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# Ovarian Neoplasms: Histopathological Patterns and Estrogen and Progesterone Receptor Expression in Epithelial Ovarian Tumors.

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## ABSTRACT

**Background:** Both the Estrogen and Progesterone hormones and their receptors are thought to be involved in the process of tumor genesis in ovarian cancer. The main aim of present study was to evaluate the histopathological pattern of ovarian neoplasms and to study the expression of estrogen and progesterone status in ovarian epithelial tumours. **Methods:** The study was carried out on 60 cases of ovarian neoplasms. Out of all 60 cases, 46 epithelial ovarian neoplasms were studied for estrogen and progesterone expression detected through IHC and their correlation with histopathological pattern, age, menopausal status and stage of tumour was studied. **Results:** Among the 60 cases, 68.3% were benign, 26.7% were malignant and 5 % were borderline. Surface epithelial tumors constituted 76.66%, Germ cell tumours constituted 15.55% and sex cord stromal tumours constituted 6.66% of all tumours. Serous cystadenoma comprised of 43.33% of all cases. Serous cystadenocarcinoma and mature teratoma both constituted 13.33% of all tumours. ER and PR expression was seen in 34.28% and 31.42% of serous neoplasms respectively. Mucinous neoplasms showed 11.11% positivity for PR expression. Among serous tumours, ER and PR both showed positivity in 75% of malignant tumours and positivity of 19.2% and 19.23% for benign tumours respectively. ER and PR showed higher expression in serous tumours. ER and PR expression was more among postmenopausal females. (66.66% and 75% respectively). Both ER and PR showed higher expression in Stage III ovarian neoplasms.(66.66% and 100% respectively). **Conclusion:** Surface epithelial tumours were most common histopathological pattern among benign and malignant tumours. Estrogen and Progesterone showed higher expression in serous tumours and in postmenopausal patients. ER and PR expression was more in higher stage of ovarian tumours. So estimation of Estrogen and Progesterone receptors may help to select the women with ovarian malignancy for hormonal therapy.

***Keywords:*** Estrogen, Ovarian Neoplasms, Progesterone.

## INTRODUCTION

Ovarian cancers constitute 15.0%-25.0% of all the primary malignancies in female genital tract and are a common cause of death in gynaecological malignancies.[2] A female's risk of having ovarian tumour at any time in her life is 6.0 %– 7.0%, of having ovarian cancer is 1.5 % and dying from ovarian cancer is almost 1.0%.[3] Increasing age, early menarche, late menopause, nulliparity and delayed child bearing are associated with increased risk of ovarian cancer. Inflammation that is incited by ovulation-induced surface damage, by retrograde menstruation-induced salpingitis, by introduction of foreign material through the vagina and uterine cavity may be responsible for ovarian carcinoma.[4,5] Familial predisposition has been noticed in about 5-10% of the cases.[6] Majority of ovarian cancers occur due to mutation in BRCA 1 or BRCA 2 gene.[7]

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Estrogen and Progesterone and their receptors are thought to be involved in the process of tumor genesis in ovarian cancer.[20] ER+ ve PR +ve, ER – ve PR+ve phenotype predicts a favourable tumor biology and long term survival, probably reflecting functional effects on tumor proliferation, differentiation, and cellular apoptosis.[9] The present study aims at studying the histopathological pattern ,incidence of ovarian neoplasms and ER, PR expression in them which can be helpful in choosing an appropriate hormonal therapy in hormone dependant tumours.

## MATERIALS AND METHODS

A study was conducted on 60 specimens of ovarian neoplasms received in the Department of Pathology, GMC Patiala. A detailed clinical data was abstracted from the patients chart. Multiple tissue pieces from representative areas, 1 cm apart were taken, kept in stainless steel cassettes. The tissue was then dehydrated by passing through ascending grades of alcohol in histokinette. Wax blocks of the embedded material were prepared by using Leukhart's 'L' blocks. The sectioning of tissue blocks was done by Leica microtome and 3-5 micron sections were obtained. Sections were placed on a slide coated with Mayers albumin. The staining of sections was done routinely with Haemotoxylin and Eosin. Ehrlich's haematoxylin was used, differentiation with 1 percent acid alcohol for ten to twenty seconds was done. Counter staining was done using 1 percent aqueous eosin for one minute. After staining, histological subtypes of the tumours were studied.

Immunohistochemical expression for ER and PR was studied in the 46 epithelial ovarian tumors that included 31 benign, 3 borderline and 12 malignant surface epithelial tumours. 4 micrometre thick sections were taken. Three percent peroxidized solution was used to quench endogenous perxidase. Retreival of the antigen was done by boiling it with citrate buffer for 40 minutes at 95 degree celcius in decloaking chamber. (Microwave antigen retrieval method). Primary antibody (rabbit monoclonal antibodies - SP1 Biocare) was applied and incubated at room temperature for 1 hr in moist chamber. Then secondary antibody (MACH-2 Polymerase Detection Kit) was applied for half an hour in moist chamber. Diaminobenzidine with hydrogen peroxide was used as the chromogen substrate. Counterstaining was done by staining the slide Harris Haematoxylin for 2 minutes.

Grading of ER and PR was performed using a semiquantitative score by Remmele and Steger (Immunoreactive score),[9] obtained by multiplying the staining intensity (grade as 0= negative, 1= weak, 2= moderate and 3= strong) by percentage of positive stained cells (0=no,1=<10%,2=11-50%,3=51-80% and 4=81% of cells). Tumour with immunoreactive score = or >2 were taken as positive. Statistical analysis was done using Chi Square tests.

## RESULTS

The tumours were observed in the range of 11 to 80 years with maximum number of cases observed between the age group of 21-30 yrs, accounting for 33.33% of cases followed by 31-40 yrs of age group being the second common. Majority of the tumours were unilateral (86.6%) and 13.33% came out to be bilateral. Benign tumours were the major component of ovarian tumours constituting 68.3% followed by malignant tumours which formed 26.7% and borderline tumours constituted 5%. The surface epithelial tumours formed the major group constituting 76.66% followed by germ cell tumours constituting 15% followed by sex cord stromal tumours constituting 6.66% [Figure 3] with metastatic tumours constituting 1.66% of all the tumours.[Table 1]

**Table 1: Histopathological Typing Of Ovarian Neoplasms as Per WHO.**

| | Type of tumour | No.of cases | % age |
|---|---|---|---|
| Serous epithelial Tumours(46) | Serous(35) | | |
| | Benign | 26 | 43.33% |
| | Borderline | 1 | 1.6% |
| | Malignant | 8 | 13.33% |
| Mucinous epithelial tumors | Mucinous(9) | | |
| | Benign | 5 | 8.3% |
| | Borderline | 2 | 3.33% |
| | Malignant | 2 | 3.33% |
| Endometrioid carcinoma | Malignant | 2 | 3.33% |
| Germ cell tumours (09) | Mature teratoma | 8 | 13.33% |
| | Dysgerminoma | 1 | 1.66% |
| Sex cord stromal Tumours(4) | Fibroma | 1 | 1.66% |
| | Granulosa cell tumour | 3 | 5% |
| Metastasis | | 1 | 1.66% |

Among the benign tumours, serous cystadenoma were the most common constituting 43.33% of all the tumours followed by mature cystic teratomas and serous cystadenocarcinomas both constituting 13.33% of all cases.

Serous cystadenocarcinoma [Figure 1] was the most common malignant tumour (13.33%) followed by mucinous carcinoma (8.33%) [Figure 2]

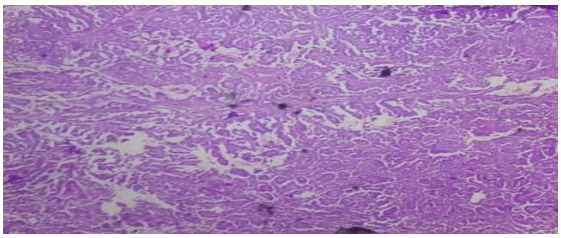

**Figure 1: Photomicrograph Of Serous Carcinoma Showing Mainly Papillae With Cells Exhibiting Marked Nuclear Atypia And Stromal Invasion. (H And E,10X).**

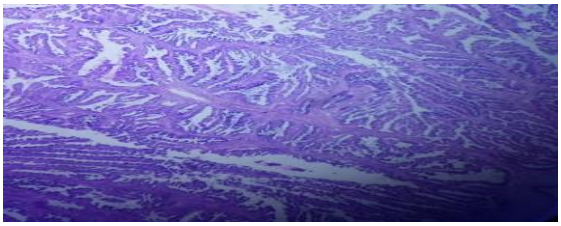

**Figure 2: Photomicrograph of Mucinous Carcinoma Showing Papillae Formation with Moderate Nuclear Atypia ANd Mucin In Glandular Lumen. (H and E, 10X).**

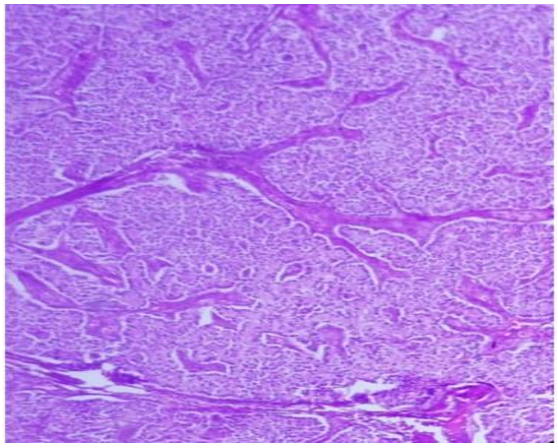

**Figure 3: Photomicrograph of Granulosa Cell Tumor Showing Micro follicular Pattern. Cells Are Arranged in Form of Micro follicles. Call Exner Bodies Seen. (H and E, 10 X)**

Majority of benign tumours were cystic in consistency (65%), 7% were solid and 21.66% had partly cystic partly solid consistency. Out of these, majority of benign tumours had cystic consistency (37 cases) while most malignant tumours had partly solid partly cystic consistency.

65% of the ovarian tumours occurred in premenopausal patients and 35% occurred in postmenopausal patients. Most of the carcinomas were observed in post-menopausal patients. Benign cases had highest incidence in premenopausal females.

Among the 46 epithelial tumours to which IHC was applied, ER as well as PR positivity were both seen in 26.08% of the total ovarian epithelial tumours.

Incidence among epithelial cancers was seen to be 50 % in ER and 58.33 % in PR.

Both ER and PR showed higher expression in serous tumours (34.28% and 31.4%) [Figure 4] as compared to mucinous tumours (PR positivity in 11.11%). [Table 2]

**Table 2: Type of Tumor.**

| Type Of Tumour | Er Positive | Er Negative | Pr Positive | Pr Negative |
|---|---|---|---|---|
| Serous tumours (35) | 12 (34.28%) | 23 (65.71%) | 11 (31.42%) | 24 (68.57%) |
| Mucinous tumours (9) | - | - | 1 (11.11%) | 8 (88.88%) |

Both ER and PR showed statistically higher expression in malignant tumours.ER was positive in 6 cases (50%) of malignant tumours, all of which were serous carcinomas and PR was positive in 58.33% cases among which 6 were serous carcinoma and 1 was mucinous carcinoma. Benign cases showed an expression of 16.12% among ER and PR receptors. The expression was more in serous carcinomas as compared to mucinous carcinomas.

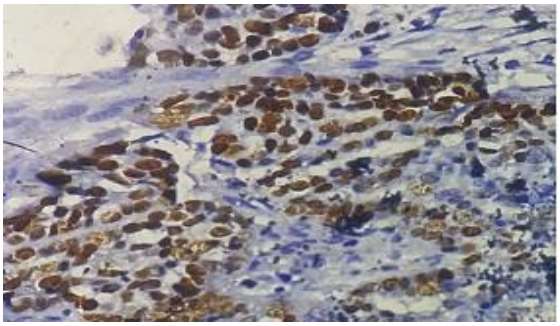

**Figure 4: Photomicrograph Showing Moderate to Strong Intensity Er Positivity in Serous Carcinoma.**

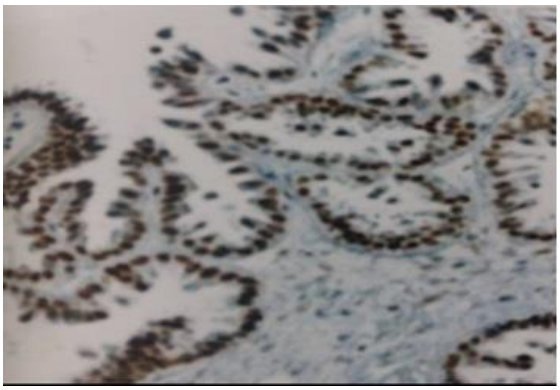

**Figure 5: Photomicrograph Showing Er Positive Mucinous Carcinoma. (40x)**

Both ER and PR showed higher expression in women >40 yr of age (75% and 66.66% respectively) as compared to females less than 40 yrs. (25% and 33.33% respectively).[Table 3]

**Table 3: Correlation of Age with Er/Pr.**

| Age | <40 yrs | >40 yrs | p value |
|---|---|---|---|
| ER positivity(n=12) | 3(25%) | 9(75%) | 0.025 |
| PR positivity(n=12) | 4(33.33%) | 8(66.66%) | 0.025 |

ER/PR expression was more in postmenopausal females (66.66% and 75%) as compared to premenopausal females.(33.33% and 25%)(Table- 4)

**Table 4: Association between Er/Pr and Menopausal Status.**

| | Premenopausal (n=39) | Postmenopausal (n=20) | P value |
|---|---|---|---|
| ER (N=12) | 4 (33.33%) | 8 (66.66%) | 0.085 |
| PR (N=12) | 3 (25%) | 9 (75%) | 0.015 |

Both ER and PR showed statistically significant higher expression in stage III as compared to stage II and Stage I tumours.[Table 5]

**Table 5: Correlation between Er/Pr and Stage of Tumour.**

| | STAGE I(N=4) | STAGE II(n=3) | STAGE III(n=3) | P value |
|---|---|---|---|---|
| ER+VE | 2(50%) | 2(66.66%) | 2(66.66%) | 0.766 |
| PR+VE | 1(25%) | 3(100%) | 3(100%) | 0.060 |

## DISCUSSION

The present study was carried out on 60 cases of ovarian neoplasms. Their histopathological type as per WHO classification and estrogen and progesterone receptor expression in primary epithelial ovarian neoplasms and their correlation with histopathology, age, menopausal status and stage of tumor was studied.

These tumours were seen in the age range of 11 to 70 years with a peak incidence in 21-30 years range. The youngest case was 11 yr old (serous cystadenoma) and the oldest case was 75 yr old (mucinous cystadenoma). The maximum number of tumours occurred in 21-30 years (33.3%) followed by 41-50 yr (18.3%) followed by 31-40 yr range (16.7%). Similar age range was reported by many authors like Saxena et al and Jagdeshwari et al.[10,11]

Out of 60 ovarian neoplasms, 68.3% cases were benign, 5 % were borderline and 26.7 % were malignant. The results were similar to findings by other workers (Pilli et al and Gupta et al) where benign were most common followed by malignant lesions followed by borderline lesions. Among the surface epithelial tumours, commonest benign epithelial tumour was serous cystadenoma (43.33%) of all neoplastic lesions followed by mucinous cystadenoma as 2nd most common benign epithelial tumour (8.3%).

Among the malignant epithelial tumours, serous carcinoma was the commonest (13.33%) followed by mucinous carcinoma (3.33%).

Germ cell tumour was the second most common group of ovarian tumours. Among the 9 cases of germ cell tumours, most common was mature cystic teratoma accounting for 13.33% of total neoplastic lesions. This result correlated with studies by Misra et al and Prabhakar et al.[12,13]

Incidence of Sex cord stromal tumours was 6.66% of all neoplastic lesions, comprising of 5% cases of granulosa cell tumour and 1.66% cases of fibroma. The results were comparable to studies conducted by Gupta et al Misra et al and Prabhakar et al.[12-14]

ER/PR expression was seen in 46 epithelial ovarian neoplasms out of which 35 were serous epithelial ovarian neoplasms and 9 were mucinous epithelial neoplasms and 2 were endometrioid cancers.

Out of these, 8 were serous carcinomas, 2 were mucinous carcinomas and 2 were endometrioid cancers of ovary. In the present study, ER positivity was seen in 26.08% (12 cases) and PR positivity was also seen in 26.08% (12 cases) of all the ovarian epithelial neoplasms (n=46). These included 2 cases of endometrioid carcinoma both of which were negative for estrogen and progesterone receptors expression.

On comparison Tangjitgamol et al in their study found ER positivity in 39.6% and PR positivity in 33% of total 106 cases of ovarian neoplasms.[15]

Similarly Sujitra Tanvanich et al in their study found ER positivity in 29.8% cases and PR positivity in 34% of all the ovarian neoplasms.

The present study showed an ER expression in serous tumours in 12 out of 35 cases (34.28%). PR expression in serous tumours was seen in 11 cases (31.4%). ER expression in mucinous tumours was seen in none of the case and PR expression in mucinous tumours was seen in 1 (11.11%) cases.

On comparison it was seen that H. Arias-pulido et al reported that 66% of serous tumours were ER positive and 54% were PR positive, in mucinous tumours 13% were ER positive and 20% were PR positive.[16]

In present study 6 cases (50%) out of 12 malignant tumours taken, showed ER positivity among which all cases were of serous carcinomas. PR positivity was a seen in 7 (58.33%) out of 12 cases of ovarian cancers which included 6 cases of serous carcinomas and 1 case of mucinous carcinoma. Among the benign tumours 5 (16.12%) cases out of 31 tumous showed ER and PR positivity.

On comparison Bergqvist et al reported that 67% and 40% cases of ovarian cancers were positive for ER and PR respectively and 35% and 45% positivity for ER/PR was seen in benign tumours in their study.[17]

Estrogen receptor showed higher expression in malignant tumours 6 (13.04%) as compared to benign 5 (10.86%) and borderline 2 (4.3%).

PR showed almost similar incidence with higher expression in malignant tumours 7 cases (15.21%) as compared to benign tumours 5 cases (10.86%).

On comparison Sylvia et al showed that ER positivity was seen in 29% of benign, 33% of malignant and 40% of borderline tumours.[18]

In the present study 8 cases (66.66%) out of 12 cases expressing ER were postmenopausal and 4 cases (33.33%) were premenopausal. Among the cases expressing PR, 9 cases (75%) were postmenopausal, 3 cases (25%) were premenopausal. Hence ER/PR expression was more among postmenopausal patients as compared to premenopausal patients. Similar results were found in studies conducted by Sylvia et al, Hahnel et al and Agarwal et al.[18-20]

As per staging, ER was expressed as 66.66% in stage III, 66.66% in stage II, 50% in stage I. PR was expressed as 100 % in stage III, 100% in stage II and 25% in stage I.

Hogdall E V et al reported that ER positivity in ovarian cancers increases with increasing FIGO stage.[21] Agarwal et al reported that receptor positivity increases with stage of tumour.[20] Similar observations were made by Sylvia et al.

## CONCLUSION

So it is concluded that knowing the various histopathological patterns of ovarian neoplasms and

ER and PR expression in tumours of specific histopathological pattern. Variability of expression of ER and PR with age of patient, nature of tumour and stage of tumour may help us choose the patients responsive to hormonal therapy that may aid in prognosis as well as response of patient to treatment.

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