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Original Research Article

Clinicopathological study of epithelial neoplasms of ovary with special reference to the expression of P53 and Her2/neu in epithelial carcinoma

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ABSTRACT

Background: Ovarian cancer represents 30% of all cancers of female genital tract. An accurate histopathological diagnosis of ovarian tumours is essential for their management and the outcome of therapy.
Aims and Objectives : Clinicopathological study of ovarian epithelial neoplasms and to study the expression of p53 and Her2/neu in epithelial carcinoma of ovary and their association with the histological grade.
Settings and Design: An observational descriptive type of study in a tertiary care hospital in Eastern India.
Materials and Methods: 72 cases diagnosed as ovarian epithelial neoplasms in the department of Pathology, CNMC&H Kolkata during the study period of January, 2019 to December, 2020 were studied. Specimens were processed routinely. Immunohistochemistry was done following standard protocol.
Statistical analysis: Statistical analysis was done using SPSS (version 21.0, Chicago inc., Chicago, Illinois, USA) software.
Results: 57 cases were benign followed by 14 malignant and 1 borderline case. Majority of the tumours were serous type (71.4%) followed by mucinous (27.2%) and seromucinous (1.4%). P53 expression was noted in 50% of the epithelial ovarian carcinoma and 85.7% of the high grade serous carcinoma. Her2/neu expression was noted in 21.4% of epithelial ovarian carcinoma cases.
Conclusion: p53 expression was more in serous carcinoma and the expression of p53 was associated with higher grade of serous carcinoma. Her2/neu expression was more in serous carcinoma. There was no significant association between Her2/neu expression and histological grade and a larger population based study is needed for further evaluation.

1. Introduction

Ovarian cancer represents about 30% of all cancers of female genital tract. It is the seventh most commonly diagnosed cancer among women in the world.[1] The prognosis of ovarian cancer largely depends on the clinical stage and grade of the cancer diagnosed. Most women with stage I ovarian cancer have an excellent prognosis. But most ovarian cancer patients (60%) are diagnosed with distant-stage disease, for which 5-year survival is just 29%.[2] An accurate histopathological diagnosis of ovarian tumours is vital for their management and to predict the outcome of the therapy. Multiple factors such as age, race, histological grade & type, FIGO stage, residual disease, CA125 levels and performance status at the time of diagnosis influence survival of ovarian tumours.[3]

TP53 is a tumor suppressor gene located on 17p13.1. It suppresses formation of tumour by inducing either transient cell cycle arrest (at G1 phase), senescence (permanent cell cycle arrest) or programmed cell death.[4]

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Loss of functional p53 protein leads to accumulation of an abnormal protein with a markedly elevated half life which can be detected immunohistochemically. Studies have shown that p53 expression is associated with higher grade and stage of ovarian carcinoma specifically high grade serous carcinoma. The Her2/neu oncogene is located on chromosome 17q11.21 and encodes for a tyrosine kinase transmembrane growth factor receptor. Activation of the Her2/neu receptor results in the activation of a cascade of intracellular proteins.[4] Her2/neu protein overexpression, assessed by immunohistochemistry (IHC), is found to be associated with higher histological grade of ovarian tumor in some studies.[5] With the availability of anti Her2/neu therapy, Her2/neu expression in ovarian cancer provides a therapeutic significance as well. Considering all the above information as background, this study is undertaken to evaluate various clinicopathological aspects associated with ovarian epithelial neoplasm and also to determine the expression of Her2/neu and p53 in ovarian epithelial cancer using standardized immunohistochemical techniques.

2. Aims of study

1. Clinicopathological study of ovarian epithelial neoplasms
2. To study the expression of p53 and Her2/neu in epithelial carcinoma of ovary
3. To study the association between the expression of p53 and Her2/Neu and histological grade of epithelial carcinoma of ovary.

3. Materials and Methods

This study included a total number of 72 cases of epithelial tumours of ovary diagnosed in the department of Pathology, Calcutta National Medical College & Hospital during the study period from January, 2019 to December, 2020. Specimens of ovarian cystectomy, total abdominal hysterectomy with oophorectomy and specimens of ovariectomy were included. All the specimens were fixed in 10% neutral buffered formalin and processed routinely. Immunohistochemistry was done following protocol.

3.1. Inclusion criteria

1. Patients admitted in the Department of Gynaecology of Calcutta National Medical College with epithelial ovarian neoplasm and operated for the same were included for histopathological study.
2. Only primary epithelial carcinoma cases were included for immunohistochemical studies.

3.2. Exclusion criteria

1. Patients who did not give consent for immunohistochemistry
2. Patients who had received preoperative radiotherapy or chemotherapy.

3.3. Immunohistochemistry

Sections taken from paraffin blocks were mounted on poly-l-lysine coated slides and baked in incubator at 60^{o}C for an hour. Antigen retrieval was done in microwave oven using antigen retrieval solution for total 15 minutes in 3 cycles of 5 minutes each. The primary and secondary antibodies for immunohistochemistry were then used followed by the staining with DAB chromogen. The slides were counterstained with haematoxylin followed by dehydration with graded alcohol and xylene and were mounted in DPX. Antibodies used in immunohistochemistry were:

3.4. Primary Antibodies

1. Primary antibody for p53 protein: Master diagnostica^{TM} rabbit anti-human p53 monoclonal antibody (clone SP5) [REF:MAD-000309QD-R-3, LOT:0309009] was used.
2. Primary antibody for Her2 antigen: PathnSitu^{TM} Her2/erbB2-EP3 rabbit monoclonal antibody [PR047-6ml] was used.

Secondary antibodies: Ready to use Master diagnostica^{TM} Master polymer plus HRP was used as secondary antibodies.

3.5. Interpretation of Immunohistochemistry

3.5.1. p53

Wild Type/ Normal: showed positive staining of an admixture of negative cells, weakly and strongly positive cells (No mutation).

Aberrant/Abnormal/Mutant Type: showed strong and diffuse nuclear positivity in > 60% tumour cell nuclei (missense mutation) or complete absence of staining in < 5% tumour cell nuclei (Loss of function mutation).[6]

3.5.2. Her2/neu

Positivity was assessed using ASCO/CAP scoring criteria.[7]

3.6. Data analysis

Analysis was done according to the objectives formulated for the study. Data analysis was done using SPSS (version 21.0, Chicago inc., Chicago, Illinois, USA) software.

Chi square test was used to associate findings. The level of significance chosen was $p < 0.05$

Reporting categories	Scoring criteria
Negative	0 : No staining is observed or incomplete membrane staining that is barely perceptible in ≤10% tumour cells 1+ : Incomplete membrane staining that is barely perceptible in >10% of cells
Equivocal	2+ : Weak to moderate complete membrane staining observed in >10% of tumour cells
Positive	3+ : Circumferential membrane staining that is complete, intense and in >10% of tumour cells

4. Result Analysis

4.1. Clinicopathological study

We studied 72 cases of epithelial ovarian tumours in the time period of January, 2019 to December, 2020 in the department of Pathology, Calcutta National Medical College & Hospital, Kolkata. Majority of the cases were diagnosed as benign (79.1%). 19.6% cases were diagnosed as malignant tumours and only 1.3% was borderline in our study (Table 1).

Most (n = 39, 68.4%) of the benign tumours were seen in the ≤ 40 years age group. Majority (n = 11, 78.6%) of the malignant tumours were seen in > 40 years age group. The only borderline tumour belongs to ≤ 40 years age group (Table 2). In this study, the lowest age in which the tumour was found was a 15 years old girl. This was diagnosed as serous cystadenoma. The oldest lady aged 63 years, presented with mass abdomen. Histopathological examination revealed a diagnosis of low grade serous carcinoma.

Among all the epithelial ovarian tumours, serous tumours (n = 51, 71.4%) predominate followed by mucinous tumours (n = 20, 27.2%). Least (n = 1, 1.4%) common tumours are of sero-mucinous type. The most frequent histological subtype of tumour was serous cystadenoma (n = 35, 48.6%). Majority (n = 11, 15.2%) of the malignant tumours were serous carcinoma. Out of 72 cases, 17 (23.6%) were diagnosed as mucinous cystadenoma, 3 (4.1%) were mucinous carcinoma and 1 case (1.4%) of seromucinous cystadenoma (Table 3).

Out of 11 serous carcinoma cases, 4 cases (36.4%) were diagnosed as low grade and 7 cases (63.6%) were high grade. (Table 4)

Majority of the patients were clinically diagnosed as FIGO stage III (57.2%) disease. 4 cases were found with stage I (28.5%) disease and 2 cases were in stage II (14.3%). In our study, none of the cases was found with stage IV disease. (Table 5)

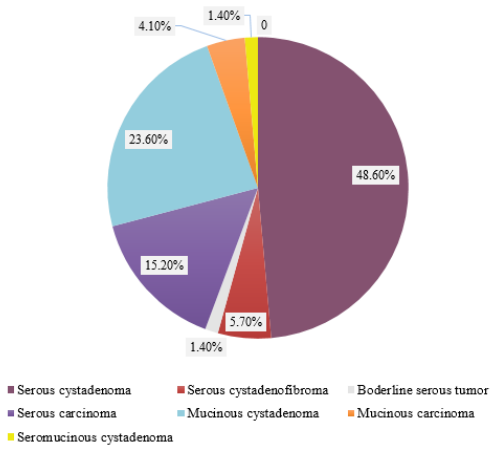

Fig. 1: Pie diagram showing distribution of epithelial ovariantumours based on histopathological subtypes (n=72)

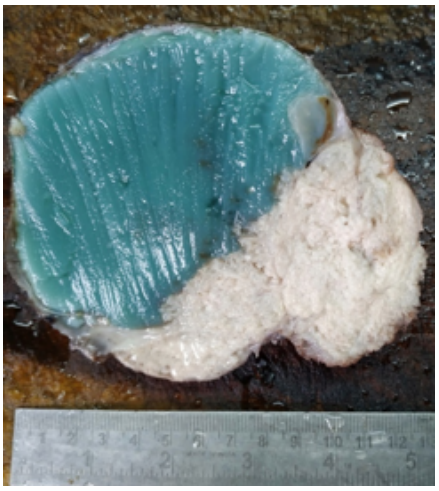

Fig. 2: Gross photograph of low grade serouscarcinoma showing cystic and solid areas

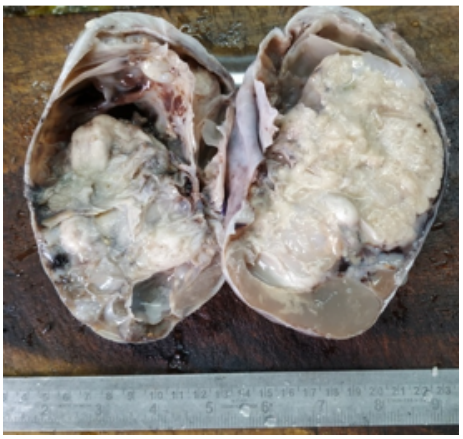

Fig. 3: Gross photograph of mucinous carcinoma showingmultiloculated cysts with solid areas

Table 1: Distribution of epithelial ovarian tumours (n=72)

Tumour	Number	%
Benign	57	79.1%
Borderline	1	1.3%
Malignant	14	19.6%

Table 2: Age distribution of epithelial ovarian tumors (n=72)

Age Groups	Benign (%)	Borderline (%)	Malignant (%)
≤ 40 years	39 (68.4%)	1 (100%)	3 (21.4%)
> 40 years	18 (31.6%)	-	11 (78.6%)
Total	57	1	14

Table 3: Distribution of epithelial ovarian tumours based on histopathological subtypes (n=72)

Histopathological subtypes	Number	%
Serous cystadenoma	35	48.6%
Serous cystadenofibroma	4	5.7%
Borderline serous tumour	1	1.4%
Serous Carcinoma	11	15.2%
Mucinous cystadenoma	17	23.6%
Mucinous carcinoma	3	4.1%
Seromucinous cystadenoma	1	1.4%
Total	72	100%

Table 4: Distribution of serous carcinoma based on histological grade (n = 11)

Grade	Number	%
Low	4	36.4%
High	7	63.6%
Total	11	100%

Table 5: Distribution of epithelial ovarian cancer based on FIGO staging system (n=14)

Stages	Stage I	Stage II	Stage III	Stage IV	Total
No of cases	4	2	8	-	14
%	28.5%	14.3%	57.2%	-	100%

Table 6: p53 expression in epithelial ovarian carcinoma

Tumour	P53(+)ve	P53(-)ve	Total
Serous carcinoma	7 (63.6%)	4 (36.4%)	11
Mucinous carcinoma	-	3(100%)	3

Table 7: Association of the expression of p53 with histological grade of serous carcinoma (n=11)

Grade	P53		Total %	P value
	Positive %	Negative %		
High	6 85.7	1 14.3	7 100	0.044 Chi-square value: 4.0548 with 1 degree of freedom
Low	1 25	3 75	4 100	

Table 8: Her2/neu expression in epithelial ovarian carcinoma

Tumour	Her2/neu(+)ve	Her2/neu(-)ve	Total
Serous carcinoma	3 (27.2%)	8 (72.8%)	11
Mucinous carcinoma	-	3 (100%)	3

Table 9: Association of the expression of Her2/neu with histological grade of serous carcinoma (n=11)

Grade	Her2/neu		Total(%)	P value
	Positive (%)	Negative (%)		
High	2(28.6)	5(71.4)	7(100)	0.898 Chi-square value: 0.0164 with 1 degree of freedom
Low	1(25)	3(75)	4(100)	

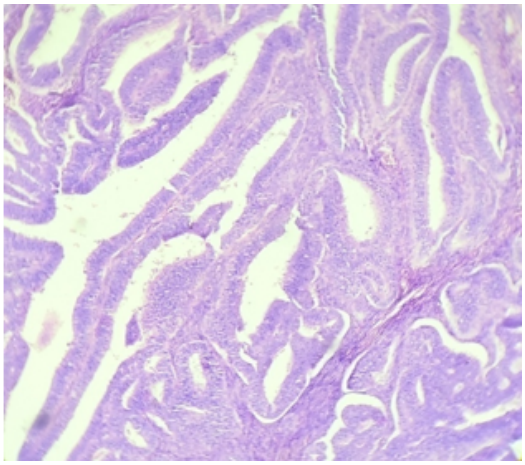

Fig. 4: Low grade serous carcinoma showing papillary architecture. H&E stain (100X)

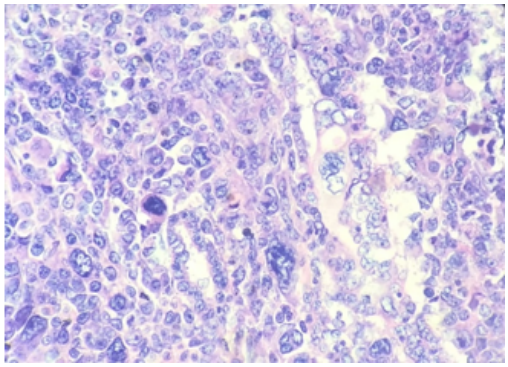

Fig. 5: High grade serous carcinoma showing nuclearatypia & atypical mitotic figures. H&E stain (400X)

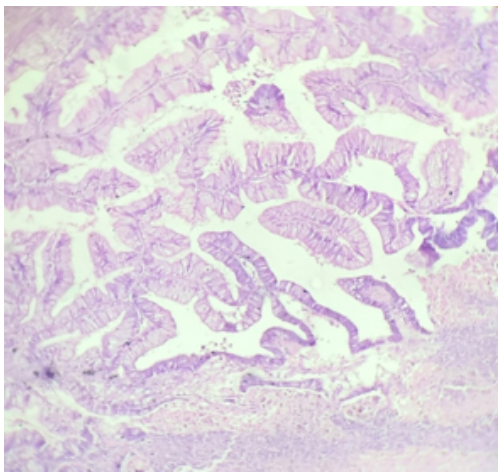

Fig. 6: Mucinous carcinoma showingexpansile invasive pattern. H&E stain (100X)

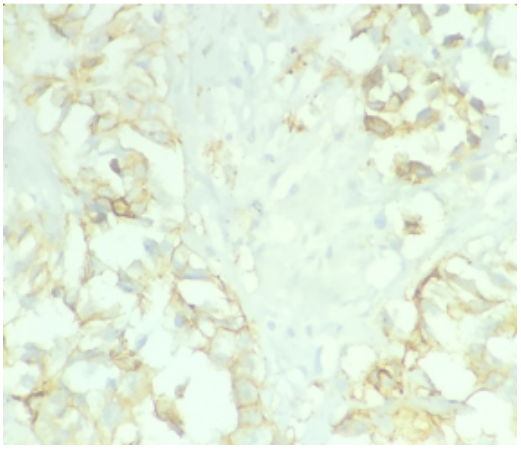

Fig. 7: High grade serous carcinomashowing strong, complete membranous staining (3+) for Her2/neu (400X)

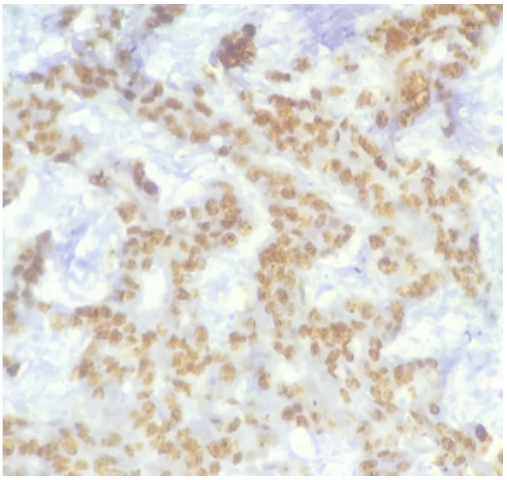

Fig. 8: High grade serous carcinoma showing strong nuclear staining (Aberrant expression) for p53 (400X)

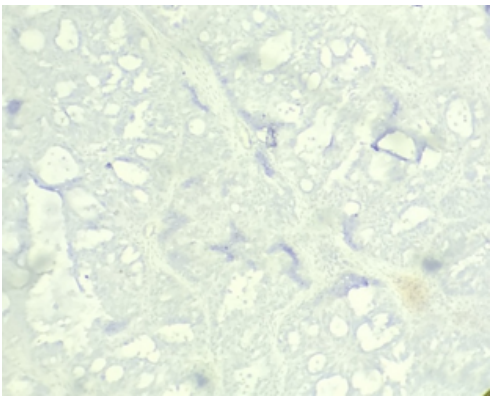

Fig. 9: High grade serous carcinoma showing lack of staining for p53 ('Null type' expression) (100X)

4.2. P53 and Her2/neu expression

85.7% of the high grade serous carcinoma cases were p53 positive. p53 expression was noted more in high grade serous carcinoma than low grade serous carcinoma. This difference was statistically significant with p value being 0.044 (P value < 0.05) (Table 7).

21.4% (n=3) cases were Her2/neu positive out of 14 total cases. 27.2% (n=3) of the serous carcinoma cases were Her2/neu positive. Majority of these cases were high grade serous carcinoma. None of the mucinous carcinoma cases showed Her2/neu positivity (Table 8).

28.6% of high grade serous carcinoma cases were Her2/neu positive. Her2/neu expression was noted more in high grade serous carcinoma than low grade serous carcinoma. However, this difference was not statistically significant (P value = 0.898) (Table 9).

5. Discussion

Benign tumours were the most frequent tumour in our study covering 79.1% of the tumours. This is similar to study conducted by Sreeja et al in 2012 where majority (64.5%) of the tumours were benign tumours.[8] Similar finding is noted in the studies of Naik et al conducted in 2015.[9] Benign tumours consisted of 74.55% of the tumours. In the study of Abbasi et al in 2016, the findings are similar, benign tumours being 67.88%.[10] However, In the studies conducted by Guirgea et al and Sylvia et al in 2012, majority of the tumours were malignant being 50% and 55% respectively.[11,12]

In our study, most of the cases (59.7%) belonged to ≤ 40 years age group which is similar to the studies of Sreeja et al (2015) and Naik et al (2015).[8,9] Their studies included 52.07% and 50% of the cases respectively, in the age group of ≤ 40 years. In the study conducted by Abbasi et al (2016), 61.46% patients were in the age group ≤ 50 years.[10]

In the present study, majority of tumours were serous cystadenoma (48.6%), followed by mucinous cystadenoma (23.6%). This is concordant with the studies of Naik et al (2015) and Abbasi et al (2016). In the study of Naik et al, 40% of the tumours were serous cystadenoma followed by 34.55% of mucinous cystadenoma[9] whereas in the study conducted by Abbasi et al (2016), 31.2% were serous cystadenoma and were the majority of the tumours, followed by 26.6% mucinous cystadenoma.[10] However, In the study of Guirgea at al (2012), majority (46.15%) of the tumours were serous carcinoma contrary to our study where serous carcinoma cases were 15.2%. There were 1.4% borderline cases in our study which consisted of borderline serous tumour only whereas in the study of Guirgea et al 28.85% tumours were borderline tumours consisting of both serous and mucinous borderline tumours.[12]

In the present study, 63.6% of serous carcinoma were high grade tumours and 36.4% tumours were low grade which is similar to the study of Naik et al. (2015) In their study, 77.77% of serous carcinoma were high grade.[9] Similarly, in the study conducted by Guirgea et al (2012), 66.66% of the serous carcinoma were high grade serous carcinoma.[12] In the study of Wang et al (2016) higher number of high grade carcinoma noted, the amount being 81% whereas 19% of the serous carcinoma were low grade.[13] Majority of the studies found in the literature followed a 3 tier grading system for serous carcinoma. The present study followed a two tier grading system. So, the results of histological grading are not compared with those studies.

In the present study, Majority (57.2%) of the epithelial ovarian cancer presented as FIGO stage III tumours. 28.5% cases were in stage I and 14.3% were in stage II. In our study none of the tumours was found in stage IV which is in contrast with the study conducted by Harlozinska et al in 1996. In their study, 75% tumours were in Stage IV followed by 35.7% stage II cases.[14] In the study of Guirgea et al (2012), 33% tumours are noted both in stage II and stage III. The study conducted by Wang et al (2016) showed majority of the tumours in stage I and stage III which is similar to the present study, 46% tumours in stage I, 37.8% tumours in stage III. Only 1.8% tumours were in stage IV. In the study conducted by Levesque et al in 1995, majority (56.6%) of the tumours were in stage III followed by 23.3% tumours in stage[15] which is a similar finding compared to the present study.

In the present study, p53 expression is noted in 50% of the epithelial ovarian carcinoma cases. Similar finding was noted in the study conducted by Harlozinska et al (1996). In their study 53.3% of malignant tumours were p53 positive. In the studies of Guirgea et al (2012) and Naik et al (2015), the percentage of p53 positivity in malignant tumours were 19.2% and 81.25% respectively. In the study of Gursan et al (2009), 40% of the malignant tumours showed p53 positivity.[16] In the study of Sylvia et al (2012), 57% malignant epithelial tumours showed p53 positivity which is close to our study finding.

In the present study, p53 positivity was noted exclusively in serous carcinoma. 63.6% of serous carcinoma were p53 positive. p53 positivity was not seen in mucinous carcinoma. In the study of Guirgea et al (2012), similar finding was noted. They found p53 positivity only in serous carcinoma whereas p53 positivity was not found in mucinous carcinoma. 41.7% of serous carcinoma showed p53 positivity. In the studies of Sylvia et al (2012) and Sreeja et al (2015), 57.89% and 63.6% serous carcinoma cases showed p53 positivity. Sreeja et al (2015) also found 25% mucinous carcinoma cases which were p53 positive. Similarly In the studies of Harlozinska et al (1996) and Naik et al (2015), serous carcinoma showed majority of the p53 positivity.

In the present study, 85.6% of the high grade serous carcinoma showed p53 positivity. p53 positivity was much higher in high grade serous carcinoma cases than low grade cases and this difference was found to be statistically significant (p value = 0.044). In the study of Naik et al (2015), 100% of the high grade serous carcinoma cases were p53 positive. There was a statistically significant difference between p53 expression and grade of tumours. ($p < 0.05$) which is concordant with our studies. A positive association between p53 expression and histological grade is also noted in the study of Levesque et al (1995) ($p = 0.01$). However, in the study of Guirgea et al (2012), 56.25% of high grade and 12.5% of low grade cases were p53 positive. But they did not find an association between p53 expression and grade ($p = 0.16$). Similar finding was noted in the study of Abbasi et al (2016) ($p = 0.578$).

In the present study, Her2/neu expression was noted in 21.4% of epithelial ovarian carcinoma cases. This finding is similar to study done by Sylvia et al (2012) where 21% of the malignant tumours showed expression of Her2/neu. In the study of Verma et al (2018), 54.17% of the malignant tumours were Her2/neu positive.[17] In the study done by Nielsen et al (2004), 35% malignant cases were Her2/neu positive. But they excluded benign and borderline cases from their study similar to the present study.[18]

In the present study, Her2/neu positivity was noted only in serous carcinoma (27.3%). Mucinous carcinoma did not show positive expression of Her2/neu. This finding is concordant with the study done by Sarkar et al (2015),[19] Verma et al (2018) and Goel et al (2014)[20] where 35%, 69.37% and 72.2% serous carcinoma were Her2/neu positive respectively. In the study done by Sarkar et al, only serous carcinoma showed Her2/neu positivity. Mucinous carcinoma cases were Her2/neu negative which is similar to the present study findings. However, in the study done by Arya et al (2018), only mucinous carcinoma (33.3%) showed Her2/neu positivity. All other histological types were Her2/neu negative.[21]

In our study, 28.6% of the high grade serous carcinoma cases were Her2/neu positive and Her2/neu positivity was noted more in high grade cases than low grade. This difference was not statistically significant in the present study ($p = 0.858$). In the study done by sarkar et al (2015) and Berchuck et al (1990),[22] high grade serous tumours showed Her2/neu positive expression similar to our studies. However, in contrast to our study, in the study of Verma et al (2018), Her2/neu positivity was noted significantly more in low grade tumours compared to high grade tumours.

6. Conclusion

From this study we can conclude that, benign tumours were more common than malignant tumours and tumours in the premenopausal age group is rising. Serous cystadenoma was the commonest type of epithelial ovarian tumour and serous carcinoma was the most common malignant epithelial tumour. The rate of p53 expression varied with histological type and grade of the tumour. p53 expression was high in serous carcinoma and showed statistically significant association with high histological grading ($p < 0.05$). But further studies with the facility of mutational analysis for p53 to correlate with the wild type and aberrant expression of the protein in the immunohistochemistry are required to establish the role of p53 as a prognostic marker. Her2/neu expression was seen in higher proportion in high serous carcinoma. But a multicentric, large population based study with the infrastructure to follow up and the facility of FISH studies to evaluate equivocal score of her2/neu in immunohistochemistry is required to establish the prognostic impact and the role of anti her2/neu therapy in ovarian carcinoma in the future.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.

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