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A CROSS SECTIONAL STUDY TO EVALUATE EXPRESSION OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR AND HER2/NEU IN OVARIAN TUMOURS

Pathology

Dr. Saroj Pachori Professor, Department of Pathology, Sawai Man Singh College & Attached Hospitals, Jaipur Rajasthan, India

Dr. Tapendra Kumar Upadhyay Resident, Department of Pathology, Sawai Man Singh College & Attached Hospitals, Jaipur Rajasthan, India.

Dr. Parmendra Pachori* Professor, Department of Immuno Hematology And Transfusion Medicine, Sawai Man Singh College & Attached Hospitals, Jaipur Rajasthan, India. *Corresponding Author

Dr. Divya Sharma Department of Biochemistry, Sawai Man Singh College & Attached Hospitals, Jaipur Rajasthan, India.

Dr. Rajendra Kumar Sharma Resident, Department of Pathology, Sawai Man Singh College & Attached Hospitals, Jaipur Rajasthan, India.

ABSTRACT

Ovarian cancer is the second most common gynaecologic malignancy and the fifth leading cause of cancer death in women in developed countries1. More effective treatment regimens like "targeted" oncologic therapies must be developed to improve morbidity and reduce mortality in ovarian cancer patients. Estrogen receptors and HER2/neu are two such targets. The purpose of present study is to study the expression of estrogen receptors, progesterone receptors and Her2/neu in ovarian tumours. **Methods:** This was a Laboratory based cross sectional study conducted between August 2021 to December 2022 on 70 Oophorectomy specimen in 10% buffered formalin in the department of pathology, SMS Medical College, Jaipur. H&E and IHC for ER, PR and Her2/neu done. **Results:** ER, PR and Her2/neu receptors positivity was highest in surface epithelial tumours cases followed by germ cell tumours, and sex cord stromal tumour. In HIGH GRADE, (mainly serous carcinomas) the ER receptor was present in 100% of the cases, the PR receptor in 76.92%, and the Her2/neu receptor was present in 100% of cases. **Conclusion:** This study reveals that ovarian cancer are influenced by classic variables such as histologic type, grade and stage of tumour. This leads to development of targeted oncologic therapies that might be more effective and less toxic. Estrogen and Her2/neu are two such targets.

KEYWORDS

Estrogen Receptors (ER), Progesterone Receptors (PR), Her2/neu (Human epidermal growth factor receptor-2), Ovarian tumours.

INTRODUCTION

Ovarian cancer is the second most common gynaecologic malignancy and the fifth leading cause of cancer death in women in developed countries[1]. Each year, over 22,000 women are diagnosed worldwide with epithelial ovarian cancer and 15,000 die of it[2]. As most ovarian cancers detected when they have spread beyond the ovary. So, they have the worst prognosis and highest case fatality rate among all gynecological malignancies. The treatment for ovarian neoplasms depends on the grade and stage of the tumour at presentation. More effective treatment regimens and better early detection tools must be developed to improve morbidity and reduce mortality in ovarian cancer patients. This has led to the development of "targeted" oncologic therapies that might ultimately be more effective and less toxic. Among the biological parameters proposed as possible prognostic factors in ovarian cancer, much attention has been focused on endocrine factors and especially on steroid hormones and their receptors (estrogen and progesterone receptors)[3]. Her-2/neu (Human epidermal growth factor receptor-2) proto-oncogene encodes a protein belonging to the EGFR (epidermal growth factor receptor) tyrosine kinase receptor family. Overexpression of her-2/neu is known to occur in ovarian cancers and initiates intracellular signaling pathways involved in cell proliferation, differentiation, migration, and apoptosis[4].With the development of immunohistochemistry and fluorescent in situ hybridization, there has been emphasis on targeted therapy. Estrogen receptors and HER2/neu are two such targets. The purpose of present study was to estimate the expression of estrogen receptors, progesterone receptors and Her2/neu in ovarian tumours and to correlate the results of immunohistochemistry with various clinicopathological parameters to guide treatment decision.

MATERIALAND METHODS

This was a Laboratory based cross sectional study conducted between August 2021 to December 2022. Detailed consent was attained from the patients or their attendants. Ethics clearance was duly obtained from Institutional Ethics Committee.

All consecutive eligible patients fulfilling following inclusion and exclusion criteria were included.

Inclusion Criteria:

- Formalin fixed oophorectomy specimen of all age groups received at the department of pathology, SMS Medical College.

Exclusion Criteria:

- Poorly fixed specimen,
- Inflammatory lesions of ovary.

A total 70 Oophorectomy specimens were received in 10% buffered formalin from the Department of Obstetrics and Gynaecology. A complete surgical pathology requisition form received in the department with patient's clinical data along with registration number, age, parity, presenting signs and symptoms, menstrual irregularities & obstetrics history, relevant serological and radiological details was obtained.

H&E and IHC for ER, PR and Her2/neu done. Scoring is based on ALLRED SCORING System for Estrogen receptor (ER), Progesterone receptor (PR). This system includes proportion scoring of the nucleus (PS) and intensity scoring (IS). Immunohistochemical assessment of HER2/neu overexpression was graded as per ASCO (American society of clinical oncology)/CAP (college of American Pathologists) guidelines.

RESULTS

Our study involved 70 oophorectomy specimen out of which 39 (55%) cases were benign, 2 (2.8%) cases were borderline and 29 (41.42%) were malignant cases.

Table 1: Distribution of cases according to er, pr, her2/neu

Nature	Total	ER Positive		PR Positive		Her2/Neu Positive	
		Case	%	Cases	%	Case	%
Benign	39	5	12.82	5	12.82	4	10.25
Borderline	2	1	50.00	0	0.00	0	0.00
Malignant	29	21	72.41	14	48.27	27	93.10
Total	70	27	38.57	19	27.14	31	44.29
P-values LS		0.004S		0.001S		<0.001S	

Among 39 benign tumour cases, 5 (12.82%) cases were ER positive, 5 (12.82%) cases were PR positive and 4 (10.25%) cases were Her2/Neu

positive. Among 2 borderline cases there was only 1 (50%) ER positive case.While in 29 malignant tumour cases, 21 (72.41%) cases were ER positive, 14 (48.27%) cases were PR positive and 27 (93.10%) cases were Her2/Neu positive showing that ER and Her2/Neu positivity was higher in malignant cases.

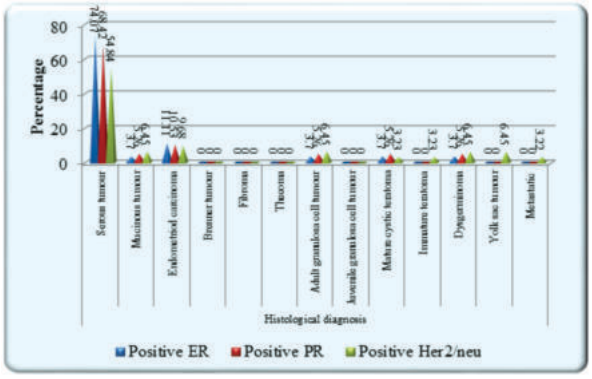


Figure 1: Status of ER, PR, Her2/neu in various ovarian tumour.

Our study reveals that with P-value significant at <0.001, ER Positivity was observed in 74.07% in serous tumours cases followed by 11.11% cases of endometriod carcinoma and 3.70% case each of mucinous tumours, Adult granulosa cell tumours, mature cystic teratoma and Dysgerminoma. Similarly PR 68.42% and Her2/neu 54.84% positivity was also higher in serous tumours cases followed by endometriod carcinoma and mucinous tumours cases.

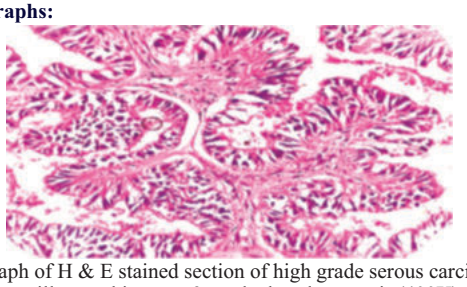
Table 2 :Status of ER, PR, Her2/neu according to tumour grade in Two-Tier Grading System (serous carcinomas and immature teratomas only)

	ER Positive		PR Positive		Her neu2 Positive	
Total (N=18)	No	%	No	%	No	%
Low grade (5)	4	80	1	20	4	80
High Grade (13)	13	100	10	76.92	13	100
P Value LS	0.006S		<0.001S		0.006S	

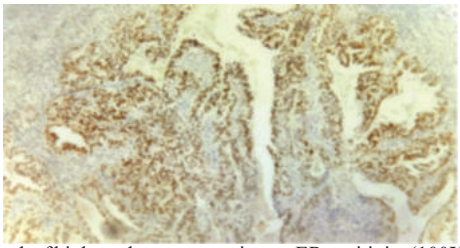
In HIGH GRADE, the ER receptor was present in 100% of the cases, the PR receptor in 76.92%, and the Her2/neu receptor was present in 100% of cases. Out of 5 low Grade cases, ER receptor was present positive in 4 (80%) cases, PR positive cases were 1 (20 %) and Her2/neu positive cases were 4 (80%). In our study three tier grading system used for endometrioid carcinoma and mucinous carcinoma and we observed that ER, PR and Her2/neu positivity was higher in grade 2. Her-2-neu was expressed both in Grade 2 and Grade 3.

ER Positivity was high in stage 3 (77.77%) followed by 76.92% in stage 2 and 66.66% in stage 1. While PR was 77.77% in stage 3, 50% in stage 2 and 30.76% in Stage 1. HER2/neu positivity was seen 100% in stage 2 and stage 3.

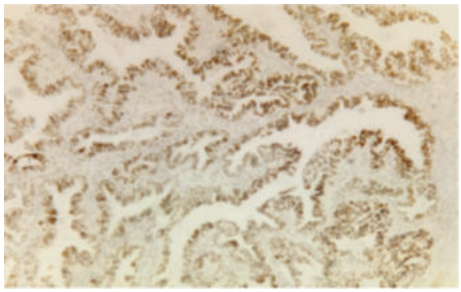
Photographs:



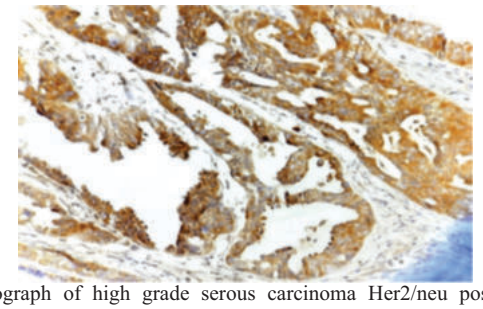
Photograph of H & E stained section of high grade serous carcinoma showing papillary architecture & marked nuclear atypia (400X).



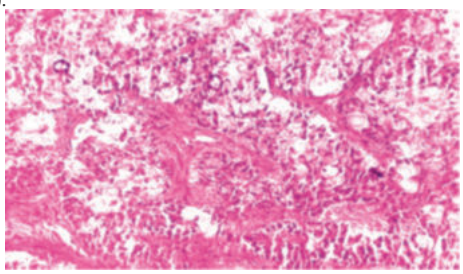
Photograph of high grade serous carcinoma ER positivity (100X)



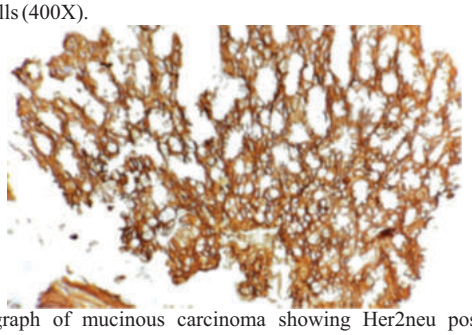
Photograph of high grade serous carcinoma PR positivity (100X).



Photograph of high grade serous carcinoma Her2/neu positivity (100X).



Photograph of H & E stained section of mucinous carcinoma showing Invasion by malignant cells having marked nuclear atypia and signet ring cells (400X).



Photograph of mucinous carcinoma showing Her2neu positivity (400X).

DISCUSSION:

Ovarian cancer is the fifth leading cause of cancer death among women in the United States and has the highest mortality rate of all gynecologic cancers. Lack of knowledge about the etiology and pathogenesis of the tumour leads to its late diagnosis at advanced stage which presents it with highest mortality rate. Therefore, new therapeutic strategies and reliable screening methods for diagnosis are urgently needed. Estrogen Receptor (ER) and Progesterone Receptor (PR) are main secreted hormones by ovary acting through specific receptors. Human epidermal growth factor receptor type 2(Her 2/Neu) a proto-oncogene that encodes a transmembrane receptor protein involved in the development and progression of the majority of cancers.

In this study, 55% cases were benign followed by malignant (41.42%) cases and borderline (2.8%) cases. Similar results were obtained in the studies done by Sofi et al (2018)[5] and Gupta N et.al (2019)[6] showing maximum cases of benign tumour. Lubna khan et al (2014)[7] studied 80 operated cases of ovarian tumours and found that benign lesions were more common the malignant lesions.

In our study, out of total 70 cases maximum number of patients were of

surface epithelial tumours 43 (61.43%), followed by sex cord stromal tumours 14 (20%), germ cell tumours 12 (17.14%) cases. Malli M. et al. (2014)[8] study also showed that out of 100 ovarian tumours included, surface epithelial tumours were most common (59%), followed by germ cell tumours (14%). Atla B et al. 2016[9] observed that Malignant surface epithelial tumours were the commonest histological type comprising of 59.5% of all the ovarian carcinomas.

Estrogen and progesterone receptors are important hormones secreted mainly by the ovaries. These hormones act through their specific receptors and have been implicated in the pathogenesis of gynecologic malignancies, including breast, endometrial, and ovarian cancers. In our study ER,PR and HER2/neu receptor positivity was higher in malignant cases followed by benign and borderline cases . Our results correlates with the study by Choudhary A et al., (2022)[10] with ER (61.76%), PR(68%) and HER2/neu (100%) receptor positivity higher in malignant cases. Sylvia MT et al (2012)[11] included 60 consecutive cases of epithelial ovarian tumours and observed that ER α had lower expression in benign (29%) and PRA higher expression in malignant (63.6%) tumours.

Our study showed that Her/neu 2 receptor was present 54.84% in serous case followed by 6.45% in mucinous cases and 9.68 % in Endometriod carcinoma but no significant difference was observed in Her 2/Neu receptor with histological diagnosis.(P=0.059NS)**.**The same PR receptor pattern was found in 68.42% of serous cases, 10.53% of endometriod carcinoma cases, and 5.26% of adult granulosa cell tumours. but no significant difference was observed in PR receptor with histological diagnosis.(P=0.171NS)

In addition, significant high positivity(74.07%) of ER receptors was present in serous cases had the ER receptor, as compared to 11.11% of endometrioid carcinoma cases and 3.70% of mucinous tumour,. significant difference was observed in ER receptor with histological diagnosis (P<0.001 S).Our results shows higher ER,PR and Her2/neu receptor positivity in serous tumour comparable to the results of Choudhary A et al, (2022)[10], Neeta Verma et al.,(2023)[11]. However, study of Rashmi k et al., (2016)[12] showed higher PR positivity in mucinous tumour compared to serous tumour. Atla et al (2016)[9] showed higher ER expression in serous cystadeno carcinomas accounting for 66.6% of all ER positive tumours. ER was positive in 2 cases of endometrioid carcinoma accounting for 22.2% of all ER positive tumours and single case (100%) of malignant Brenner. PR was positive in 3 cases of serous cystadenocarcinoma, 2 cases of endometrioid carcinoma accounting for 66.6% of all endometriosis tumours, 2 cases of germ cell tumours, 2 cases of metastatic tumours/ Krukenberg tumours accounting for 50% and 1 case of sex cord stromal tumour accounting for 25%.

In our study we used two type of grading system Tier 2 and Tier 3. ER, PR and Her2/neu receptors was observed (100%,76.92%,100%) in High Grade which is Significant over Low Grade. In Three Tier Grading System Expression of PR and Her2/neu receptors were higher in Grade 2 and Grade 3 in comparison of Grade 1. Atla B et al.,(2016)[9] observed that Her2 was negative in all grade 1 tumours. The association of Her2 with higher grade, suggest an aggressive tumour type. According to Sylvia MT et al (2012)[13] who followed WHO grading, majority of their cases of ovarian carcinomas were of grade 2 accounting for 49% in these studies also observed that ERα, PRA had higher expression in advanced stage (63.63%, 52.38%), grade 3 (45.45%, 38.09%). Her-2-neu was expressed in grade 3 (57.14%).

When status of ER, PR, Her2/neu were compared according to stage of tumours we found that ER, PR and Her2/neu positivity were high in Stage 3 which correlates with the study of Verma N et al., (2018)[11].

CONCLUSION:

Ovarian cancer was known “the silent killer” as its early detection is difficult because the initial symptoms in majority of women experience a variety of no specific symptoms before diagnosis, so the cancer goes undiagnosed until the disease is far advanced and spread throughout the abdomen or to distant organs. Estrogen is considered a primary culprit in the development of ovarian cancer as 70% of ovarian cancers express estrogen receptors (ERs), whereas progesterone and its receptors are protective against ovarian cancer. This has lead to the development of targeted oncologic therapies that might ultimately be more effective and less toxic. Estrogen and Her2/neu are two such targets.

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