# Expression of Her2/Neu, VEGF, and Ki-67 in Epithelial Ovarian Carcinomas: An Experience from a Tertiary Care Center, West Bengal, India

**Palas Bhattacharyya[1], Rama Das[2], Abhisek Lath[3], Debasish Guha[4]**


## ABSTRACT

**Introduction:** Ovarian carcinomas is still maintaining pivotal role among gynecological malignancy regarding cancer death in women. This study aims to observe expression pattern of VEGF, Her2/Neu and Ki-67 in lieu of targeted therapy for ovarian carcinoma.

**Materials and Methods:** It was retrospective observational study carried out for last 3 years (2020-2022). A total of 160 cases of Ovarian tumors were received from different departments. The specimens were processed, histopathological sections were examined under Hematoxylin and Eosin stain, Immunohistochemical stains like VEGF, Her2/Neu and Ki-67. Evaluation was done by trained and independent pathologists. Correlation of Histological type, grade, age group. FIGO stage with expression of VEGF, Her2/Neu, and Ki-67 done.

**Results:** Out of 160 specimens of histological examination proved 143 EOC- serous type constituted maximum (53.1 %) number. Among them (63.7%) were high grade and most of the cases belonged to 41.3% (59/143) in FIGO stage I in our study. Grade 3+ HER2/neu immunostaining was identified in 22.37% cases and had significantly correlated with tumor grade ($\chi 2$ = 19.7981 with Yates correction; P <0.00001) and FIGO Staging (p=0.00024). Among High grade EOC, High proliferation index (HPI) was 19.5% for Ki-67. we could observe significant statistical association of Ki-67 HPI and tumor differentiation. Moreover, significant correlations was found between the high-grade EOC and HPI of Ki-67/Her2-neu co-expression (p<0.05).

Though significant association was found between tumor grade and VEGF expression ($\chi 2$ = 11.1041; P = .000861) but no correlation were in VEGF/Her-2/neu HPI and the degree of tumor differentiation (chi-square, p>0.05).

**Conclusion:** Role of Her2/Neu and Ki-67 expression and their association should be considered in the progression and tumor grade and stage of EOC.


**Keywords:** Epithelial Ovarian Carcinoma, HER2/NEU and KI-67 Co-expression.

## INTRODUCTION

Ovarian surface epithelial carcinomas are most common type of ovarian malignancy almost accounting ninety percent of all ovarian malignancy. The new case of ovarian cancer is 1% of all reported cancers in 2023 and responsible for 2.2%of all cancer death worldwide reported by American Cancer Society.[1,2] It affects mostly the post-menopausal women. The surface epithelial tumor is heterogenous in nature and has several histological types. The pathogenesis, genetic expression and prognosis often varies among them. The present study aims to categorize different subtypes and evaluation the expression pattern of their molecular markers like Her2/Neu, VEGF, Ki-67 by IHC. The correlation among these IHC markers and relevant clinico-pathological factors like age, grade, FIGO stage of respective category are also searched for.

The Her2/Neu acts through PI3K/AKT signaling pathway. Dysregulated HER2 signaling leading to faster cell growth, impaired DNA repair, and increased tumor colony formation foundin several cancers like breast cancer, gastric cancer including ovarian cancer.[3,4] This property could be applied for targeted immunotherapies in women with HER2-positive ovarian cancer.[5,6,7]

VEGF is an angiogenetic factor of all cancer growth. It promotes endothelial cell proliferation, inhibition of apoptosis, activation of enzymes causing ECM degradation and regulation of vascular permeation. Overexpression of VEGF in ovarian epithelium cancer is associated with high tumor grade, stage, early onset of metastasis, development of ascites and poor prognosis.[8,9] The VEGF family is composed of seven members-VEGF(A-E) and placental growth factor PIGF 1and 2 and acts through Tyrosine kinase receptor. Moreover, few studies show that Serum VEGF-A estimation could be a strong diagnostic biomarker for early stages of ovarian cancer.[10,11] The Positive expression of tissue VEGF is also found be a prognostic marker in other cancer like gastric adenocarcinoma.[12,13]

Ki-67 is a proliferation marker on malignant cells. It is overexpressed in malignant EOC and associated with tumor aggression, vascular invasion, reserved prognosis and poor response to chemotherapy.

In Present study we find out the correlation of VEGF, Her2/Neu, Ki-67 expression in borderline, and malignant EOC with histologic subtype, grade, and FIGO staging. Their expression profile guide management protocol as

[1]Associate Professor, Department of Pathology, [2]Associate Professor, Department of Pathology, [3]Demonstrator, Department of Pathology., [4]Professor, Department of Pathology, NRS Medical College and Hospital, West Bengal, India

**Corresponding author:** Dr. Rama Das, Chinsurah, Hooghly, West Bengal, India.

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well as prognostic tool.[14,15]

## MATERIAL AND METHODS

A total of 160 selected ovarian cancers diagnosed between 2020–2023 were included in this study in the Department of Pathology Laboratory of tertiary careHospital. The specimens wereof total and partial hysterectomy with salpingo-oophorectomy, ovarian-cystectomy which were processed by common histopathological technique using 10% formalin fixation, paraffin embedding and Hematoxylin–Eosin stain. Clinicopathological data were analyzed and the histopathological diagnosis was done.

Inclusion criteria: well-preserved tissue blocks with adequate data from record sections and adequate tissue left for sectioning. normal ovaries with unremarkable histology in these laboratories were also retrieved to serve as controls. Available sections diagnosed as borderline and malignant ovarian epithelial neoplasm were included in the study.

Benign ovarian epithelial tumors, patients received neoadjuvant chemotherapy, poorly preserved/poorly fixed tissue were excluded from this study.

**IHC**: For immunohistochemical analysis, paraffin-embedded specimens were cut at <2 µm, using conventional histological techniques and transferred to poly-l-lysine coated slides. The immunohistochemical staining for Her-2/Neu was performed Her-2/Neu (SP3) Rabbit monoclonal antibody of Sigma/Aldrich company using 1:300 as working dilution. For VEGF and Ki67 we use Rabbit monoclonal / Bio SB in 1:20 dilution and Ki-67(SP6)/ Cell Marque using 1:100 dilution respectively. Placental tissue for VEGF and breast carcinoma for Her2/Neu and Ki-67 were used as positive external control.

**Interpretation**

***Her2/Neu*** : American Society of Clinical Oncology/ College of American Pathologists, the Dako scoring system was used for interpretation[16]: Score 0- no staining or membrane staining in ≤1 10% of the tumor cells;Score1+, Incomplete membrane staining which is faint within >10% of the tumor cells; score 2+, a weak to moderate staining of the entire membrane in >10% of the tumor cells; and score 3+, a strong staining of the entire membrane in >30% of the tumor cells.

scored as 0 or 1+ were considered to be negative for Her2/Neu expression, 2+ weakly positive, and 3+ strongly positive.

***VEGF:*** positive staining was considered as granular, brown cytoplasmic/cell surface staining in the ovarian tumor cells. The scoring was done by evaluating the intensity of cytoplasmic staining and the percentage of positive tumor cells. Intensity score considered as 0-absent staining; 1+- mild staining;2+moderate staining;3+ strong staining. Percentage Score were 0= <1% tumor cell positive;1=1-10% positive cells;2=11-50% positive cells;3=51-100% positive cells

The two scores were added to get the final scores. Based on the scores, the surface epithelial tumors were categorized as high VEGF expressors (Scores 5 and 6) and low VEGF expressors (Scores 4 and below).[8,17]

***Ki-67*:** The ki-67 proliferation index is assessed by counting 500 cells (X 400 magnification) and reported as percent of brown stained nuclear positive cells. We use 40% positive cells as cut off value for the Ki -67 index. We divide the tumors as Low Proliferation Index (<40%Ki-67) and High Proliferation Index (≥40% Ki-67).

The assessment of immunohistochemical staining was carried out by two independent pathologists separately.

## STATISTICAL ANALYSIS

Histopathology of the tumors considered as gold standard for diagnosis. Statistical relationship among qualitative parameters was determined using SPSS- 20. Nominal categorical data between the groups were compared using Chi-squared test. For all statistical tests, p value less than 0.05 was considered significant.

**Ethical Considerations**

Ethical approval for this study was obtained from the Institutional Ethics committee before the review of case records and data collection. Ethical principles according to the Helsinki declaration were considered during this study.

## RESULT

This present study included 160 number of histologically proven epithelial ovarian borderline and malignant tumors within the study period. The ages of the patients with ovarian tumors ranged from 14 to 78 years with a mean of 46 ± 32years. The EOC cases consisted of 85 (53.1%) serous carcinoma, 15(9.3%) serous borderline tumors, 24 (15%) mucinous carcinoma, 12 (7.5%) sero-mucinous carcinoma (Now considered as ovarian endometroid carcinoma-endocervical type -WHO 5$^{TH}$ Edition 2020), 8(5%) clear cellcarcinoma and 14 (8.75%) endometrioid carcinomas as well as 2 (1.25%) metastatic carcinoma in Ovary [Figure1].

Among EOC (143) fifty-two (36.3%) of the tumors were low-grade neoplasms, and ninety-one cases (63.7%) were high grade [Table 1]. We found maximum number of cases 41.3% (59/143) in FIGO stage I followed by 37.7% (54/143) in stage III and 21.7% (30/143) in stage II.

Her2/neu-immunostaining was identified strongly positive (score3+) in 32 (22.37%) of the EOC, while thirteen (9.1%) were weakly positive (a score of 2+). Of the histological subtypes studied, serous carcinoma showed the highest Her2/Neu-positive rate with 41.17%(35/85%) of them being positive. This is %followed by mucinous EOC which showed only 29.16%(7/24%)positivity rate. However, no association was found between Her2/Neu expression and histological subtyping ($\chi 2$ = 7.9309; P = 0.094) [Table 2, Figures 2 and 3].There was significant association between tumor grade and Her2/Neu expression ($\chi 2$ = 19.7981 with Yates correction;

| Tumor Grade | Serous (85) | Mucinous (24) | Seromucinous (12) | Clear cell (8) | Endometroid (14) | Total (143) |
|---|---|---|---|---|---|---|
| Low | 20 | 18 | 6 | 2 | 5 | 51(35.7%) |
| High | 65 | 6 | 6 | 6 | 9 | 92(64.3%) |
| Tumor Stage FIGO | | | | | | |
| I | 35 | 12 | 6 | 2 | 4 | 59(41.25%) |
| II | 21 | 4 | 3 | 3 | 0 | 31(21.69%) |
| III | 29 | 9 | 3 | 3 | 10 | 53(37.06%) |

**Table-1:** Distribution of tumors across histological grades and stage

| | HER2-Neu Expression (n=143) | | | | | |
|---|---|---|---|---|---|---|
| **Histologic type** | **Negative 98(68.53%)** | **Weakly Positive 13(9.1%)** | **Strongly Positive 32(22.37%)** | **Total (%)** | **χ2** | **p** |
| Serous | 50 | 10 | 25 | 85 | | |
| Mucinous | 17 | 2 | 5 | 24 | | |
| Seromucinous | 10 | 1 | 1 | 12 | | |
| Clear cell | 7 | 1 | 0 | 8 | | |
| Endometroid | 12 | 0 | 2 | 14 | | |
| Histologic Grade | | | | | | |
| Low | 47 | 2 | 2 | 51 | 22.7874 | <.000011 |
| High | 49 | 12 | 31 | 92 | | |
| FIGO stage | | | | | | |
| I | 44 | 6 | 9 | 59(41.25%) | 16.6461 | 0.00024 Significant |
| II | 24 | 1 | 6 | 31(21.69%) | | |
| III | 22 | 17 | 14 | 53(37.06%) | | |

**Table-2:** Comparison of human epidermal growth factor receptor 2 expression across histologic subtypes, Tumor grades and FIGO stages

| | VEGF Expression (n=143) | | | | |
|---|---|---|---|---|---|
| **Histologic type** | **Low Expressors** | **High Expressors** | **Total** | **χ2** | **p** |
| Serous | 61 | 24 | 85 | | |
| Mucinous | 21 | 3 | 24 | | |
| Seromucinous | 9 | 3 | 12 | | |
| Clear cell | 6 | 2 | 8 | | |
| Endometroid | 12 | 2 | 14 | | |
| Total | 109(76.2%) | 34(23.77%) | | | |
| Histologic Grade | | | | | |
| Low | 47 | 4 | 51 | 11.1041 | Significant at p<.05 |
| High | 62 | 30 | 92 | | |

**Table-3:** Comparison of VEGF expression in histologic subtypes and tumor grades.

P <0.00001). Her2/Neu positivity was predominantly observed among High-grade carcinomas (45.65%) of which of which mostly are serous. Among Low-grade carcinomastwo mucinous EOC show strong positivity for Her2/Neu [Table 2, Fig 2a and 2b].

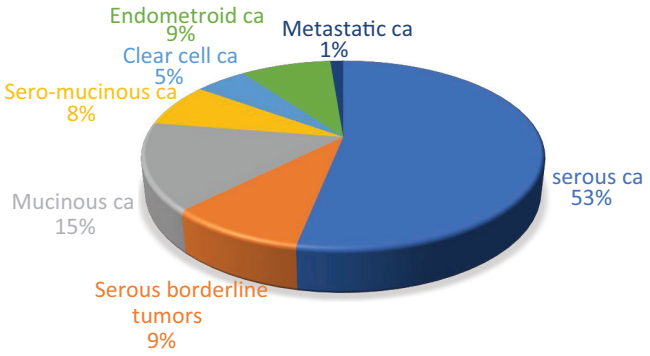
On statistical analysis there was significant correlation found between HER2neu expression and FIGO Staging of tumor (p=0.00024) [Table 3]. The present study showed highest number of EOC in FIGO Stage I, among which 44 cases (74.57%) showed negative expression of HER2/neu. T2 stage revealed maximum no. of cases showing negative expression 24/31 (77.41%). Positive expression of her2/neu 14/53 (54.5%) was found to be maximum number in FIGO stage III. [Table2]

EOC were VEGF positive in 34(23.7%) of cases. Low Expressors heterogeneous stain was found in maximum number of (76.2%) cases. Positive cells were located in solid areas in cases of high grade carcinomas and cystic areas or to the surface of low grade tumors (Table3, Figure3a and 3b).Significant association was found between tumor grade and VEGF expression ($\chi2 = 11.1041$; P = .000861).

Ki67 nuclear immunostain shows High Proliferation Index (>40% tumor cells) in two cases of low-grade tumor only. Among High grade malignant tumors High proliferation index (HPI) was 19.5%.we observed significant statistical association of Ki-67 HPI and tumor differentiation. (chi-square, p>0.05, Table4). In addition, significant correlations between the high-grade adenocarcinomas and high intensity of Ki-67/Her2-neu co-expression was established chi-square, p<0.05). But There were no correlation in VEGF/Her-2/neu co-expression

| Tissue sample of EOC | | Ki-67 | | Ki-67/Her2-Neu co Expression | | | VEGF- HE/Her2-Neu Co-Expression | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | HPI | χ2 | P value | Ki-67 HPI/ Her2 -Neu 3+ | Pearson χ2 | P value | VEGF-HE/ Her2-Neu 3+ | Pearson χ2 | P value |
| Low Grade | 51 | 2(1.3%) | 13.9129 | .000191 Significant | 2 | 8.0017 | .004673 Significant at <.05 | 1 | 0.5541 | .456659 Not significant |
| High Grade | 92 | 28(19.5%) | | | 20 | | | 4 | | |

**Table-4:** Association between KI67 /HER2-Neu and VEGF/Her2-Neu Immunohistochemical Staining in Low grade and high grade EOC.




**Figire-1:** Distribution of Ovarian tumors according to histological types (n=160)

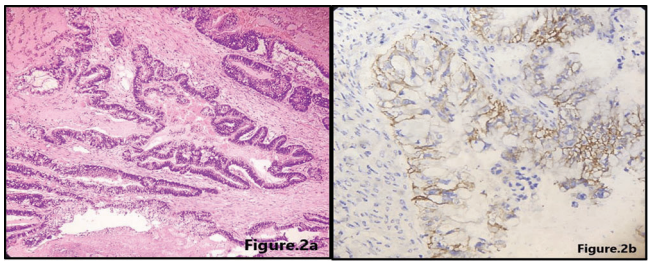



**Figure-2:** (a) Low grade mucinous carcinoma, H&E stain 20X; (2) Low grade mucinous carcinoma, Her2/Neu positive 2+

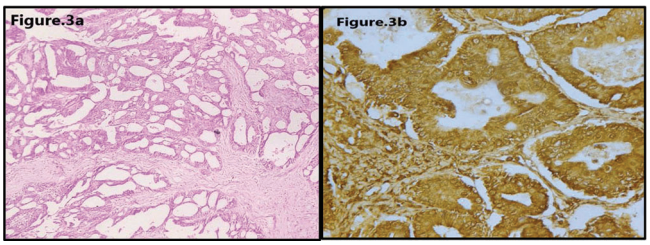



**Figure-3:** (a) Low grade serous carcinoma of ovary, H&E stain x 20X; (b) Low grade serous carcinoma, VEGF-High expressor

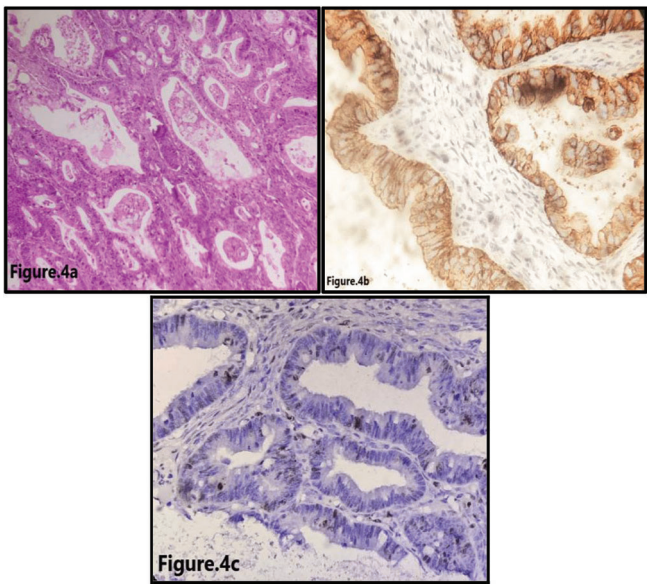



**Figure-4:** (a) Sero-mucinous carcinoma of ovary (Now considered as ovarian endometroid carcinoma-endocervical type -WHO 5TH Edition 2020), H&E stain x 20X; (b) Sero-mucinous carcinoma of ovary, Her2/Neu positive ,3+ ; (c) Sero-mucinous carcinoma of ovary, Ki-67, LPI

associated with degree of tumor differentiation (chi-square, p>0.05).

## DISCUSSION

Among Indian women ovarian cancer is third most common gynaecological cancer.[18] The age range of patients of ovarian cancer in this present study was 14 - 78 years with a mean of 46 ± 32 years. 68 % of cases occurred in those between 43 - 62 years of age, while 40 % of patients were 50 years of age or younger. Similar findings from other studies are found within and outside West Bengal.Such as age range of malignant Ovarian tumors was 40 to 49 years with prevalence of EOC after 50 years in a Study from rural area of West Bengal.[19] and age range of 18-85 years with median age 50 in another study from North India.[20] The age range of patients with EOC in a study of southeast Nigeria was 23– 90 years, with a mean of 50.2 ± 13.0 years, and age range of 24–78 years with mean of 51.26 ± 14.75 years reported in China.[21,22]

Epithelial ovarian carcinomas are a group of heterogeneous malignancies with various histological subtypes. In the present study expression of HE2/neu, VEGF and Ki67 was correlated with sub type, grade of the tumors and FIGO staging. Malignant serous ovarian tumors which are found to be the predominant type 53.1% are aggressive in nature and have a poor prognosis. Dysregulated HER2 signaling due to gene amplification or overexpression leads to rapid cell division, defected DNA repair and increased production of tumor cell colonies. That is why HER2 is an important target molecule for immunotherapy in HER2 positive ovarian cancer cases. In our studyHER2 expression in serous carcinoma is highest 41.17% whereas serous borderline tumors show positivity of 9%.

Aggressiveness of ovarian carcinoma is due to its de novo development in contrast to its borderline counterpart which develops progressively from cystadenoma. In Our study Mucinous carcinoma (15%) followed by sero-mucinous carcinomas(7.5%) [ Figure 4a, 4b,4c] care the next group of epithelial ovarian cancers. Endometrioid carcinoma and Clear cell carcinoma constitute about 8.75% and 5% respectively. Metastatic carcinomas are the least occurring tumor 1.25% in this study. Similar type of distribution of ovarian cancer cases were seen in the study of Sarkar M et.al[23] and they also found HER2 neu expression higher in malignant serous tumors.

We have got highest number of EOC cases which are of FIGO stage I(74.57%), lowest are of stage II and cases of stage III lies in between the two. Considering grade of the tumors 64.3% are of high grade and 35.7% are of low grade. This observation is similar to a published data from a Nigerian study as well as other studies from other countries.[24]

Expression of HER2 in ovarian cancer cases is quite variable. Strong positivity of HER 2/Neu immune-stain in ovarian carcinoma predominantly found in high grade serous carcinoma followed by mucinous carcinomas. The second most common EOC is mucinous variety which showed HER2/NEU positivity of 29.16%. In our observation there was significant association between tumor grade and HER2/neu expression ($\chi 2$ =22.7874, p=<.000011) but no association was found between HER2/new expression and histological subtyping of the tumor. Published international works ofDemir L et al and national work of Grover A et al shows a positive comparison with our study. [25,26] Significant correlation was found between HER2neu expression and FIGO Staging of tumor (p=0.00024) like Di Wang's multivariate study[22] but other study could not find.[26]

Statistically significant correlation was found between the histologic grade and VEGF expression statusin previous studies ofMukherjee S et al and Duncan TJ et al[8,27] like our study.

We observed that both Ki-67 and Her2/Neu positive co-expression was significantly related to histologic grade, though we could not find any correlation between VEGF and Her2/Neu co-expression with tumor grade. But other study could not found any significant association of Ki-67 and HER2/NEU.[23] The level of Ki- 67 expression was significantly associated with tumor grade.[28,29] If we could follow prognosis by estimating overall survival and metastasis by these independent ki-67 and Her/2 neu biomarkers then individual treatment plan can be optimized by use of Trastuzumab/Pertuzumabin addition to surgery.

## CONCLUSION

This study may enrich our knowledge about the role of Her/2 Neu and Ki-67 and their association in the progression and tumor grade and stage of EOC.

These are our limitations as we have relative a smaller number of EOC patients and short multivariate analysis. But results of this study would provide agood evidence-using these two novel biomarkers I.e. KI-67 and Her2/Neu combinedwith treatment strategy and survival of post-operative EOC patients. Then we could determine nature of tumor and can modify individual treatment plan.

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