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THE ROLE OF P53 EXPRESSION IN ENDOMETRIAL CARCINOMA AND ITS RELATION TO CLINICOPATHOLOGICAL PARAMETERS

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ABSTRACT

Background: Endometrial carcinoma is a primary malignant epithelial tumor, typically with glandular differentiation, that develops in the endometrium and has the potential to invade and metastasize. It ranks sixth among all female cancers, occurring primarily in postmenopausal women. Its incidence is rising due to aging populations and obesity-related factors. The p53 protein is an Immunohistochemical marker assists in prognosis of differentiating tumor subtypes. **Aim of the Study:** To evaluate the role of immunohistochemical expression of p53 in endometrial carcinoma and study the relationship with the clinical and pathological parameters. **Methods:** A cross-sectional retrospective and prospective study was carried out in Basra province. The Data were collected from Basra Teaching Hospitals and private laboratories during the period from January 2020 through September 2025. The study includes 170 histopathological diagnosed cases of endometrial carcinoma representing different histological variants, of which only 57 cases of available paraffin wax blocks were evaluated for p53 expression. Statistical analysis was carried out using SPSS software version 29.0; the collected data were presented as frequency and percentage tables, and Pearson's chi-square test and Exact Fisher test were used to determine if any statistical association was significant or not, and the p-value < 0.05 was considered significant in this study. **Results:** A total of 170 histopathological diagnosed cases of endometrial carcinoma were included in the study. Of these, only 57 cases of available paraffin wax blocks were stained for p53 expression. The mean age 59.7 ±9.47years, age distribution of women ranged from 30 - 77 years old, predominantly in the

age group of 61-70 years, with 38.7% and this was statistically significant. Endometrioid EC was the most common variant (82,4%). The majority of cases were diagnosed in grade 2 (44.7%). Stage 1 tumors were the most frequent (76.5%). Immunohistochemical staining revealed a 52.6% for wild subtype for p53 expression, (47.4%) for mutant strong expression subtypes. **Conclusions:** Endometrioid carcinoma was the most common variant, with high incidence of EC Between Postmenopausal Women, and the peak incidence occurring in the 6th and 7th decades of life. A significant statistical association was observed between p53 expression with non-endometrioid tumor variants (serous, clear cell carcinoma and carcinosarcoma) but not with tumor grades.

KEYWORDS: Endometrial Carcinoma, Immunohistochemistry, P53 expression, Tumor Grade, histological subtypes.

1. INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Endometrial carcinoma is a primary malignant epithelial tumor, typically with glandular differentiation, that develops in the endometrium and has the potential to invade and metastasize. it is the most common invasive cancer of the female genital tract in developed countries.[1]

Endometrial carcinoma (EC) ranks sixth among all female cancers, occurring primarily in postmenopausal women. Its incidence is rising due to aging populations and obesity-related factors.[2] Although an excellent prognosis is associated with early-stage disease, treatment for late-stage cases is challenging, and options remain limited.[3] It is typically classified into two major types based on clinical and pathological features[3]:

- Type 1 (endometrioid endometrial carcinoma and mucinous carcinoma).
- Type 2 (non-endometrioid endometrial carcinoma) includes histological subtypes like serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated, and dedifferentiated carcinoma.

P53 is a protein made by the TP53 gene and works as a tumor suppressor.

It controls the cell cycle, DNA repair, and apoptosis. When everything is normal, p53 prevents cells from turning into cancer cells.

The p53 protein is a prognostic Immunohistochemical marker in endometrial carcinoma, its expression assists in prognosis of differentiating tumor subtypes. Its separates high-grade

carcinoma, which usually shows abnormal mutant-type p53 expression, from low-grade endometrioid carcinoma, which usually shows a wild-type pattern.

Abnormal expression of this suppressor protein is linked to tumor aggressiveness. Abnormal p53 expression shows TP53 mutations that drive rapid cell growth and cause instability.

Consequently, p53 status is closely linked to prognosis, with p53-abnormal expression endometrial carcinomas demonstrating higher recurrence rates and poorer clinical outcomes compared to other molecular subgroups. It may also influence treatment decisions.[4]

1.2 Aim of study

To evaluate the Immunohistochemical expression of p53 in endometrial carcinoma and study the relationship with the clinical and pathological parameters.

1.3 LITERATURE REVIEW

1.3.1 Endometrial Carcinoma

Endometrial carcinoma (EC) is a malignant tumor arising from the lining of the uterus. It is the most common gynecologic malignancy in developed countries and predominantly affects postmenopausal women. Most common in women aged 55-65 years. Incidence differs worldwide, with elevated rates in developed nations.[1]

1.3.2 Epidemiology

Endometrial cancer (EC) is the most common gynecologic malignancy in women worldwide. In the past two decades, cases of endometrial cancer have seen a significant increase. EC shows regional variation, with numbers that can be ten times higher in some places than in others. The highest figures are seen in North America, Europe, Micronesia/Polynesia, and Australia/New Zealand.

The lowest figures appear in African regions and South-Central Asia. Globally, EC ranks 15th among all cancer types.[1] Around 70% of EC cases are diagnosed at an early stage. EC primarily affects postmenopausal women, with an average age at diagnosis of 60 years, although 14–20% of cases occur in premenopausal women.[5]

In Iraq, EC ranks 16th among all cancers, with 688 new cases and 196 deaths, according to GLOBOCAN 2022. The Iraq National Cancer Registry (2023) reports that EC is among the top 15 cancers in Iraqi women, with an age-standardized incidence rate (ASIR) of 4.7 per

100,000 women.[6,7]

A study on the frequency and incidence of the ten most common types of cancer found that endometrial cancers are the most prevalent in adult females in Basra, Iraq, in 2017.[8]

1.3.3 Risk factors and pathophysiology

Endometrial carcinoma (EC) develops through multiple hormonal, metabolic, genetic, and iatrogenic mechanisms. These risk factors differ between Type I (endometrioid) and Type II (non-endometrioid) tumors.[5]

- **Hormonal and Reproductive Factors:** Prolonged unopposed estrogen exposure, whether due to endogenous overproduction (PCOS, granulosa cell tumors, ovarian hyperthecosis, and stromal hyperplasia) or inadequate progesterone opposition, drives endometrial hyperplasia and increases the risk of endometrial carcinoma by approximately threefold.[9]

- **Iatrogenic and Medication-Related.**
  - **Tamoxifen:** increases the risk of endometrial carcinoma two- to threefold via its partial estrogen-agonist effect on the endometrium, with elevated incidence of both Type I and aggressive Type II tumors, necessitating vigilant monitoring among breast cancer patients receiving long-term therapy.[10]
  - **Tibolone:** has been associated with increased risks of ovarian and endometrial carcinoma, particularly hormone-sensitive subtypes, while the impact of HRT on EC risk varies by formulation and BMI, as evidenced by differential risk patterns observed among estrogen-only users with elevated BMI.[11]
  - **Pelvic radiation:** Although pelvic RT improves locoregional control in early-stage endometrial cancer, it does not enhance overall survival and may increase second primary malignancy risk, particularly in women under 60, underscoring the need for individualized risk–benefit assessment.[12]

- **Metabolic and Lifestyle Factors**
  - **Obesity:** it contributes to nearly half of all EC cases by increasing aromatase-mediated estrogen production, with EC risk rising 2.6-fold in obese and 4.7-fold in severely obese women compared with those of normal BMI.[13]
  - **Diabetes mellitus**: Hyperinsulinemia and insulin resistance appear to promote endometrial carcinogenesis independently of obesity, with high insulinemic lifestyle

patterns and elevated markers such as the TyG index significantly associated with increased EC risk.[14]

- **Hypertension:** Hypertension may modestly increase EC risk, but the association remains inconclusive due to confounding by obesity and diabetes.[15]
- **Smoking:** Associated with reduced risk of type I EC, no effect on type II.[16]

- **Age:** EC risk and poor prognosis increase with age, and later menopause (> 46 years) further elevates risk due to extended estrogen exposure.[17]
- **Genetic and Familial Syndromes**: Hereditary cancer syndromes such as Lynch syndrome, Cowden syndrome, and Muir-Torre syndrome significantly elevate EC risk due to defects in MMR and PTEN pathways, while Turner syndrome carries risk primarily when long-term unopposed estrogen therapy is used.[18]

1.4 Histotypes and Immunophenotypes of Endometrial Carcinoma according to WHO 2020. Appendix I.[19]

1.4.1 Endometrioid Adenocarcinoma, low grade

Type I endometrial carcinoma is an estrogen-dependent malignancy and represents approximately 80% of all EC cases. It is typically associated with a favorable prognosis and a high five-year disease-free survival rate. Most tumors are classified as FIGO grade 1 or 2 and commonly arise from precursor lesions such as endometrial hyperplasia or endometrial intraepithelial neoplasia (EIN).

At the molecular level, Type I EC frequently exhibits alterations in genes involved in key signaling pathways, including PTEN, KRAS, and PIK3CA, which contribute to tumor development and progression.[5,20]

Histologically, these tumors are characterized by neoplastic glands resembling normal proliferative endometrium. The glands are typically oval or round with smooth outlines and are lined by columnar to cuboid epithelial cells showing pseudo-stratification and low-grade, round to oval nuclei. Squamous or mucinous metaplasia may be present, and the tumor is often associated with background EIN, the recognized precursor lesion of most Type I ECs.[21]

According to the International Federation of Gynecology and Obstetrics (FIGO) grading system, ECs are classified primarily by the percentage of non-squamous solid growth.

Tumors with less than 50% solid growth are classified as low grade. However, the presence of severe nuclear atypia is defined by marked nuclear pleomorphism, irregular nuclear contours, coarse chromatin, and prominent nucleoli visible at low power, resulting in upgrading the tumor by one grade.[19,21]

Immunophenotype

- Positive for (ER/PR, INI1 Retained, PAX8, Pan ck)
- Negative for (p53 wild pattern, p16, AMACR, NAPSIN A, AMACR, MMR - proficient (40-60%))
- Variable: (HNF1B, PTEN, ARID 1A, B-catenin).

- FIGO 1: predominant glandular growth, < 5% non-squamous solid component; glandular architecture is characterized by a patent lumen in the gland, relatively preserved polarity of the epithelium, and absent to mild epithelial stratification.[19]
- FIGO 2: 6−50% non-squamous solid component.[21]

1.4.2 Endometrioid Adenocarcinoma, high grade

More than 50% solid growth, or 6%–50% solid growth with diffuse marked nuclear atypia; oval or round glands with smooth outlines lined by columnar to cuboidal cells with pseudostratified, low-grade, oval to round nuclei, with or without squamous or mucinous metaplasia, with or without background EIN.[19]

Immunophenotype

- Positive for (ER/PR, retained INI1, PAX8, Pan ck, abn p53 25%)
- Negative for (p16, AMACR, NAPSIN A, AMACR, MMR focal (40-60%))
- Variable: (HNF1B, PTEN, ARID 1A, B-catenin).

- FIGO 3: > 50% non-squamous solid component. High-grade endometrioid carcinoma has a worse prognosis compared to FIGO 1–2 tumors.[21]

1.4.3 Endometrioid Adenocarcinoma histological variants

Different variants of Endometrioid Adenocarcinoma share a common gland structure but may differ in appearance, growth morphology, and molecular structure, among other features.[19]

- **The glandular (Villous) variant:** It has papillary or villous structures with delicate fibrovascular cores. This variant contains tumor cells with mild to moderate atypia. It is

common in women and typically has a good prognosis. The primary diagnostic obstacle is to differentiate the Villous variant from serous carcinoma. Serous carcinoma generally has abnormal p53 expression.[22]

- **Secretory variant:** It has a glandular or tubular architecture. The variant shows tumor cells with subnuclear vacuoles mimicking secretory endometrium. This variant typically has nuclei that are uniform and of low-grade equivalent to FIGO grade 1. It is associated with a favorable prognosis.[23]
- **Ciliated cell variant:** Tumor glands are lined by ciliated columnar epithelial cells whose nuclei are bland and uniform. It is rare and, for the most part, has an indolent clinical course.[23,24]
- **Squamous differentiation:** occurs in up to 25% of cases, such as non-keratinizing morules or keratinizing foci. It does not affect prognosis but closely mimics mixed carcinoma.[23,24]

Immunophenotype: Negative for (p53, ER/PR, HNF-1B, Napsin –A, AMACR, PTEN, ARID 1A, β-catenin, MMR, IN1, PAX8)

- **Mucinous differentiation:** The tumor cells have intracytoplasmic mucin resembling endocervical-type glands. When > 50% of the tumor is mucinous, it is classified as mucinous carcinoma. The prognosis of the tumor is comparable to the prognosis of endometrioid carcinoma.[23,24]
- **Sertoli form variant:** This variant takes on the appearance of Sertoli cell tumors, with tube-like or cord-like structures. It remains ER and PR positive. This variant tumor is usually of low-grade p53 type, slow acting.[24,25]
- **Corded and hyalinized variant:** With cords or nests of tumor cells in a hyalinized stroma. It may be misdiagnosed as stromal, and this variant may have CTNNB1 (β-catenin) mutations. It has a favorable prognosis with a risk of local recurrence.[24,25]
- **Morular (β-catenin)** demonstrates squamous morules without keratinization, and most notably in the gland regions. CTNNB1 mutations that keep β-catenin in the nucleus associated with morular (β-catenin) metaplasia are also known to result from nuclear β-catenin accumulation. Morular (β-catenin) metaplasia is a benign feature and has no adverse effect on prognosis.[25,26]
- **Mesonephric differentiation:** It is a very rare variant. It consists of glands and tubules reminiscent of remnants. Mesonephric-like differentiation, on the other hand, is aggressive. It typically exhibits more aggressive behavior than the regular endometrioid

carcinoma.[25,26]

Immunophenotype

- Positive for (MMR focal, INI1 retained, PAN–CK)
- Negative for (null p53, P16, ER/PR, HNF-1B, Napsin -A, AMACR, PTEN, ARID 1A, β-catenin)
- Variable (PAX8, GATA 3, TTF1).

1.4.4 Serous Adenocarcinoma

It is a high-grade estrogen-independent type of endometrial carcinoma, which accounts for 5-10 % of all cases. It predominantly affects non-obese postmenopausal women and is typically associated with endometrial polyps or within a background of thin atrophied endometrium.

Despite being small or minimally invasive at diagnosis, Uterine Serous Carcinoma (USC) demonstrates a strong propensity for early extra-uterine spread and is frequently detected at an advanced stage.[24]

Histologically, USC is characterized by papillary and solid architectural patterns accompanied by marked cytological atypia. Tumor cells show pronounced nuclear pleomorphism, coarse chromatin, prominent nucleoli, and high mitotic bodies.

Additional microscopic features include tumor cell budding and tufting, slit-like glandular spaces, complex branching papillae, psammoma bodies, and variable areas of necrosis. Morphologically, USC closely resembles high-grade serous carcinomas of the ovary and fallopian tube.[24,27]

At the molecular level, USC is strongly associated with TP53 mutations, which correlate with aberrant p53 Immunohistochemical staining patterns. These molecular alterations underpin the aggressive biological behavior and poor clinical prognosis characteristic of this tumor subtype.[27]

Immunophenotype

- Positive for (mutant p53, PTEN (mutated), p16, ARIDA 1A, MMR, INI1, PAX8, Pan ck)
- Negative for (HNF1, AMACR, b-catenin)
- Variable (ER/PR, NAPSINA).

1.4.5 Clear cell endometrial carcinoma

It is a rare type II EC, accounting for less than 5% of all cases. Histologically, it resembles ovarian clear cell carcinoma and is characterized by clear or eosinophilic (oxyphilic) cytoplasm and distinctive hobnail cells.[28]

The tumor exhibits variable architectural patterns, most commonly solid, but glandular and papillary configurations may also occur. Hobnail cells, which show apical cytoplasmic protrusions and dark, irregular nuclei, are atypically present in tubular and papillary areas and may be less evident in solid tumor nests.[26]

Immunophenotype

- Positive for (abnormal (mutated) p53 30%, HNF-1b, NapsinA, AMACR, PTEN).
- Negative for (p16, ER/PR, B-catenin).
- Variable: (ARID1A, proficient MMR).

1.4.6 Carcinosarcoma (Malignant Mixed Müllerian tumor) (MMMT)

Uterine carcinosarcoma is a rare, highly aggressive malignancy of the uterus. It accounts for less than 5% of gynecologic cancers and is most commonly diagnosed in post-menopausal women, with a mean age of approximately 65 years. It is more frequently observed in black women.[3,29]

Clinically, the tumor often presents as a polyploid mass accompanied by excessive uterine bleeding and areas of necrosis.[3]

Histologically, carcinosarcoma is characterized by a biphasic pattern consisting of malignant epithelial and mesenchymal components. The epithelial part usually resembles endometrioid or serous carcinoma, while the mesenchymal parts may be homologous, such as endometrial stromal sarcoma, or highly aggressive behavior, poor clinical outcomes, and an elevated mortality rate.[30]

Immunophenotype

- Positive for (mutant p53, P16, INI1 retained).
- Negative for (HNF-1B, Napsin –A, AMACR deficient, PTEN, ARID 1A, B-catenin).
- Variable (ER/PR, MMR, PAX8, PAN-CK, Myogenin).

1.4.7 Undifferentiated/ dedifferentiated endometrial carcinoma

It is a rare type, accounting for about 2% of all ECs.[21] Differentiated carcinoma consists of a low-grade endometrial component alongside an undifferentiated component, forming a biologically aggressive entity which is called dedifferentiated endometrial carcinoma. Histologically, these tumors show solid sheets of discohesive cells with no glandular differentiation, often mimicking sarcomas or hematopoietic malignancies, which is called undifferentiated.[31]

Distinguishing them from FIGO grade 3 endometrioid carcinoma is crucial, as they carry a significantly poorer prognosis.[32]

Most cases arise in peri and post-menopausal women, with rare but highly aggressive presentations in younger patients.

Molecular alteration frequently involves loss of SWI/SNF complex components such as SMARCA4, SMARCB1, ARID1A, or ARID1B, supporting their classification within molecular subtypes of EC.[31,32]

Immunophenotype

- Negative for (mutant P53, p16, ER/ PR, HNF-1b, NAPSIN A, AMACR, B-catenin, ARID 1A, (50-6-%) MMR, INI1 -30%, PAX8).
- Variable: (PTEN, pan ck, Cd138, neuroendocrine).

1.5 Molecular Classification

The Cancer Genome Atlas (TCGA) has divided cancer into four molecular categories. Each group has its own Immunohistochemical characteristics, clinical behavior, and genetic changes. Treatment decisions are increasingly informed by molecular classification, and prognosis information becomes available.[33]

- **The POLE Ultra-Mutated (Ultra-Mutated)**

The POLE ultra-mutated subtype of EC is characterized by pathogenic mutations in the exonuclease (DNA) proofreading domain of the POLE gene, resulting in an exceptionally high tumor mutational burden.

Histologically, these tumors may display aggressive features; however, despite this appearance, the POLE ultra-mutated subtype is associated with an excellent prognosis. The

favorable clinical outcome is attributed to a strong antitumor immune response triggered by the abundance of neoantigens generated by the high mutation rate.[33,34]

POLE-mutated carcinomas typically show a wild-type p53 immunostaining pattern and occur around 60-62 years of age. Owing to their favorable outcomes, reduced adjuvant therapy is often appropriate despite the presence of high-risk pathological features.[34]

- **Microsatellite Instability-High (Hyper-mutated)**

Microsatellite Instability-High EC is defined by a mismatch repair deficiency due to loss of MLH1, MLH2, MSH6, or PMS2, resulting in a high mutational burden that is lower than that seen in POLE-mutated tumors.[35] These cancers usually show wild-type p53 expression, occur around 65-66 years of age, and have an intermediate prognosis, worse than POLE-mutated tumors but better than p53 abnormal carcinomas. Owing to their high neoantigen load, MSI-H tumors respond well to immune checkpoint inhibitors and are increasingly important in precision oncology.[35]

- **Copy Number Low (CN Low)**

The copy-number low (CN-Low), also termed the non-specific molecular profile (NSMP) subtype, is characterized by minimal somatic copy-number alterations and the absence of POLE mutations, mismatch repair deficiency, and p53 abnormalities, distinguishing it from other molecular subtypes. These tumors are most commonly low to intermediate grade Type I ECs and frequently harbor mutations in PTEN, PIK3CA, CTNNB1, and KRAS, while retaining wild-type p53 expression.[35]

Clinically, CN-Low ECs typically occur in older women (around 72 years of age), show hormone receptor positivity, and have a stable genomic profile. Prognostically, they demonstrate an intermediate but generally favorable outcome, with slower tumor behavior and potential responsiveness to hormonal therapy.[36]

- **Copy Number High (CN High)**

The version of copy-number high (CN-High) refers to the p53-serous-like copy-number of the cancer, which is the most genetically unstable type of endometrial carcinoma and is characterized by extensive somatic copy-number changes.[3]

These tumors consistently show abnormal p53 immunoexpression, either diffuse or

overexpression or complete absence, reflecting underlying TP53 mutations.[35] CN-High carcinomas are frequently associated with Type II histology, especially uterine serous carcinoma, but also include a subset of high-grade endometrioid tumors.[37]

Clinically, this subtype carries the poorest prognosis among TCGA molecular classes, with aggressive behavior and a high recurrence rate. CN-High tumors typically occur in older women (mean age 72 years) and are considered high risk, usually requiring intensive treatment.[36,37]

1.6 Presentation and Clinical Diagnosis

Irregular vaginal bleeding is the main warning sign of endometrial carcinoma, and EC accounts for 20 % of postmenopausal bleeding. Other symptoms include intermenstrual bleeding, pelvic pain, and abnormal or heavy bleeding in premenopausal women. Most cases are detected early because symptoms appear early.[38]

Women aged 65 and older should be educated about EC symptoms, while screening is not recommended for asymptomatic women.[39] Transvaginal ultrasound is the initial test for assessing endometrial thickness, with suspicious findings confirmed by hysteroscopy and biopsy.[38,40]

MRI is preferred for staging due to its accuracy in detecting myometrial invasion, whereas CT is mainly used to evaluate advanced or metastatic diseases.[40]

1.7 Staging

1.7.1 The Federation International of Gynecology and Obstetrics (FIGO) staging 2023 of cancer of the endometrium, as explained below[21]

Appendix II

1.7.2 TNM Staging of cancer of the endometrium according to the American Joint Committee on Cancer AJCC[40]

Appendix III

1.8 Treatment

Early-stage EC is primarily treated with total hysterectomy and bilateral salpingo-oophorectomy, usually via minimally invasive surgery. Lymph node dissection is reserved for intermediate and high-risk cases, while sentinel lymph node biopsy is increasingly used

for staging in specialized centers.[38,41]

Omentectomy is recommended for high-risk histology such as serous carcinoma, carcinosarcoma, and undifferentiated tumors. In advanced disease (FIGO III, IV), cytoreductive surgery is advised when feasible, with palliative surgery considered for symptom control in selected metastatic cases.[42]

Selected patients with grade 1, endometrium-confined disease may undergo fertility-sparing treatment using progestin therapy, followed by definitive surgery after childbearing.[43]

1.9 Role of p53 in Endometrial Carcinoma

Consequently, accurate interpretation of p53 immunohistochemistry (IHC) is fundamental to the differential diagnosis of endometrial carcinoma. Correct interpretation of p53 immunohistochemistry (IHC) alters how doctors categorize risk and treatment considerations. Tumors of p53 (p53abn) have always demonstrated worse progression-free survival and overall survival than NSMP tumors. Abnormal p53 (p53abn) tumors affect outcome prediction.[44]

The more recent ESGO–ESTRO–ESP guidelines suggest that physicians provide combined external-beam radiotherapy and chemotherapy to patients with stage I disease with myometrial invasion up to stage IVA p53abn disease. The p53abn disease has clinical features, as the guidelines explain.[41]

The newly available targeted therapies are PARP inhibitors for the recombination-deficient tumors and anti-HER2 therapy for HER2-amplified disease. Since changes are more common in the p53abn subtype, the doctors are now seeking out the new targeted therapies. Numerous studies have reported an agreement between p53 IHC staining patterns and TP53 mutation state. This agreement shows that the p53 IHC and the TP53 mutation status can be used instead of each other if the p53 abnormalities are found correctly. Next-generation sequencing (NGS) methods covering the whole TP53 gene are good alternatives for molecular classification as an alternative to p53 IHC in both the clinic and studies.[44]

Thus, interpretation of p53 Immunohistochemical (IHC) staining is essential to estimate the molecular status of the TP53 gene in endometrial carcinoma. Four prominent staining patterns are identified[43], each corresponding to distinct types of TP53 changes:

- In wild-type, Heterogonous nuclear staining of medium strength can be observed in 10 to 60 percent of tumor cell nuclei. The pattern of wild type indicates p53 expression. The wild-type configuration generally indicates no TP53 mutation.[45]
- The overexpression pattern is characterized by very intense, spread-out staining in more than 80 percent of tumor cells. Missense TP53 mutations are a usual cause of our overexpression pattern. With missense TP53 mutations present, the p53 protein doesn't break down.[45]
- The null (aberrant) pattern shows an absolute absence of nuclear staining in tumor cells, with positive staining of the background non-neoplastic tissue functioning as the internal control; this signature is most frequently associated with nonsense, frameshift, or splice site mutations resulting in truncated, nonfunctional protein and lost expression.[46]
- Cytoplasmic (aberrant) pattern is a less frequent pattern that shows the predominance of cytoplasmic staining alongside absent or insignificant nuclear staining and is associated with specific TP53 mutations that attenuate the nuclear signal, leading to p53 mislocalization. Taking into consideration these patterns render p53 IHC is an appropriate surrogate for TP53 mutation profiling in endometrial carcinoma.[47]

2. PATIENTS AND METHOD

2.1 *Sources of data*

This research was a cross-sectional, retrospective study conducted in Basra. The data were collected from Basra Teaching Hospitals and private laboratories during the period from January 2020 through September 2025.

All cases of Endometrial carcinoma were diagnosed after hysterectomy during the last five years, and only 57 cases with available wax blocks were included for immunohistochemistry stain with p53.

2.2 *Patients and data collection*

The study included 170 cases of newly diagnosed endometrial carcinoma, but only 57 available blocks. Formalin-fixed, paraffin-embedded sections 3-5 μm thick were prepared for immunohistochemistry with p53.

The following parameters were recorded

- Age of the patient
- Histological type of endometrial carcinoma

- Grade of endometrial carcinoma
- Stage of endometrial carcinoma, if it's available.

2.3 *Methods*

2.3.1 *Instruments and equipment*

The equipment used in the processing and staining of the histological sections was displayed in the following box:

Box 1: Instruments and equipment
Positively charged microscopic slides.
Super frosted microscopic slides
Slide holder
Coverslips
Drying oven
Microwave
Microtome
Water bath
Glass staining jar
Light microscope
Hydrophobic slide marking pen
Timer
Rubber gloves
Tissue papers for drying the slides

2.3.2 *Tissue marker*

The study was carried out by using p53 Primary antibody (Mouse monoclonal anti-p53 antibody, clone BP-53-12, PathnSitu Biotechnologies or equivalent).

2.3.3 *Chemicals*

The chemicals used to obtain paraffin-embedded sections for IHC staining are displayed in the following box:

Box 2: Chemicals
Ethanol Alcohol with different concentrations (50%, 70%, 90%, absolute)
PathnSitu 's Biotechnologies multiple epitope retrieval system (MERS)
Primary Mouse monoclonal anti-p53 antibody (clone BP-53-12,PathnSitu Biotechnologies or equivalent)
Xylene
Distilled water
Mayer's hematoxylin and eosin solutions
DPX (Dibutylphthalate Polystyrene Xylene)

2.3.4 *Immunohistochemical specific detection kit*

The Immunohistochemical specific detection kit is shown in the following box:

Box 3: Immunohistochemistry-specific detection kit
Peroxidase Block, PolyExcel hydrogen peroxide vol. 50 ml (PathnSitu's)
PolyExcel Target Binder PolyExcel HRP-labeled polymer
PolyExcel Stunn DAB Substrate Chromogen
PolyExcel Stunn DAB Substrate Buffer

2.3.5 *Method*

Formalin-fixed, paraffin-embedded blocks were collected. Sections with a thickness of 3 to 5 µm were obtained and stained using routine hematoxylin and eosin stains. The slides were examined to define the histological type and grade. (In accordance with the updated WHO classification 2020 and the Histological grading system).

Additional sections using positively charged slides were provided for Immunohistochemical staining for the p53 marker.

2.3.6 *Immunohistochemistry staining*

1. The tissue sections were mounted on positively charged slides and put in a hot air oven at 70 C˚ for one-hour duration for baking.
2. Deparaffinization and rehydration of the tissue section at room temperature were done by the following steps:

- The slides were immersed in three xylene jars, each jar for 5 minutes.
- Then the slides were immersed in alcohol of different concentrations, 100%, 70%, and 50% respectively, each jar for 3 minutes.
- Then the slides were immersed in two jars of distilled water, each jar for 2minutes.

3. Antigen retrieval was done by putting the slides in pathnsitu's staining jar and adding sufficient amount of 1x Tris-EDTA buffer pH (8.0 -9.0) according to manufacturer's instructions. to cover tissue sections on the slides. The jar then was placed in pathnSitu MERS for 15minutes.
4. The staining jar then was taken out and let cool at room temperature for 10 minutes.
5. Pap pen was used to encircle the representative tissue section to minimize the usage of the reagents used.
6. Endogenous peroxidase was blocked by adding PolyExcel hydrogen peroxide and incubated at room temperature for 10 minutes.
7. The peroxidase block was drained off by tilting the slides and washing with an immuno-

wash buffer in 3 jars, each jar for one minute.

8. p53 primary antibodies (Mouse monoclonal anti-p53 antibody, clone BP-53-12, PathnSitu Biotechnologies or equivalent) were added and incubated for (30-60) minutes at room temperature, then washed with an immuno-wash buffer in 3 jars, each jar for one minute.
9. Apply the mouse-linker (EnVision FLEX+Mouse LINKER), the reagent is intended for signal amplification of primary mouse antibodies, incubated for 10-15 minutes.
10. PolyExcel Target Binder was added and incubated at room temperature for 10 minutes, then washed with an immuno-wash buffer in 3 jars, each jar for one minute.
11. Using PolyExcel HRP labelled polymer and 10 minutes' incubation followed by washing with an immuno-wash buffer in 3 jars, each jar for one minute.
12. Staining is completed by a 5-10-minute incubation in the dark. PolyExcel Stunn DAB working solution (prepared by adding 1ml of Stunn DAB Buffer, adding a drop of Stunn DAB chromogen, mixing well, and storing it in the dark) followed by washing in distilled water for 2 minutes, then with immuno-wash buffer in 2 jars, each jar for one minute.
13. The slides were then counterstained with hematoxylin, washed with tap water till the counterstain washed away.
14. Dehydrate and mount the tissue sections with DPX.

The interpretation of p53 immunoreactivity was based exclusively on nuclear staining patterns and categorized into:

- Mutant overexpression pattern
- Complete absence (null) pattern
- And wild-type (heterogeneous) pattern, (in comparison with an external positive control slide stain).

2.4 *Statistical analysis*

The statistical analysis: IBM SPSS Statistics version 29.0 was used for the statistical analysis of qualitative data, which are represented as percentages (%) and the number of respondents, are examined using the Pearson Chi-squared test. Differences are deemed statistically significant at $p < 0.05$.

3. RESULTS

This study included 170 histopathologically confirmed cases of endometrial carcinoma, representing different histological variants, of which only 57 cases of available paraffin wax

blocks were evaluated for p53 expression.

3.1 *Age Distribution*

Table (3-1) shows that the age distribution of cases ranged from 30 to 77 years, with a mean age of 59.7 ±9.47 years, and that the majority (86%) of patients were older than 50 years.

Most patients, 38.9%, were 61-70 years old, followed by those aged 51-60 (37.1%), and only 1 woman (0.6%) was ≤ 30 years old. This distribution was statistically significant ($p < 0.05$).

Table 3-1: Age distribution of study Population.

Age (Year)	Frequency	Percent	P- value
≤30	1	0.6	<0.001*SA
31-40	7	4.0	
41-50	15	8.8	
51-60	63	37.1	
61-70	66	38.9	
>70	18	10.6	
Total	170	100	

*** Chi-square test**

3.2 *Variants of endometrial carcinoma*

Regarding the type of carcinoma variants, the most common variant was Endometrioid EC, accounting for 140 (82.4%) of cases. This is followed by serous carcinoma (18 cases,10.6%), while carcinosarcoma (7 cases,4.1%) and clear cell carcinoma (5case,2.9%) represent relatively small proportions. As illustrated in Figure 3-1.

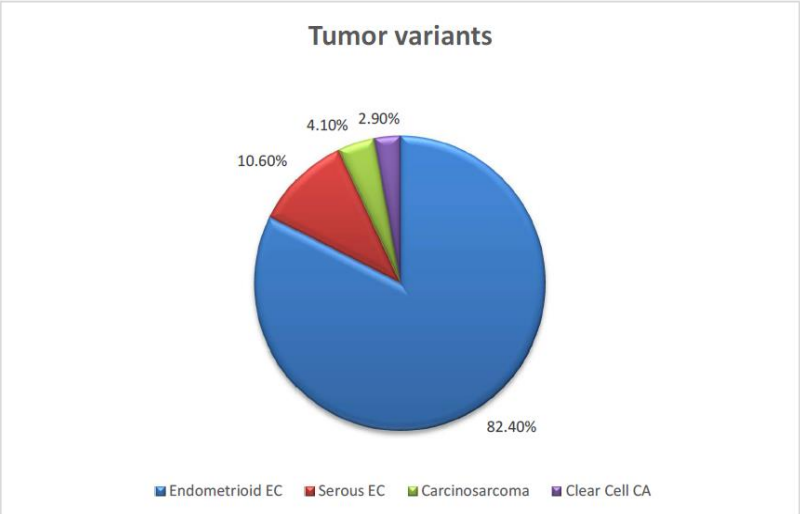


Figure 3.1: Pie chart showing variants of endometrial carcinoma.

3.3 *Grades of endometrial carcinoma*

Most patients 76 cases (44.7%) fall into grade 2, followed by grade 1 was 57 cases (33.5%) and then grade 3 was 37 cases (21.8%), as shown in Table 3-2.

Table (3-2): Distribution of study population according to tumor grade frequency.

Grade	Frequency	Percent
Grade 1	57	33.5
Grade 2	76	44.7
Grade 3	37	21.8
Total	170	100

3.4 *Association between variants of endometrial carcinoma and age of study population*

The table (3-3) demonstrates that endometrioid EC is the predominant subtype across all age groups, accounting for 82.4% of cases. It is most frequent in women aged 51-70 years, while serous EC represents 10.6% of cases and occurs mainly in older age groups > (51 years), with no cases observed below 30 or above 70 years.

Carcinosarcoma (4.1%) and clear cell carcinoma (2.9%) are relatively rare and are almost seen in patients aged > 51 years, particularly in the elderly >71 years.

Younger women < 40 years show a nearly predominance of endometrioid. A statistically significant association between histological variants of EC and patient age group ($p < 0.05$)

Table (3-3): Association between variants of the endometrial carcinoma and age groups. *Exact Fisher test.

Variant	Age group (Year) N (%)							P-value
	≤30	31-40	41-50	51-60	61-70	>70	Total	
Endometrioid EC	1(100)	6(85.7)	14 (9.3%)	51(80.9)	55(83.4)	13(72.2)	**140(82.4)**	**<0.001 *SA**
Serous EC	0(0)	1(14.3)	1(6.7)	8 (12.7)	8(12.1)	0(0)	**18(10.6)**	
Carcinosarcoma	0(0)	0(0)	0(0)	2 (3.2)	2(3.0)	3(16.7)	**7(4.1)**	
Clear Cell CA	0(0)	0(0)	0(0)	2(3.2)	1(1.5)	2(11.1)	**5(2.9)**	
Total	**1(100)**	**7(100)**	**15(100)**	**63(100)**	**66(100)**	**18(100)**	**170(100)**	

3.5 *Association between grades of endometrial carcinoma and age of study population*

The distribution of tumor grades across age groups shows a shift toward higher-grade tumors in older age groups, which are most frequently observed in individuals over 50 years old. The peak of grade 2 occurs in the 61-70 age group (54.6%), followed by the 51-60 age group (42.9%). Additionally, high-grade (grade 3) tumors are more common in women (61- 70) years, with a prevalence of 38.9%. This association is statistically significant ($p < 0.001$), as shown in Figure 3-2.

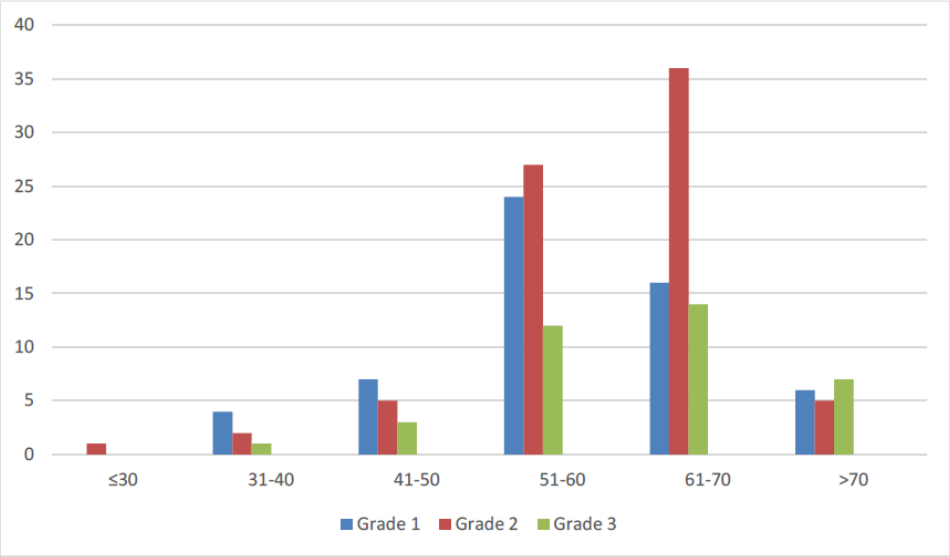


Figure (3-2): Distribution of endometrial carcinoma grades by age groups.

3.6 *Distribution of the study patients according to tumor stage*

Figure (3-3) shows that Stage 1 was the most common in the study sample 130 cases (76.5%), followed by Stage 2 was 35 cases (20.6%), and the least was Stage 3 was 5 cases (2.9%).

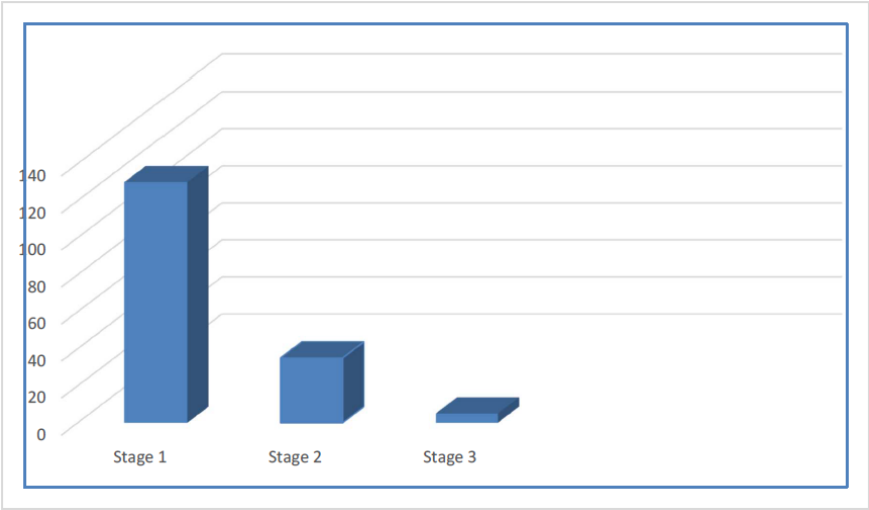


Figure (3-3): Distribution of the study population by tumor stage.

3.7 *Distribution of the study population according to p53 expression results*

Among the 57 patients assessed for p53 expression, 52.6% showed a wild-type p53 pattern, while 47.4% demonstrated a mutant-type p53 pattern in the patients with endometrial carcinoma. This is illustrated in Figure 3-4.

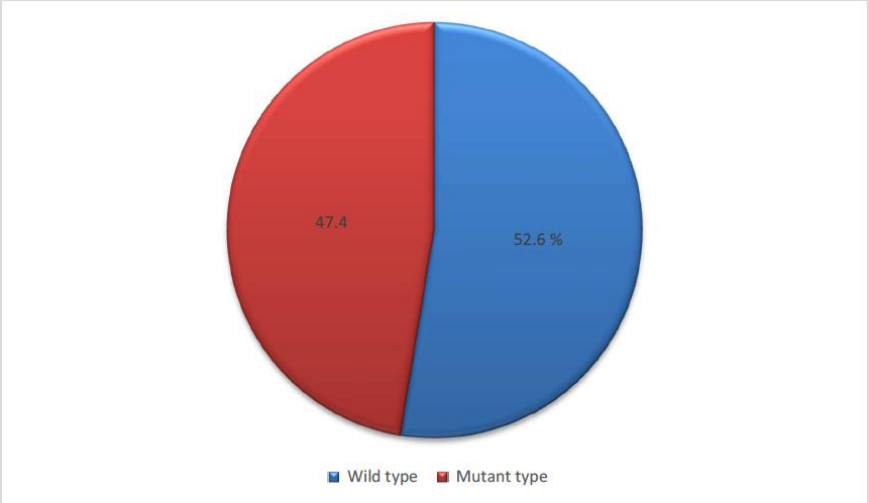


Figure (3-4): Pie chart of the distribution of the study population by the result of p53 expression.

3.8 *Association between variants of Endometrial Carcinoma and p53 Expression*

Among the p53-stained cases, Endometrioid EC constitutes the majority of cases (71.9%), which showed the highest proportion of wild-type p53 expression (96.7%), with fewer cases showing mutant type (42.8%) of all mutant cases. While Serous EC, carcinosarcoma, and Clear Cell CA showed predominant mutant-type p53 expression. Serous EC accounted for 25% of all mutant p53 cases despite its low overall frequency, and carcinosarcoma (21.4%) and Clear Cell CA (7.1%) were exclusively associated with mutant-type p53, as also shown in Figure 3-5.

Overall, mutant-type p53expression clustered strongly in non-endometrioid, high-grade histology, and this was statistically significant ($p < 0.05$).

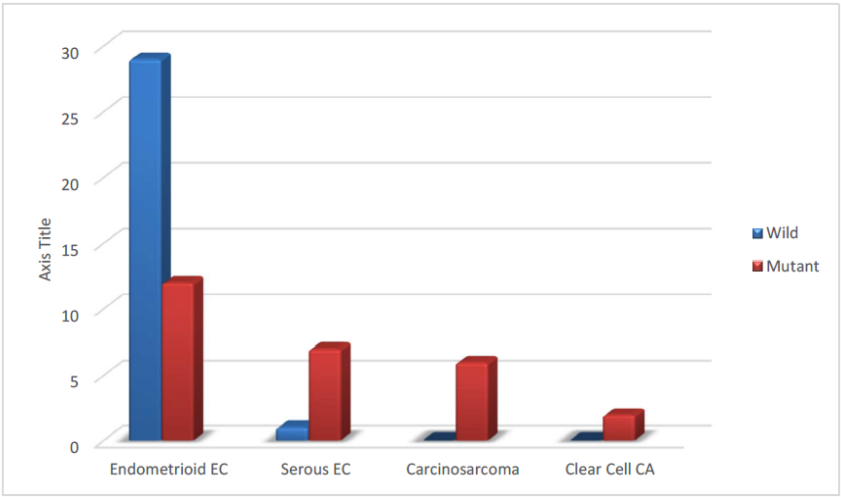


Figure (3-5): Association between Tumor variants and p53 expression.

3.9 *Association between Grades of Endometrial Carcinoma and p53 expression*

Evaluating the relationship between tumor grade and p53 expression pattern shows that wild-type cases were mainly distributed in grades 1 and 2 (11 cases, 36.7%) and (18 cases, 60%), respectively. Whereas the mutant group was predominantly observed in grade 3 (17 cases, 63%) with fewer cases in grade 1 (3 cases, 11.1%) and grade 2 (7 cases, 25.9%), notably 94.4% of all grade 3 cases were mutant, indicating a strong association between mutation status and disease activity as shown in Figure 3-6.

This association between the grade of tumor and p53 expression was not statistically significant ($p > 0.05$).

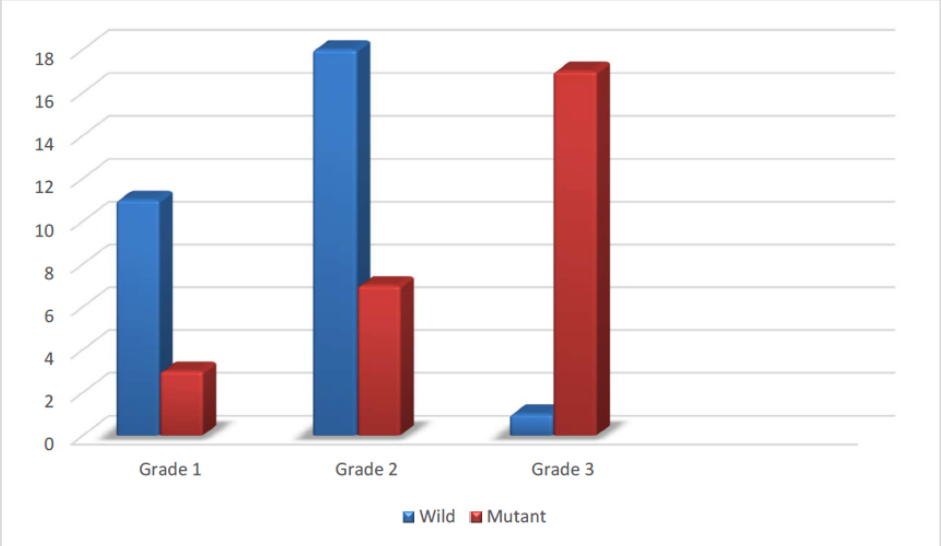
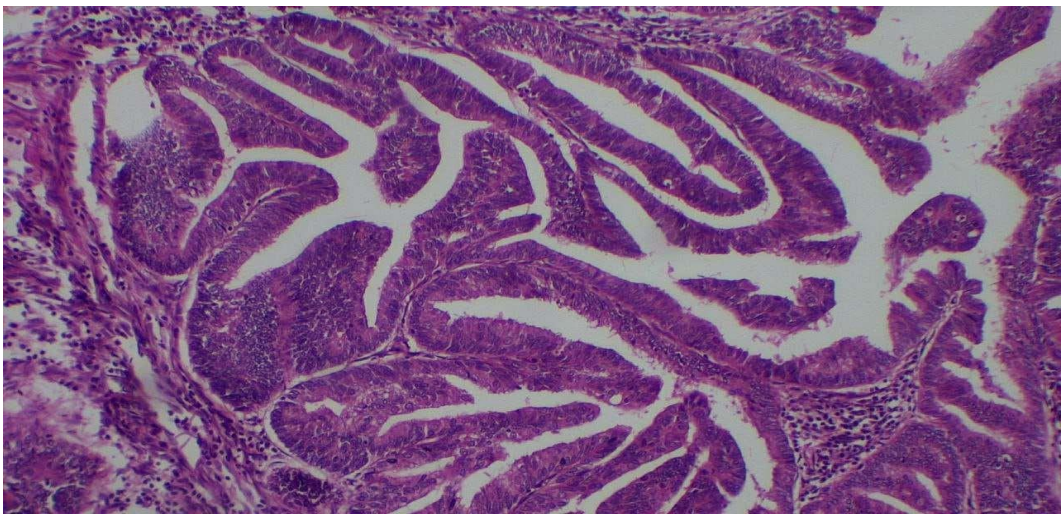


Figure 3-6: Association between endometrial carcinoma grades and p53 expression.

A.



B.

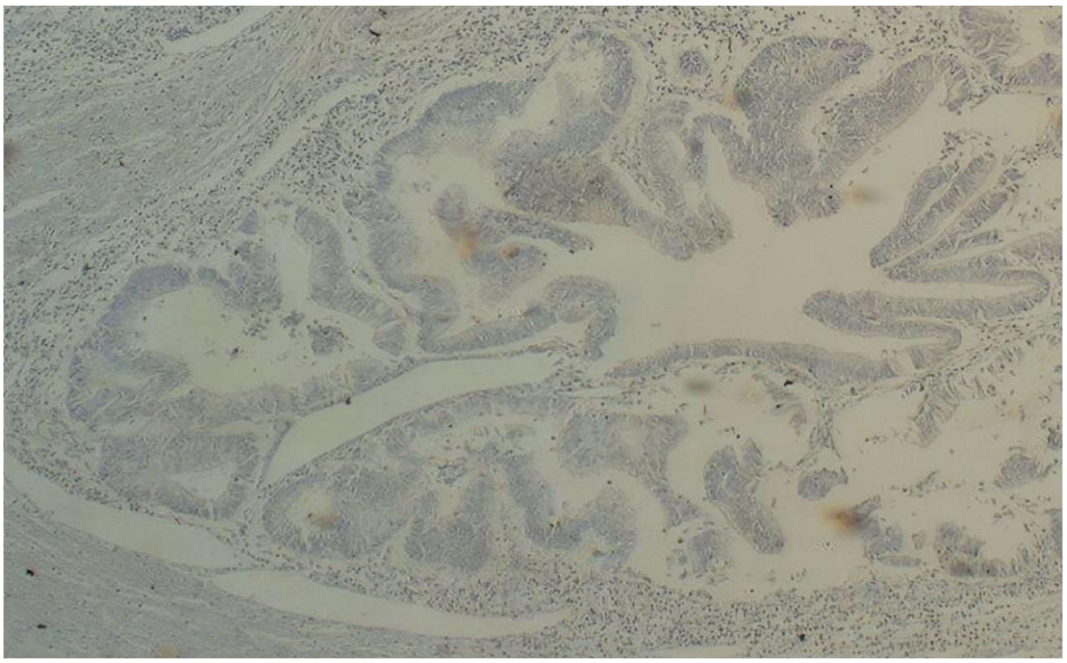
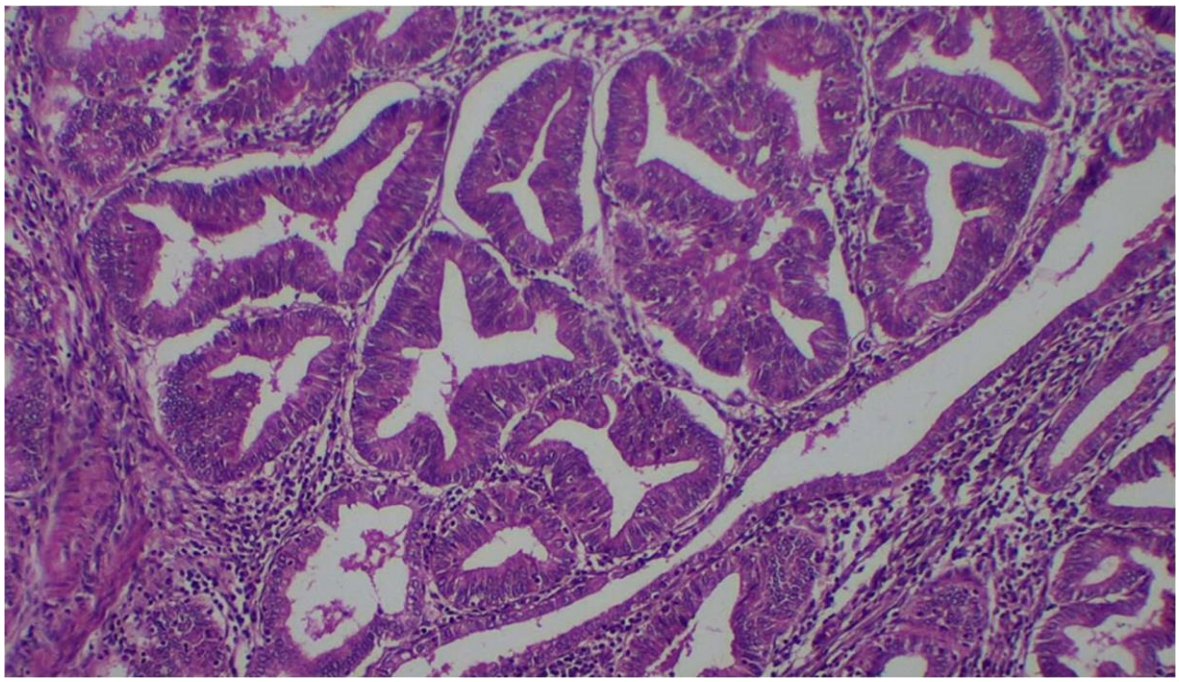


Figure (3-7): Endometrioid endometrial carcinoma ،grade 1.

A. H&E staining(100X).

B. p53 null nuclear pattern(100X).

A.



B.

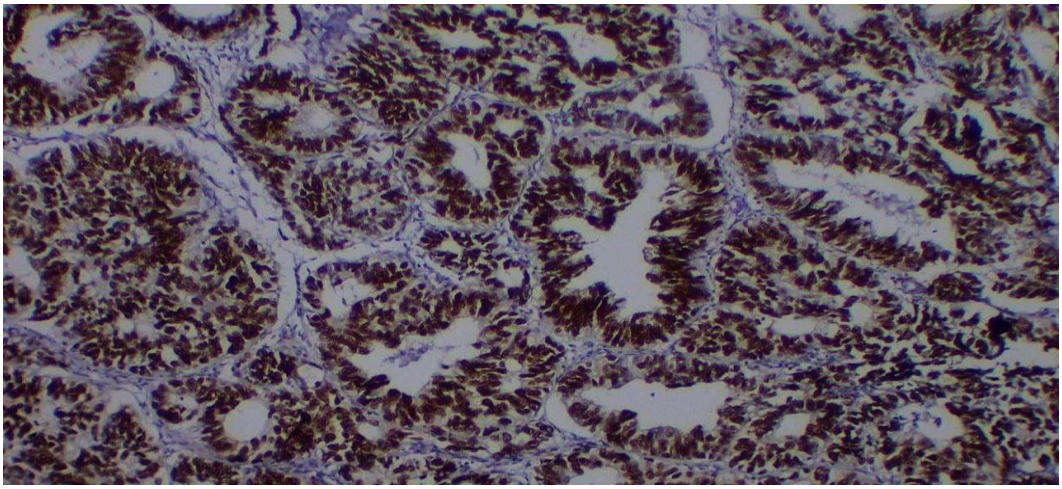
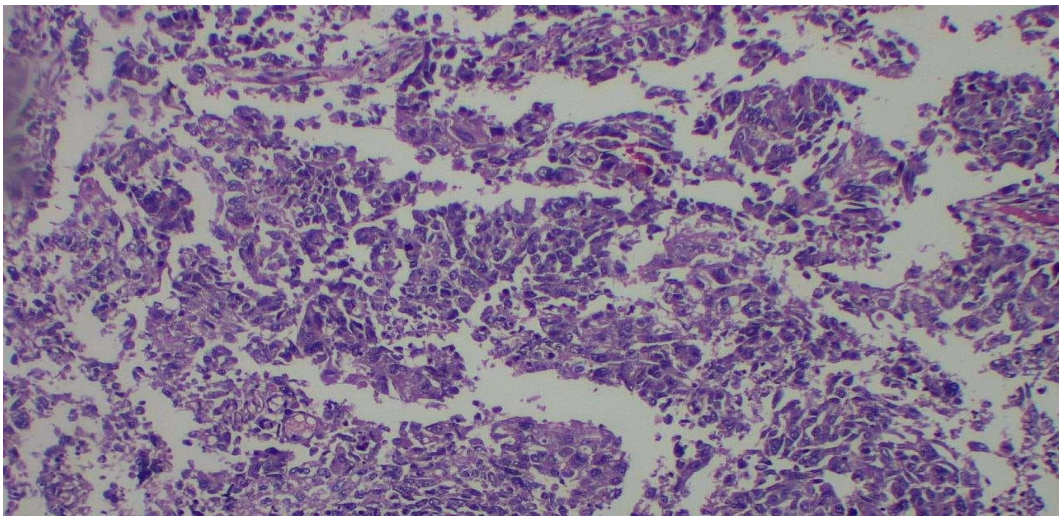


Figure (3-8): Endometrioid endometrial carcinoma ،grade 2.

A. H&E staining(100X).

B. p53 mutant overexpression diffuse-type nuclear expression(100X).

A.



B.

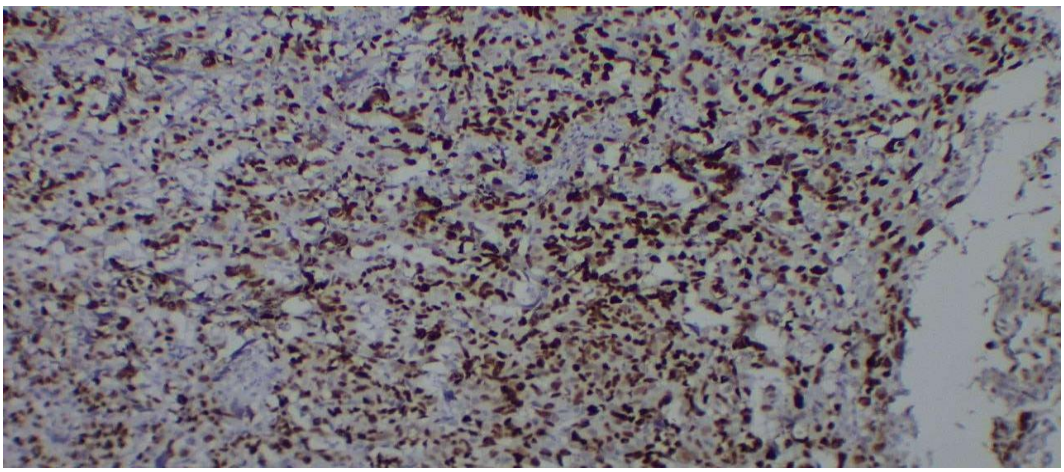
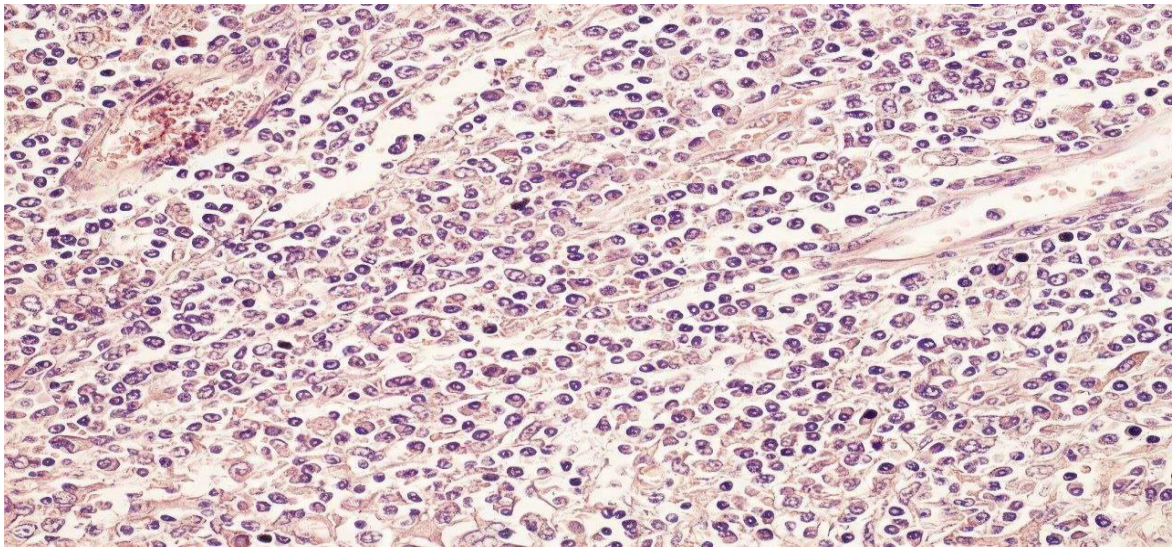


Figure 3-9: Endometrioid endometrial carcinoma, grade 3.

A. H&E staining(100X).

B. p53 mutant-type nuclear expression(100X).

A.



B.

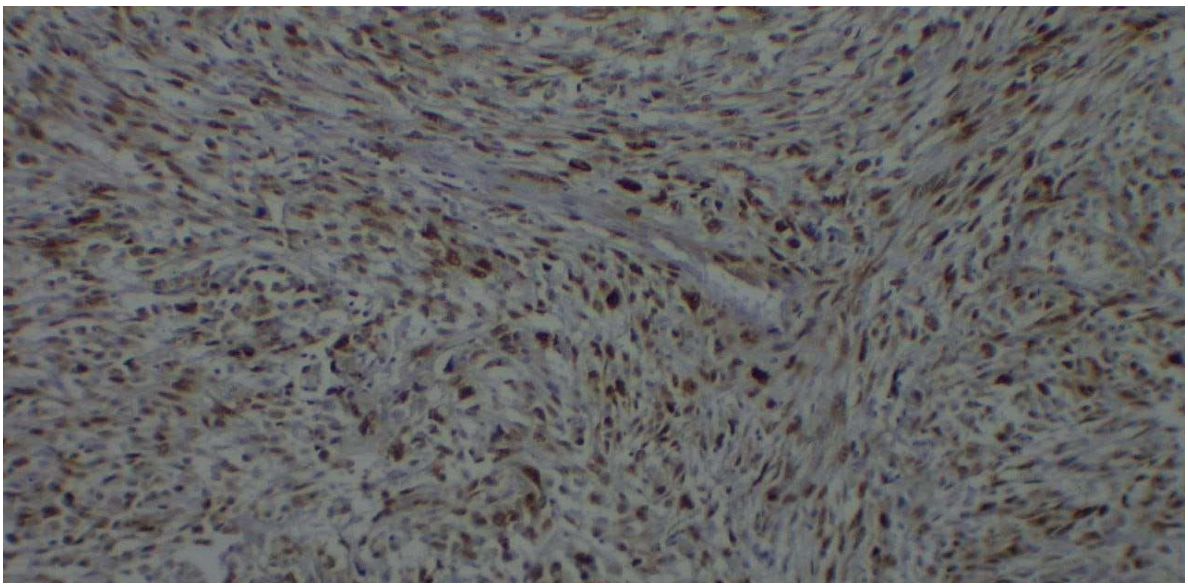
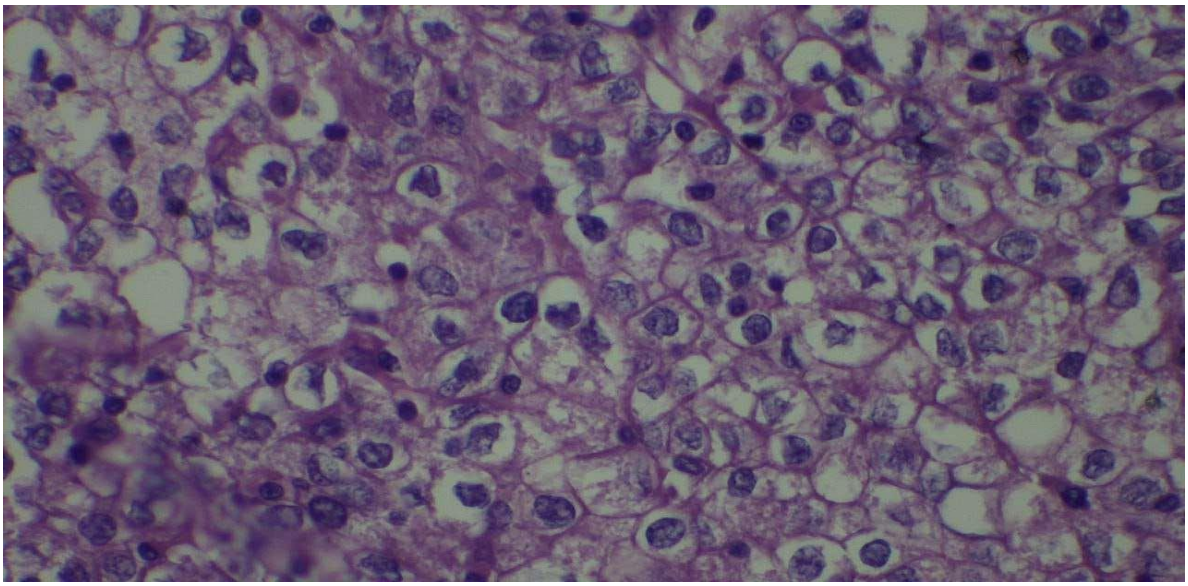


Figure (3-10): Endometrial carcinoma with sarcomatoid features, grade3

A. H&E staining(100X).

B. Tumor cells showing mutant-type p53 diffuse and strong nuclear expression (100X).

A.



B.

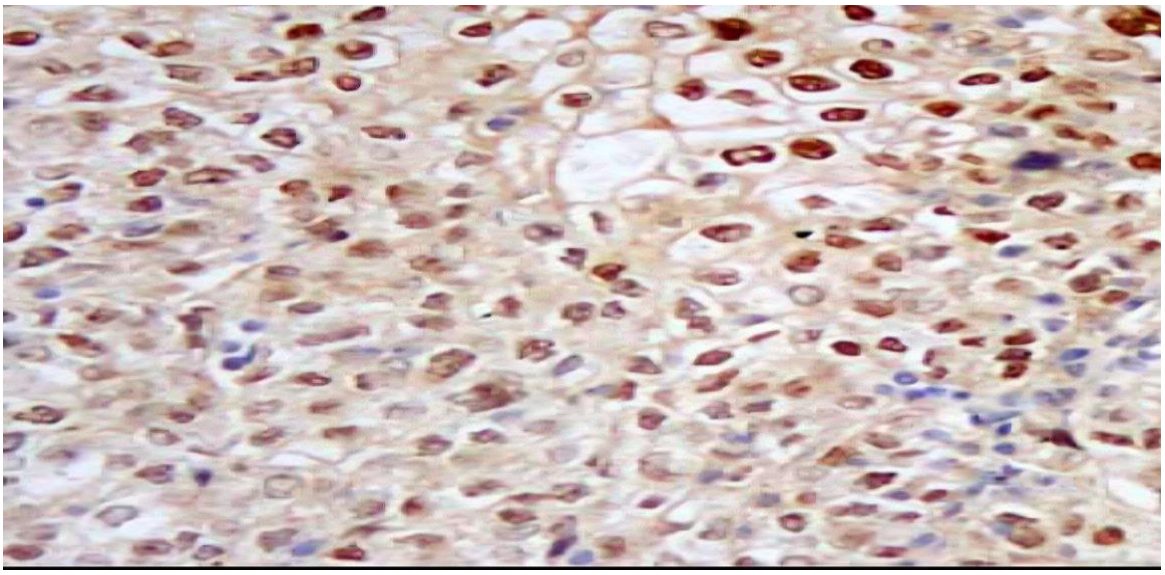
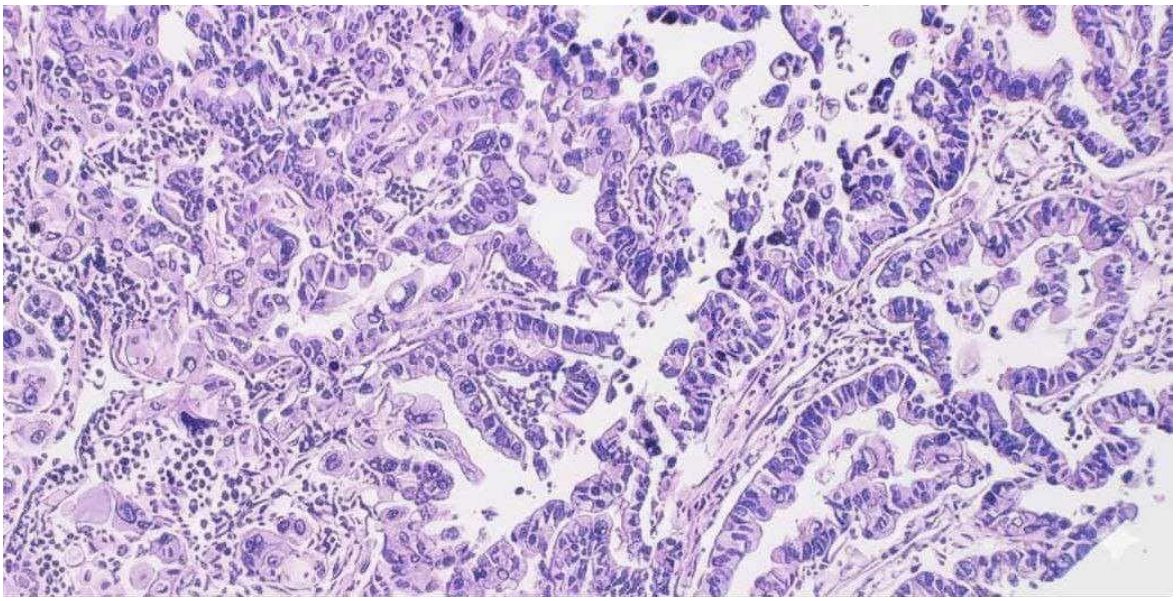


Figure 3-11: Clear cell variant endometrial Adenocarcinoma.

A. H&E staining(400X).

B. p53 mutant-type diffuse and strong nuclear expression (400X).

A.



B.

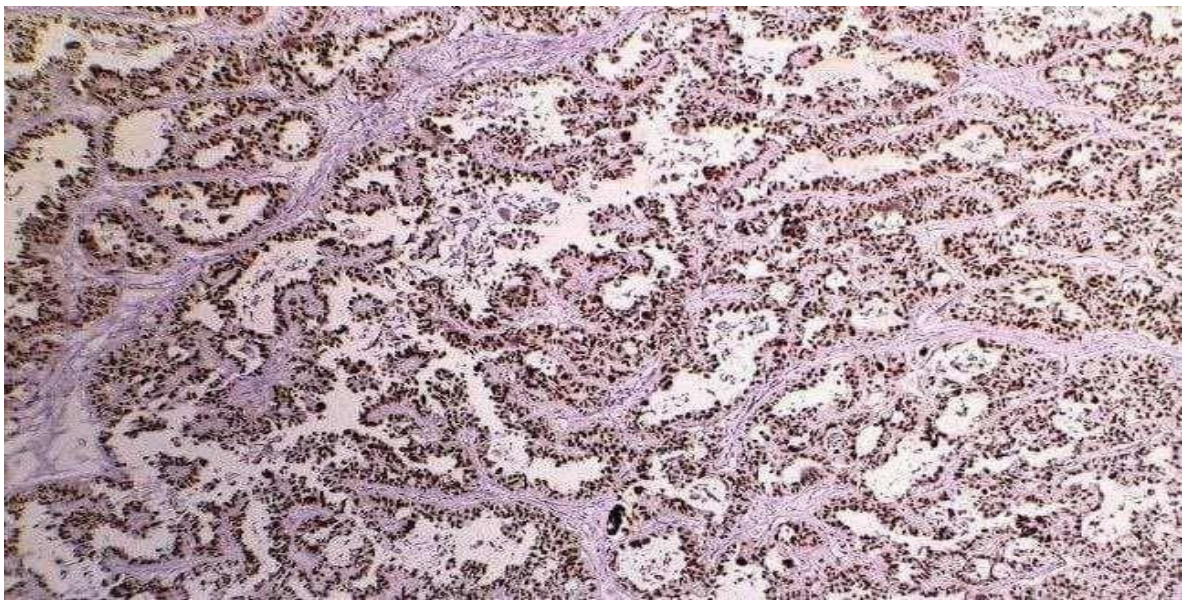
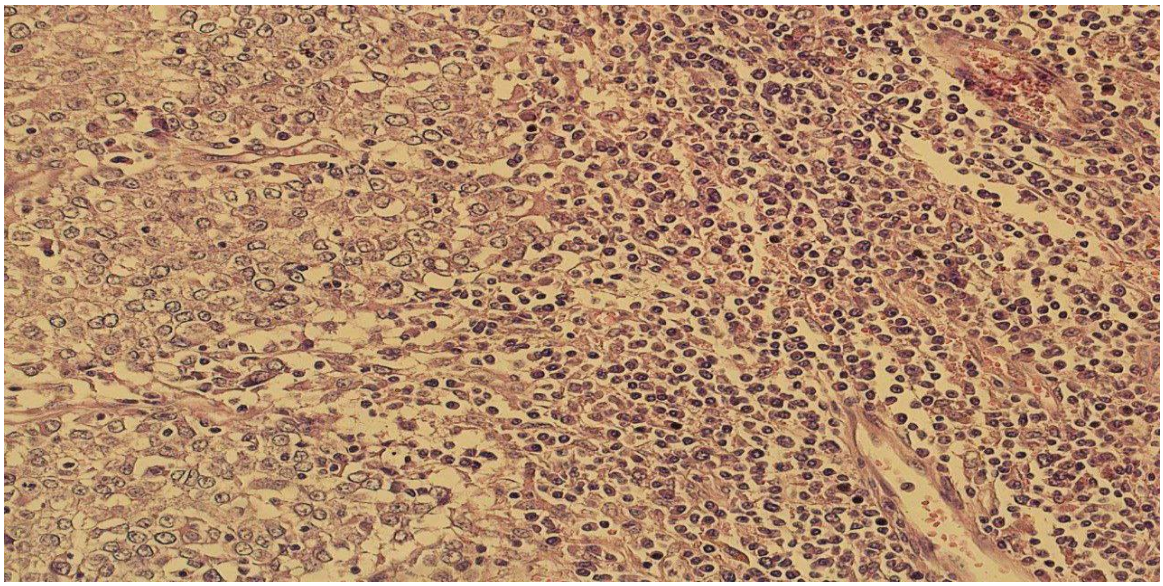


Figure (3-12): Serous endometrial Carcinoma.

A. H&E staining(400X).

B. Serous carcinoma showing mutant-type p53 overexpression nuclear expression(100X).

A.



B.

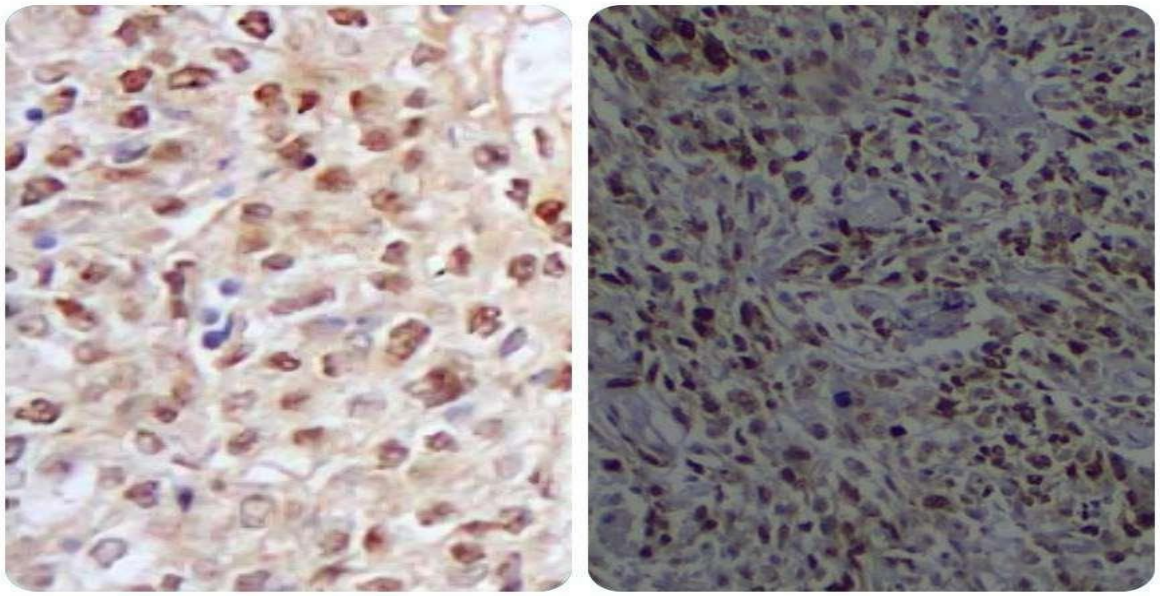


Figure (3-13): Endometrial carcinosarcoma (MMMT).

A. H&E staining showing biphasic tumor components(40X).

B. Tumor cells showing mutant-type p53 overexpression nuclear expression(400X).

4. DISCUSSION

The current study offers new insights into the importance of p53 expression patterns in endometrial carcinoma and their association with key clinicopathological features. By examining p53 immunohistochemistry across various histological subtypes and tumor grades, the study aimed to better understand its potential as both a diagnostic and prognostic biomarker in EC.

The age distribution of the study sample reflects the typical epidemiology of EC (mostly older and post-menopausal women). When compared with earlier reports, the age data of this study are compatible with the majority of published literature, such as a study by Wang et al of 576 EC patients classified by molecular subtypes with an age range of 24-80 across the cohort.[48]

Similarly, an Indian study reported that 81% of EC cases occurred in women aged above 50 years, matching the classical age-risk profile of the disease, suggesting that age is an important factor influencing the variant types of EC.[49] In contrast, a large recent epidemiologic analysis of U.S. cancer registry data (2000-2019) found a disproportionate increase in endometrial cancer incidence among women under age 50.[50]

The histological distribution observed indicated the predominance of endometrioid EC. This trend aligns with global epidemiologic data, which shows that endometrioid carcinoma is the most common histologic subtype of EC, accounting for 75–80% of cases. High-grade tumors remain rare but are clinically important.[51] Also, a study from Jeddah supports a dominant proportion of Endometrioid carcinoma (70%), reinforcing this finding across diverse geographic and demographic settings.[52]

Endometrioid EC is typically estrogen-dependent, often presents at an early stage, and is associated with a favorable prognosis. Its high prevalence explains why endometrioid EC dominates most institutional and population-based series.[53] In contrast, serous EC, although representing only 10.6% of cases in this study, is clinically significant due to its aggressive behavior, high likelihood of extra-uterine spread, and poor prognosis. This proportion is consistent with published reports indicating that serous carcinoma accounts for approximately 5-10% of ECs but contributes disproportionately to EC-related mortality.[42]

Carcinosarcoma and clear cell carcinoma are rare variants, together constituting less than 10% of cases, which aligns with published data reporting incidence of approximately 3-5% and 1-5%, respectively. Despite their low prevalence, these subtypes are recognized as high-risk grade tumors with aggressive clinical behavior and unfavorable outcomes, underscoring their importance in histopathological classifications and treatment planning.[42]

According to the FIGO grading system, low-grade endometrioid carcinomas (grade 1 and 2) generally behave less aggressively, whereas grade 3 tumors show a higher risk.[54]

The predominance of low to moderate grade (1 and 2) tumors in this study agrees well with multiple recent studies, which report that the majority of EC cases present as low-grade disease, as Verde et al found that more than 85% of patients present with low-grade variant.[55] A large retrospective study of 776 patients with endometrioid EC found that although grade 2 tumors had distinct pathological features compared to grade 1 and grade 3, their oncologic outcomes (overall survival) largely trended towards those of grade 1, supporting the practice of grouping grade I and grade II as lower risk in many settings.[56]

The observed age-related distribution of EC variants aligns well with established clinicopathological and molecular classifications. Endometrioid EC, typically classified as Type I EC, is estrogen-dependent and commonly present in perimenopausal and early postmenopausal women, often arising from endometrial hyperplasia. This explains its dominance across most age groups, particularly between 51 and 70 years. However, recent molecular studies suggest that tumor biology may not always correlate strictly with age or histological subtype. High-risk molecular profiles, particularly p53-abnormal tumors, can occasionally occur in younger patients, while favorable molecular subtypes may be identified in older women, as reported by Talhouk et al.[57] Also, a study by Lax et al. reported that, although uncommon, serous carcinoma can occur in younger women.[23] This highlights the growing importance of molecular classification alongside conventional clinicopathological parameters.

In the present study, a statistically significant association was observed between patient age and tumor grade, with higher-grade EC occurring more frequently in older age groups; Grade 1 tumors were predominantly diagnosed in women aged 51-60 years, whereas Grade 2 tumors were most common among those aged 61-70 years. Notably, Grade 3 tumors showed their highest frequency in women older than 70 years. This pattern aligns with recent studies that demonstrate a strong association between advancing age and more aggressive histologic features and higher-grade EC. A similar result was reported by Ercelep et al and Singh et al that high-grade and Poorly Differentiated tumors are more prevalent in older women, and that increasing age is an independent predictor of adverse pathological features, deeper myometrial invasion, and poorer outcomes.[58,24]

Furthermore, large study analyses have shown that the incidence of high-grade and type II EC rises significantly after the age of 60, reflecting age-related changes in tumor biology and molecular pathways, including increased frequency of p53 mutation among older patients.[5]

The distribution of p53 expression in this investigation shows that most patients (52.6%) had wild-type p53 immunohistochemically expressed, which is consistent with the established epidemiology of EC.[60] Wild-type p53 expression, which represents the majority of cases, is characteristic of type I (endometrioid, low-grade) tumors, which typically demonstrate estrogen-driven pathogenesis and favorable clinical outcomes. In contrast, the p53-abnormal tumors represent a smaller but clinically significant proportion, similar to findings from a recent meta-analysis of high-grade endometrioid EC reporting a prevalence of abnormal p53 of about 30% with increased risk of death and disease progression compared with patients with wild-type EC.[59]

Similarly, p53 wild patterns were predominantly observed in endometrioid carcinoma. In 292 consecutive EC cases, 77% p53 wild type, 14.7% p53-abnormal, and all serous CA and carcinosarcoma were p53-abnormal, which were common in high-grade EC.[61]

The findings of this study reveal a strong and significant association between p53 expression patterns and tumor histologic subtypes, which is consistent with the molecular classification of EC proposed by The Cancer Genome Atlas and validated by multiple international studies.[42]

Low-grade (well and moderately differentiated) EC in this study demonstrated wild-type p53 expression, with 60%, 36.7% respectively. This agrees with the existing literature by Leon-Castillo et al. and Singh et al., where EC, especially low-grade types, is strongly associated with wild-type p53.[26,45]

In contrast, p53-abnormal expression was most frequent in serous CA (31.8%), clear cell carcinoma (27.3%), and carcinosarcoma (9.3%), which is fully consistent with established evidence identifying these histotypes as strongly linked to p53 abnormalities.[60]

Kobel et al. demonstrated that p53-abnormal tumors are associated with aggressive pathological characteristics and poor prognosis, which further supports the findings of the present study.[46]

The overall trend supports established molecular evidence that p53 abnormal tumors are typically high grade, whereas p53 wild-type tumors are usually low grade, despite the absence of statistical significance. This is likely because of the small sample size of the study population.

CONCLUSION

1. Endometrial carcinoma primarily affects postmenopausal women with predominance of low-to-moderate grade EC exhibiting a wild-type p53 expression pattern.
2. The prevalence of high-grade endometrial carcinoma variants is increasing with age, expressing mutant p53 patterns such as serous and clear cell carcinoma, and is linked to aggressive disease behavior and poor prognosis.
3. This study demonstrates the role of p53 expression patterns in EC and reinforces its association with clinicopathological factors such as tumor histologic subtypes, grades, and patient age.
4. Integration of p53 into the molecular classification framework alongside traditional histopathological grading.

Recommendations

1. Routine incorporation of p53 immunohistochemistry, especially in identifying high-risk histological subtypes and high- grade tumors.
2. Age-Sensitive Clinical Surveillance: Given their increased risk profile, older patients should be given more careful clinical surveillance and possibly aggressive treatment options because growing older is linked to higher-grade and p53 mutant EC.
3. Further large- scale prospective studies are recommended to validate the prognostic utility of p53 expression patterns in endometrial carcinoma.
4. A multimodal diagnostic approach combining histopathology and immunohistochemistry, and molecular profiling to optimize risk stratification to improve patient outcomes in EC.
5. Long-term follow-up studies with larger sample sizes are recommended in endometrial carcinoma to improve the reliability and validity of the results.
6. Routine assessment of lymphovascular invasion is recommended due to its significant prognostic value and its role in guiding further management**.**

APPENDICES

Appendix I: Genomic-based endometrial carcinoma subtypes (37)

Table 33.1 Genomic-based endometrial carcinoma subtypes

TCGA CATEGORY[223]	GENOMIC ALTERATION	SURROGATE MARKER	FORMER DESIGNATION[229]	AGE[217]	PROGNOSIS	HISTOTYPE
CN low	Few mutations, low # of somatic copy number alterations	Absence of POLE EDM, MMR-D and p53 abn	Type I	65 years	Intermediate	Endometrioid (usually grade 1 or 2)
CN high	Few mutations, low # of somatic copy number alterations	p53 abn	Type II	72 years	Poor	Serous and some grade 3 endometrioid
Hypermutated	Many mutations	MMR-D	NA	66 years	Intermediate	Mostly endometrioid, may be high grade
Ultramutated	Very many mutations	POLE EDM	NA	62 years	Favorable	Endometrioid, may be high grade

CN high, High numbers of somatic copy number abnormalities; *CN low*, low numbers of somatic copy number abnormalities; *MMR-D*, mismatch repair deficient; *NA*, not applicable; *p53 abn*, abnormal p53 expression by immunohistochemistry that is either complete absence of expression or strong diffuse overexpression; *POLE EDM*, mutations in the POLE exonuclease domain; *TCGA*, The Cancer Genome Atlas.

Appendix II: The International Federation of Gynecology and Obstetrics (FIGO) staging 2023 of cancer of the endometrium, as explained below: (21).

FIGO 2023	Description
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIB1	Metastasis or direct spread to the vagina and/or the parametria
IIIB2	Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
IIIC1	Metastasis to the pelvic lymph nodes
IIIC1i	Micrometastasis
IIIC1ii	Macrometastasis
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
IIIC2i	Micrometastasis
IIIC2ii	Macrometastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Appendix III: TNM Staging of cancer of the endometrium according to the American Joint Committee on Cancer AJCC (40).

Stage	Stage grouping	Stage description*
I	T1 N0 M0	The tumor is growing inside the uterus and/or is limited to the uterus and ovary for non-aggressive types. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IA	T1a N0 M0	The tumor is limited to the endometrium (inner lining of the uterus) [IA1]. Or The tumor is a non-aggressive histologic type with growth less than halfway through the underlying muscle layer of the uterus (the myometrium) with no or focal lymphovascular space involvement (LVSI)** [IA2]. Or The tumor is a non-aggressive histologic type limited to the uterus and ovary [IA3]. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IB	T1b N0 M0	Non-aggressive histologic types with growth more than halfway through the myometrium, but not beyond the body of the uterus, with no or focal LVSI [IB] The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IC		Aggressive histologic types are limited to the endometrium.
II	T2 N0 M0	The cancer has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix (called the cervical stroma). Or There is substantial LVSI. Or The cancer is an aggressive histologic type with any invasion into the myometrium. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IIA		Non-aggressive histologic type with invasion of the cervical stroma
IIB		Non-aggressive histologic type with substantial LVSI
IIC	T2 N0 M0	Aggressive histologic type with any myometrial invasion
III	T3 N0 M0	The cancer has spread outside the uterus but has not spread to the inner lining of the rectum or urinary bladder (T3).
IIIA	T3a N0 M0	The tumor has spread to the ovary or fallopian tube (and the criteria for stage IA3 is not met) [IIIA1] The tumor has spread to the outer surface of the uterus (called the serosa) [IIIA2]. The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IIIB	T3b N0 M0	The cancer has spread to the vagina or to the tissues around the uterus (the parametrium). [IIIB1] The cancer has spread to the pelvic peritoneum (The peritoneum is a sheet of smooth tissue that lines the abdomen and pelvis). [IIIB2] It has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
IIIC1	T1-T3	The cancer has spread to pelvic lymph nodes (N1, N1mi, or N1a), but

	N1, N1mi or N1a M0	not to lymph nodes around the aorta or distant parts of the body (M0). IIIC1iMicrometastasis+ IIIC1ii Macrometastasis^
IIIC2	T1-T3 N2, N2mi or N2a M0	The cancer has spread to lymph nodes around the aorta (para-aortic lymph nodes) (N2, N2mi, or N2a), but not to distant parts of the body (M0). IIIC2i The cancer has spread but is very small. It is a micrometastasis. IIIC2ii The cancer has spread but is very small. It is a macrometastasis.
IVA	T4 Any N M0	The cancer has spread to the inner lining of the rectum or urinary bladder (called the mucosa) (T4). It may or may not have spread to nearby lymph nodes (Any N), but has not spread to distant parts of the body (M0).
IVB	Any T Any N M1	The cancer has spread to the abdominal peritoneum. The cancer can be any size (Any T) and it might or might not have spread to other lymph nodes (Any N).
IVC		The cancer has spread to distant parts of the body such as lungs, liver, brain or bone or has spread to lymph nodes outside of the abdomen or lymph nodes above the kidneys.

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