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IMMUNOHISTOCHEMICAL EXPRESSION OF ER, PR AND HER 2/Neu STATUS IN SURFACE EPITHELIAL TUMORS OF THE OVARY

Pathology

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ABSTRACT

Background: Surface epithelial ovarian tumors form the major group of ovarian neoplasms with diverse biological behavior. This study assessed the immunohistochemical (IHC) expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) and correlated these markers with key histopathological features to evaluate their prognostic significance. **Aims And Objectives:** To assess the expression of ER, PR, and HER2/neu in surface epithelial ovarian tumors and to correlate these markers with clinicopathological features for their prognostic significance. **Methods:** A cross-sectional observational study was conducted on 42 histologically confirmed surface epithelial ovarian tumors over 18 months at Gandhi Medical College and Associated Hospitals, Bhopal. Clinical data, imaging, and gross and microscopic features were recorded. IHC staining for ER, PR, and HER2/neu was performed and interpreted using ASCO/CAP guidelines. Associations with tumor grade, type, and TNM stage were analyzed using chi-square and ANOVA tests. **Results:** The tumors occurred across a wide age range (mean 41.7 ± 17.9 years), with a peak incidence at 21–40 years (42.8 %). Benign tumors constituted 71.4 %, borderline 12 %, and malignant 16.6 %. ER was positive in 66.7 % of cases (51 % of malignant tumors), PR in 47.6 % (46 % of malignant tumors), and HER2/neu in 26.2 % (29.7 % of malignant tumors). HER2/neu positivity was more frequent in high-grade and advanced-stage tumors. Significant associations were observed between IHC marker expression and tumor grade ($p < 0.001$), TNM stage ($p = 0.001$), and tumor type ($p < 0.001$). **Conclusion:** ER, PR, and HER2/neu are valuable biomarkers in surface epithelial ovarian tumors. ER was the most frequently expressed marker, while HER2/neu positivity correlated with aggressive histology. Combined evaluation of these markers with routine histopathology can improve diagnostic stratification, refine prognostication, and help identify patients who may benefit from targeted or hormone-based therapies.

KEYWORDS

Ovarian neoplasms; Surface epithelial tumors; Estrogen receptor; Progesterone receptor; HER2/neu; Immunohistochemistry

INTRODUCTION

Surface epithelial tumors constitute nearly two-thirds of all ovarian tumors, and their malignant forms account for about 90 % of ovarian cancers. These neoplasms are believed to arise directly or indirectly from the ovarian surface epithelium. The ovary is composed of three primary cell types—Müllerian epithelium, sex-cord stromal cells, and germ cells—each capable of giving rise to distinct tumor types [1]. Most primary ovarian tumors originate from the Müllerian epithelium, and surface epithelial tumors are further classified according to epithelial differentiation patterns and the degree of cellular proliferation. Histologically, they include serous, mucinous, endometrioid, clear-cell, transitional, and epithelial-stromal types [2].

Serous cystic tumors are the most common malignant ovarian neoplasms, representing roughly 40 % of all ovarian cancers. When benign, borderline, and malignant serous tumors are combined, they account for about 30 % of all ovarian tumors and more than half of epithelial tumors. Approximately 70 % of these are benign or borderline, while 30 % are malignant. Benign and borderline serous tumors typically occur between 20 and 45 years of age, whereas serous carcinomas present later in life. Mucinous tumors comprise 20–25 % of ovarian neoplasms, and transitional cell (Brenner) tumors represent around 10 % of epithelial ovarian tumors [2].

Worldwide, ovarian cancer remains a major public health concern because of its high incidence and mortality. The disease is usually asymptomatic in early stages, leading to delayed diagnosis and poor prognosis. Among all gynecological malignancies, ovarian cancer carries the highest fatality rate, making it a key focus of clinical management and research [3]. Understanding its etiological factors, risk determinants, and molecular biomarkers is critical for early detection, individualized treatment, and improved survival.

Although the precise etiology is not fully understood, several risk factors have been implicated, including early menarche, delayed menopause, nulliparity, obesity, postmenopausal hormone-replacement therapy, and certain ethnic backgrounds. These influences are thought to act partly through altered circulating levels of estrogen and progesterone [3]. Prognosis is still largely based on established clinicopathological indicators such as stage, histological type, tumor grade, and the volume of residual disease after surgery. Of these, the stage-from I (localized) to IV (metastatic)—remains the most powerful predictor of outcome, while tumor grade and histopathological architecture provide additional insight into aggressiveness [4].

However, patients with apparently similar clinicopathological profiles often exhibit markedly different clinical courses and treatment responses. This underscores the need for additional biomarkers capable of more accurately predicting tumor behavior and survival [5]. Advances in molecular biology and immunology have highlighted several promising biomarkers, notably estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu). These molecules influence the biology of many cancers, including ovarian malignancies [6]. Epidemiologic studies suggest a key role of steroid hormones—especially estrogen and progesterone-in ovarian carcinogenesis, and expression of ER and PR in tumor cells has been associated with better clinical outcomes and longer survival [7].

Conversely, HER2/neu overexpression—well recognized in breast and gastric cancer—has also been documented in ovarian tumors. Its presence is generally linked to aggressive disease and poorer outcomes and has been proposed as a negative prognostic factor, particularly in chemoresistant cases. Nevertheless, clinical trials of HER2-targeted therapies in ovarian cancer have shown inconsistent benefit, leaving its precise role under investigation [8].

Evaluating ER, PR, and HER2/neu expression can therefore deepen understanding of tumor biology, refine risk stratification, and guide individualized treatment. Patients with strong ER or PR positivity may benefit from hormone-based therapy, while those with HER2/neu overexpression could be considered for targeted interventions [9,10]. Immunohistochemistry (IHC) offers a practical method to visualize these proteins in tumor tissues, providing both prognostic and predictive data to support personalized therapy [11]. Continued research on the molecular pathways involving ER, PR, and HER2/neu promises to advance tailored management strategies and improve

survival outcomes for women with ovarian cancer [1].

MATERIALS AND METHODS

Study Setting and Design

This cross-sectional observational study was conducted in the Department of Pathology, Gandhi Medical College and Associated Hospitals, Bhopal, over 18 months (1 May 2023 – 31 October 2024), after obtaining approval from the Institutional Ethics Committee (Letter No. 18923/MC/IEC/2023, dated 09 May 2023).

Study Population

All histopathologically confirmed cases of surface epithelial ovarian tumors—benign, borderline, and malignant—received in the Department of Pathology during the study period were included. Patients with multiple malignancies or specimens showing autolysis were excluded.

Data Collection

Clinical and radiological details, including age, parity, presenting symptoms, menstrual status, tumor size, consistency, and bilaterality, were recorded in a structured proforma. Preoperative imaging findings from ultrasonography, computed tomography, or magnetic resonance imaging were reviewed.

Specimen Processing And Histopathology

Ovarian tumor specimens were fixed in 10 % buffered formalin, grossed, processed, and embedded in paraffin. Sections 4–5 µm thick were cut on a microtome and stained with hematoxylin and eosin for routine histopathological evaluation, including tumor typing, grading, and staging.

Immunohistochemistry

Additional 2–4 µm sections were prepared on poly-L-lysine–coated slides for immunohistochemistry (IHC). After deparaffinization and antigen retrieval (pressure-cooker method), endogenous peroxidase activity was blocked using peroxidase-blocking solution. Slides were incubated with primary antibodies against estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) for 30 minutes each, followed by secondary antibody incubation and visualization with 3,3′-diaminobenzidine (DAB) chromogen. Harris hematoxylin was used for counterstaining [128].Fibroadenoma tissue sections served as positive controls for ER, PR, and HER2/neu staining.

Interpretation Of Immunostaining

IHC slides were independently evaluated by two experienced pathologists. Staining was assessed qualitatively and semi-quantitatively, considering the location of reactivity (nuclear, cytoplasmic, or membranous) and its intensity, which was graded on a 0–3+ scale [74]. For ER and PR, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines were followed: tumors showing nuclear staining in ≥1 % of invasive cancer cells were classified as positive [129]. Results were further categorized as ER/PR-negative (<1 %), low-positive (1–10 %), or positive (>10 %). HER2/neu expression was evaluated based on membrane staining scored from 0 to 3+: score 0 indicated no staining or faint, incomplete staining in ≤10 % of tumor cells (negative); 1+ denoted incomplete, faint staining in >10 % of cells (negative); 2+ represented weak or moderate, complete membrane staining in >10 % of cells (equivocal); and 3+ indicated circumferential, complete, intense membrane staining in >10 % of cells (positive). HER2/neu positivity was defined as a 3+ score, while 0 and 1+ were regarded as negative [26]. Additionally, the Allred score—calculated as the sum of the proportion and intensity scores—was recorded for supplementary assessment [27].

Statistical Analysis

All data were coded and compiled in Microsoft Excel. Descriptive statistics were presented as numbers and percentages. The chi-square test was applied to compare categorical variables, and one-way analysis of variance (ANOVA) was used to compare means. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 42 histologically confirmed surface epithelial ovarian tumors were analyzed during the 18-month study period. Specimens included unilateral or bilateral salpingo-oophorectomy, total abdominal hysterectomy with salpingo-oophorectomy, and excised ovarian masses. The main clinical and pathological findings are summarized below.

Demographic and Clinical Characteristics

Surface epithelial ovarian tumors affected a wide age range (Table 1). The mean age was 41.7 ± 17.9 years (range: < 20 to > 60 years). The largest proportion of cases occurred in the 21–40 year age group (42.8 %), while 19.1 % of patients were older than 60 years, reflecting a bimodal age distribution.

Table 1. Age-wise Distribution Of Cases (N = 42)

Age group (years)	n	%
< 20	5	11.9
21–30	9	21.4
31–40	9	21.4
41–50	7	16.7
51–60	4	9.5
> 60	8	19.1
Total	42	100.0

Abdominal pain was the most frequent presenting symptom (38.1 %), followed by abdominal distension with pain (31.0 %). Most women reported regular menstrual cycles (45.2 %), whereas 31 % had irregular cycles and 23.8 % were menopausal.

Table 2. Presenting Complaints (N = 42)

Complaint	n	%
Abdominal pain	16	38.1
Abdominal distension with pain	13	31.0
Abdominal distension	5	11.9
Dysfunctional uterine bleeding (DUB)	4	9.4
Abdominal pain with DUB	2	4.8
Abdominal distension with amenorrhea	1	2.4
Amenorrhea with urinary tract infection (UTI)	1	2.4

Two-thirds of patients (66.4 %) had no significant past medical or surgical history. A positive family history of ovarian or other malignancies was documented in 16.7 %, and a similar proportion (16.7 %) reported smoking, tobacco, or alcohol use. Only 7.1 % had a history of hormone-replacement therapy or oral contraceptive pill (OCP) use.Radiologically, serous and mucinous cystadenomas were the most frequent imaging impressions (14.3 % and 11.9 %, respectively), although a wide variety of cystic and complex masses were described.

Laterality And Gross Findings

Most tumors were unilateral (88.1 %), with bilaterality in 11.9 % of cases. Grossly, multiloculated masses were most common, followed by uniloculated and biloculated types.

Histopathological Spectrum

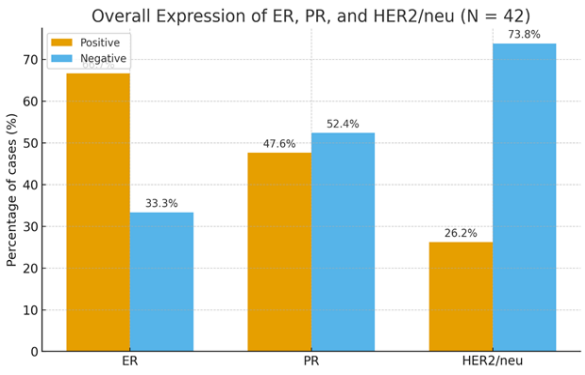
Histologically, benign tumors predominated (71.4 %), while borderline and malignant tumors accounted for 12 % and 16.6 %, respectively (Table 3).

Table 3. Histopathological Classification Of Surface Epithelial Ovarian Tumors (N = 42)

Category	n	%
Benign	30	71.4
Borderline	5	12.0
Malignant	7	16.6

Among individual entities, serous cystadenoma (14 cases) and mucinous cystadenoma (8 cases) were most frequent. High-grade serous carcinoma accounted for two cases, while other malignant forms included mucinous carcinoma and low-grade serous carcinoma.

Expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) was evaluated in all cases (Graph 1).ER positivity was most common (66.7 %), followed by PR (47.6 %) and HER2/neu (26.2 %).HER2/neu positivity tended to occur at a higher mean age (47.3 years) than ER-positive (39.7 years) or PR-positive (40.3 years) tumors, although this difference was not statistically significant ($p > 0.05$).



Graph 1 Overall expression of ER, PR, and HER2/neu (N = 42)

Correlation of IHC Markers with Pathological Variables

ER and PR expression was observed across both uniloculated and multiloculated tumors, whereas HER2/neu positivity was more frequent in multiloculated masses; however, this association was not statistically significant ($p = 0.712$).Tumor grade showed a significant correlation with marker expression ($p < 0.001$): all high-grade tumors demonstrated HER2/neu positivity, while PR positivity was largely limited to benign and low-grade lesions.Regarding TNM stage, ER and HER2/neu were expressed even in early stages (T1a/T1b), and a significant association between stage and marker status was observed ($p = 0.001$).Analysis by tumor type revealed that ER was chiefly expressed in benign tumors (23 of 29 ER-positive cases), whereas HER2/neu positivity was more common in borderline (4 of 11) and malignant (5 of 11) tumors, yielding a significant relationship between marker expression and tumor type ($p < 0.001$).

Table 4. Correlation Of IHC Markers With Tumor Type (N = 42)

Tumor type	ER positive n	PR positive n	HER2/neu positive n
Benign	23	18	2
Borderline	2	2	4
Malignant	4	0	5

DISCUSSION

This study analyzed 42 cases of surface epithelial ovarian tumors over an 18-month period at a tertiary care center in Bhopal and compared the findings with published data to highlight demographic patterns, clinical features, histopathological spectrum, and biomarker expression. The majority of tumors occurred in women aged 21–40 years (42.8 %), while malignant tumors were more frequent after 60 years—a trend consistent with reports by Ameli et al. [12], Naik et al. [13], and Dhatwalia et al. [14], who documented higher malignant incidence in older women and a predominance of benign tumors in the reproductive age group.

Clinically, ovarian mass was the most frequent preoperative diagnosis (38 %), reflecting the nonspecific imaging findings that typically guide initial evaluation. Comparable patterns of nonspecific or mixed adnexal masses have been described by Bassiouny et al. [15] and Abdel Hamid et al. [16], whereas Priyadarshini et al. [17] and Dhatwalia et al. [14] noted serous cystadenoma as the most common entity when postoperative histology was included. In the present series, abdominal pain (38.1 %) and abdominal distension with pain (31 %) were the commonest symptoms, in agreement with Choudhary et al. [18] and Pandey et al. [19].

Menstrual and medical histories likewise paralleled earlier studies. Here, 45.2 % of patients reported regular cycles, 31 % had irregular cycles, and 23.8 % were post-menopausal, confirming that ovarian tumors occur across hormonal phases. Similar distributions were documented by Naik et al. [13] and Ameli et al. [12]. Two-thirds of patients had no significant comorbidities; among those with associated illness, hypothyroidism and hypertension predominated, echoing Choudhary et al. [18] and Mohapatra et al. [20]. Tumors were predominantly unilateral (88.1 %), a finding consistent with Jasmine Kaur et al. [21] and Priyadarshini et al. [17]. Imaging most often suggested serous or mucinous cystadenoma, together accounting for more than one-quarter of cases, again supporting the largely benign nature of these tumors and aligning with Naik et al. [23], Pandey et al. [19], and Priyadarshini et al. [17].

Histopathologically, benign tumors formed the majority (71.4 %), with borderline and malignant tumors comprising 12 % and 16.6 %, respectively. These proportions are comparable to those reported by Priyadarshini et al. [17] and Jasmine Kaur et al. [21], though higher malignant rates have been noted by Pandey et al. [19] and Choudhary et al. [18], possibly reflecting referral bias to specialized oncology centers.

Immunohistochemically, estrogen receptor (ER) was the most frequently expressed marker (66.7 % overall; 51 % in malignant tumors), consistent with Ameli et al. [22], Pandey et al. [19], and Priyadarshini et al. [17]. Progesterone receptor (PR) positivity was 47.6 % overall and 46 % in malignant tumors, closely matching values reported by Ameli et al. [22] and Pandey et al. [19]. HER2/neu overexpression was documented in 26.2 % of all tumors and 29.7 % of malignant ones, similar to Pandey et al. [19] but markedly lower than the 100 % positivity noted by Choudhary et al. [18]. Increased HER2/neu expression in high-grade serous carcinomas has also been highlighted by Verma et al. [23] and Rajarajan et al. [25]. Overall, ER positivity predominated, PR was less frequent, and HER2/neu expression was observed mainly in borderline and malignant tumors.

Significant associations emerged between immunohistochemical expression and tumor grade, TNM stage, and tumor type. All high-grade tumors demonstrated HER2/neu positivity, and ER expression persisted across stages, suggesting that these markers can help identify aggressive behavior and guide individualized therapy. These findings concur with earlier studies that proposed ER, PR, and HER2/neu as important prognostic and predictive biomarkers [18,24,25].

This study has certain limitations. The relatively small sample size limits the generalizability of results. Molecular profiling or gene-expression analysis was not performed, and long-term follow-up was unavailable, precluding survival correlation. In addition, inter-observer variability in immunohistochemical scoring was not assessed. Larger, multi-institutional studies incorporating genomic and outcome data are needed to validate and expand these observations.

In summary, most surface epithelial ovarian tumors in this series were benign, yet ER, PR, and particularly HER2/neu expression provided valuable insights into tumor biology. The significant associations of these markers with tumor grade, stage, and type underscore their potential role as prognostic indicators and therapeutic targets in epithelial ovarian tumors.

CONCLUSION

This study comprehensively evaluated the immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu in surface epithelial ovarian tumors and correlated these markers with detailed histopathological features. A higher proportion of malignant tumors exhibited ER and PR positivity, indicating their potential roles in tumor aggressiveness and hormonal responsiveness. HER2/neu overexpression, though confined to a subset of cases, was largely restricted to high-grade malignant tumors of serous and mucinous type, highlighting its value in identifying candidates for targeted therapy. Significant associations of ER, PR, and HER2/neu expression with tumor grade, tumor type, and TNM stage reinforce the prognostic and therapeutic relevance of these biomarkers. The consistent pattern of high ER in malignant tumors and relatively higher PR expression in benign and borderline lesions further supports their incorporation into routine histopathological evaluation. Collectively, these findings emphasize the benefit of integrating immunohistochemical profiling with conventional morphology for more accurate classification and personalized management of ovarian epithelial tumors.

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