Section: Pathology

Original Research Article

STUDY OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR AND HER 2/NEU IN SURFACE EPITHELIAL OVARIAN TUMORS

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ABSTRACT

Background: Ovarian cancer is among the most aggressive malignancies of the female reproductive system and constitutes about 4% of all female cancers. Surface epithelial tumors form the majority, comprising serous, mucinous, endometrioid, and Brenner's tumors. Immunohistochemical (IHC) markers such as estrogen receptor (ER), progesterone receptor (PR), and HER2/neu play an important role in determining tumor behavior, prognosis, and therapeutic response. **Objectives:** This study aimed to evaluate the expression of ER, PR, and HER2/neu in surface epithelial ovarian tumors and correlate their expression with different histopathological subtypes.

Materials and Methods: Immunohistochemistry was performed using ER, PR, and HER2/neu antibodies on paraffin-embedded tissue sections of ovarian epithelial tumors. Positive and negative controls were applied for standardization. ER/PR expression was assessed based on nuclear staining, with >10% positivity considered positive. HER2/neu expression was scored from 0 to 3+, with 0/1+ as negative, 2+ as equivocal, and 3+ as strongly positive.

Results: ER positivity was observed predominantly in malignant and high-grade tumors, indicating estrogen's role in ovarian carcinogenesis. PR expression was variable across subtypes, with reduced expression in higher-grade tumors. HER2/neu overexpression (3+) was more frequently associated with aggressive histological subtypes and recurrent disease, while equivocal expression (2+) required further evaluation. The findings suggest that ER and PR expression may serve as prognostic indicators, while HER2/neu overexpression correlates with tumor aggressiveness and resistance to chemotherapy.

Conclusion: Immunohistochemical profiling of ER, PR, and HER2/neu provides valuable insights into the biology of surface epithelial ovarian tumors. ER and PR expression patterns may help predict tumor behavior, whereas HER2/neu overexpression could identify patients who may benefit from targeted therapies. Incorporating these markers into diagnostic and therapeutic protocols could improve prognostication and individualized treatment planning.

Keywords: Ovarian cancer, surface epithelial tumors, estrogen receptor, progesterone receptor, HER2/neu, immunohistochemistry.

INTRODUCTION

Tumours affecting the ovary have a diverse spectrum of features which vary according to the particular tumour entity. They include benign, low-malignant potential/borderline and malignant subtypes. Incidence of malignant tumours increases with age, occurring predominantly in pre-menopausal and perimenopausal women.[1,2] Among cancers of female genital tract, the incidence of ovarian cancer rank below only carcinoma of the cervix and the endometrium.[3] Ovarian cancer is one of the most aggressive malignancies of female reproductive reproductive system and is the seventh most common

cause of cancer related deaths in females constituting about 4.4 % of all female malignancies worldwide.[4] The World Health Organization (WHO) has given a Histological Classification,[5] of ovarian tumors according to which ovarian neoplasms are separated based on the most probable tissue of origin: surface epithelial tumours (65%) constitute majority, followed in decreasing order of frequency by germ cell tumours (15%), sex cord-stromal tumours (10%), metastases (5%) and miscellaneous tumours 5. Surface epithelial tumors are further sub-classified by cell type (serous, mucinous, endometrioid, etc) and atypia (benign, borderline or malignant)

- Serous tumors (30% of all ovarian tumours)
- Mucinous tumors (25 % of all ovarian tumours)
- Endometrioid tumors (20% of all ovarian tumours, mostly malignant)
- Clear cell tumors
- Transitional cell tumors

There have been constant efforts in the analysis of molecular markers in epithelial ovarian tumors by immunohistochemical (IHC) studies6. The high expression of estrogen receptor(ER) and progesterone receptor (PR) in epithelial ovarian cancer samples has led to the assumption that expression patterns of ER and PR may be related to tumour behaviour, prognosis, or both.[7]

Steroid hormones, estrogen and progesterone have been associated with ovarian carcinogenesis.[8]

Estrogens primarily regulate growth and differentiation in normal ovaries. The association between estrogen and cancer is linked to the mutagenic properties of estrogen and its derivatives in normal ovarian epithelial cells.[9-11] In contrast, progesterone and its receptors exert protective effects by reducing the exposure to high levels of estrogen and suppressing ovulation; antagonizing the growth-promoting effect of estrogen; and by inducing cell differentiation and apoptosis.[8-15] Loss of heterozygosity at the 11q23.3–24.3 region which contains the PR gene has been associated with an elevated risk for ovarian cancer and poorer prognosis.[13-15] Estrogen is considered a primary perpetrator in the development of ovarian carcinomas as 70% of ovarian cancers express estrogen receptors (ERs), whereas progesterone and its receptor are protective against ovarian cancer. In patients with breast malignancies and tumours of the endometrium the association between tumor estrogen and progesterone receptor levels and prognosis is well established. However, the clinical significance of ER and PR content in ovarian carcinomas has not been well documented.[15-19]

HER2/neu oncogene is a part of tyrosine kinase family, together with HER-1, HER-3 and HER-4. HER-2 is positioned on chromosome 17q21 and codes for a 185 kD transmembrane receptor protein.[20] HER2 gene is involved in intracellular signaling transduction pathways leading to cell growth and differentiation.[21] Over expression of extracellular domain of HER-2/neu is common as ovarian carcinoma progresses. HER-2/neu expression has been known to be quite common in ovarian carcinomas relapsing after chemotherapy.[22] 25% of primary ovarian carcinomas express the HER-2/neu encoded receptor, however it is controversial to what extent HER-2/neu amplification and protein overexpression correlates with prognosis, as noted in case of breast cancer. Only few studies have been carried out so far in this regard.

Dysregulation of HER2 signaling in ovarian neoplasms may occur as a result of either gene amplification or overexpression and may lead to faster cell growth, impaired DNA repair, and increased colony formation. These features would appear to make HER2 an attractive molecule for targeted immunotherapies in women with HER2-positive ovarian cancer.[23]

In the present study, an attempt was made to evaluate the expression of Her-2/neu along with ER and PR expression in surface epithelial tumours of ovary, their relationship to the type of malignancy and correlation with the various clinicopathological parameters, histological grading and staging.[21-23]

Aims and Objectives

1. To study the expression of estrogen receptor (ER), progesterone receptor (PR) and HER2/ neu immunohistochemical markers in surface epithelial ovarian tumors.
2. To correlate expression of markers (ER, PR and HER 2 neu) with histological subtypes.

MATERIALS AND METHODS

Study Setting: This retrospective study is based on ovarian tumour specimens received in the Department of Pathology, FMHS, SGT Hospital, Gurugram referred by the Department of Obstetrics and Gynaecology and Department of Surgery.

Study Size: Total of 42 cases of ovarian tumours were included.

Inclusion Criteria: All types of surface epithelial tumours of ovary were considered in this study.

Exclusion Criteria

- Metastatic tumors
- Other ovarian tumors like germ cell tumors and sex cord tumors
- Recurrent tumors

Methods: Hematoxylin & Eosin staining was done on paraffin sections of ovarian specimens received in the department. Immunohistochemical staining for ER, PR and Her 2/ neu were done as per standard procedure.

ER/PR expression

Nuclear staining was considered positive (dark brown colour)

Negative	% of stained cells less than 10%
Positive	% of stained cells more than 10%

Scoring

Score for proportion	Score for intensity
0 = No staining	0 =No staining
1< 1% staining	1 =Weak staining
2 =(1-10%) staining	2 =Moderate staining
3 = (11-33%) staining	3 =Strong staining
4 =(34-66%) staining	
5 =(67-100%) staining	

Total score ranges from 0 to 8
Tumors scoring <2 are regarded as negative and have a negligible chance of response

HER2/neu INTERPRETATION

Score	HER2/neu overexpression	Staining pattern
0	Negative	No staining is observed ,or membrane staining is observed in <10% of tumor cell
1+	Negative	Faint/barely perceptible membrane staining is detected in >10% tumor cell. Incomplete membrane staining
2+	Weakly positive (equivocal)	A weak to moderate complete membrane staining in >10% of tumor cell
3+	Strongly positive	A strong complete membrane staining is observed in >10% of tumor cell.

RESULTS

1. Age of the patient: The age of the patients studied ranged from 19 – 75 years, youngest being a 19 years old patient with serous cystadenoma and the oldest being a woman who had serous cystadenocarcinoma. Maximum number of cases, i.e 10 were seen in the age group of 31 to 40 years

2. History: The most common presenting complaints overall were abdominal pain and palpable lump, both of which were seen in 27 patients each (64.3 %). These were also the most common complaints in the malignant tumour group.

3. Type of surgical specimen: The most common surgical specimen was Total abdominal hysterectomy (TAH) +Bilateral salpingo-ophorectomy (BSO) comprising approx. 33.3% of the total specimens received

4. Gross appearance of the tumours: The mean size of the tumours was 9.20 ± 3.76 cms.

20 (47.6%) of the tumours were right sided lesions. 19 (45.2%) of the tumours were left sided lesions. 3 (7.1%) of the tumours were bilateral.

As far as consistency of the tumours was concerned, 30 (71.4%) of the tumours were cystic lesions. Purely solid tumours were seen 3(7.1%) in number. The rest (21.4%) of the tumours had mixed appearance on gross examination.

5. Histological Diagnosis: 29 (69.0%) of the tumours were found to have benign morphological features on histopathology. 1 (2.4%) of the tumours had borderline histopathological features whereas 12 (28.6%) of the cases proved to be malignant on histopathology.

The most common histopathological diagnosis, overall and also in the benign category was Serous Cystadenoma (SCA). In the malignant group, the most common tumour type was Serous Cystadenocarcinoma (SCAC). Only one case of borderline tumour was included in our study which was Borderline Mucinous Tumour (BMCA).

Purely cystic tumours were all benign on histopathology whereas the malignant tumours showed solid components. The only case of borderline tumour in our study was purely cystic

6. ER Expression: 39 (92.9%) of the tumors had positive ER expression and 3 (7.1%) of the tumors showed negative ER expression. The ER expression was almost equal in benign and malignant subgroups being 93.1% and 92.3% respectively. (Table 6.1)

There was a statistically significant association between ER expression and the histological subtypes (p value 0.036). Highest ER expression was seen in cases of serous tumours. Overall 27 out of 28 serous tumours (96.4%) included in the study showed positive ER expression. All benign serous tumours (n=21) in the study showed ER expression.

Table 6.1: Association Between ER: Expression and Tumor Classification (n = 42)

Tumor Classification	ER: Expression			Fisher's Exact Test	
	Positive	Negative	Total	χ2	P Value
Benign	27 (93.1%)	2 (6.9%)	29 (100.0%)	0.009	1.000
Malignant/Borderline	12 (92.3%)	1 (7.7%)	13 (100.0%)		
Total	39 (92.9%)	3 (7.1%)	42 (100.0%)		

7. PR expression: The PR expression was positive in 38 (90.47%) tumours and negative in 4 (9.52%) tumours. The PR expression was marginally greater in malignant subgroup than the benign subgroup being 91.7% and 89.73% respectively (Table 7.1)

There was a statistically significant association between PR expression and the histological subtypes

(p value 0.038). Most of the tumours in the study showed PR expression except 3 cases of mucinous cystadenoma and 1 case of PSAD comprising 42.9% and 50% of their respective categories.

Table 7.1: Association Between PR: Expression and Tumor Classification (n = 42)

Tumor Classification	PR: Expression			Fisher's Exact Test	
	Positive	Negative	Total	χ2	P Value
Benign	26 (89.7%)	3 (10.3%)	29 (100.0%)	0.073	1.000
Malignant/Borderline	12 (92.3%)	1 (7.7%)	13 (100.0%)		
Total	38 (90.5%)	4 (9.5%)	42 (100.0%)		

The ER parameters like cell count, proportional score, intensity score and final score showed greater area under the curve (AUROC) values indicating an excellent diagnostic performance with a statistically significant p value (< 0.05) .

On the other hand similar PR parameters showed smaller AUROC values which were statistically insignificant and demonstrated poor diagnostic parameters with the exception of PR final score which showed a 97% specificity at a cut -off of >/= 8.

8. Her 2 neu Expression

Only two tumours in our study showed Her 2 neu expression, one case each of serous cystadenocarcinoma and papillary serous adenocarcinoma. None of the benign tumours in our study showed Her 2 neu expression. There was no statistically significant association between the histological tumour type and Her 2 neu expression (p value 0.124).

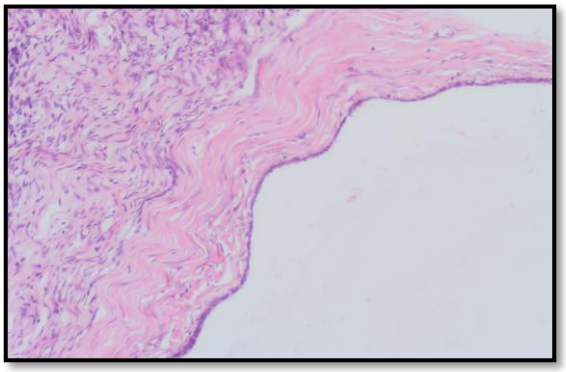

Figure 1: H and E stained section of Serous Cystadenoma

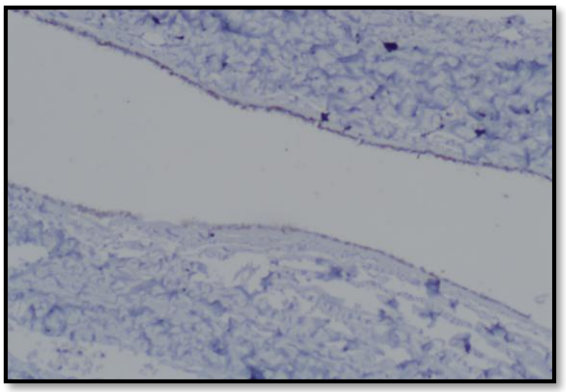

Figure 2: Strong ER positivity seen in Serous cystadenoma

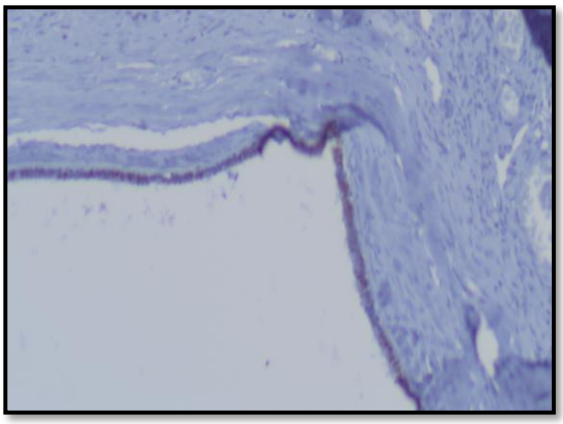

Figure 3: Strong PR positivity seen in Serous cystadenoma

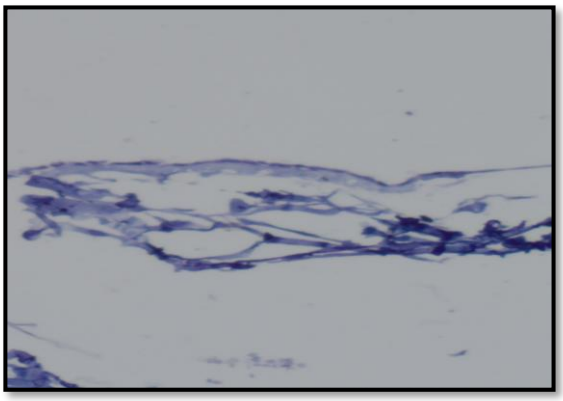

Figure 4: Negative expression of Her 2/neu seen in Serous cystadeno

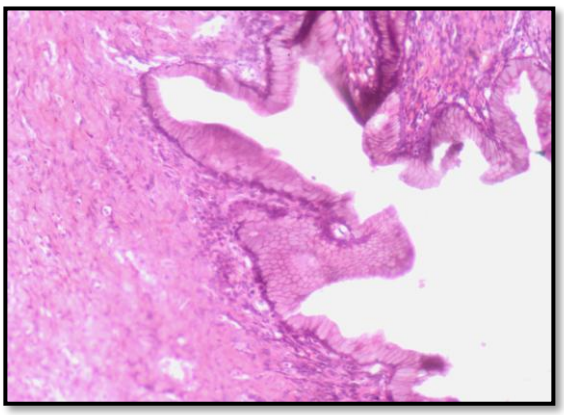

Figure 5: H and E stained section of Mucinous cystadenom

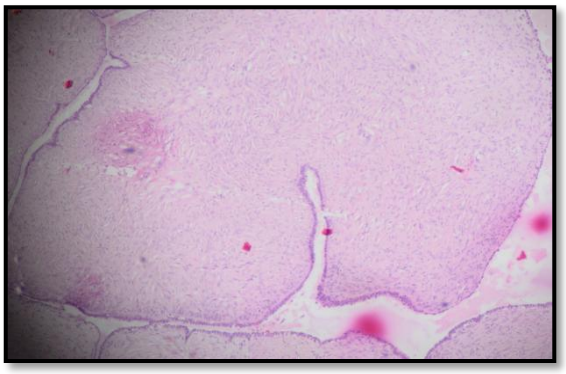

Figure 6: H and E stained section of Serous Cystdenofibroma

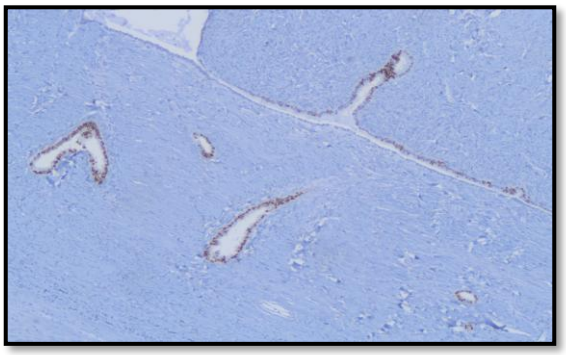

Figure 7: Strong positive expression of PR in Serous cystadenofibroma

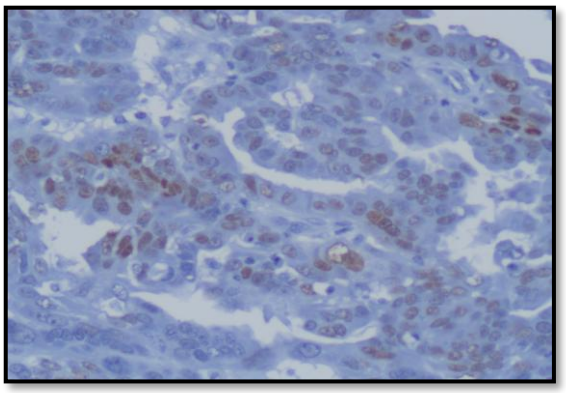

Figure 8: Positive expression of ER in Papillary serous carcinoma

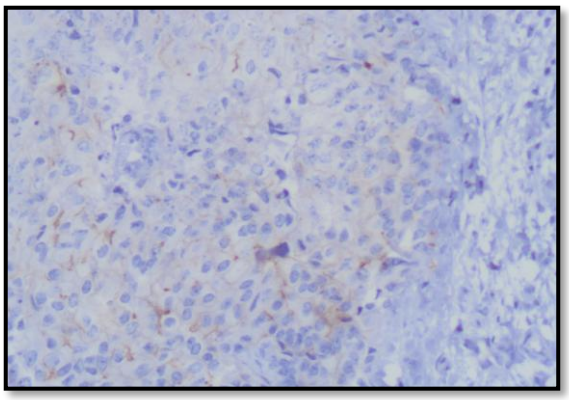

Figure 9: Positive expression of Her 2/ neu in Serous cystadenocarcinoma

DISCUSSION

The youngest patient in our study was aged 19 years and the eldest patient was of 75 years age. Naik et al24 in their study of 110 cases of surface epithelial tumours had a similar age distribution of cases, ranging from 14-75 years.

The common presenting complaints were abdominal pain, palpable lump and abdominal distension. Similar clinical manifestation were mentioned by Kumar V et al.[25] In a study conducted by Sarkar et al,[26] too, pain abdomen was the most common chief complaint overall.

In our study, 22 patients were premenopausal whereas the rest 20 patients were postmenopausal. In our study we found that the prevalence of epithelial ovarian cancer was slightly higher in postmenopausal women (40%) than in premenopausal women (18%). However, all the cases of borderline and malignant mucinous tumours in our study were seen in pre-menopausal women. Similar observations were recorded by Fang Shen et al in a study conducted in Chinese women.[27]

A family history of ovarian carcinoma was seen in 19% (8/42) of the overall cases and in 50% (6/12) of the malignant cases. Many studies have established higher ovarian cancer risk in women with a family history of ovarian cancer, breast cancer and cancers of other sites Negri E et al,[28] Soegaard M et al.[29]

The most common surgical specimen received was TAH + BSO comprising of 14 cases (33.3% of total specimens received). In our study, the mean size of the tumour in the benign group was 8.67 cms. The mean size in the malignant group was 9.92 cms. 38 tumors (90.5%) had average size ranging from 5-14 cm and only 4 (9.5%) had size more than 15 cm. No tumour was found to be less than 5 cm in size. However, there was no statistically significant difference between the groups in terms of size ($\chi 2$ = 3.057, p = 0.217). In a study conducted by Gupta N et al 30, 66% of the tumours were in the size range if 5-14 cms. A similar observation was made by Manoja V 31 et al in their study on ovarian tumours.

On gross examination, the majority of the tumours were cystic in appearance comprising of 30 (71.4 %) cases. Next common category of tumours had a mixed appearance with both cystic and solid components contributing to 9 (21.4%) cases. 3 cases were purely solid in appearance (7.1%). A similar proportion of cases was seen in studies conducted by Sarkar et al,[26] and Gupta N et al.[30] There was a statistically significant correlation between the tumour consistency and the histological diagnosis in our study (p value < .001)

In our study, 92.9.% of ovarian tumors were unilateral. Tyagi et al,[32] reported incidence of unilaterality in 90% of ovarian tumors. Saxena HMK et al,[33] also gave similar results with incidence of unilaterality in 83.7% cases.

29 (69.0%) of the tumours were found to have benign morphological features on histopathology. 1 (2.4%)

of the tumours had borderline histopathological features whereas 12 (28.6%) of the cases proved to be malignant on histopathology. Similar incidences of histopathological subtypes have been noted in many previous studies (Makwana et al,[34] Vaidya et al,[35] Abdullah et al,[36]). Purely cystic tumours were all benign on histopathology whereas the malignant tumours showed solid components. The only case of borderline tumour in our study was purely cystic. A similar observation was made in many previous studies like Sarkar et al,[26] Basu et al.[37]

The most common histopathological diagnosis, overall and also in the benign category was serous cystadenoma (SCA) comprising 50.0% of the total cases (21/42) and 75 % of the serous tumours (21/28). According to Saxena HMK et al 33. incidence of serous cystadenoma among serous tumors was 72%. Jha et al,[38] and Makwana et al,[34] had an incidence of serous tumours of 47.8% and 44.4% respectively in their studies on ovarian tumours.

In the malignant group, the most common tumour type was Serous Cystadenocarcinoma. 4 (9.5%) of the patients had histological diagnosis of serous cystadenocarcinoma and it comprised 33% of the cases in the malignant group. Commonest histopathological malignancy in most of the the studies done so far is serous carcinoma. Basu et al,[37]-41.6%, Saini et al 39-49.69%, Se le Kim et al40-49.5%, Yogambal et al41-45%, Mondal et al,[42]-38.3% , reported even higher incidences of serous carcinomas in their studies.

39 (92.9%) of the tumors in our study had positive ER expression and 3 (7.1%) of the tumors showed negative ER expression. The ER expression was almost equal in benign and malignant subgroups being 93.1% and 92.3% respectively. This is in stark contrast to many studies done previously which have shown a higher ER positivity in malignant subgroups but a lower expression in benign tumours. In a study done by Naik PS et al,[24] the expression of ER was more in malignant tumors-13(81.25%) than borderline-9(75%) and benign-20(24.39%) tumours. Expression of ER was also low in benign tumors (5/17cases, 29%) compared to malignant (11/33 cases, 33%) and borderline (4/10 cases, 40%) in another study (Sylvia et al6).

The mean proportional score in ER expression was 2.69 in benign, 4.0 in borderline and 3.92 in malignant cases (p value = 0.003). The ER scores were statistically significant, with p values less than 0.05, hence demonstrating excellent diagnostic performance.

Sevelda P et al,[43] demonstrated a higher incidence (63%) of ER+/PR+ in patients older than 60 years of age than in younger subjects (36%). In our study, ER expression was seen in 14 out of 15 patients (93%) above the age of 50 years.

There was a statistically significant association between ER expression and the histological subtypes (p value = 0.036). Highest ER expression was seen in cases of serous tumours. Overall, 27 out of 28 serous tumours (96.4%) included in the study showed positive ER expression. Similar incidences of ER expression were found in a large-scale study comprising of 1742 high-grade serous carcinomas. ER expression was seen in 81% of such tumors (Sieh W et al.[44]). In a study by Sylvia et al,[6] mucinous tumours were negative for ER expression. Mucinous ovarian tumours were reported to express very low levels in many other earlier studies as well (Toppila et al,[45] Gronroos et al,[46] Scambia et al.[47])

In our study, the PR expression was positive in 38 (90.47%) tumours and negative in 4 (9.52%) tumors; the PR expression being marginally greater in malignant subgroup (91.7%) than the benign subgroup (89.7.3%). Our study included 21 patients above the age of 40 years. Out of these 19 (90%) showed positive PR expression. In many earlier studies as well (Sevelda et al,[43] Scambia et al,[47]) it was reported that PR positivity is more frequently associated with older age .

Only two patients in our study (4.76%) showed Her 2 neu expression, one case each of serous cystadenocarcinoma and papillary serous carcinoma. The percentage of Her 2 neu positivity among malignant tumours was 16.66 % (n=2). None of the benign tumours (n=29, 72.5 %) in our study showed Her 2 neu expression , thus showing that Her 2 neu expression is generally a feature of malignant tumours. According to a study done by Goel et al,[48] 18(48.6%) malignant tumours showed positive expression for Her2/ neu, while no benign or borderline tumour showed Her2/neu expression.

CONCLUSION

In our study the incidences of ER and PR expression were almost equal in benign and malignant subgroups. However the ER positive malignant tumours showed ‘strong’ expression than the ER positive benign tumours. On the other hand, the PR positive benign tumours showed a relatively ‘strong’ PR expression than PR positive malignant tumours. Only two tumours showed Her 2/ neu expression and both of these were malignant tumours.

In our study there was statistically inconsistent correlation of clinicopathological parameters and the expression of ER, PR and Her 2 /neu, probably due to a limitations like including a single subset of ovarian tumours and also due to less number of cases included. Hence an absolute conclusion could not be derived. Thus, further studies following similar immunohistochemistry protocols and well marked cut-off levels are recommended to be carried out with larger sample sizes.

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