Clinicopathological Correlation of Surface Epithelial Ovarian Carcinomas with Special Reference to Er, Pr and Ki 67 Expression - an Observational Study in a Tertiary Cancer Hospital

[1] Dr. Afreen Fatima, [2] Dr. Swati srivastava, [3] Dr. Beenish bano,
[4] Dr. Farheen Khan, [5] Dr. Andleeb zehra
[1,2,3] Assistant Professor, [4] Junior resident, [5] Assistant Professor
[1,2,3,4,5] Department of pathology, Era's lucknow medical college and hospital, India

Corresponding Author : Dr Afreen Fatima

Abstract
Background: Ovarian cancer is the eighth most common cancer and cause of cancer-related deaths among women globally. This study aimed to analyze the clinicopathological correlation of surface epithelial ovarian carcinomas with special reference to estrogen receptor (ER), progesterone receptor (PR), and Ki-67 expression. **Objectives**: Assess the proportion of high-grade ovarian carcinomas. Evaluate the association of ER, PR, and Ki-67 status with tumor type, grade, and stage. Determine the correlation of these markers with tumor recurrence. **Methods:** A hospital-based prospective observational study was conducted at Chittaranjan National Cancer Institute, Kolkata, over 18 months (January 2020–June 2021). Surgically resected tumor samples from 48 patients diagnosed with malignant surface epithelial ovarian tumors were analyzed. Inclusion criteria comprised women with malignant surface epithelial ovarian neoplasms who provided consent; non-surface epithelial malignancies and post-chemotherapy cases with no residual tumor were excluded. **Results:** Serous carcinoma was the most common histopathological type (64.6%), predominantly affecting women aged 51–60 years (56.3%). Abdominal pain was the most frequent presenting symptom (54.2%), and solid-cystic space-occupying lesions were noted in 75% of cases on imaging. High-grade tumors accounted for 64.6% of cases, with 37.5% in Stage I. ER expression was observed in 83.3% of cases, with 50% showing strong positivity (3+), while PR expression was weaker (41.7% showing 1+ positivity). Ki-67 expression was high (>50%) in 56.3% of cases, indicating significant proliferative activity. Statistical analysis revealed significant associations of ER and Ki-67 expression with serous carcinoma, high-grade tumors, advanced stages, and tumor recurrence. PR expression was more common in serous carcinoma but showed no significant correlation with recurrence. **Conclusion:** Serous carcinoma is the predominant histological type of ovarian cancer, mainly affecting perimenopausal and postmenopausal women. ER and Ki-67 are valuable prognostic markers for tumor grade, stage, and recurrence, whereas PR has limited prognostic significance. The study highlights the need for thorough evaluation of vague abdominal symptoms in women and recommends immunohistochemical testing for ER, PR, and Ki-67 in suspected ovarian carcinoma cases. **Limitations:** The study had a small sample size, was single-center, and may have hospital-related bias. Large-scale, multi-center studies are recommended to validate these findings.

Keywords: Ovarian carcinoma, estrogen receptor, progesterone receptor, Ki-67, serous carcinoma, tumor grade, tumor stage, recurrence

Introduction

Ovarian cancer is a significant global health challenge, ranking as the eighth most common malignancy and the eighth leading cause of cancer-related deaths among women worldwide [1]. According to GLOBOCAN 2020, more than 313,000 new ovarian cancer cases and nearly 207,000 deaths were reported annually, underscoring its aggressive nature and poor survival outcomes [2]. In India, ovarian cancer is the third most common gynecological malignancy after cervical and uterine cancers, with an increasing trend in incidence, particularly in urban populations [3].

Surface epithelial ovarian carcinomas constitute nearly 90% of all ovarian malignancies, with serous carcinoma being the predominant histological subtype [4]. Despite advances in surgery and chemotherapy, prognosis remains poor due to late-stage presentation, tumor heterogeneity, and high recurrence rates [5]. Hence, identifying reliable biomarkers for early diagnosis, prognostication, and therapeutic decision-making is of paramount importance.

Hormone receptors, including estrogen receptor (ER) and progesterone receptor (PR), have long been studied in breast and endometrial cancers for their prognostic and therapeutic implications. Their role in ovarian carcinoma, however, remains less clearly defined. ER expression has been linked to tumor aggressiveness and adverse outcomes, while PR has been suggested as a favorable prognostic indicator in some studies [6–8]. The proliferative marker Ki-67, reflecting tumor cell proliferation, has emerged as an important biomarker in several malignancies, with high expression correlating with poor prognosis and recurrence [9,10].

Previous studies evaluating ER, PR, and Ki-67 in ovarian carcinoma have yielded inconsistent results. Some reports indicate significant associations with tumor type, grade, and recurrence, while others suggest limited prognostic utility [11–13]. Moreover, there is limited data from the Indian population, where distinct genetic, lifestyle, and environmental factors may influence tumor biology.

Given these gaps, the present study was conducted at a tertiary cancer hospital in Eastern India to analyze the clinicopathological correlation of surface epithelial ovarian carcinomas with special reference to ER, PR, and Ki-67 expression. The study aimed to assess the prevalence of these markers across histological subtypes, grades, and stages, and to determine their prognostic significance in relation to tumor recurrence.

Materials and Methods

This was a **hospital-based prospective observational study** conducted at the **Chittaranjan National Cancer Institute (CNCI), Kolkata**, a tertiary referral center for cancer care in Eastern India. The study duration was **18 months (January 2020 – June 2021)**. The primary objective was to evaluate the clinicopathological correlation of malignant surface epithelial ovarian carcinomas with **estrogen receptor (ER), progesterone receptor (PR), and Ki-67 expression**, and their association with histological type, tumor grade, stage, and recurrence.A total of **48 patients** diagnosed histologically with malignant surface epithelial ovarian carcinomas were included in

the study. The diagnosis was established on surgically resected tumor specimens submitted to the Department of Pathology during the study period.

The inclusion criteria were:

- Women of any age diagnosed with malignant **surface epithelial ovarian tumors**.
- Availability of adequate tissue specimen for histopathological and immunohistochemical (IHC) analysis.
- Patients who provided informed consent.

The exclusion criteria were:

- Patients with **non-surface epithelial ovarian malignancies** (e.g., germ cell tumors, sex cord-stromal tumors).
- Cases with **no residual tumor** following neoadjuvant chemotherapy.
- Patients with **incomplete clinical data** or inadequate paraffin blocks for IHC.

Ethical Approval

The study protocol was reviewed and approved by the **Institutional Ethics Committee of CNCI, Kolkata**. Written informed consent was obtained from all participants prior to inclusion.

Clinical and Radiological Evaluation

Baseline demographic data (age, menopausal status), presenting symptoms, and clinical examination findings were documented. Radiological investigations, primarily **ultrasonography (USG)** and **contrast-enhanced computed tomography (CECT)** of the abdomen and pelvis, were performed for initial tumor evaluation. Common clinical presentations included **abdominal pain, distension, and incidental asymptomatic findings**.

Histopathological Examination

Surgically resected specimens were grossed according to **standard protocols**. Representative sections were taken, processed, and embedded in paraffin. **Hematoxylin and eosin (H&E)-stained slides** were examined to confirm the diagnosis and classify the tumors based on the **WHO 2020 classification of ovarian tumors** [14]. Tumors were graded as **low grade** or **high grade** according to established morphological criteria, and staging was performed using the **FIGO 2014 staging system** [15].

Immunohistochemistry (IHC)

Immunohistochemical analysis was carried out on formalin-fixed paraffin-embedded (FFPE) sections using monoclonal antibodies against:

- **Estrogen receptor (ER)**
- **Progesterone receptor (PR)**
- **Ki-67 (proliferation index marker)**

The sections were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0). Following blocking of endogenous peroxidase activity, slides were incubated with primary antibodies, followed by detection using a **horseradish peroxidase (HRP)-labeled polymer system** and visualization with **3,3′-diaminobenzidine (DAB)** chromogen. Counterstaining was performed with hematoxylin.

Scoring of IHC results:

- **ER and PR expression** was assessed semi-quantitatively using the **Allred scoring system** (1+, 2+, 3+) based on staining intensity and percentage of positive tumor cells [16]. Cases with no nuclear staining were recorded as **negative**.
- **Ki-67 index** was evaluated by counting positively stained tumor nuclei in at least **1000 cells across high-power fields**, and results were categorized as **<50% (low proliferative activity)** or **>50% (high proliferative activity)** [17].

Follow-up and Recurrence

Patients were followed up clinically and radiologically every 3 months for the first year and every 6 months thereafter. Recurrence was defined as the appearance of new lesions on imaging or histologically confirmed disease after initial treatment response.

Statistical Analysis

Data were compiled in Microsoft Excel and analyzed using **SPSS version 25.0 (IBM Corp., Armonk, NY, USA)**. Continuous variables were expressed as means ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages.

Associations between categorical variables (e.g., ER/PR/Ki-67 expression and clinicopathological features) were tested using the **Chi-square test or Fisher's exact test** where appropriate. **p-values <0.05 were considered statistically significant**.

Results

Patient Demographics

A total of **48 patients** with malignant surface epithelial ovarian carcinomas were included. The **mean age** of presentation was 53.7 years (range: 34–68 years). The highest frequency of cases occurred in the **51–60 years age group (56.3%)**, followed by 41–50 years (31.3%), 61–70 years (8.3%), and 31–40 years (4.2%). This age distribution was statistically significant (**p = 0.01352**), indicating that surface epithelial ovarian

carcinomas most commonly affect **perimenopausal and postmenopausal women** [18,19].

Clinical Presentation

The most common symptom at presentation was **abdominal pain**, reported in **26 patients (54.2%)**, followed by **abdominal distension** in 15 patients (31.3%). A small proportion (14.6%) were **asymptomatic** and diagnosed incidentally during imaging or routine examinations. The association between presenting symptoms and disease was statistically significant (**p = 0.0232**). Similar findings have been reported in other Indian and global studies, where **abdominal pain and distension** constituted the major complaints [20].

Histological Subtypes

Among the histological subtypes, **serous carcinoma was predominant (31 cases, 64.6%)**, followed by **endometrioid carcinoma (16.7%)**, **mucinous carcinoma (12.5%)**, and **clear cell carcinoma (6.3%)**. The predominance of **serous carcinoma** is consistent with previously published reports, where it has been documented as the most common subtype of ovarian cancer worldwide [21,22].

Tumor Grade and Stage

Most tumors were classified as **high grade (64.6%)**, while **low-grade tumors constituted 35.4%**. With respect to stage, **Stage I tumors were the most common (37.5%)**, followed by **Stage III (31.3%)**, **Stage II (16.7%)**, and **Stage IV (14.6%)**. These findings highlight that a significant number of patients still present at an **early stage**, although a considerable proportion harbor advanced disease at diagnosis [23].

Immunohistochemical Expression

Estrogen Receptor (ER)

ER positivity was observed in **83.3% of cases**, with **3+ strong positivity in 50%**, 2+ in 22.9%, and 1+ in 10.4%. Only 16.7% of cases were **ER negative**. A statistically significant correlation was observed between **ER expression and histological type (p < 0.0001)**, with serous carcinomas demonstrating the highest ER positivity. ER expression also showed a strong association with **high tumor grade (p = 0.0008)**, **advanced stage (p = 0.0005)**, and **recurrence (p = 0.0092)**. These findings corroborate prior research, which suggests that ER positivity plays an important role in **tumor aggressiveness and recurrence risk** [24,25].

Progesterone Receptor (PR)

PR positivity was seen in **83.3% of cases**, but staining intensity was generally weaker, with **1+ expression in 41.7%** and **2+ in 37.5%**. Only **4.2% showed strong 3+ expression**, while 16.7% were negative. Although PR expression was significantly associated with **histological subtype (p < 0.0001)**, it did not show significant

correlation with **tumor grade (p = 0.1001)**, **stage (p = 0.0848)**, or **recurrence (p = 0.2802)**. These findings indicate that, unlike ER, PR expression has **limited prognostic value**, consistent with earlier studies [26].

Ki-67 Proliferation Index

Ki-67 expression was **high (>50%) in 56.3% of cases** and low (<50%) in 43.8%. High Ki-67 expression showed statistically significant associations with **histological subtype (p = 0.0157)**, **high grade (p < 0.0001)**, **advanced stage (p < 0.0001)**, and **recurrence (p = 0.0009)**. This emphasizes the role of Ki-67 as a **robust marker of proliferative activity and aggressive tumor biology** [27,28].

Summary of Associations

- **ER**: Strongly associated with histological type, high grade, advanced stage, and recurrence.
- **PR**: Associated with histological type only; no significant prognostic correlation.
- **Ki-67**: Associated with histological type, high grade, advanced stage, and recurrence.

Overall, ER and Ki-67 demonstrated strong prognostic value, whereas PR was less informative.

Discussion

This study analyzed the clinicopathological correlation of surface epithelial ovarian carcinomas with ER, PR, and Ki-67 expression in a cohort of 48 patients. The majority of patients were in the perimenopausal and postmenopausal age groups, which is consistent with global epidemiological patterns of ovarian carcinoma [29]. The predominance of serous carcinoma (64.6%) observed in our study aligns with prior reports from both Indian and Western populations, where serous carcinoma accounts for nearly two-thirds of ovarian malignancies [30,31].

Most tumors were of high grade (64.6%), supporting earlier findings that high-grade tumors represent the majority of malignant ovarian carcinomas and often determine overall prognosis [32]. Although over one-third of patients presented in Stage I, a substantial proportion still had advanced disease, underscoring the need for strategies to improve early detection.

The expression profile of hormonal receptors and proliferation markers provided meaningful prognostic information. **ER positivity (83.3%)** was significantly associated with serous histology, high grade, advanced stage, and recurrence. This association reinforces previous studies that highlight ER as a biomarker of aggressive tumor biology and poor outcomes [33,34]. In contrast, **PR expression**, although relatively frequent, did not correlate significantly with recurrence, consistent with reports suggesting its limited prognostic role compared to ER [35].

Ki-67 expression (>50% in 56.3% of cases) demonstrated strong association with high grade, advanced stage, and recurrence, confirming its value as a marker of

proliferative activity and adverse prognosis. This finding corroborates earlier evidence where high Ki-67 index predicted shorter survival and increased recurrence risk in ovarian carcinoma [36,37].

Overall, the study highlights that **ER and Ki-67** serve as reliable adjuncts for assessing tumor aggressiveness and recurrence risk, while the prognostic utility of PR remains inconclusive. Routine incorporation of these markers into pathological evaluation may enhance prognostication and guide follow-up strategies.

Conclusion

This study demonstrates that serous carcinoma is the most common histological type of malignant surface epithelial ovarian carcinoma, predominantly affecting perimenopausal and postmenopausal women. The age distribution emphasizes that ovarian carcinoma risk increases with advancing age, reinforcing the importance of heightened clinical vigilance in women over 50 years. High-grade tumors were more frequent in our cohort, and a considerable proportion of patients presented with advanced-stage disease, reflecting the often silent and insidious progression of ovarian carcinoma, which may delay diagnosis until the disease has reached a more aggressive stage.

The study also highlights the prognostic value of immunohistochemical markers, particularly ER and Ki-67. ER positivity was strongly associated with serous histology, high grade, advanced stage, and recurrence, suggesting that ER expression may serve as an important biomarker for identifying patients at higher risk of aggressive disease and early relapse. Similarly, a high Ki-67 proliferation index (>50%) correlated significantly with tumor aggressiveness, advanced stage, and recurrence, indicating its utility as a marker of proliferative activity and poor prognosis. These findings suggest that integrating ER and Ki-67 testing into routine pathological evaluation could provide clinicians with valuable information for risk stratification, treatment planning, and post-operative surveillance.

In contrast, PR expression in our study, although present in a substantial number of cases, demonstrated limited prognostic significance beyond histological subtype, suggesting that its clinical utility as a predictor of tumor behavior or recurrence may be modest. Nevertheless, assessing PR expression may still provide complementary information alongside ER and Ki-67 in certain clinical scenarios.

From a clinical perspective, this study underscores the importance of early evaluation of non-specific abdominal symptoms, such as pain or distension, especially in perimenopausal and postmenopausal women. Routine immunohistochemical analysis for ER, PR, and Ki-67 in ovarian carcinoma patients may help in identifying high-risk individuals who may benefit from more intensive follow-up or tailored therapeutic approaches.

Finally, while this study provides valuable insights, the findings emphasize the need for larger, multi-center studies to validate the prognostic significance of ER and Ki-67 across diverse populations, refine risk prediction models, and ultimately improve

patient outcomes. Incorporating these markers into standardized diagnostic protocols may enhance the precision of prognostication and guide personalized management strategies in ovarian carcinoma.

Clinical implications:

1. **Early evaluation of vague abdominal symptoms** in perimenopausal and postmenopausal women is critical for timely detection.
2. Routine **immunohistochemical testing for ER, PR, and Ki-67** should be considered in suspected ovarian carcinoma cases to aid prognostication and guide follow-up strategies.
3. Patients with high ER or Ki-67 expression may benefit from **closer surveillance** and personalized treatment planning.
4. Further **large-scale, multi-center studies** are warranted to validate these findings across diverse populations and refine the prognostic utility of these biomarkers .

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Figures and Table

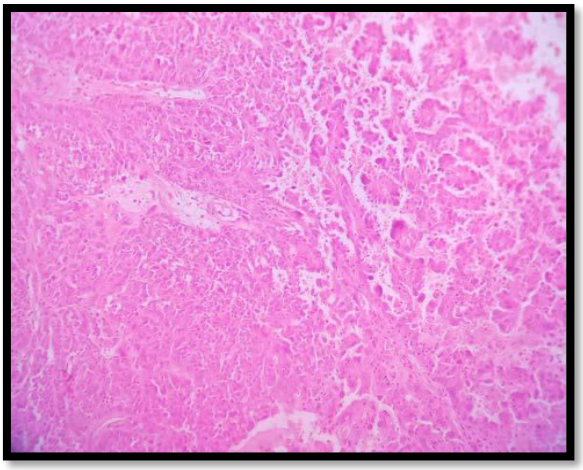

Figure 1: Serous Papillary Carcinoma of Ovary.

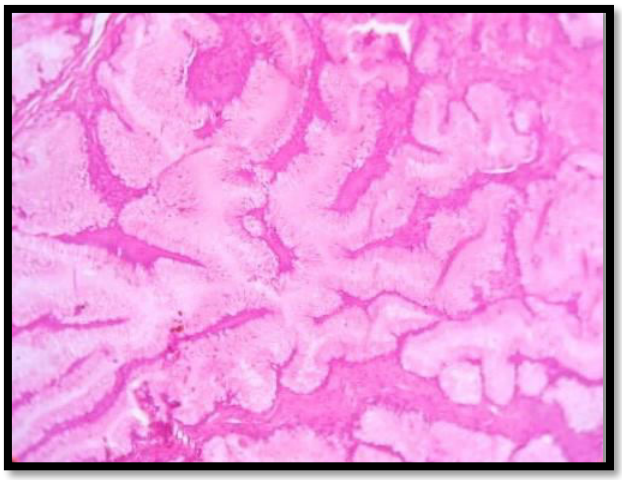

Figure 2: Mucinous Carcinoma of Ovary.

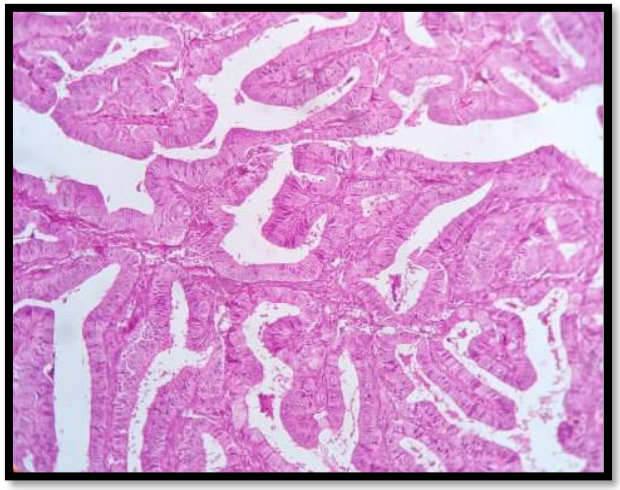

Figure 3: Endometrioid Carcinoma of Ovary

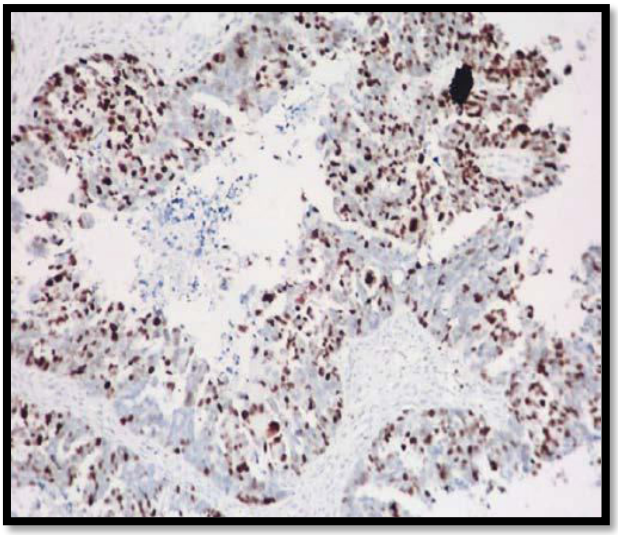

Figure 4: Serous Papillary Carcinoma showing strong ER expression.

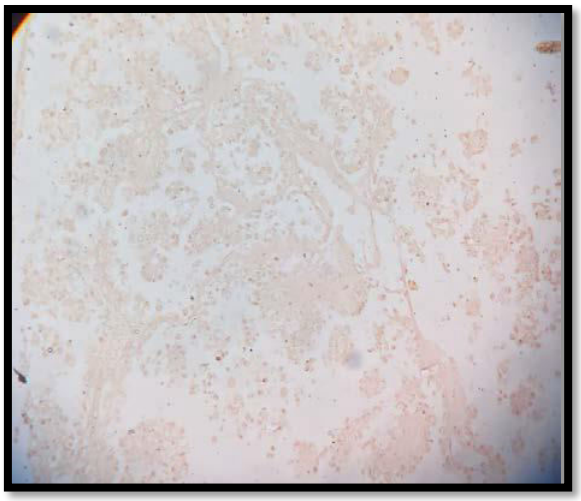

Figure 5: Serous Papillary Carcinoma showing weak PR expression.

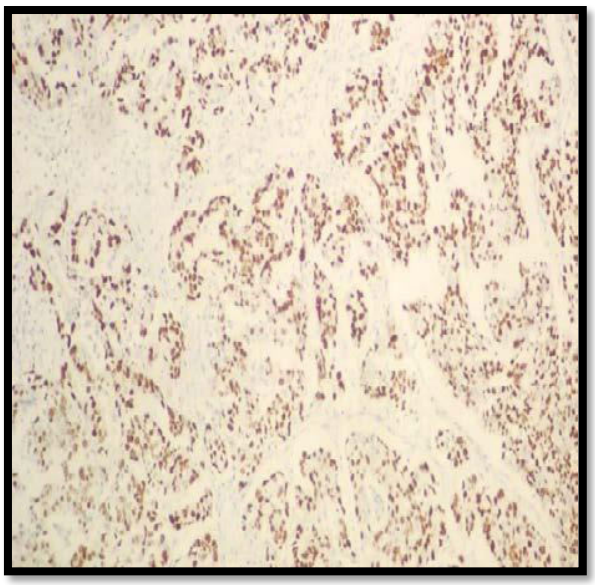

Figure 6: Ki 67 positive in Serous Papillary Carcinoma

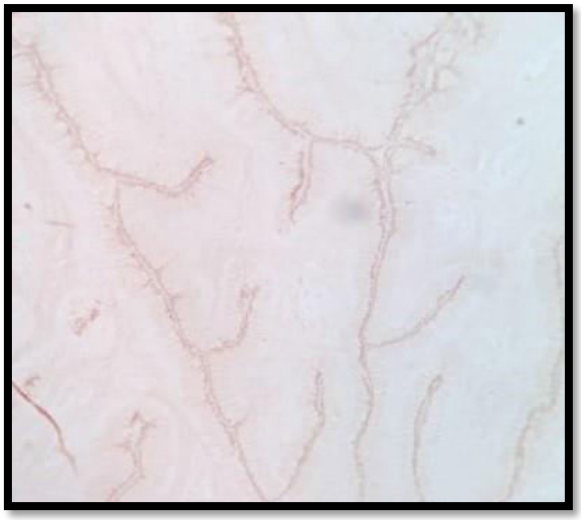

Figure 7: Weak ER expression in Mucinous Carcinoma.

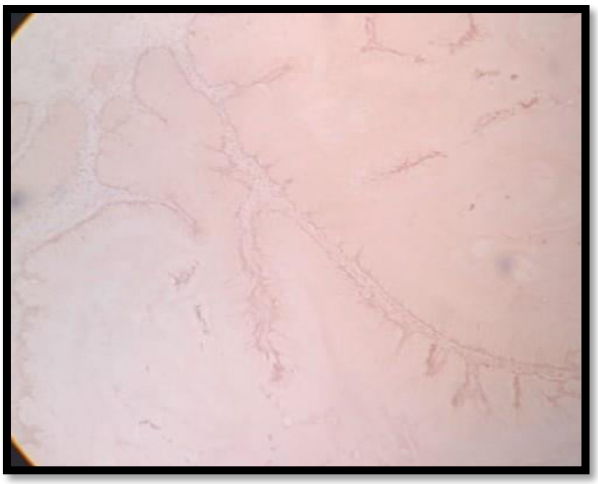

Figure 8: Weak PR expression in Mucinous Carcinoma.

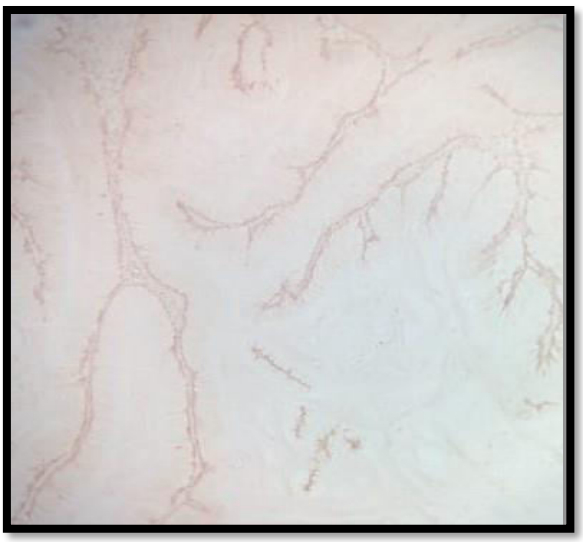

Figure 9: Ki 67 expression in Mucinous Carcinoma

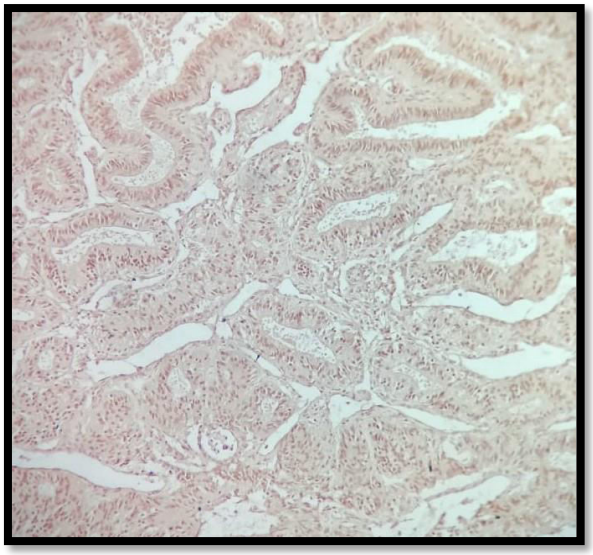

Figure 10: Endometrioid Carcinoma showing strong ER expression.

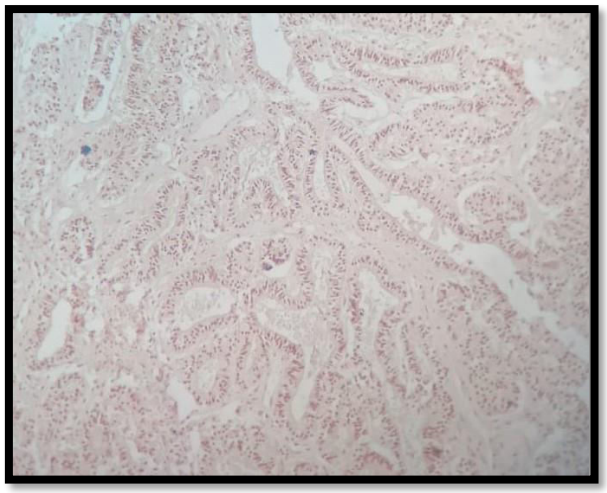

Figure 11: Strong PR expression in Endometrioid Carcinoma.

Tables

1. Age Distribution

Age Group (Years)	Frequency	Percentage
31–40	2	4.2%
41–50	15	31.3%
51–60	27	56.3%
61–70	4	8.3%

2. Symptoms

Symptoms	Frequency	Percentage
Abdominal distension	15	31.3%
Asymptomatic	7	14.6%
Abdominal pain	26	54.2%

3. Histological Types

Histological Type	Frequency	Percentage
Serous carcinoma	31	64.6%
Endometrioid carcinoma	8	16.7%
Mucinous carcinoma	6	12.5%
Clear cell carcinoma	3	6.3%

4. Grades

Grade	Frequency	Percentage
High grade	31	64.6%
Low grade	17	35.4%

5. Stages

Stage	Frequency	Percentage
Stage I	18	37.5%
Stage II	8	16.7%
Stage III	15	31.3%
Stage IV	7	14.6%

6. ER Expression

ER Expression	Frequency	Percentage
1+ Positive	5	10.4%
2+ Positive	11	22.9%
3+ Positive	24	50.0%
Negative	8	16.7%

7. PR Expression

PR Expression	Frequency	Percentage
1+ Positive	20	41.7%
2+ Positive	18	37.5%
3+ Positive	2	4.2%
Negative	8	16.7%

8. Ki 67 expression

Ki-67 Expression	Frequency (n)	Percentage (%)
<50% Expression	**21**	**43.8**
>50% Expression	**27**	**56.3**

9. p-Values for Associations

Association	p-Value	Significance
Age Distribution	0.01352	Significant
Symptoms	0.0232	Significant
ER Expression vs Histological Type	<0.0001	Significant
PR Expression vs Histological Type	<0.0001	Significant
Ki-67 Expression vs Histological Type	0.0157	Significant
ER Expression vs Grade	0.0008	Significant
PR Expression vs Grade	0.1001	Not Significant
Ki-67 Expression vs Grade	<0.0001	Significant
ER Expression vs Stage	0.0005	Significant
PR Expression vs Stage	0.0848	Not Significant
Ki-67 Expression vs Stage	<0.0001	Significant
ER Expression vs Recurrence	0.0092	Significant
PR Expression vs Recurrence	0.2802	Not Significant
Ki-67 Expression vs Recurrence	0.0009	Significant