A study of her-2/neu oncogene expression in benign and malignant ovarian tumors

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**Background:** Ovarian cancers are very common worldwide with serous epithelial tumors being the most common. Her-2/neu oncoprotein encodes a protein belonging to the EGFR tyrosine kinase receptor family. Overexpression has been shown for poor prognosis in breast cancer. The study was done to find the association of ovarian tumors with Her-2/neu expression.

**Aim and objectives:** To assess the clinicopathological profile of various ovarian tumors with special reference to age, histological type, grade, and stage of the tumor. To assess and compare the expression of Her-2/neu oncogene in benign and malignant ovarian tumors in relation to age, histological type, grade, and stage of the tumor.

**Method:** The prospective study was done on 37 specimens received in the Department of Pathology; NIMS medical college from the period between 2015 to 2019.

**Results:** All the benign and borderline tumors were negative for her-2/neu. 48.6% of malignant tumors were her-2/neu positive.

**Conclusion:** Her-2/neu positivity was seen in 24.3% of ovarian tumors. All the benign and borderline tumors were negative for her-2/neu. 48.6% of malignant tumors were her-2/neu positive.

**Keywords:** Her-2/neu oncoprotein, Ovarian cancer, Epithelial tumors

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Introduc...
Guidelines provided by FIGO. For assessing the association of tumor stage with Her-2/neuexpressions, tumors were divided into early-stage tumors (stage I and II) and tumors with late-stage (III and IV). The sections with tumor and adjacent normal ovarian tissue were processed for her 2 neu immunohistochemical staining.

A case of her 2 neu positive breast carcinoma was used as the positive control. For Her-2/neu staining, after antigen retrieval, slides were stained with a polyclonal antibody against Her-2/neu oncoprotein. No ethical permission was required in this study as it was done on surgical specimens received postoperative.

All the immunostained slides were reviewed and evaluated using the following criteria- Assessment of the immunohistochemical staining for her-2/neu overexpression. The negative expression included cases with either no staining or faint to weak membranous positivity in less than 10% of tumor cells. The positive expression was considered in cases of moderate to strong membranous positivity in more than 10% of tumor cells.

Results

In study 32 ovarian tumors were studied, out of which 44.5% of tumors were benign, 5.5% were borderline and 50% were malignant.

It was found that out of 32 studied ovarian tumors, 64.9% were epithelial tumors, 21.6% were germ cell tumors, 8.1% were sex cord-stromal tumors and 5.4% were metastatic tumors.

Serous tumors were most common among all epithelial tumors (68.8%) (Table 1).

| Table 1: Distribution of various ovarian neoplasm. |
|---------------------------------------------------|
| **Total case=37** | Benign | Borderline | Malignant | Total |
|-------------------|--------|------------|-----------|-------|
| Epithelial Tumors | 9      | 2          | 13        | 24 (64.9%) |
| Germ cell Tumors | 4      | 0          | 4         | 8 (21.6%) |
| Sex-cord Tumors  | 3      | 0          | 0         | 3 (8.1%) |
| Metastatic Tumors| 0      | 0          | 2         | 2 (5.4%) |
|                   | 16     | 2          | 19        | 37    |

Out of a total 16 serous tumors, 45.5% were benign.

Serous adenocarcinoma was the most common malignant tumor accounting for 37.5% of all epithelial tumors and 54.5% were serous tumors (Table 2).
The positive expression of Her-2/neu was more in patients with high-grade ovarian tumors in comparison to low grade. Out of all studied malignant ovarian tumors, maximum Her-2/neu positivity (72.2%) was present in serous adenocarcinoma and its association with Her-2/neu was statistically significant as compared to others.

The current study suggested that her-2/neu deserves further evaluation as a prognostic marker in epithelial tumors (Figure 2) (Figure 3-7).

Fig-1: Distribution of various ovarian neoplasm.

Fig-2: Status of HER-2/NEU and histological type of cancer.

Fig-3: Microphotograph of metastatic adenocarcinoma (Krukenberg tumor) (H and E 400 X).

Fig-4: Microphotograph of grade III serous adenocarcinoma showing membranous positivity in tumor cells (Her-2/neu immunostain).

Fig-5: Microphotograph of grade II serous adenocarcinoma showing membranous positivity of tumor cells (Her-2/neu immunostain).
**Fig-6:** Microphotograph of poorly differentiated epithelial neoplasm showing membranous positivity of tumor cells (Her-2/neu immunostain).

**Fig-7:** Microphotograph of yolk sac tumor showing membranous positivity of tumor cells (Her-2/neu immunostain).

## Discussion

Ovarian cancer is the fifth leading cause of cancer death among women and has the highest mortality rate of all gynecologic cancers [5]. Ovarian cancer is diagnosed in later stages because the inaccessible anatomic location of the ovaries and asymptomatic nature of the disease hinders the detection of cancer while it is still confined to the ovary.

The prognostic factors include the FIGO stage, histological type, tumor grade, and clinic-surgical parameters include residual disease after debulking surgery, presence or absence of ascites, performance status, and age. FIGO stage is the most important independent prognostic factor.

The current study evaluated the clinicopathological profile of various ovarian tumors and expression of Her-2/neu in ovarian lesions, its relationship to its type of malignancy, and correlation with clinico-

Pathological factors like age of the patient, size of the tumor, histological grading, and staging.

In the current study, 16 cases were benign, 2 cases were borderline and 19 cases were malignant with surface epithelial tumors were most common (68.8%).

The majority of benign tumors were in age between 30-39 years and the majority of malignant epithelial tumors were in the range between 40-49 years in comparison with other studies [6]. In the current study, benign cystic teratoma was commonest among all germ cell tumors accounting for 56.2% of all germ cell tumors and 12.1% of all ovarian tumors, and most of them presented in the age range of 30-39 years.

However malignant germ cell tumors were present at the age of fewer than 30 years. Sex cord tumors, granulosa cell tumors, and fibromas were most common each constituting around 2.7% of all ovarian tumors. 66.7% of sex cord tumors were in age between 40-49 years. Metastatic tumors constituted 5.4% of all ovarian tumors and were seen in the age above 30 years.

63.5% tumors had a size of 5-14 cms, 28.4% had size more than 15 cm only and 8.1% had size less than 5 cms.

24.3% of ovarian tumors were seen in nulliparous women and 75.7% of ovarian tumors were seen in multiparous women. Among epithelial tumors, 89.6% were seen in multiparous women. The majority of germ cell tumors were seen in nulliparous women probably due to the young age of onset.

78.4% of ovarian tumors were unilateral and all the metastatic tumors were bilateral. 21.2% of malignant tumors were stage I; 27.3% were stage II and 51.5% were stage III. Out of a total of 13 epithelial tumors, whose grading was done; 7.7% were grade I, 34.6% were grade II, 57.7% were grade III.

The proportion of ovarian cancers overexpressing her -2 /neu is a matter of debate. Various studies have reported that between 5% and 30 % of ovarian tumors overexpress her 2 neu [7]. In the current study, 24.3% of all ovarian tumors showed her -2/neu positivity of which all were malignant (48.6%) comparable to another study [8,9].

No statistically significant association of her 2 neu positivity with age and size of the tumor was found.
In concordance with another study [10,11]. Among all malignant epithelial tumors, 61.5% of cases were her-2/neu positive and 39.5% were negative. In germ cells, tumor 18.2% cases were her 2 neu positive and rest 81.8% were negative. So, her-2/neu was statistically significantly associated with epithelial tumors than with other ovarian tumors compared to another study [12] and with non-cordance with another study [13,14]. The non-epithelial tumors of ovary rarely showed her-2/neu expression comparable to another study [8]. HER2 expression is associated with a worse outcome of ovarian cancer, implicating HER2 may be a potential prognostic indicator for ovarian cancer patients [16].

In the present study out of 8 (48.5%) patients with early-stage ovarian cancer (Stage I and 2); 43.7% patients were her-2/neu positive and 56.3% were her-2/neu negative while out of 51.5% patients were with advanced-stage ovarian cancer (stage III/IV), with 64.7% cases were her-2/neu positive and 35.3% were her-2/neu negative; concluding the expression of her-2/neu is independent of ovarian cancer stage [14,15]. The number of cases the current study received during the period of study was limited. Hence the association of various ovarian tumor type and Her-2/neu co-relation need to be a further study in a large sample size.

**Conclusion**

Epithelial tumors were commonest among all ovarian tumors studied; most common being serous tumors. The majority of tumors were unilateral and were seen in multiparous women and the majority had a size between 5-14 cms. The majority of tumors were in high grade and presented in advanced stages. Her-2/neu positivity was seen in 24.3% of ovarian tumors. All the benign and borderline tumors were negative for her-2/neu. 48.6% of malignant tumors were her-2/neu positive. Epithelial tumors were significantly associated with her-2/neu with serous adenocarcinoma showing maximum association as compared to other tumors.

**What does the study add to the existing knowledge**

Her-2/neu expression is significantly associated with tumors of high grade but had no correlation with the stage of the tumor. No association is found with the age of the patient and the size of the tumor. Though the stage and grade of the tumor are the most important prognostic indicator.

**Author’s contribution**

Dr. Sumit Gupta: Concept, study design, manuscript preparation
Dr. Manju Mehra: Manuscript preparation
Dr. Jyotsana Khattri: Statistical analysis
Dr. Madhvi: Study design

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