Original Article

Role of Estrogen Receptor, Progesterone Receptor, Human Epidermal Growth Factor Receptor Type 2/neu, and Ki-67 in Surface Epithelial Ovarian Tumors and Its Histopathological Correlation

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Abstract

Background: This study aims to evaluate the expression of estrogen receptor (ER), progesterone receptor (PR), HER-2/neu, and Ki-67 in epithelial ovarian tumors and their correlation with various clinicopathologic variables.
Methods: This study included 50 cases of surface epithelial ovarian tumors. Formalin-fixed paraffin-embedded blocks were prepared from the surgical resection specimens. Hematoxylin and Eosin (H & E) stained sections were examined. Appropriate blocks with tumor tissue were selected for immunohistochemical (IHC) analysis. IHC was performed using commercially available monoclonal antibodies for ER, PR, Ki-67, and HER-2/neu.
Results: Amongst a total of 50 malignant ovarian tumors encountered, the most common tumor was of the serous type (30 cases, 60%). Expression of ER was mainly noted in the serous and endometrioid type of surface epithelial tumors. Expression of PR was less in comparison to ER. Expression of HER-2/neu was rarely found. Out of the total 50 cases studied, 10 were post-chemotherapy patients. Expression of Ki-67 in post-chemotherapy patients was reduced.
Conclusion: ER positivity is seen in most of the serous tumors. Ki-67 nuclear expression should be considered as a prognostic factor. HER-2/neu overexpression is sparse in our study, so further research with a large sample size, followed by gene amplification, is necessary to rule out HER-2/neu expression in surface epithelial ovarian tumors.

Keywords: Immunohistochemistry, ER, PR, HER-2/neu, Ki-67, Surface Epithelial Ovarian Tumors

Introduction

Worldwide, there were over 0.3 million cases of ovarian cancer in 2020, almost 0.2 million deaths, and more than 0.8 million women are presently living after 5 years of diagnosis [1]. Ovarian cancer is the seventh disease and eighth cause of deaths in females [1]. Relapse is seen in 16 months in half of the patients after primary treatment, including staging or debulking surgery and platinum-based adjuvant chemotherapy. Therefore, immediate treatment and clinicopathological correlation is required [1]. In India, most of the cases are seen in post-menopausal females above 60 years of age [2].

Due to limited clinical symptoms, it is diagnosed relatively late and, hence, has a bad prognosis. Conventional treatment of serous ovarian cancer (SOC) comprises surgical removal of the tumor, followed by Platinum/Taxane-based chemotherapy. Currently, neoadjuvant chemotherapy (NACT) is preferred for advanced-stage disease (stage IIIC or IV, of the FIGO staging system). The outcome of this line of treatment is under trial [2].

Breast and prostate cancers are treated successfully with hormone therapies. Hormonal expression could help in more detailed characterization, and different staining patterns could help to guide therapeutic decisions in different subtypes of ovarian cancer [3].

Materials and Methods

This study was a combined retrospective and prospective study including cases from March 2022 to March 2023 seen in the Department of Pathology, D. Y. Patil Medical College, Kolhapur. Institutional Ethical Committee approval was obtained (IEC no. DYPMCK/IEC/138/2022). Written informed consent was taken from all the participants. Fifty cases of surface epithelial tumor diagnosed on histopathology were included. Formalin-fixed paraffin-embedded blocks were prepared from the surgical resection specimens. Hematoxylin and Eosin (H & E) stained sections were examined. Appropriate blocks with tumor tissue were selected for immunohistochemical (IHC) analysis. IHC was performed using commercially available monoclonal antibodies for Estrogen Receptor (Rabbit Monoclonal; AN701-5M, prediluted), Progesterone Receptor (Rabbit Monoclonal; AM328-5ME), Ki-67 (Mouse Monoclonal; AN726-2ME), and Human Epidermal Growth Factor Receptor-2 (HER-2/neu) (Rabbit Monoclonal; AN711-5M). Sections were cut from the selected blocks on poly-L-lysine coated slides. The sections were deparaffinized, and antigen retrieval was done. Overnight incubation with the primary antibody at 4 °C was performed. Incubation with a polymer-based biotinylated secondary antibody, followed by DAB (Di-amino Benzidine) visualization and Hematoxylin counterstain, was done. With each batch, appropriate positive and negative controls (omitting the primary antibody) were also run. Since ER, PR, and Ki-67 are nuclear transcription factors and HER-2/neu is a membranous transcription factor involved in gene regulation, the percentage of cells showing nuclear staining was considered positive in ER, PR, and Ki-67, and the percentage of cells showing membranous staining was considered positive in HER-2/neu. Immunohistochemistry (IHC) slides were reviewed by two pathologists. Data was analyzed using MS Excel. Descriptive statistics were done by frequency and percentage.

Results

A total of 50 cases were seen in the two-year study period. The mean age of the patients was 54.6 years, with the youngest patient being 30 years and the oldest being 88 years. The malignant surface epithelial ovarian tumors encountered were serous, mucinous, endometrioid, clear, and malignant mixed mullerian tumor (MMMT). Expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 for serous epithelial tumor is shown in Figures 1, 2, and 3. As shown in Table 1, the most commonly encountered tumor was of the serous type (30 cases, i.e., 60%). Expression of Estrogen Receptor (ER) was mainly noted in the serous type (23 cases out of 30, i.e., 76.67%) and endometrioid type (5 cases out of 6, i.e., 83.33%), with some seen in the mucinous type (3 cases out of 9, i.e., 33.33%).

Expression of Progesterone Receptor (PR) was less in comparison to ER and was mainly seen in the endometrioid type (4 cases out of 6, i.e., 66.67%). Few cases were also seen in the serous type (7 cases out of 30, i.e., 23.33%) and mucinous type (3 cases out of 9, i.e., 33.33%).

Expression of HER-2/neu was rarely found in the cases studied, with only 3 cases showing HER-2/neu positivity. Both PR and HER-2/neu were found positive only in cases showing ER positivity.

As shown in Table 2, out of the total 50 cases studied, 10 were post-chemotherapy patients. ER positivity in post-chemotherapy (6 cases out of 10, i.e., 60% cases) and pre-chemotherapy (25 cases out of 40, i.e., 62.5%) was similar. Similarly, PR positivity was also identical in post-chemotherapy (3 cases out of 10, i.e., 30%) and pre-chemotherapy (11 cases out of 40, i.e., 27.5%).

Ki-67, when studied in post-chemotherapy patients (mean Ki-67 index - 16.9), a marked decrement was seen in comparison to pre-chemotherapy patients (mean Ki-67 index – 52.58).

Following NACT, significant differences in tumor histomorphology were observed as compared to the native neoplasms. ER was found to be positive in most of the serous tumors. It has a variable role in prognosis. ER expression in tumors with adverse prognostic factors supports the mitogenic role of estrogen in ovarian tumors. PR was expressed in almost equal levels in all histomorphological grades of the tumor. HER-2/neu reactivity was found to be associated with poor prognosis, suggesting their carcinogenic role.

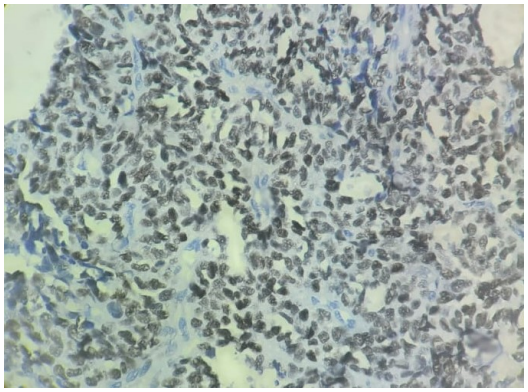

Figure 1: High power view-strong ER positivity in serous carcinoma (IHC, 400x).

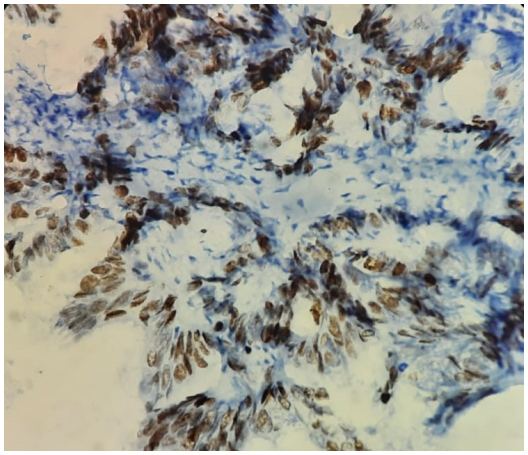

Figure 2: High power view-strong PR positivity in serous carcinoma (IHC, 400x).

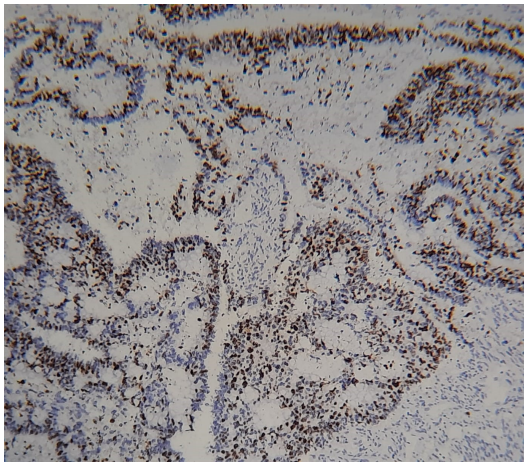

Figure 3: High power view-strong Ki-67 positivity in serous carcinoma (IHC, 400x).

Discussion

As shown in Table 3, data indicated that estrogen favors the neoplastic transformation of the ovarian surface epithelial cells, whereas progesterone offers protection against ovarian cancer development. HER-2/neu is a proto-oncogene that encodes a protein belonging to the EGFR tyrosine kinase receptor family. Overexpression of HER-2/neu indicates defects in intracellular signaling pathways involved in cell proliferation, differentiation, migration, and apoptosis. HER-2/neu-positive status is associated with a poor prognosis [4].

According to our study, ER positivity was found to be maximum in serous tumors, with strong nuclear positivity in >50% of cells. The intensity of PR expression was found to be strong in serous tumors, moderate in mucinous tumors, and weak in other surface epithelial tumors, which was approximately in concordance with Sylvia et al. [4].

The ovarian neoplasms are characterized by changes in their receptor status. They can either be primarily receptor-negative

Table 1: Comparison of various tissue biomarkers in different histopathological diagnoses.

Histological Diagnoses	Cases	Only ER	Only PR	ER & PR +ve	ER, PR & HER-2/neu -ve	ER & HER-2/neu +ve	ER, PR & HER-2/neu +ve
Serous	30	14	-	6	7	2	1
Mucinous	9	-	-	3	6	-	-
Endometrioid	6	1	-	4	1	-	-
MMMT	1	-	-	-	1	-	-
Clear	4	-	-	-	4	-	-
Total	**50**	**15**	-	**13**	**19**	**2**	**1**

Table 2: Comparison of expression of ER & PR tissue biomarkers after surgery & post-chemotherapy.

ER & PR expression	Surgery	Post-chemotherapy
ER+ve, PR+ve (14 cases)	11 (27.5%)	3 (30%)
ER+ve, PR-ve (17 cases)	14 (35%)	3 (30%)
ER-ve, PR+ve (0 case)	0 (0%)	0 (0%)
ER-ve, PR-ve (19 cases)	15 (37.5%)	4 (40%)
Total (50 cases)	**40**	**10**

or may lose the receptors with disease progression, and expression varies with histological subtypes [2]. This can be a cause for low PR positivity as seen in our study.

In this study, ER was expressed in 62% of surface ovarian carcinomas without any statistically significant difference across the treatment groups. A study by Miller and co-workers showed diffuse ER positivity in 90% of cases without any difference in expression in the post-neoadjuvant tumor samples [2]. Expression of PR observed in this study was very low, with PR being positive in only 28% of cases. In contrast to the extent of ER expression, our cases showed only focal weak expression of PR. In a study done by Lee and his coworkers on 322 ovarian cancers, the serous subtype was mostly ER-positive (77.3%), while PR was more frequently expressed (64.2%) in endometrioid cancers [2].

Like the previous study of Luo et al. [13], who found a decrease in PR expression with grade 3 and advanced-stage tumors, we too found similar results.

HER-2/neu has been found to have significant prognostic and predictive value in breast cancer [2]. Its amplification is also seen in several other tumors and has been correlated with a poor prognosis. The results in ovarian cancer regarding HER-2/neu overexpression show wide variability. Expression of HER-2/neu in ovarian cancer, ranging from 8% to 66%, has been reported in various studies [2].

The reason is attributed to the different detection methods, namely, immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or chromogenic in situ hybridization (CISH), used. Differences in the sources of tissue material and tumor heterogeneity may also be responsible for the wide variability [2]. In our study, 94% of cases were HER-2/neu negative, with only occasional tumor cells showing faint nonspecific cytoplasmic staining, similar to the study by Binny et al. [2].

This study analyzes the expression of tissue biomarkers in malignant surface epithelial tumors across the conventionally treated and the neoadjuvant chemotherapy-treated group of patients. Tumor cells differ significantly in their proliferation capacity following NACT, which is indicated by a lower Ki-67 percentage in post-NACT samples, similar to the study by Binny et al. [2]. Grade 3 serous malignant tumors had a significant higher proliferation index, similar to previous results [4].

Pitfalls: Data on prognosis and mortality was not available.

Conclusion

This study highlights the significance of hormone receptor expression in ovarian cancer subtypes, particularly the strong ER positivity observed in serous and endometrioid carcinomas. PR expression was lower and mainly seen in endometrioid tumors, while HER-2/neu positivity was rare. Notably, chemotherapy had minimal impact on ER and PR expression but significantly reduced Ki-67 levels, indicating decreased tumor proliferation. These findings suggest that hormone receptor profiling could provide valuable insights for personalized treatment strategies in ovarian cancer. Further research is needed to explore the potential role of targeted hormonal therapies in improving patient outcomes.

Table 3: Estrogen receptor, progesterone receptor, HER-2/neu, and Ki-67 expression in ovarian malignancies.

Study by	ER	PR	HER-2/neu	Ki-67 (mean)
Verma N et al. (2022) [5]	77.14%	51.43%	57.14%	-
Pandey V et al. (2022) [8]	51.35%	51.35%	29.73%	42.43%
Bhagora R et al. (2017) [7]	80.77%	50.00%	-	-
Naik PS et al. (2015) [6]	81.25%	56.25%	-	64%
Pils D et al. (2007) [9]	-	-	27.6%	-
Verri E et al. (2005) [10]	-	-	27.3%	-
Mahadevappa A et al. (2017) [11]	-	-	-	62.19%
Saurabh S et al. (2019) [12]	71.43%	-	-	74.95%
Present study (2023)	**62%**	**28%**	**6%**	**45.44%**

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Competing Interests: None.

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