen appears to be important to induce the progesterone receptors. When there is no binding hormone , the carboxyl terminal inhibits transcription process. The hormone binds and induces a structural change removing the inhibitory action.Progesterone is an important regulator of normal female reproductive function, with various tissue-specific effects[51.]

The physiological effects of progesterone appears to be dependent completely on the presence of the human progesterone receptor (hPR), which is a member of the steroid receptor.Progesterone has a numerous physiological effects amplified in the presence of estrogen. Estrogen along with the estrogen receptors causes up regulation of the expression of progesterone receptors[57,59].

The functions of progesterone through its receptors appears to be important in the reproductive system. Progesterone is known as the "hormone of pregnancy",and appears to be important in the development of the fetus[58.] Progesterone prepares the uterus for implantation by causing thickening of the vaginal epithelium and cervical mucus, making it impermeable to sperm. If there is no pregnancy, the levels of progesterone levels decrease, leading to bleeding. Normal menstrual bleeding occurs when there is withdrawal of progesterone[30]

When implantation occurs, progesterone decreases the maternal immune response allowing the pregnancy. Progesterone decreases the contractility of the uterine smooth muscle and also causes inhibition of lactation during pregnancy. The decrease in levels of progesterone after delivery is one of the triggers for milk production, and also the fall in

progesterone levels facilitates the onset of labor[45,57]. The fetus is able to metabolise placental progesterone in the production of adrenal steroids.

A selective progesterone receptor modulator (SPRM) is an agent which acts on the progesterone receptor. A characteristic feature distinguishing such substances from progesterone (full agonists) and mifepristone (full antagonists) is that these exert different action in different tissues. This mixed agonist/antagonist profile of action leads to selective stimulation or inhibition of progesterone-like action in different tissues[60] and raising the possibility of dissociation of desirable therapeutic effects from undesirable side effects in synthetic progesterone receptor drug candidates[61]

ER AND PR IN NORMAL ENDOMETRIUM [62,63,64]

In the human uterus, the concentrations of receptors for both estrogen (ER) and progesterone (PR) undergo characteristic variations throughout the menstrual cycle in response to the hormonal change.

The endometrium appears to express estrogen receptors (ER) and progesterone receptors (PR). There is difference in expression of the steroid receptors in the epithelial and the stromal cells indicating, the autocrine and paracrine regulation of cyclic functional and morphological

changes in these cells.In the normal postmenopausal endometrial tissue, there is down-regulation of ER alpha, ER beta and PR-B with higher expression of PR-A.

Steroid receptors ERalpha, ERbeta, PR-A and PR-B are expressed differently in normal and atrophic human endometrium which has been observed by Mylonas I, P. M. L. Snijder and many other groups[62,63,64]

During the menstrual cycle, there occurs a significant change in the estrogen receptor present in the glands and stroma of the endometrium basalis and functionalis and in smooth muscle cells of the myometrium. Mostly in all types of cells in the endometrium, estrogen receptor expression was found to be maximum in the late proliferative phase.

The estrogen receptor staining sharply decreases during the early secretory phase of the endometrium in stromal and smooth muscle cells, while, in glandular epithelium, estrogen receptor expression aapears to decrease gradually[63].There is increase in estrogen receptor in the predecudualising stromal cells and smooth muscle cells during the mid and late phases of secretory endometrium.

ER AND PR IN NEOPLASTIC ENDOMETRIUM

Endometrial carcinoma is one of the most common gynecologic

malignancies in industrialized and developing countries. Various prognostic factors have been extensively studied to improve the treatment and follow-up of these patients.

Prognostic significance of steroid hormone receptors has been well established in breast cancer. Several studies on breast cancer have confirmed the validity of ER/PR immunohistochemical assay and have shown its prognostic and therapeutic usefulness. Analogous Studies in endometrial carcinoma are scanty and largely limited to clinoco-pathological correlation.

Patients suffering from advanced or recurrent endometrial carcinoma and having significant concentrations of both receptors in the tumor tend to have a more indolent clinical course than patients with absent or low tumor receptors.

Patients whose lesions are progestin receptor-rich respond to regular treatment than those with receptor-poor tumors. In contrast, patients with advanced or recurrent disease after regular treatment and with low tumor estrogen and progestin receptor concentrations respond more often to combination cytotoxic chemotherapy than patients with higher tumor receptor levels.

Many studies have noted the influence of the steroid receptor content on survival. Geisinger et al. found that progestin-positive as well as quantitative level of the progestin receptor were significantly related to survival.

Creasman et al.showed that estrogen receptor-positive status, progestin receptor-positive status,and combined estrogen receptor and progestin receptor-positive status had a significantly better disease-free survival than those with negative receptor status tumors.

Myolonas I stated that the loss of receptor positivity for ER-alpha resulted in a poorer survival in endometrial cancer patients, while ER-beta did not affect survival.

IMPORTANCE OF p53

p53 is a tumour suppressor gene which is situated on the chromosome 17p13.1. It is found to be the most frequent target for genetic alteration in human tumours[65]. p53 controls the neoplastic transformation by three interlocking mechanisms:

a) Activating arrest of the temporary cell cycle
b) Inducing arrest of the permanent cell cycle.
c) Triggering the programmed cell death.

Mutation of p53 were seen in 10% of all endometrioid carcinomas, with 50% occurring in grade 3 tumour and which were not identified in grade I tumour or endometrial hyperplasia.

In serous carcinomas about 90% of cases show p53 gene mutation[53,54]. In serous carcinomas p53 mutations occurs earlier which is the reason for its aggressive course. Since p53 mutation occurs in high grade endometrioid (type I) carcinomas and also in serous papillary carcinomas (type II), p53 is considered as an indicator of aggressive tumours[55].

KRAS and PTEN mutations are very rare in serous carcinomas. Microsatellite instability is not observed in the serous type[56]. Recently PIK3A mutation has been described in 15% of serous carcinomas indicating that PIK3A/PTEN/AKT pathway may have a role in the pathogenesis of a subset of the serous tumours.

From the above discussion, it is understood that very little is known about the molecular pathogenesis of the two types of endometrial carcinomas. However from the studies so far conducted it is evident that endometrioid and serous carcinomas of the endometrium are two different entities, with distinct molecular pathways and prognosis.

The current study has been undertaken to evaluate the steroid hormone receptor status and p53 status in endometrial carcinomas using immunohistochemical method and to assess its significance in disease progression.

Materials and Methods

MATERIALS AND METHODS

STUDY PLACE:

Coimbatore Medical College and Hospital.

STUDY DESIGN:

The present cross-sectional study was a prospective study conducted in the Department of Pathology on "HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS" during the period of October 2012 to July 2014. The ethical clearance was obtained from the Ethical Committee of Coimbatore Medical College, Coimbatore.

A sample of 30 cases of endometrial carcinomas were analysed during the period of October 2012- July 2014.

INCLUSION CRITERIA:

All specimens of endometrial carcinomas were received in the Department of Pathology, Coimbatore Medical College and Hospital, Coimbatore - 18

EXCLUSION CRITERIA

1. Patients who received prior radiotherapy and chemotherapy.

2.Illfixed specimen

3.Endocervical carcinomas.

COLLECTION OF DATA:

All the hysterectomy specimens sent to the Department of Pathology were included. Thorough history of the patients were recorded on predesigned and pretested proforma (Annexure I).

METHODOLOGY AND TECHNIQUES

The specimens were received in 10% formalin. The macroscopic features are noted and the tissue will be then processed routinely , paraffin sections were cut at 4 -5 micrometers thickness and stained with Haematoxylin and Eosin and were examined by light microscopy.

They are then classified into Type l or Type ll based on their histomorphology. Then Immunohistochemistry study was done. For immunohistochemistry sections of 4 microns thickness are cut and then taken on coated slides(slides coated with gelatin chrome alum mixture) and incubated at 58 degrees overnight and these slides are used for running immunohistochemistry by a two step indirect technique.

Immunohistochemical markers:

The panel of markers used in the present study were ER,PR and p53.

PROCEDURE OF IMMUNOHISTOCHEMISTRY

METHOD : Two step indirect technique.

PRINCIPLE OF THE PROCEDURE

The antigens that are present in tissues and cells are detected by two stage process which is as follows:

The binding of the primary antibody to specific epitopes and its subsequent detection by a calorimetric reaction.

Tissue sections which were taken on coated glass slides (coated with gelatin- chrome alum mixture) are incubated overnight at 37 degrees. Antigen retrieval is done by heating the tissue sections in buffer solution in microwave. The buffer solution used are tris-EDTA and citrate buffer. In the present study ER, PR and P53 antigens were retrieved in tris EDTA which has a ph of 9.

REAGENTS USED

1. Peroxide block: 3% hydrogen peroxide in water.

2. Power block reagent: It's a protein blocking reagent containing casein and propriety additives in PBS with 15Mm sodium azide.

3. Chromogen: DAB-3,3'-diaminobenzidine.

4. Liquid DAB Substrate:Contains Tris buffer with the peroxide and stabilizers.

5. Superenhancer reagent

6. Poly-HRP Reagent

7. Counter stain with Mayer's Hematoxylin.

8. Buffer solutions:

TRIS EDTA :

Distilled water – 1000 ml

TRIS Buffer salt – 6.05 grams

Disodium EDTA – 0.744 grams

CITRATE BUFFER : (ph – 6)

Distilled water – 1000 ml

Trisodium citrate – 2.94 grams

1N Hydrochloric acid 5 ml

TRIS BUFFER :

Distilled water 1000 ml

TRIS Buffer salt – 0.605 grams

Sodium chloride – 8 grams

1 N Hydrochloric acid -3 ml

PROCEDURE

1. The sections are deparaffinised in xylene for 15 minutes in 2 changes.
2. Washed in alcohol for 5minutes in 2 changes.
3. Washed in 50% alcohol for 5 minutes
4. Washed in running tap water for 5 minutes.
5. Then rinsed in distilled water for 5 minutes.

6. Next step is the antigen retrieval which is done by placing the slides with tris EDTA buffer solution in microwave:Medium - 5 mins for three times and then in High – 5 mins for two times.

7. It is then cooled to room temperature .

8. Then rinsed in distilled water.

9. Washed in TBS buffer for 5 minutes in 2 changes.

10. Treated with Peroxide block for 10 minutes.

11. Washed in TBS buffer for 5 minutes in 2 changes.

12. Treated with power block for 10 minutes.

13. Then the power block is drained and the sections are covered with primary antibody (BIOGENEX) for 2 hours.

14. Washed in TBS buffer for 5 minutes in 2 changes.

15. Then the slides are covered with Superenhancer for 30 minutes.

16. Washed in TBS buffer for 5 minutes in 2 changes.

17. Slides are then covered with SS label(HRP Polymer reagent) for 30 minutes.

18. Washed in TBS buffer for 5 minutes in 2 changes.

19. The slides are then treated with 1ml of DAB buffer,1 drop of of peroxide block,4 drops of DAB chromogen for 5-8 minutes. The diaminobenzidine gives brown colour to the antigen antibody reaction. This is carcinogenic and hence should be used with precautionary measures including wearing of gears like apron,mask and gloves.

20. Washed in TBS for 5 minutes in 2 changes.

21. Then the slides are washed in running tap water for 5 minutes.

22. Counterstaining is done with Ehrlich's Hematoxylin for 30 seconds. Then washed in tap water for 5 minutes.

23. Sections are then air dried.

24. Slides are then mounted with DPX.

Tumour cells are scored positive if there is golden brown cytoplasmic staining in the neoplastic cells.

INTERPRETATION :

ER, PR and p53 expression will be indicated by nuclear positivity in glandular cells. The positivity of both ER and PR were scored as the sum of the percentage of stained cells and intensity of nuclear staining.

Based on the percentage of cells there are three grades

Grade 1 – 0-25% of the nuclei stained.

Grade II – 26-75% of the nuclei stained

Grade III - >76% of the nuclei stained

Based on the staining intensity

Grade I – absent or weak

Grade II – strong

Grade III - very strong.

The sum of both the parameters determine the score.

Tumours were classified into three categories depending on the

immunohistochemistry score

Category I – score of 2 indicates immunonegativity

Category II – score of 3 or 4 indicates immnunopositivity

Category III – score of 5 or 6 indicates immnunopositivity[100]

The most common distribution patterns of p53 were:

a) diffuse (>70%) of intense nuclear staining.

b) no staining or cytoplasmic staining only

c) focal weak to intense staining of scattered neoplastic cells(<30%)

d) complete absence of staining in all tumour cell nuclei

e) abrupt transition from minimal to marked staining.

STATISTICAL ANALYSIS:

The data was coded and entered into Microsoft excel spread sheet (Annexure II) and was analysed using ratios and percentage. Correlation between the histopathological results and immunohistochemistry results were calculated by using chi-square test.

Results

RESULTS AND OBSERVATION

Our present study was conducted in the Department of Pathology during the period of October 2012 – July 2014 on **"HISTOMORPHOLOGY AND ROLE OF IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMAS".** Ethical committee clearance was obtained from the Ethical Committee of Coimbatore Medical College and Hospital, Coimbatore.

A total of 30 cases of endometrial carcinomas were studied during the period.

STATISTICS

TABLE : 1

AGE WISE DISTRIBUTION OF ENDOMETRIAL CARCINOMAS IN THE PRESENT STUDY POPULATION

AGE GROUP	NUMBER OF PATIENTS	PERCENTAGE
40-49 years	08	26.66%
50-59 years	10	33.33%
60-69 years	10	33.33%
70 years and above	02	6.66%

Women in the age group in which endometrial carcinomas usually presented were those who were above 55 years. Most common age group according to the present study is 50-69 years. Mean age according to the above study was 52.7 years.

CHART : 1

AGE WISE DISTRIBUTION OF ENDOMETRIAL CARCINOMAS IN THE PRESENT STUDY POPULATION

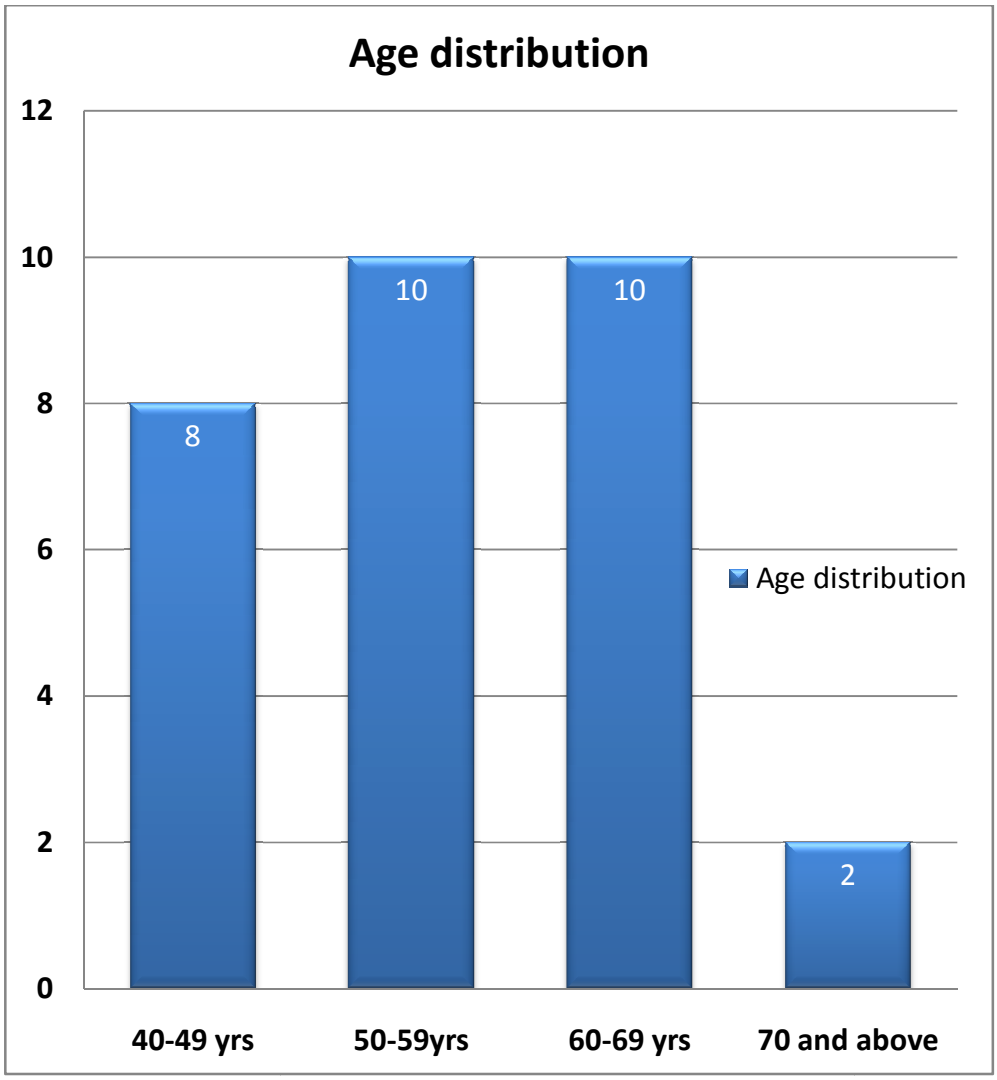


TABLE : 2

FREQUENCY OF PRESENTATION OF SYMPTOMS IN ENDOMETRIAL CARCINOMA IN THE STUDY

SYMPTOMS	NUMBER OF CASES	PERCENTAGE
Bleeding per vagina	18	60%
Abdomen pain	06	20%
Amenorrhea	04	13.33%
Others	02	6.67%

The most common presentation of endometrial carcinomas in the present study is bleeding per vagina comprising 60% followed by pain abdomen, amenorrhea, menorrhagia, mass per abdomen, difficulty in passing urine and mass per vagina.

CHART : 2

FREQUENCY OF PRESENTATION OF SYMPTOMS IN ENDOMETRIAL CARCINOMA IN THE STUDY

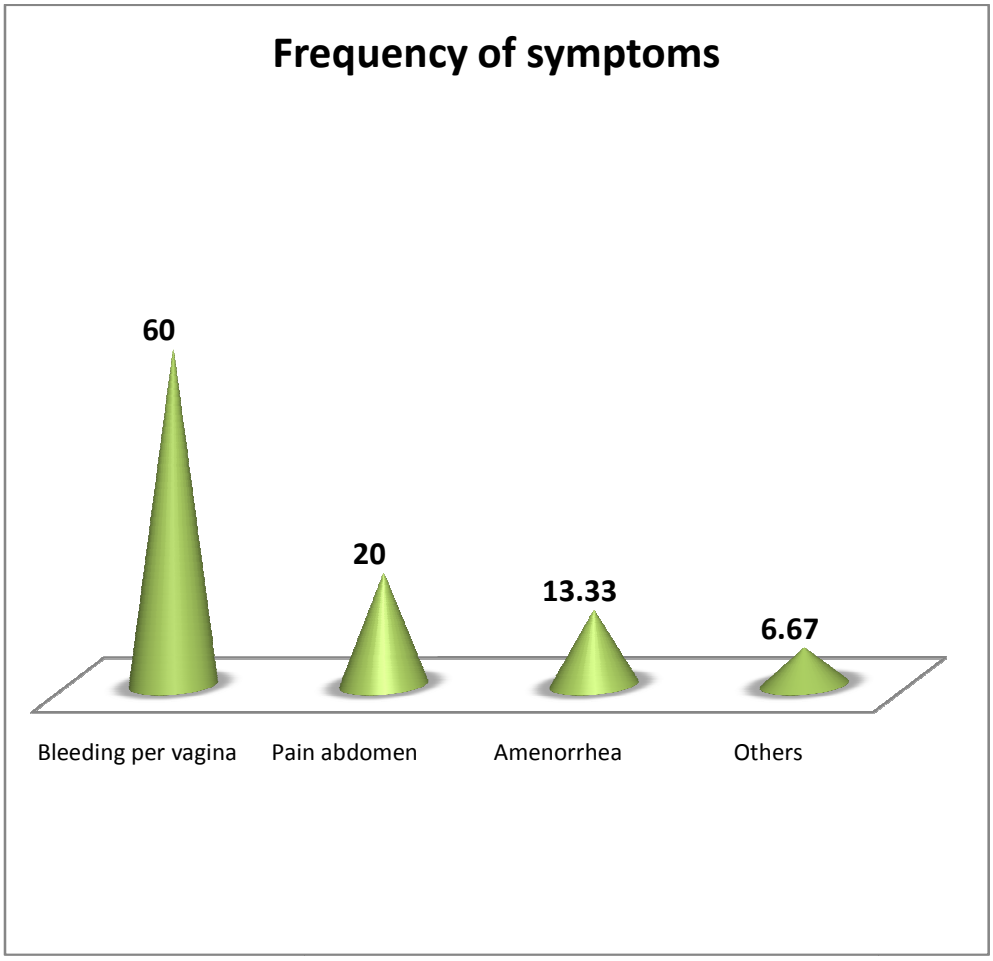


TABLE : 3

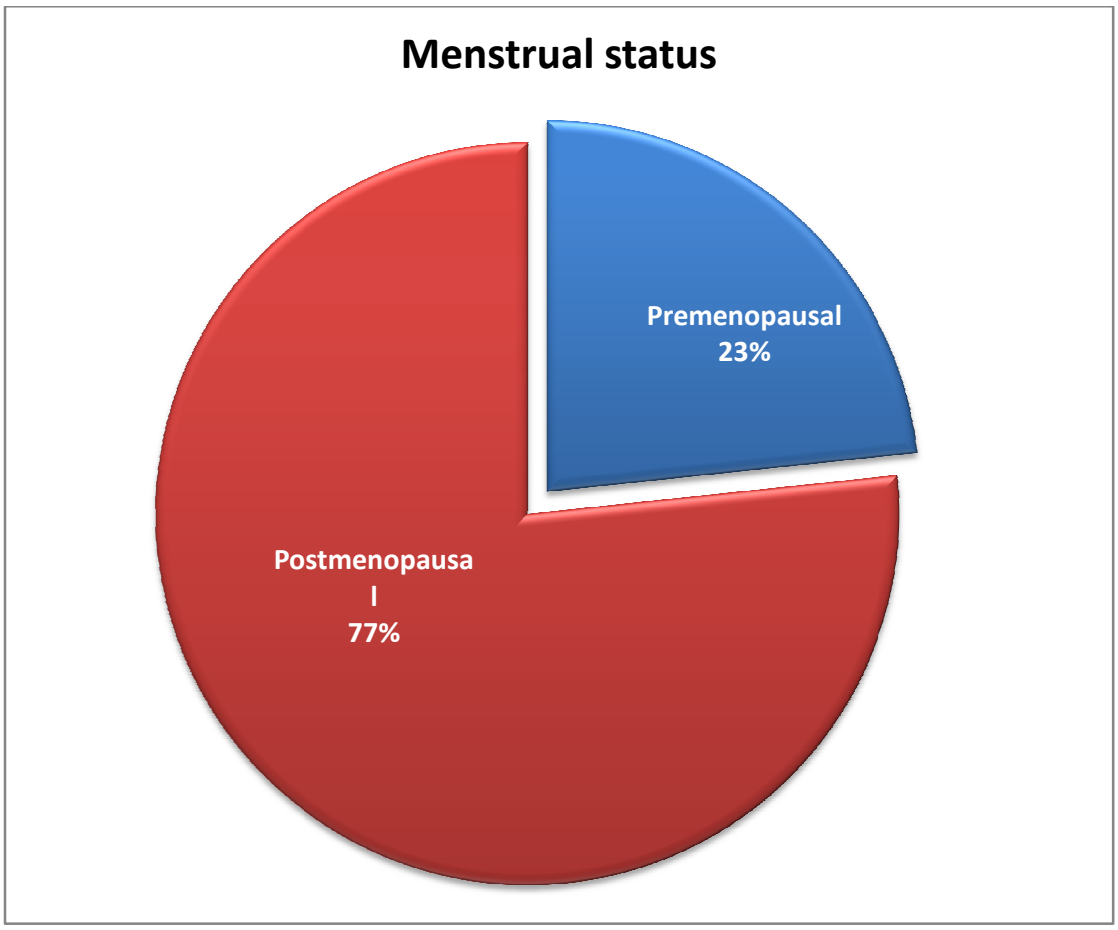
THE DISTRIBUTION OF ENDOMETRIAL CARCINOMAS WITH RESPECT TO THE PERIOD OF REPRODUCTIVE LIFE

STATUS	NUMBER OF PATIENTS	PERCENTAGE
Premenopausal	07	23.33%
Postmenopausal	23	76.66%

Usually endometrial carcinomas are found to be distributed in postmenopausal age group which in the present study constitutes 76.66%, the remaining were found to be perimenopausal and premenopausal comprising 23.33%.

CHART : 3

THE DISTRIBUTION OF ENDOMETRIAL CARCINOMAS WITH RESPECT TO THE PERIOD OF REPRODUCTIVE LIFE



According to the present study population, women in their postmenopausal age group were more vulnerable to develop endometrial carcinomas than women in the other age group.

TABLE : 4

THE DEPTH OF INVASION OF ENDOMETRIAL CARCINOMA IN THE PRESENT STUDY

MYOMETRIAL INVASION	NUMBER OF PATIENTS	PERCENTAGE
Less than half of myometrium	18	60%
More than half of myometrium	12	40%

The depth of invasion of endometrial carcinomas were illustrated as above and it was found that in the present study, endometrial carcinomas usually were found confined to less than half of the myometrium or there was minimal involvement of the myometrium in around 60% of the cases. About 40% of the cases showed more than half of the myometrial invasion.

CHART : 4

THE DEPTH OF INVASION OF ENDOMETRIAL CARCINOMA

IN THE PRESENT STUDY

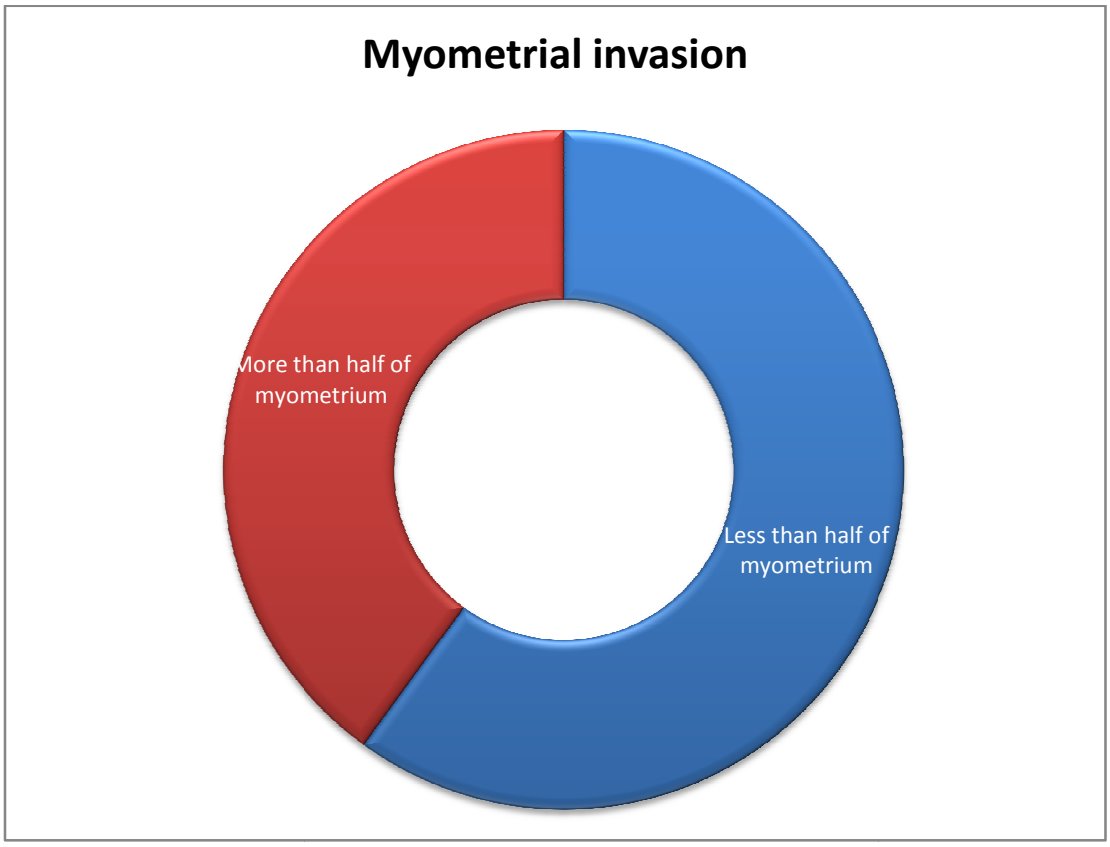


TABLE : 5

THE DISTRIBUTION OF HISTOLOGIC TYPES IN ENDOMETRIAL CARCINOMA IN THE PRESENT STUDY

HISTOLOGIC TYPE	NUMBER OF CASES	PERCENTAGE
Type I carcinoma	16	53.33%
Type II carcinoma	14	46.66%

In the present study, type I constituted 53.33% which is the most common histologic type among endometrial carcinomas and 46.66% were among type II.

CHART : 5

THE DISTRIBUTION OF HISTOLOGIC TYPES IN ENDOMETRIAL CARCINOMA IN THE PRESENT STUDY

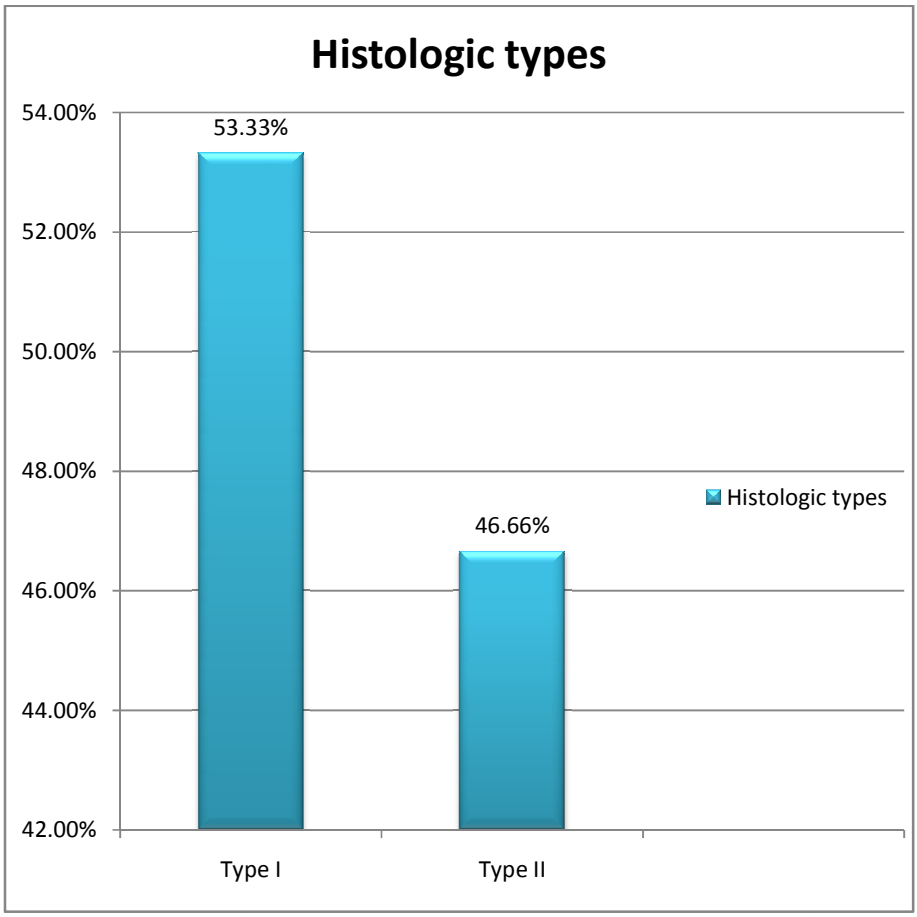


TABLE : 6

HISTOLOGIC TYPES IN ENDOMETRIAL CARCINOMA TYPE I

HISTOLOGIC TYPE	NUMBER OF CASES	PERCENTAGE
Well differentiated grade endometrioid	8	50%
Moderately differentiated grade endometrioid	6	37.5%
Higher grade endometrioid	2	12.5%

In the present study,16 cases of type I endometrioid tumors were studied. Among the sixteen cases, well differentiated endometrioid constituted 50%, moderately differentiated endometrioid tumors constituted 37.5% and higher grade endometrioid constituted 12.5%.

CHART: 6

HISTOLOGIC TYPES IN ENDOMETRIAL CARCINOMA TYPE I

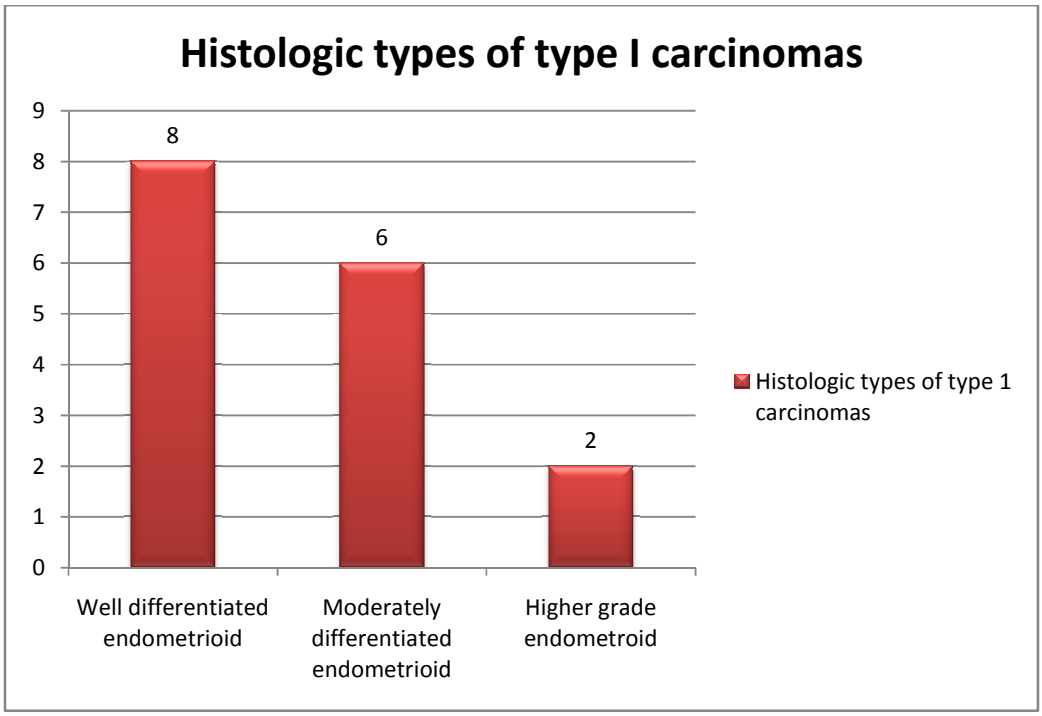


TABLE 7

HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMA TYPE II

HISTOLOGIC TYPE	NUMBER OF CASES	PERCENTAGE
Uterine papillary serous carcinoma	8	57.14%
Clear cell carcinoma	6	42.86%

In the study, fourteen cases of type II carcinomas were studied. Among the fourteen cases, 57.14% were uterine papillary serous carcinomas and 42.86% were clear cell carcinomas.

CHART : 7

HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMA TYPE II

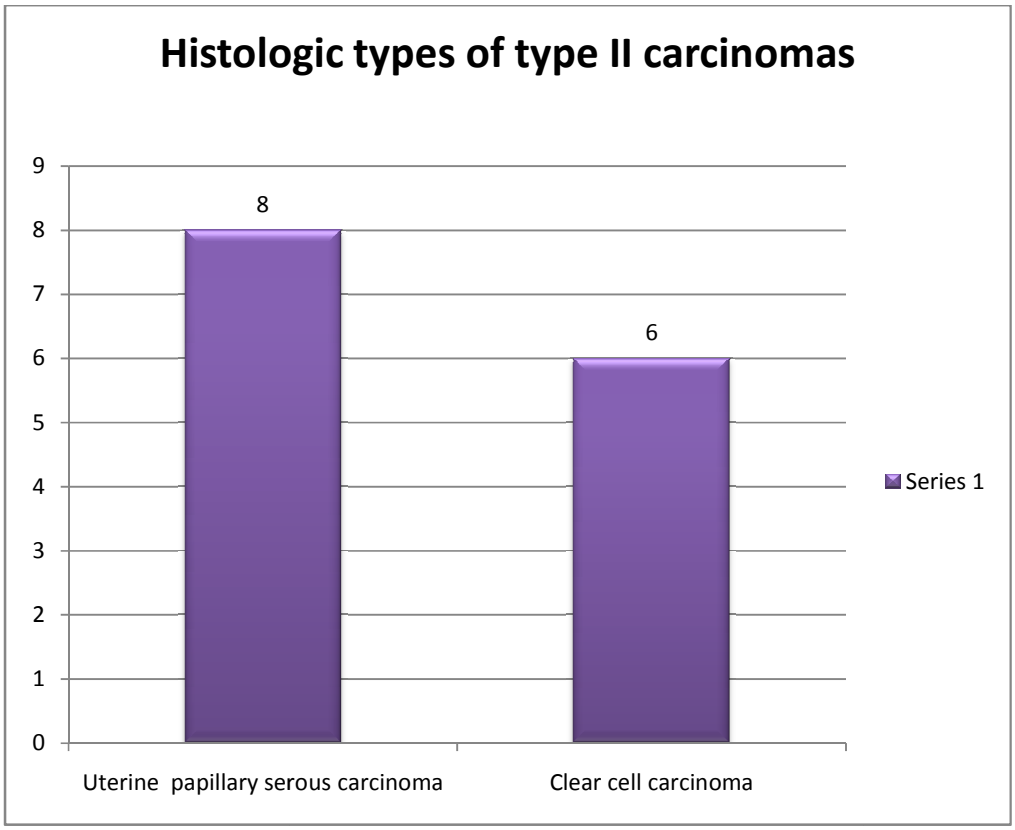


TABLE : 8

THE DISTRIBUTION OF ARCHITECTURAL GRADING IN ENDOMETRIAL CARCINOMA

ARCHITECTURE	NUMBER OF CASES	PERCENTAGE
Glandular pattern	09	30%
Glandular admixed with sheets	12	40%
Sheet	08	26.67%
Papillary pattern	01	3.33%

Most common architectural pattern in the present study is glands and sheets comprising 40%, next in the grading were tumours composed entirely of glands consisting of 30% and then 26.67 % of the tumours were entirely composed of sheets / solid pattern.

CHART : 8

THE DISTRIBUTION OF ARCHITECTURAL GRADING IN ENDOMETRIAL CARCINOMA

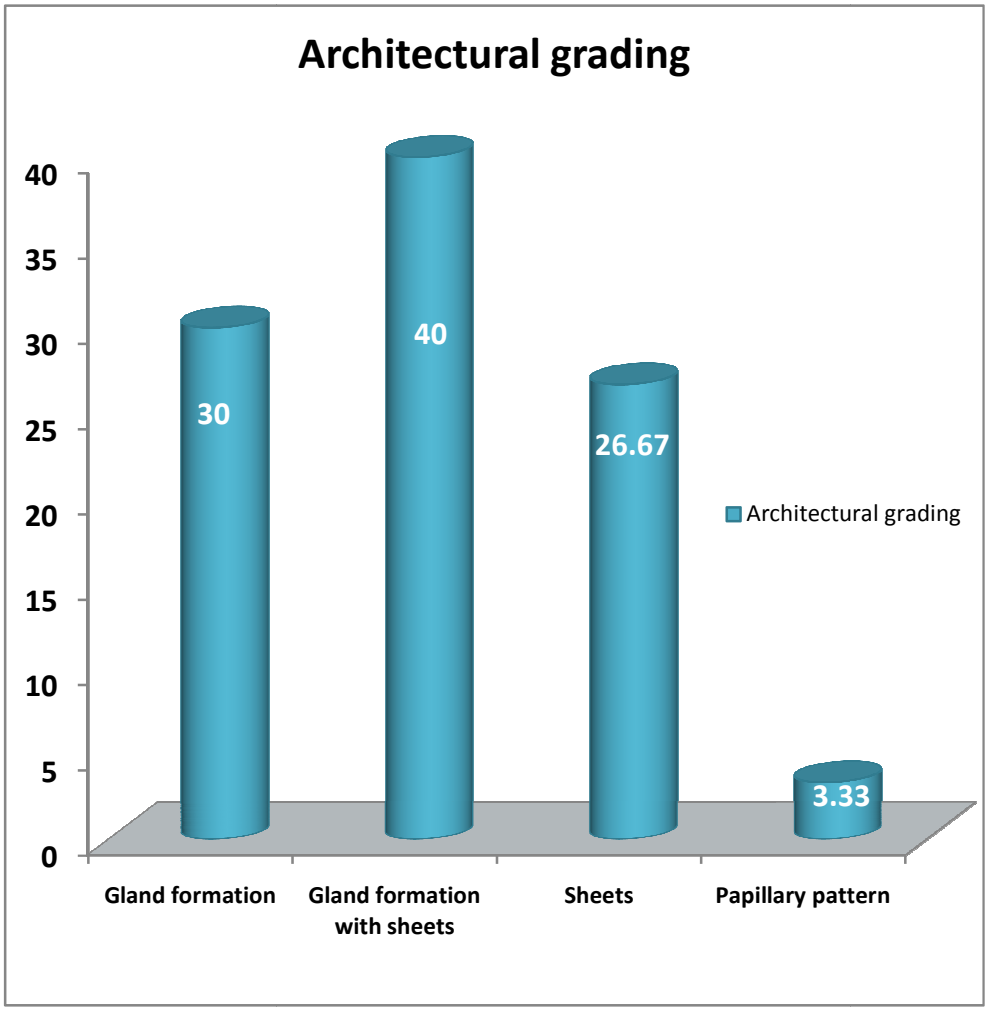


TABLE : 9

THE EXPRESSION OF ESTROGEN RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

EXPRESSION OF ESTROGEN RECEPTOR	NUMBER (PERCENTAGE) OF POSITIVE CASES	NUMBER (PERCENTAGE) OF NEGATIVE CASES
Type I	13 (81.25%)	03 (18.75%)
Type II	03 (21.43%)	11 (78.57%)

In the present study, out of 16 cases in type I -13 cases were positive constituting 81.25% and 3 cases were negative comprising 18.75% and out of 14 cases of type II – 3 were positive constituting 21.43% and 11 cases were negative comprising 78.57%.

CHART : 9

THE EXPRESSION OF ESTROGEN RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

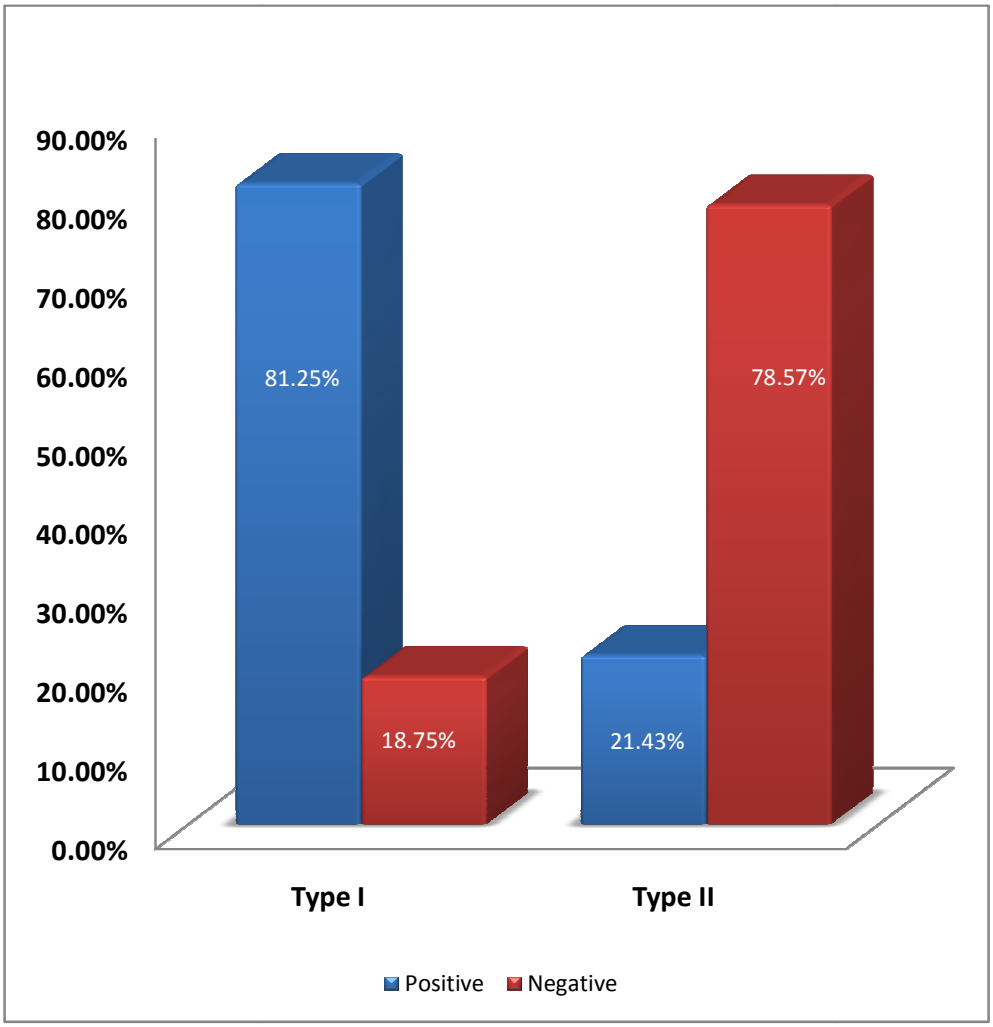


TABLE : 10

THE EXPRESSION OF PROGESTERONE RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

EXPRESSSION OF PROGESTERONE RECEPTOR	NUMBER (PERCENTAGE) OF POSITIVE CASES	NUMBER (PERCENTAGE) OF NEGATIVE CASES
Type I	12 (75%)	04 (25%)
Type II	04 (28.75%)	10 (71.42%)

In the above study out of 16 cases in type I - 12 cases were positive constituting 75% and 4 cases were negative constituting 25% and out of 14 cases of type II - 4 cases were positive comprising 28.75% and 10 cases were negative constituting 71.42%.

CHART : 10

THE EXPRESSION OF PROGESTERONE RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

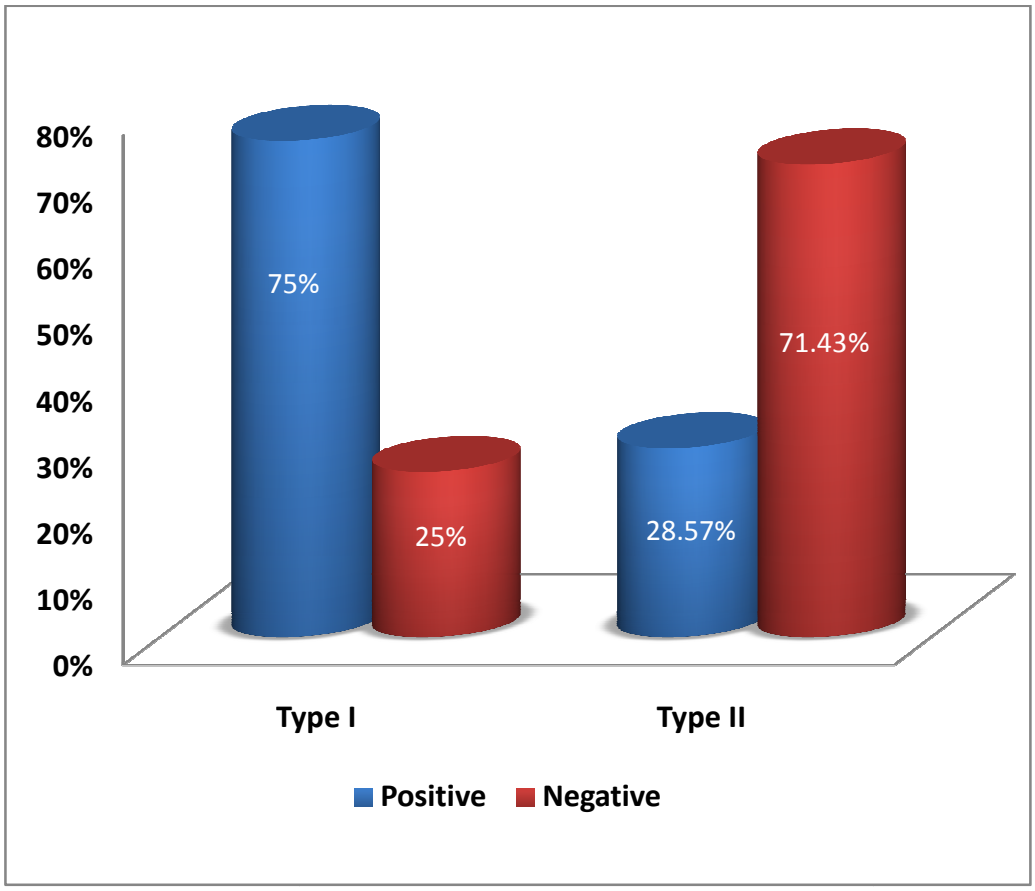


TABLE : 11

THE EXPRESSION OF p53 IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

EXPRESSION OF p53	NUMBER (PERCENTAGE) OF POSITIVE CASES	NUMBER (PERCENTAGE) OF NEGATIVE CASES
Type I	07 (43.75 %)	09 (56.25%)
Type II	11 (78.57%)	03 (21.43%)

In the present study out of 16 cases in type I – 7 cases were positive constituting 43.75% and 9 cases were negative which constitutes 56.25%, and out of 14 cases of type II – 11 cases were positive comprising 78.57% and 3 were negative constituting 21.43%.

CHART: 11

THE EXPRESSION OF p53 IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

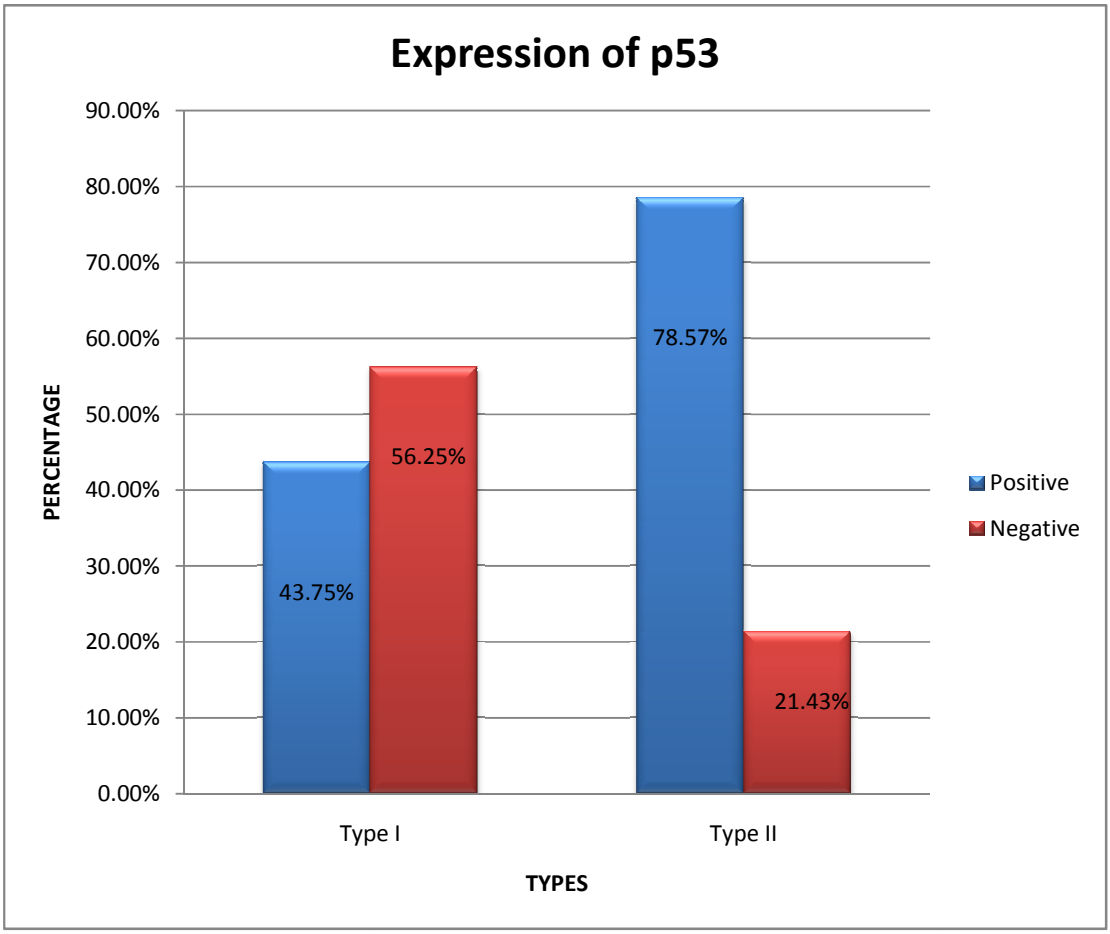


TABLE : 12

THE EXPRESSION OF ESTROGEN RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS BY IMMUNOHISTOCHEMICAL SCORE

	NEGATIVE	**POSITIVE**		**Total**
	Category 1	**Category 2**	**Category 3**	
Type I	03	05	08	16
Type II	11	02	01	14

The association of histologic types with estrogen receptor was tested using chi-square analysis,the value was found to be 10.75 with the p value less than 0.01(significant at 1% level) which implies a significant association between the type I carcinoma and expression of estrogen receptor.

The positivity of both ER and PR were scored as the sum of the percentage of stained cells and intensity of nuclear staining.

Based on the percentage of cells there are three grades

Grade 1 – 0-25% of the nuclei stained.

Grade II – 26-75% of the nuclei stained

Grade III - >76% of the nuclei stained

Based on the staining intensity

Grade I – absent or weak

Grade II – strong

Grade III - very strong.

The sum of both the parameters determine the score.

Tumours were classified into three categories depending on the

immunohistochemistry score

Category I – score of 2 indicates immunonegativity

Category II – score of 3 or 4 indicates immnunopositivity

Category III – score of 5 or 6 indicates immnunopositivity[76]

CHART : 12

THE EXPRESSION OF ESTROGEN RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS BY IMMUNOHISTOCHEMICAL SCORE

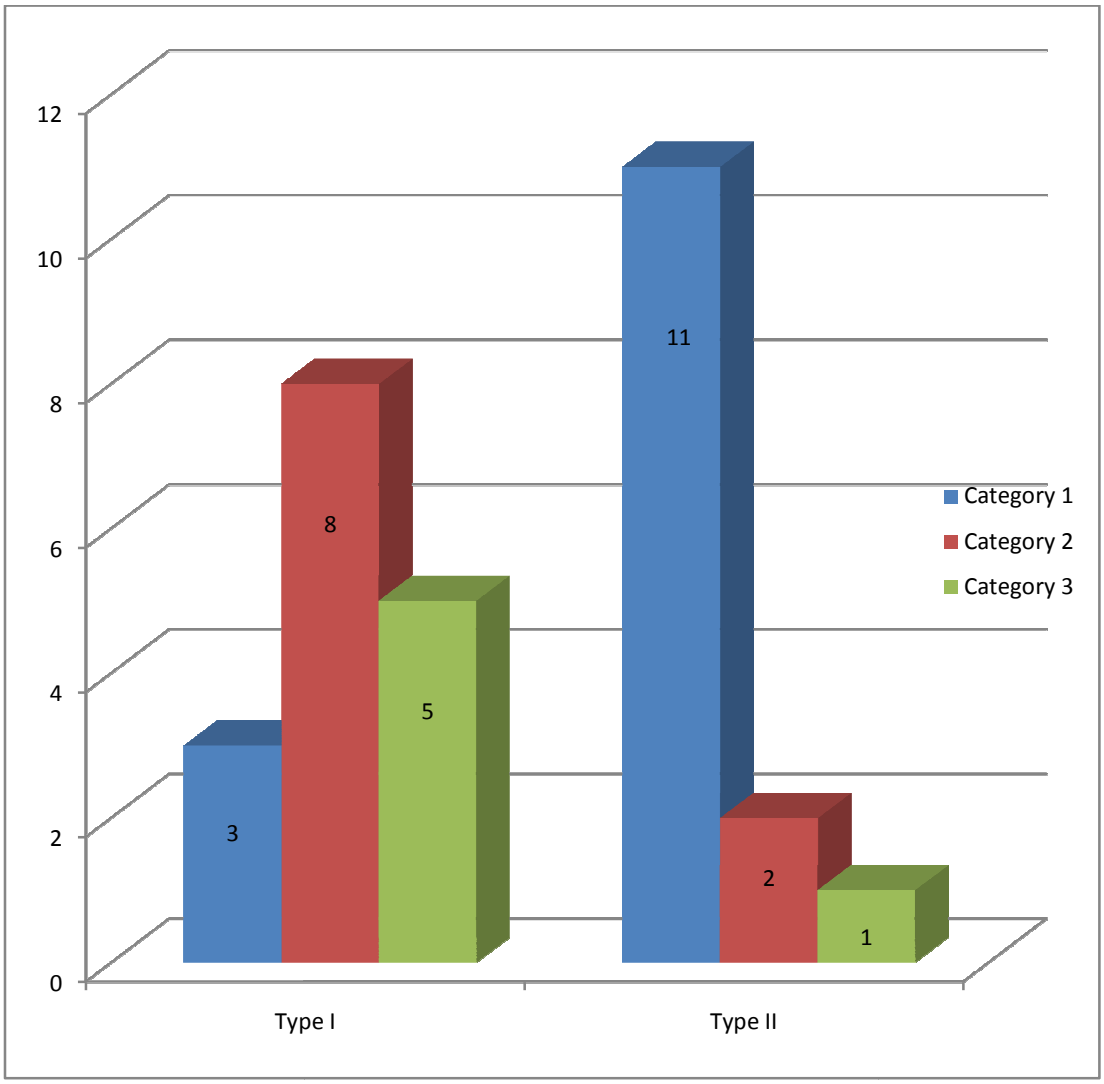


TABLE : 13

EXPRESSION OF PROGESTERONE RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS BY IMMUNOHISTOCHEMICAL SCORE

	NEGATIVE	**POSITIVE**		**Total**
	Category 1	**Category 2**	**Category 3**	
Type I	04	05	07	16
Type II	10	02	02	14

The association of histologic types with progesterone receptor was tested using chi-square analysis,the value was found to be 6.53 with the p value less than 0.05(significant at 5% level) which implies a significant association between the type I carcinoma and expression of progesterone receptor

CHART : 13

EXPRESSION OF PROGESTERONE RECEPTOR IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS BY IMMUNOHISTOCHEMICAL SCORE

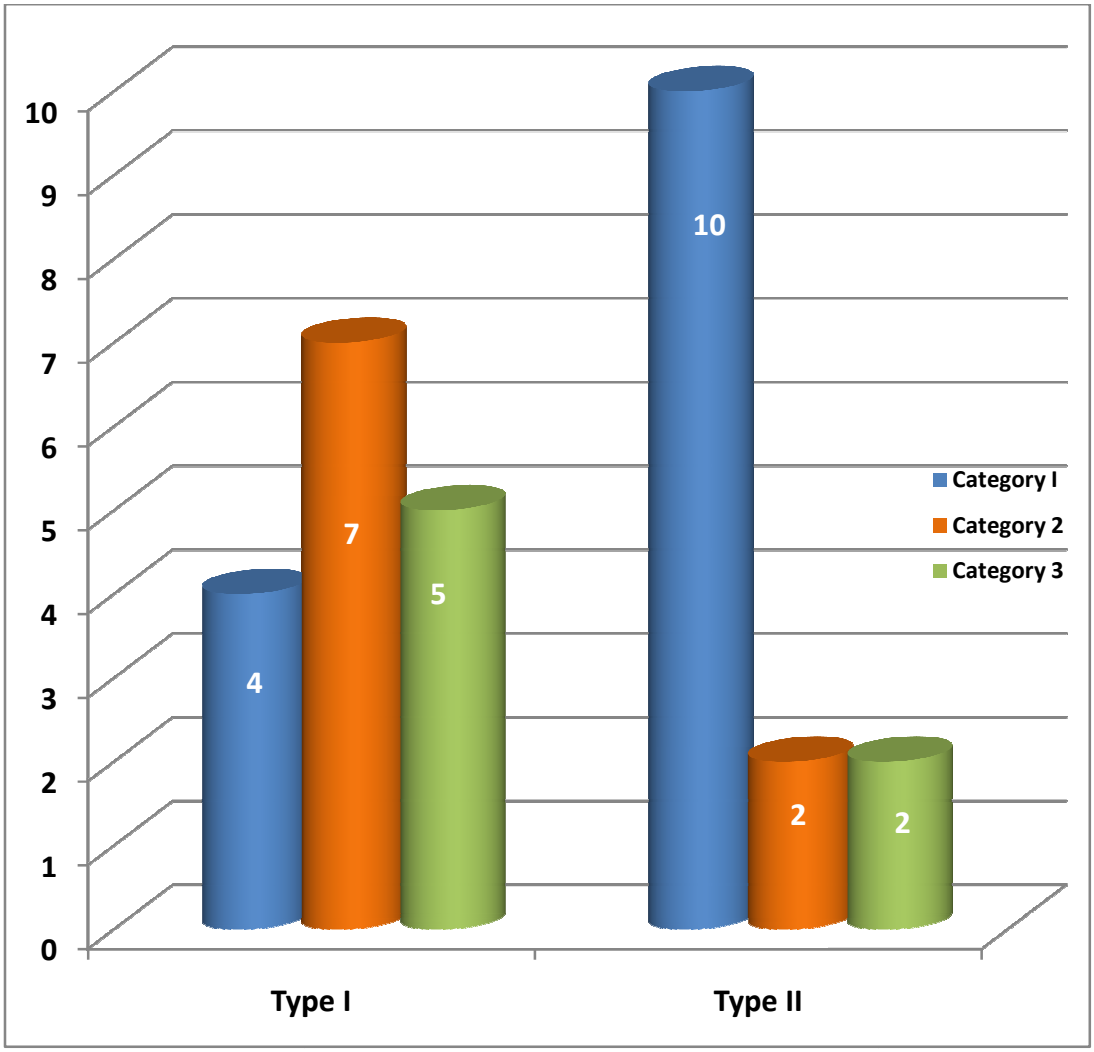


TABLE : 14

EXPRESSION OF p53 IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMA BY IMMUNOHISTOCHEMISTRY

	NEGATIVE	**POSITIVE**			**Total**
	Negative	<30%	30-70%	>70%	
Type I	9	2	2	3	16
Type II	3	2	4	5	14

The association of histologic types with p53 was tested using chi-square analysis,the value was found to be 3.77 with the p value less than 0.05(significant at 5% level) which implies a significant association between the type II carcinoma and expression of p53.

The most common distribution patterns of p53 were:

a) diffuse (>70%) of intense nuclear staining.

b) no staining or cytoplasmic staining only

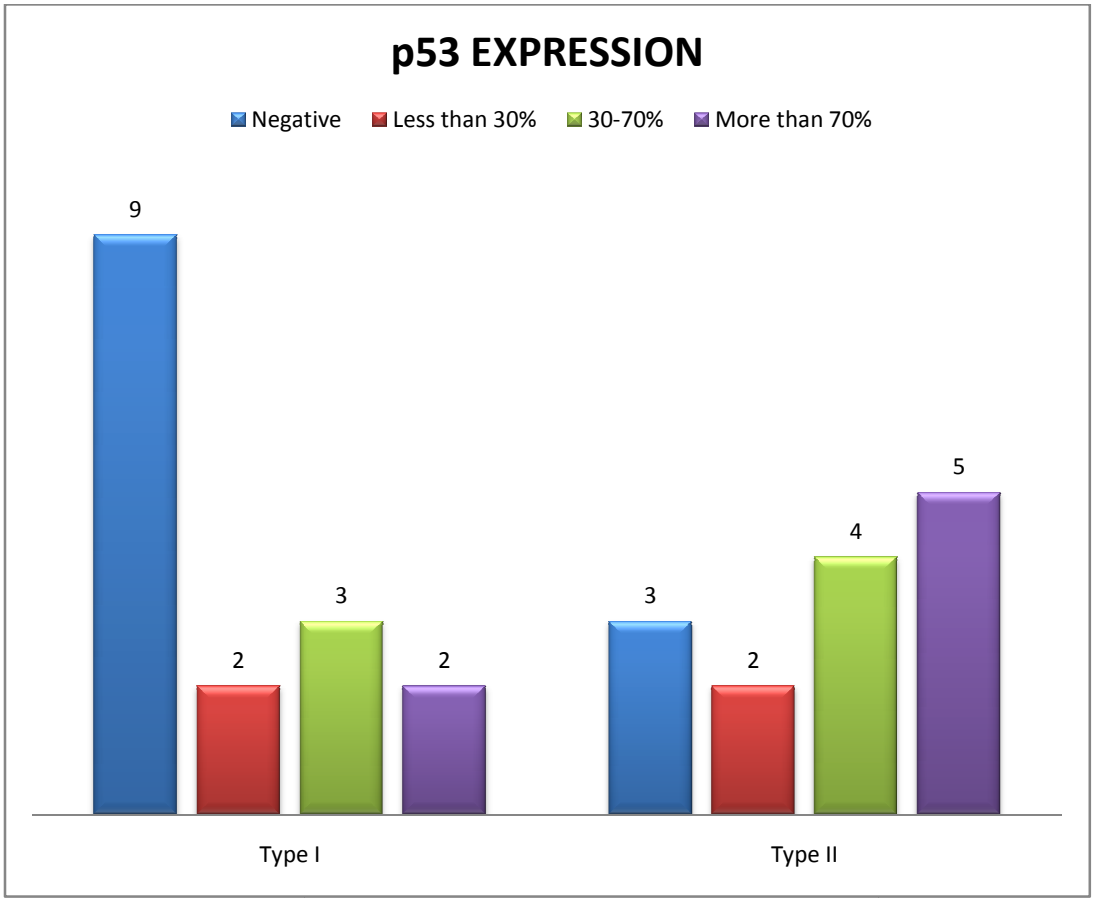
c) focal weak to intense staining of scattered neoplastic cells(<30%)

d) complete absence of staining in all tumour cell nuclei

e) abrupt transition from minimal to marked staining.

CHART : 14

EXPRESSION OF p53 IN TYPE I AND TYPE II ENDOMETRIAL CARCINOMA BY IMMUNOHISTOCHEMISTRY



List of Colour Plate

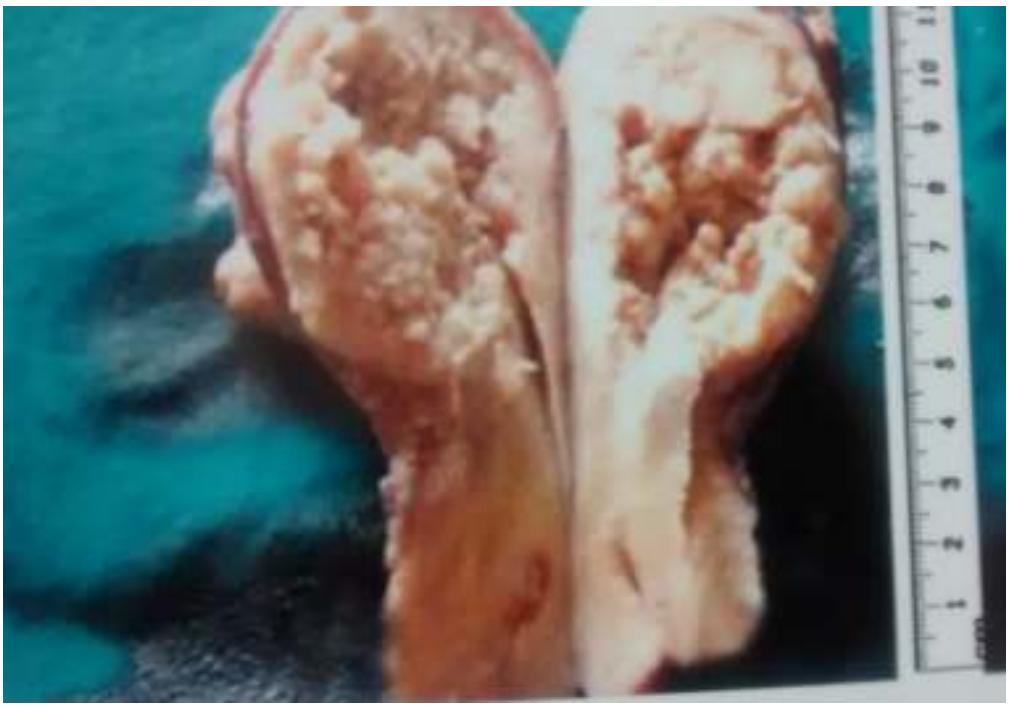


Figure 3 : Gross picture of endometrial carcinoma of uterus showing a proliferative growth filling the entire endometrial cavity and extending upto the serosa.

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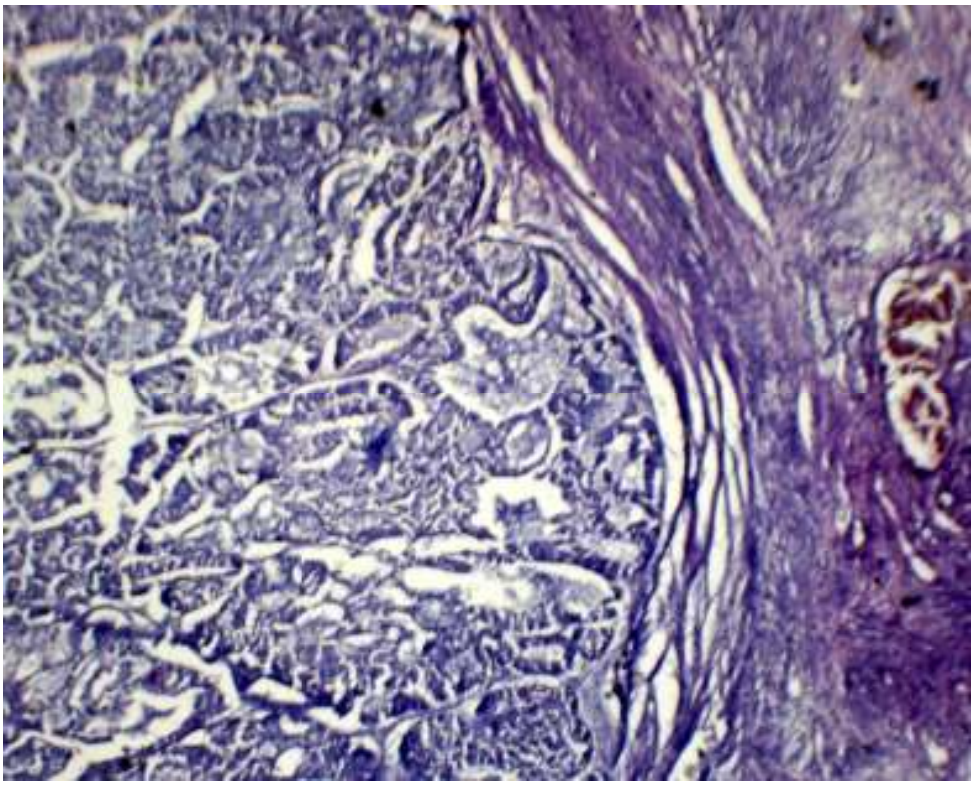

Figure 4 : H& E shows well differentiated endometrioid carcinoma (10 X)

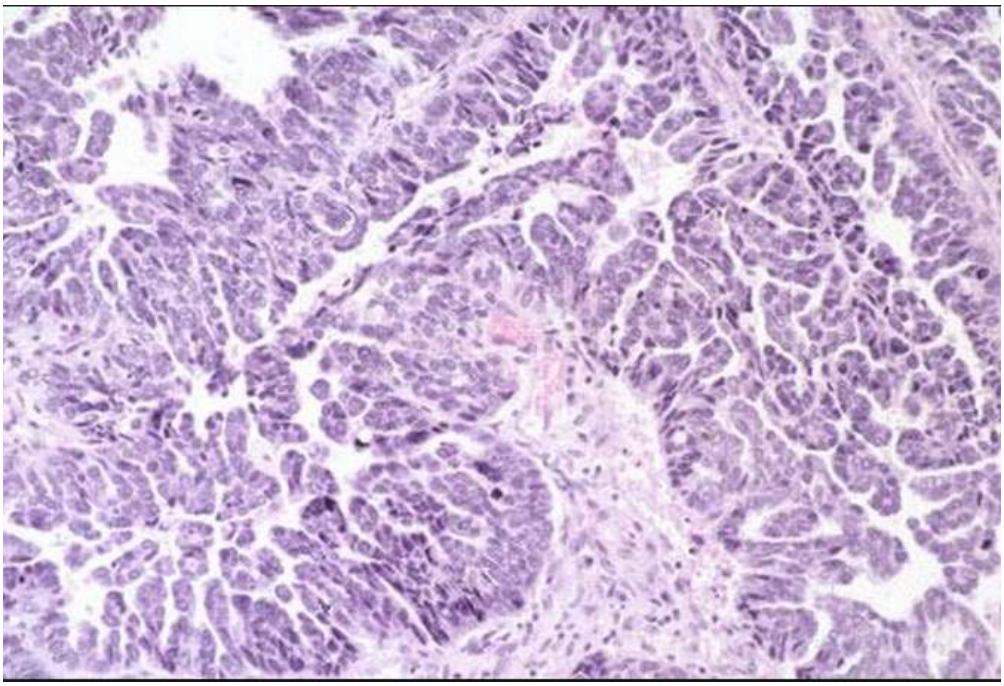

Figure 5: H & E shows papillary serous carcinoma (40 X)

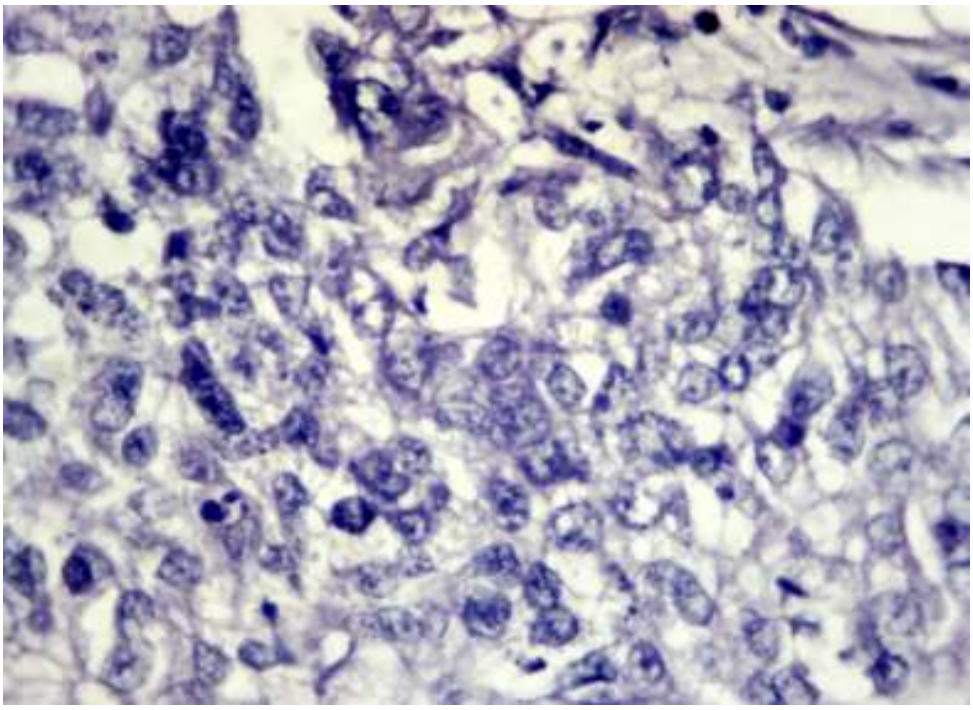

Figure 6 : H & E showing clear cell carcinoma (40 X)

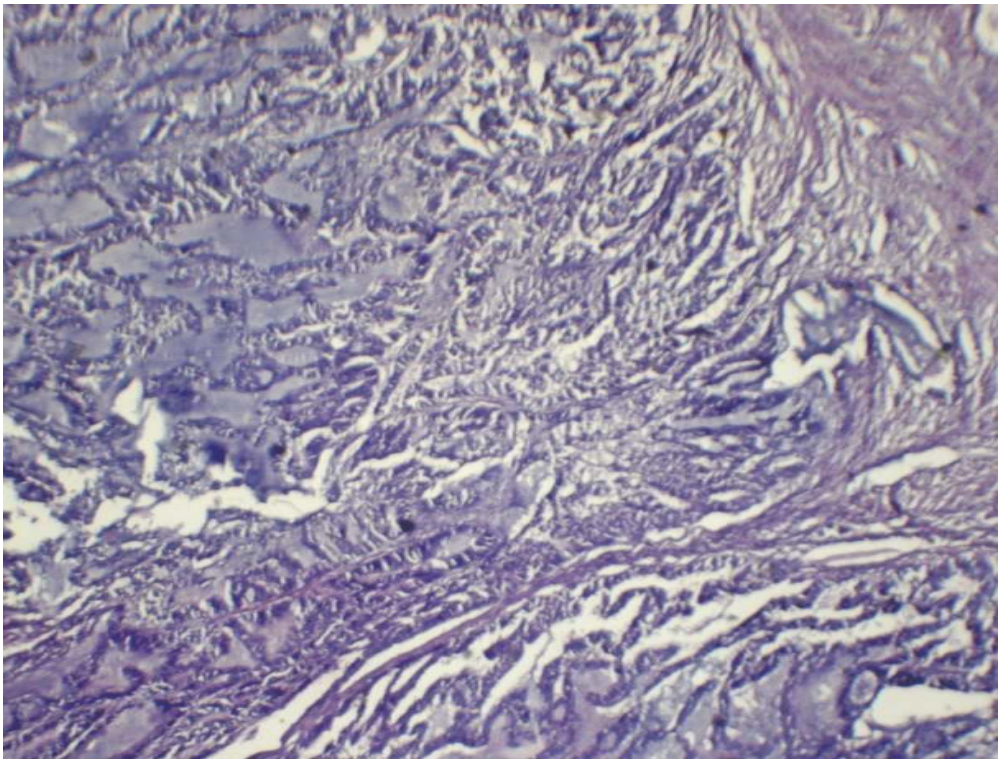

Figure 7 : H & E showing mucinous type of endometrial carcinoma(10 X)

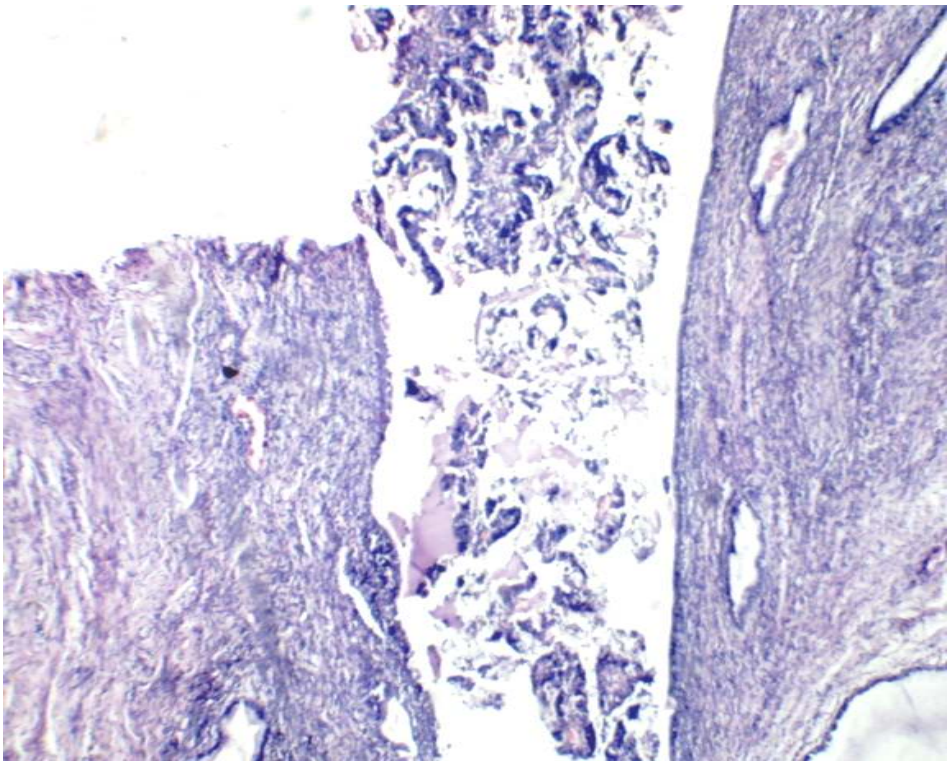

Figure 8 : H & E showing involvement of the cervical canal by endometrioid carcinoma(10 X)

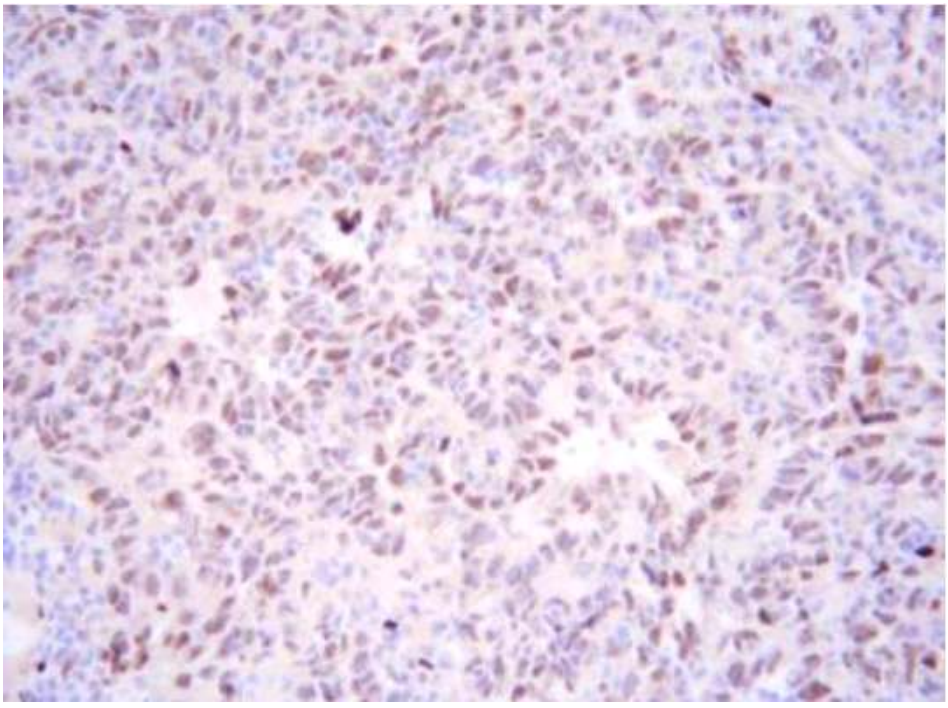

Figure 9: Immunohistochemistry showing ER expression,

Category 2 in type I carcinoma (10 X)

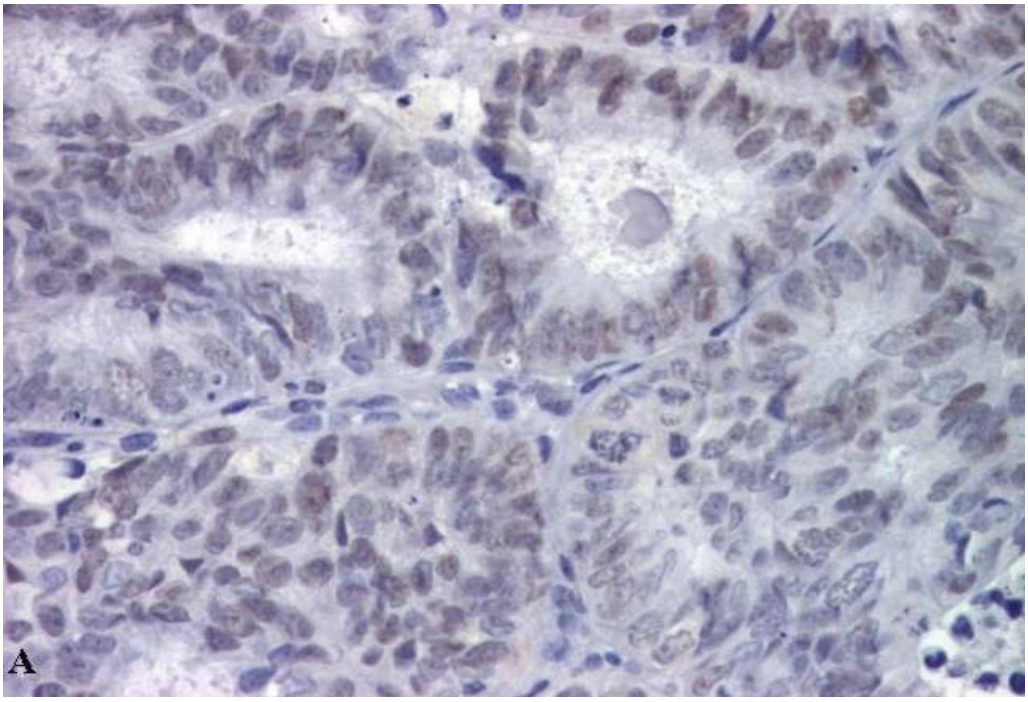

Figure 10: Immunohistochemistry showing nuclear staining of ER Category 3 in type I carcinoma (100 X)

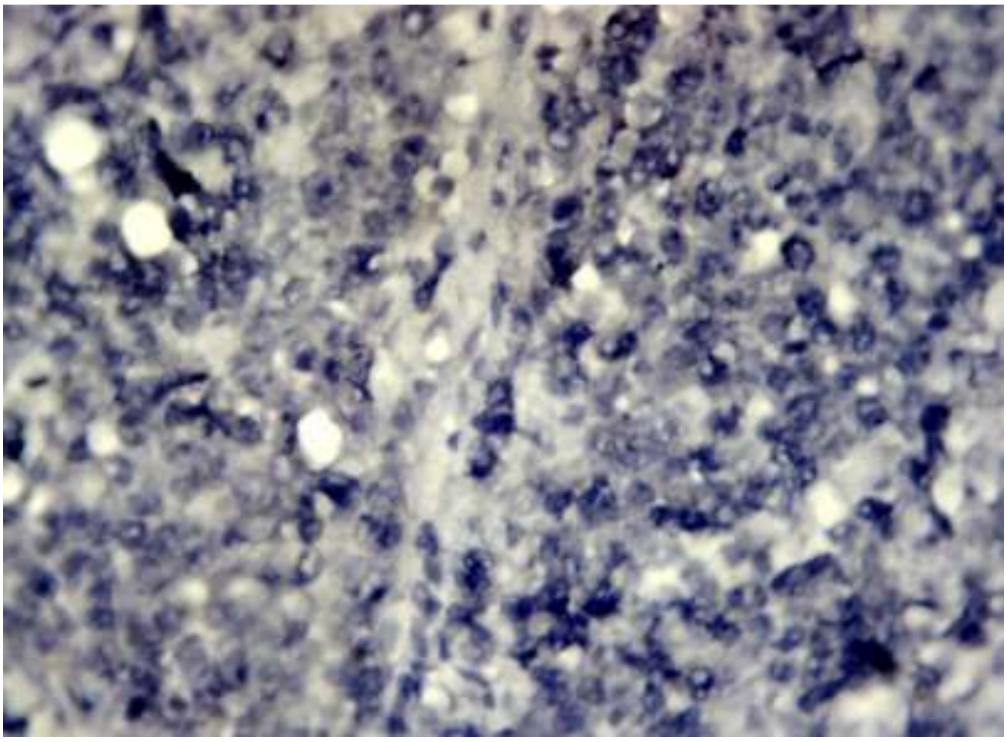

Figure 11 : Immunohistochemistry showing ER negative in

type II carcinoma (40 X)

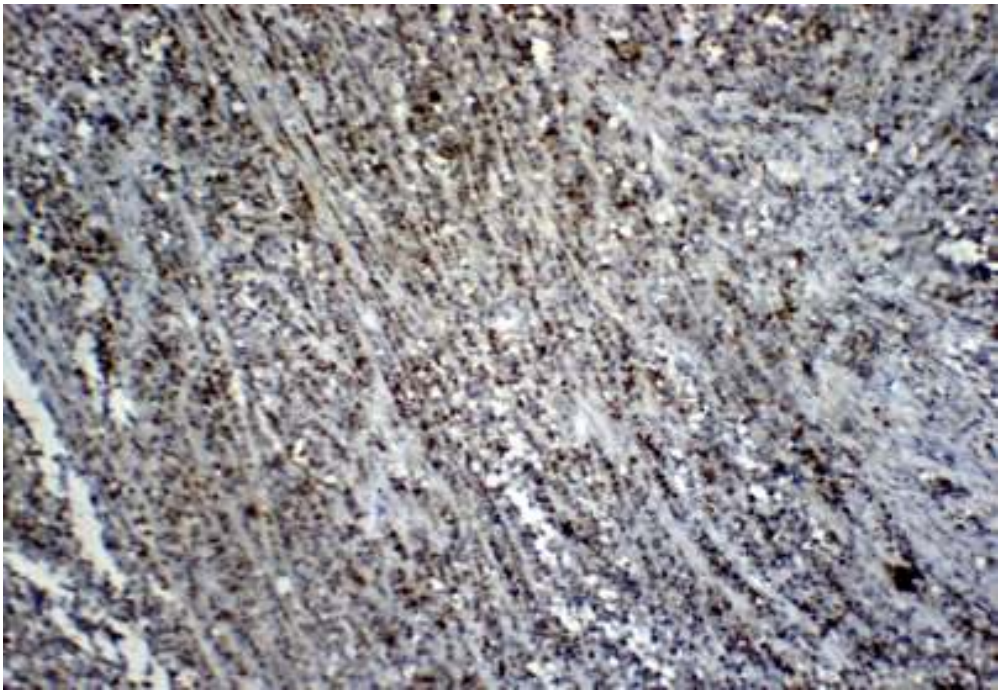

Figure 12 : Immunohistochemistry showing positive nuclear staining of PR Category 3 in type I carcinoma (10 X)

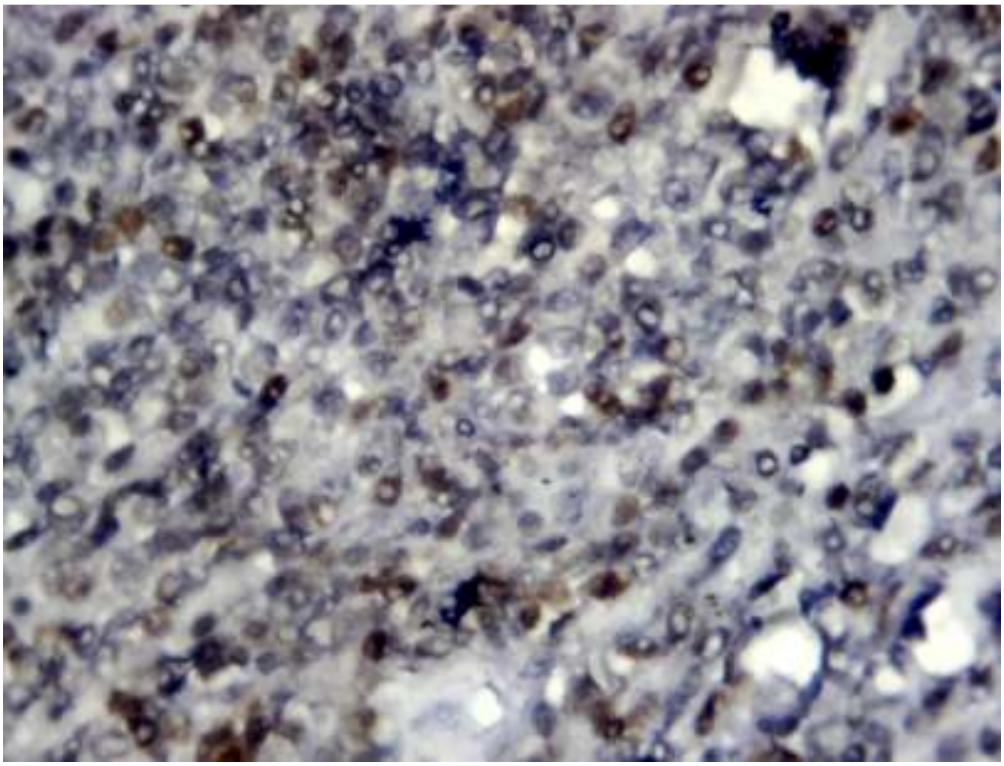

Figure 13 : Immunohistochemistry showing nuclear staining of PR in type I carcinomas. Category 2 (40 X)

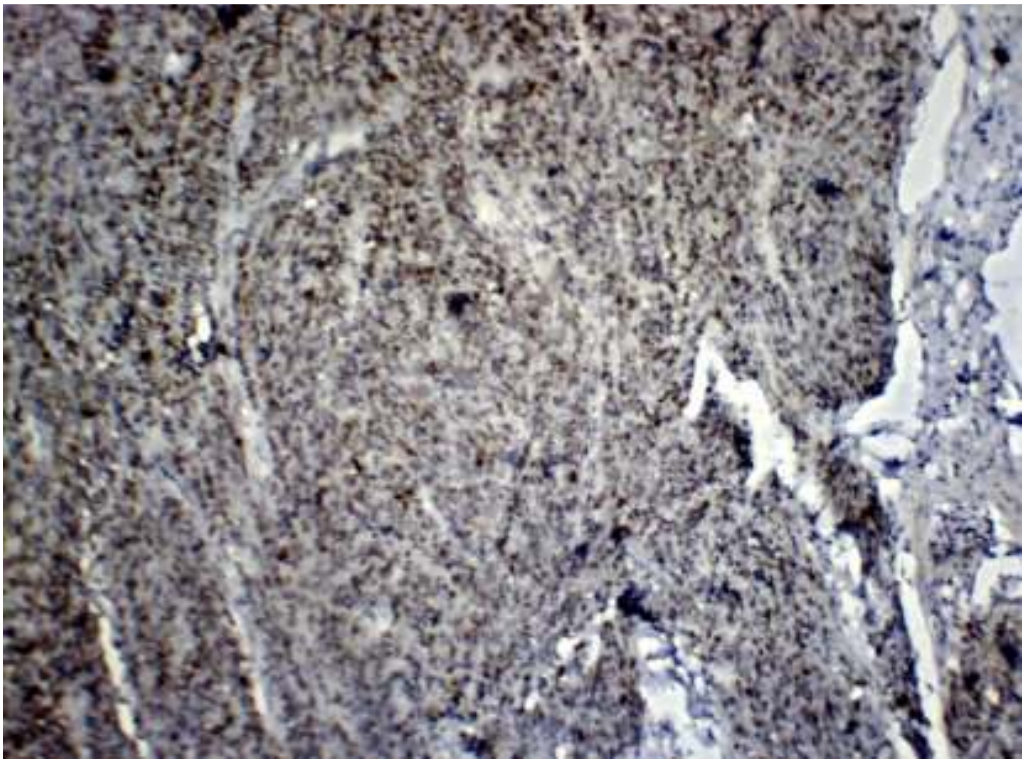

Figure 14: Immunohistochemistry showing nuclear positivity for p53 (>70% staining) (10 X)

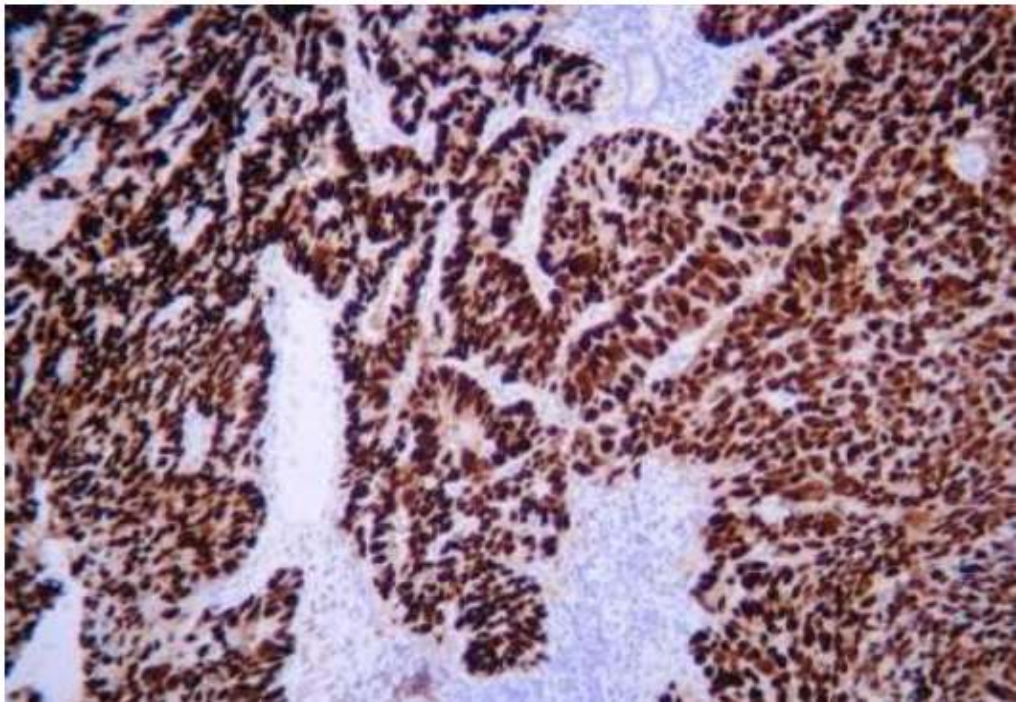

Figure 15 : Immunohistochemistry showing nuclear positivity for p53 in type II carcinomas(>70%) (10 X)

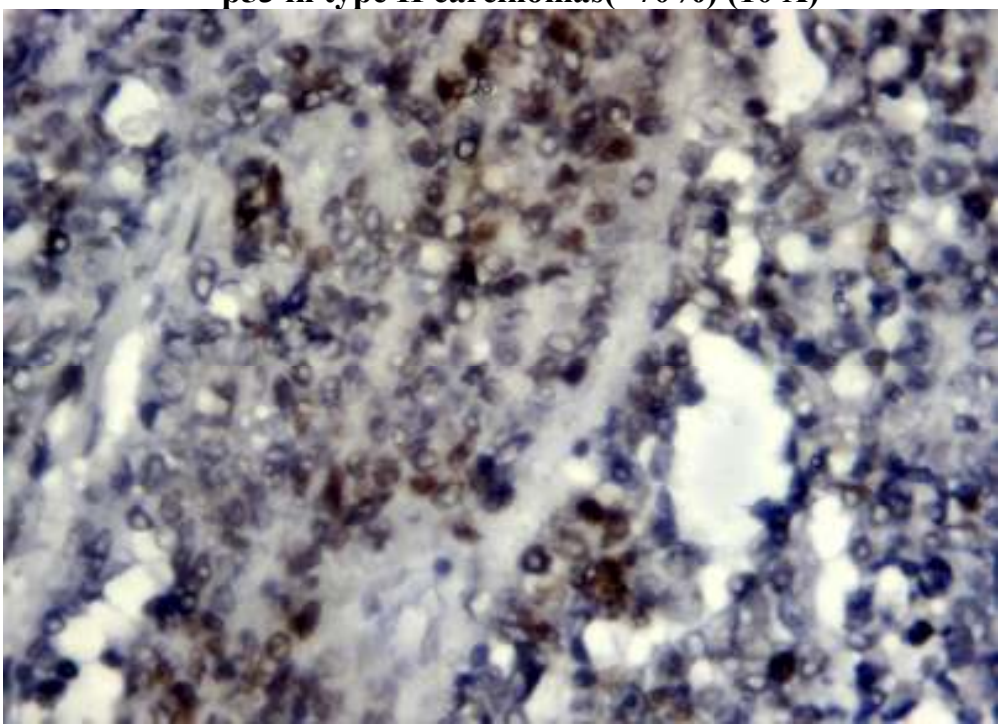

Figure 16 : Immunohistochemistry showing p53 nuclear positivity in type II carcinoma (30-70%) (40 X)

Discussion

DISCUSSION

The endometrial carcinomas are class of neoplasms in which pathologic factors play an important role in determining the prognosis of the patient. Basically endometrial carcinomas are of two types: type I- estrogen dependent tumors and type II – non estrogen dependent tumors.

Type I are usually seen in premenopausal and perimenopausal women in patients with hyperplastic endometrium, usually does not involve the myometrium. Most of them are well to moderately differentiated and rarely presents with distant metastasis and hence usually have a better prognosis.

Whereas type II tumours, occur in females little older than the estrogen dependent type. They are usually of higher grades and presents with distant metastasis and are associated with poor prognosis.

There are few well established prognostic factors which includes, stage of the tumor, grade of the tumor and the depth of invasion of the myometrium.

Recently nuclear grade of the tumor and vascular invasion of the tumor were also recognized as important prognostic factors.

The advent of immunohistochemistry proved to be of significance in many malignancies like the breast, soft tissue tumours etc., to arrive at a diagnosis and were helpful in assessing the prognosis and in the management of the patients.

There are numerous studies showing inverse correlation between the steroid hormone receptor status and the grade of the tumour and direct relationship of p53 positivity with higher grade of tumours.

In the present study: A total of 30 cases of endometrial carcinomas were studied histologically and the immunohistochemistry expression for ER, PR and p53 were correlated. Among the thirty cases sixteen were type I and fourteen were type II.

Expression of ER: Out of 16 cases in type I -13 cases were positive and 3 cases were negative and out of 14 cases of type II – 3 cases were positive cases and 11 cases were negative.

Expression of PR: Out of 16 cases in type I - 12 cases were positive and 4 cases were negative and out of 14 cases of type II - 4 cases were positive and 10 cases were negative.

Expression of p53: Out of 16 cases in type I – 7 cases were positive and 9 cases were negative and out of 14 cases of type II – 11 cases were positive and 3 were negative.

In the present study women in the age group in which endometrial carcinomas usually presented were those who were above 55 years. Most common age group according to the present study is 50-69 years. Mean age according to the above study was 52.7 years.

According to G. Plataniotis and Castiglione[66] the median age of occurrence is 63 years and more than 90% of women were found to be older than 50.

The most common presentation of endometrial carcinomas in our present study was bleeding per vagina comprising 60% followed by pain abdomen, amenorrhea, menorrhagia, mass per abdomen, difficulty in passing urine and mass per vagina.

Usually endometrial carcinomas are found to be distributed in postmenopausal age group which in the present study constitutes 76.66%, the remaining were found to be perimenopausal and premenopausal comprising 23.33%.

The depth of invasion of endometrial carcinomas in the present study, were usually found confined to less than half of the myometrium or there was minimal involvement of the myometrium in around 60% of the cases. About 40% of the cases showed more than half of the myometrium showing invasion.

In the present study, among the various histologic types, type I constituted 53.33% of endometrial carcinomas and 46.66% were type II carcinomas.

In the present study, 16 cases of type I endometrioid tumors were studied. Among the sixteen cases, well differentiated endometrioid constituted 50%, moderately differentiated endometrioid tumors constituted 37.5% and higher grade endometrioid constituted 12.5%.

In the study, fourteen cases of type II carcinomas were studied. Among the fourteen cases, 57.14% were uterine papillary serous carcinomas and 42.86% were clear cell carcinomas.

Most common architectural pattern in the present study is glands and sheets comprising 40% next were tumours composed entirely of glands consisting of 30% and then 26.67% of tumours were entirely composed of sheets or solid pattern.

In the present study, expression of ER was determined by the immunohistochemical score. A total of 16 cases were evaluated in type I carcinomas – in which 13 cases were found to be positive comprising of 81.25% (which included weakly positive and strongly positive cases) and 3 cases were found to be negative constituting 18.75% and among the 13 positive cases, five of them were weakly positive categorized as category two and eight were strongly positive categorized under category three. Whereas among the 14 cases of type II (higher grade, serous papillary carcinomas and clear cell carcinomas) 3 positive cases consisting of 21.43 %, two were weakly positive and one was strongly positive and 11 cases were negative comprising 78.57%.

As per Sidonia Catalina Stoian[70] et al a retrospective analysis on endometrial carcinomas , ER positivity was seen in 86.3% of type I tumors and 13.4% of the type I tumors cases were found to be negative for ER.

The association of histologic types with estrogen receptor was tested using chi-square analysis, the value was found to be 10.75 with the p value less than 0.01 (significant at 1% level) which implies a significant

association exist between the type I carcinoma and expression of estrogen receptor.

In the given study, the expression of PR was determined by the immunohistochemical score. A total of 16 cases were evaluated in type I endometrioid carcinomas – in which 12 cases were found to be positive comprising of 75% (includes weakly positive and strongly positive cases) among which five cases were weakly positive and seven cases were strongly positive and 4 cases were found to be negative constituting 25%. Whereas among the 14 cases of type II (higher grade, serous papillary carcinomas and clear cell carcinomas) 4 cases were positive comprising of 28.75% (among them two were weakly positive and two was strongly positive) and 10 cases were negative comprising 71.42%.

Sidonia Catalina Stoian[70] et al analysed 22 cases retrospectively and observed 81.1% of type I tumors to be positive for PR while 18.9% of type I tumors were reported to be negative.

The association of histologic types with progesterone receptor was tested using chi-square analysis,the value was found to be 6.53 with the p value less than 0.05 (significant at 5% level) which implies a significant association exist between the type I carcinoma and expression of progesterone receptor.

Expression of p53: In the present study, from a total of 16 cases in type I (endometrioid type) – 7 cases were positive constituting 43.75%, among them two cases stained less than 30%, two cases stained 30-70% and three cases stained more than 70% and 9 cases were negative comprising about 56.25%, while in type II a total of 14 cases were evaluated –in which 11 cases were positive comprising 78.57% , in which two cases stained less than 30%, four cases stained 30-70% and five cases stained more than 70% and 3 were negative constituting 21.43%.

The association of histologic types with p53 was tested using chi-square analysis,the value was found to be 3.77 with the p value less than 0.05 (significant at 5% level) which implies a significant association between the type II carcinoma and expression of p53.

A study conducted by Nicola Ragina[69] et al, on 240 specimens of endometrial carcinomas showed that nearly 100 % of the uterine papillary serous tumors (type II) were positive for p53 when compared to 60% of the endometrioid tumors (type I). There was a trend for immunopositivity in advanced stage tumors constituting 86.2% while compared to 64.3% in early stage tumors. Positive p53staining was observed in 111 of the 182 (61%) endometrioid tumors (type I) and in 47 of the 58 (81.0%) type II.

p53 expression was significantly higher in papillary serous carcinomas (type II) than in the endometrioid type (type I).

Recent reports suggest that ER, PR and p53status, as determined by immunohistochemical studies, can be used as an independent predictor for disease recurrence also. The numbers in this study were too small to make a definitive statement on the importance of hormone receptors and p53 to predict the recurrence of the disease.

Summary

SUMMARY OF THE STUDY

The present study is a cross sectional prospective study on endometrial carcinomas. A sample of 30 specimens were collected and studied during this period.

The following were observed in the course of this study:

1. The incidence of endometrial carcinomas in our hospital was found to be 1.73%

2. The mean age of the patients diagnosed with endometrial carcinomas was 52 years.

3. 60% of the patients were postmenopausal.

4. Around 60% of the cases showed no involvement or less than than half of the thickness of the myometrium showing involvement by the tumor.

5. Of the 30 samples studied, 53.33% were type I tumours and 46.66% were type II tumors.

6. In the present study, 16 cases of type I endometrioid tumors were studied. Among the sixteen cases, well differentiated endometrioid constituted 50%, moderately differentiated endometrioid tumors constituted 37.5% and higher grade endometrioid constituted 12.5%.

7. In the study, fourteen cases of type II carcinomas were studied. Among the fourteen cases, 57.14% were uterine papillary serous carcinomas and 42.86% were clear cell carcinomas.

8. The most common architectural pattern was tumour cells in glands and sheets forming around 40% of the total tumours followed by tumour cells arranged in glandular pattern comprising 30%, tumour cells in sheets forming 26.6% and the remaining cases forming papillary pattern.

9. The expression of ER in type I carcinomas were 81.25% and in type II tumors 21.43% of cases showed ER positivity. It was found that there was a positive correlation between the expression of ER and type I tumors.

10. The expression of PR in type I carcinomas were 75% and in type II tumors 28.75% of the cases showed PR positivity. In the present study there was a positive correlation between the expression of PR and type I tumors.

11. The expression of p53 in type I carcinomas were 43.75% and in type II tumors 78.57% of the cases showed p53 positivity. In the present study there was positive correlation between the type II endometrial carcinomas and p53 expression.

The immunohistochemical study of ER, PR and p53 and its significance on the prognosis are few in literature when compared to breast carcinoma. Our data will be definitely an important addition to the existing literature and this has to be standardized by further studies.

FURTHER STUDIES

1. The patients with endometrial carcinomas after surgery have to be followed up along with the immunohistochemical status of ER, PR and p53 for assessing the prognosis and to standardize treatment protocols.
2. Expression of additional immunohistochemical markers have to be studied and its implication in the treatment and prognosis of endometrial carcinomas have to be standarised.
3. Based on the above criteria, follow up protocol and management strategies can be standardized.
4. The patients has to be divided into type I and type II, since the type I carcinomas are managed by hysterectomy and hormonal therapy and type II carcinomas are managed by surgery along with chemotherapy and radiotherapy. Further studies with more number of patients are required.
5. Novel markers like expression of ER and PR for type I carcinomas and expression of p53, p16 for type II carcinomas can be made available and their utility for choosing treatment and predicting prognosis has to be standardized.

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Annexur-I

ANNEXURE I - PROFORMA

Department of Pathology

Coimbatore Medical College

Coimbatore

Patientt's name:

Age/Sex

IP No

Occupation

Income

Address

HPE No.

PRESENTING ILLNESS:

History of presenting illness

History of bleeding: Amount- Heavy/moderate/scant

Duration

History of dusmenorrhea

History of white discharge

OBSTETRIC HISTORY

Married since …….. years

Para:…….History of abortions

Last child birth:

Sterilisation history:

MENSTRUAL HISTORY

Age at menarchy

Menstrual cycle:regular/ irregular,Duration

Amount of bleeding

PERSONAL HISTORY

Diet history

Appetite

Bladder and bowel habits

PAST HISTORY

History of diabetes/hypertension

History of any other major illness

History of drug intake

GENERAL EXAMINATION

Built and nourishment

Pallor/icterus/lymphadenopathy

Pulse

Blood pressure

SYSTEMIC EXAMINATION

Cardiovascular system

Respiratory system

Per abdomen: Liver- palpable/normal

Spleen- palpable/normal

Central nervous system

LOCAL EXAMINATION

Speculum examination

Vulva: Healthy/unhealthy

Vagina

Cervix

Vaginal examination

Cervix: Direction

Consistency

Bleeds on touch

Cervical erosion

Uterus: Anteverted/Retroverted

Normal/bulky/small.

Mobile/fixed

LABORATORY EXAMINATION

1.URINE: Albumin

Sugar

Microscopy

2.HAEMATOLOGY

Haemoglobin…….gms%

RBC :……..millions/cumm

WBC count:……/cumm

PCV:……%

MCV……..%

MCH:……%

MCHC:……%Differential count:……./cumm

ESR:……..mm/hr

Blood group and RH type:

Bleeding time…

Clotting time

Peripheral smear

3.BIOCHEMICAL TEST

Blood glucose:…..mg/dl

Blood urea:……mg/dl

Serum creatinine:…..mg/dl

4.RADIOLOGICAL INVESSTIGATION:

Ultrasound findings

Others:

BIOPSY AND HYSTERECTOMY SPECIMEN:

Biopsy

Gross appearance

Microscopy

Hysterectomy specimens

Gross appearance: Size of the specimen

Size of the growth

Proliferative/Irregular/Polypoidal/Infiltrative growth

Myometrial involvement.Serosal involvement

Cervical involvement, Isthmic involvement

Parametrial involvement, Vaginal cuff involvement

Lymph Node status

Annexure - II

ANNEXURE II- MASTER CHART

S.NO	AGE	I.P NO	HISTOPATHOLOGY NO	DIAGNOSIS	HISTOPATHOLOGIC TYPE	HISTOLOGIC TYPE	ER	PR	P53
1	53/F	465	G65	DUB	I	H.G.E	NEGATIVE	NEGATIVE	POSTIVE
2	65/F	71940	G177	DUB	I	WDE	POSTIVE	POSTIVE	NEGATIVE
3	55/F	6325	G332	PAIN ABDOMEN	II	UPSC	NEGATIVE	NEGATIVE	POSTIVE
4	52/F	17474	G367	DUB	II	UPSC	NEGATIVE	NEGATIVE	POSTIVE
5	37/F	38847	G394	DUB	I	MDE	POSTIVE	POSTIVE	NEGATIVE
6	42/F	47084	G497	DUB	II	CC	POSTIVE	NEGATIVE	POSTIVE
7	42/F	50724	G538	PAIN ABDOMEN	I	MDE	POSTIVE	POSTIVE	POSTIVE
8	55/F	52648	G544	DUB	I	MDE	POSTIVE	POSTIVE	NEGATIVE
9	52/F	74411	G995	DUB	II	CC	NEGATIVE	NEGATIVE	POSTIVE
10	60/F	15976	G1287	PAIN ABDOMEN	II	CC	NEGATIVE	NEGATIVE	POSTIVE
11	45/F	56728	G1288	PAIN ABDOMEN	I	H.G.E	NEGATIVE	NEGATIVE	POSTIVE
12	60/F	16728	G1324	DUB	II	CC	NEGATIVE	NEGATIVE	NEGATIVE
13	45/F	24432	G1809	DUB	II	UPSC	POSTIVE	POSTIVE	POSTIVE
14	60/F	568299	P752	DIFFICULTY IN PASSING URINE	I	MDE	POSTIVE	NEGATIVE	POSTIVE
15	60/F	17300	G603	DUB	II	UPSC	NEGATIVE	NEGATIVE	POSTIVE

16	60/F	22669	G632	AMENORRHEA	I	WDE	POSTIVE	POSTIVE	NEGATIVE
17	54/F	804879	G1811	DUB	II	UPSC	NEGATIVE	NEGATIVE	POSTIVE
18	43/F	7654235	P1100	AMENORRHEA	I	WDE	POSTIVE	POSTIVE	NEGATIVE
19	50/F	765	E514	DUB	II	UPSC	NEGATIVE	POSTIVE	POSTIVE
20	48/F	588921	P146/14	DUB	I	WDE	POSTIVE	POSTIVE	NEGATIVE
21	77/F	57161	P665	PAIN ABDOMEN	II	CC	NEGATIVE	NEGATIVE	POSTIVE
22	50/F	568292	P624	DUB	I	MDE	POSTIVE	POSTIVE	POSTIVE
23	55/F	58648	G803	PAIN ABDOMEN	I	WDE	NEGATIVE	POSTIVE	POSTIVE
24	62/F	599766	P559	DUB	I	WDE	POSTIVE	NEGATIVE	NEGATIVE
25	60/F	66662	MLC283	AMENORRHEA	II	UPSC	NEGATIVE	POSTIVE	POSTIVE
26	60/F	57055	G105/14	DUB	I	WDE	POSTIVE	POSTIVE	NEGATIVE
27	60/F	27321	G1871	DUB	I	WDE	POSTIVE	POSTIVE	NEGATIVE
28	50/F	37205	G1164	PAIN ABDOMEN	II	UPSC	POSTIVE	POSTIVE	NEGATIVE
29	70/F	44035	G1298	DUB	I	MDE	POSTIVE	POSTIVE	POSTIVE
30	48/F	47835	G1814	AMENORRHEA	II	CC	NEGATIVE	NEGATIVE	NEGATIVE

ABBREVIATIONS FOR MASTERCHART

WDE	-	WELL DIFFERENTIATED ENDOMETRIOID
MDE	-	MODERATELY DIFFERENTIATED ENDOMETRIOID
HGE	-	HIGHER GRADE ENDOMETRIOID
UPSC	-	UTERINE PAPILLARY SEROUS CARCINOMA
CCC	-	CLEARCELL CARCINOMA
ER	-	ESTROGEN RECEPTOR
PR	-	PROGESTERONE RECEPTOR

Annexure - III

ANNEXURE III

ABBREVIATIONS

ER	-	ESTROGEN RECEPTOR
PR	-	PROGESTERONE RECEPTOR
CEA	-	CARCINOEMBRYONIC ANTIGEN
EIN	-	ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA
CK	-	CYTOKERATIN