ANALYSIS OF ESTROGEN RECEPTOR (ER) AND PROGESTRONE RECEPTOR (PR) EXPRESSION IN SURFACE EPITHELIAL TUMORS OF OVARY AND ITS CORRELATION WITH THEIR CLINICAL STAGE

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ABSTRACT

Objective: To evaluate ER and PR expression in epithelial ovarian cancers (EOC) and to determine its association with clinical stage.

Study Design: Cross sectional study.

Place and Duration of Study: Histopathology department, Armed Forces Institute of Pathology (AFIP) Rawalpindi, from Mar to Oct 2017.

Material and Methods: A total of thirty three (n=33) histologically confirmed EOCs were analyzed. ER and PR expression status was assessed by immunohistochemistry using Allred scoring system and was compared with the clinical stage defined by The International Federation of Gynecology and Obstetrics (FIGO) staging system.

Results: A total of thirty three (n=33) females were enrolled. Mean age of the study females was 50.8 ± 12.9 years. Most frequent histologic type was serous carcinoma (SC) 60.6% (n=20) followed by mucinous carcinoma (MC) 15.2% (n=5), endometrioid carcinoma (EC) 9.1% (n=3), clear cell carcinoma (CC) 9.1% (n=3), Brenner tumor (MBT) 3% (n=1) and seromucinous carcinoma (SMC) 3% (n=1). Most patients were in clinical stage I 61% (n=20) followed by stage II 24%, (n=8) and stage III 15% (n=5). Among SC, 90.0% (n=18/20) were ER and 65% (n=13/20) were PR-positive. All MC and CC were ER/PR negative. Two of the three ECs were ER and one was PR-positive. Higher percentage of stage I tumors exhibited ER 65% (n=13/20) and PR 45% (n=9/20) positive status (p>0.5). The correlation was very weak positive between clinical stages and both ER and PR scores (Allred) r=0.11 and 0.15 respectively p>0.05.

Conclusion: Higher percentages of stage I tumors exhibited ER and PR positive status yet not statistically significant from stage II/III. Estimation of ER and PR receptor status may help to select the women with ovarian malignancy for hormonal therapy, which is more likely to improve the response rate.

Keywords: Clinical stage, Estrogen receptor, Immunohistochemistry, Ovarian cancer, Progesterone receptor.

INTRODUCTION

Ovarian cancer is considered the second most common gynecological cancer. More than 90% of ovarian tumors are epithelial in origin[1]. Ovarian cancer is one of the most complex tumors of women in terms of histogenesis, clinical behavior and malignant potential[2]. World Health Organization classifies surface epithelial tumors by cell type into serous, mucinous, endometrioid, clear cell, Brenner cell, epithelial-stromal and by atypia and invasion into benign, borderline and malignant tumors[3]. Although the surgical techniques and chemotherapy regimens have been improved, yet the 5-year survival rate remains between ten to thirty percent[4,5]. The high lethal potential of these tumors and poor survival are mainly attributed to delayed detection and rapid progression. There have been persistent efforts in the investigation of molecular markers in epithelial ovarian tumors by immuno-histo-chemical (IHC) studies and search for new bio-markers is going on, which could serve as reliable predictors of prognosis[6-7]. The ovaries are not only a source of estrogen and progesterone but they appear to be targets for these hormones. Estrogen is considered a primary culprit in the development of ovarian cancer, as 70% of ovarian cancers express estrogen receptors (ER), whereas

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progesterone and its receptor are protective against ovarian cancer[8-10]. Several investigators tried to evaluate the prognostic implication of ER expression in epithelial ovarian cancer, but results remain controversial[11]. It has been reported that PR expression was associated with improved survival for EC and high-grade serous carcinoma and ER expression was associated with improved EC survival[10]. The evidence from local population is limited and there is hardly any study on ER and PR status among ovarian cancers[12-14]. Present study was designed to study the ER and PR status in malignant ovarian tumors through immunohistochemical analysis. Our main objective was to evaluate ER and PR expression in epithelial ovarian cancers and to determine their association with clinical stage.

PATIENTS AND METHODS

This cross-sectional study was carried out at the Armed Forces Institute of Pathology, Rawalpindi, from March to October 2017 after taking approval from the Institutional Review Board. A total of 33 radical surgical specimens of ovarian tumors, subsequently diagnosed malignant surface epithelial tumors on histopathology were included in the study by non-probability convenience sampling. Benign or borderline surface epithelial tumors were excluded, as were germ cell tumors, sex cord neoplasms, undifferentiated tumors and metastases. Poorly fixed tissues and core biopsy specimens were also excluded. Immunohistochemistry (IHC) analyses of ER and PR were performed on formalin-fixed, paraffin embedded malignant surface epithelial ovarian tumor tissue. Tissue blocks were sectioned at 3µm thickness and deparaffinized in xylene and rehydrated with decreasing concentration of ethanol. Heat induced epitope retrieval in Tris/EDTA buffer at pH 9.0 buffer was used for ready to use primary antibodies ER and PR (clone by Dako Corporation). ER and PR expression status was analyzed using allred scoring system in each case by taking into consideration the proportion of positive cells and staining intensity[15]. The expression status was then compared with their clinical stage (defined by FIGO staging system)[16]. SPSS-version 22 was used for analysis of the data. Association between ER/PR status and clinical stage was determined. Chi-square test was applied and $p \leq 0.05$ was considered significant. Bivariate correlation analysis was performed between Allred scores of ER and PR and clinical stages. Pearson correlation coefficient (r) was determined and $p \leq 0.05$ was considered significant.

RESULTS

A total of thirty three (n=33) females were included in the period. Mean age of the patients was 50.8 ± 12.9 years. Most frequent histological

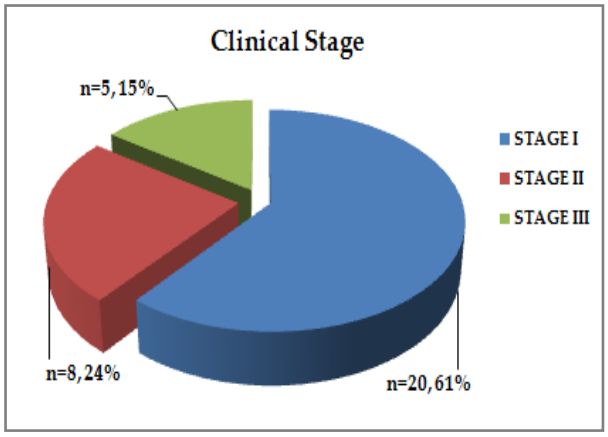

Figure-1: Clinical stage distribution in study sample.

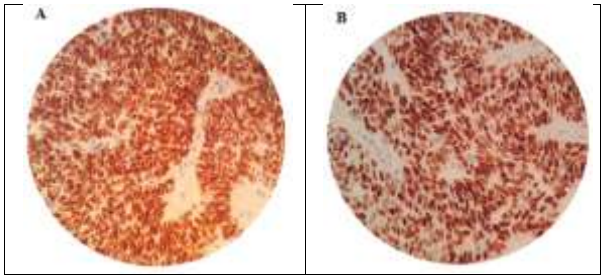

Figure-2: Immunohistochemistry showing ER nuclear positivity (A) and PR (B) nuclear positivity.

type was serous carcinoma (SC) followed by mucinous carcinoma (MC), endometrioid carcinoma (EC), clear cell carcinoma (CC), malignant brenner tumor (MBT) and seromucinous carcinoma (SMC) (60.6% n=20, 15.2% n=5, 9.1% n=3, 9.1% n=3, 3% n=1, and 3% n=1 respectively). Clinical stage distribution is presented in fig-1. Among SC, 90.0% (n=18/20) were ER- and 65% (n=13/20) were PR-positive. All MC, CC and MBT were ER/PR negative (fig-2). Two of the

three EC were ER- and one was PR-positive. Only case of SMC was ER-positive but PR-negative. Higher percentage of stage I tumors exhibited ER- (65.0% n=13/20) and PR- (45.0% n=9/20) positive status yet the difference was not statistically significant with stage II and III (p>0.5). These results are tabulated in tables-I & II. The correlation was not significant and was very weak positive between clinical stages (Mean ± SD; 3.5 ± 2.6) and Allred scores of both ER (4.2 ± 2.4) and PR (2.5 ± 3.0), (r=0.11 and 0.15 respectively p>0.05).

Table-I: Association between clinical stage and ER and PR status

Clinical stage	Er status		Total	p-value chi-square
	Positive	Positive		
Stage-I	13	7	20	0.976
	65.0%	35.0%	100.0%	
Stage-II	5	3	8	
	62.5%	37.5%	100.0%	
Stage-III	3	2	5	
	60.0%	40.0%	100.0%	
Total	21	12	33	
	63.6%	36.4%	100.0%	

Table-II: Association between clinical stage and PR status.

Clinical stage	Pr status		Total	p-value chi-square
	Positive	Negative		
Stage-I	9	11	20	0.431
	45.0%	55.0%	100.0%	
Stage-II	2	6	8	
	25.0%	75.0%	100.0%	
Stage-III	3	2	5	
	60.0%	40.0%	100.0%	
Total	14	19	33	
	42.4%	57.6%	100.0%	

DISCUSSION

Our study results showed that mean age of the study females was 50.8 ± 12.9 years. Most frequent type was serous carcinoma (SC) followed by mucinous carcinoma (MC) and endometrioid carcinoma (EC). In a study on local population, Zubair *et al* analyzed more than 2000 ovarian tumors. Their results are quite similar with the results of present study. They reported that malignant ovarian tumors were common in 5th and 6th decades. SC was the commonest malignant surface epithelial tumors followed by MC and EC[15]. In another local study, Sohail *et al* reported that most of the women with malignant tumors were above 40 years of age with mean age of 52.79 years. The commonest malignant tumor was found to be SC followed by MC[14]. Another study demonstrated that majority of the ovarian carcinomas occurred in the age group of third and fifth decades and the commonest histological type was SC[17]. Similar demographic characteristics were reported in another local study by Malik *et al*, which demonstrated mean age of women with malignant ovarian tumors was 49.5 (±13) years. The commonest histological subtype was SC followed by the MC. Seventy eight percent of the patients had stage III or IV disease at the time of diagnosis. However, in our study the percentage of patients with clinical stage II and III was approximately 40%. The difference might be attributed to the fact that during the time (from 2002 to recent years) screening and diagnostic

methods have markedly improved and most patients are diagnosed at an earlier stage. The difference might also be due to relatively lower sample size of the present study (286 vs 33 in our study)[13]. It has been reported that ER expression showed marked differences across various subtypes of malignant ovarian tumors. Our results also showed that among SC 90.0% (n=18/20) and 66.7% (n=2/3) EC were ER-positive and all MC, CC and MBT were ER negative. The findings are concordant with the already published data. Sieh *et al*[10] in their series on approximately three thousand ovarian cancer patients with various epithelial histological types by IHC, demonstrated that the expression of ER was much higher in SC and EC than in MC and CC. In another similar study it was demonstrated that ER expression was much lower in the MC and CC subtype than ER positivity in SC[18]. These results highlighted a possible role of ER in ovary carcinogenesis across different malignant subtypes. It may be suggested that expression of ER may be a prognostic biomarker in non-serous epithelial ovarian cancer rather than SC and we suggest further longitudinal studies to clarify this prognostic role of ER in each non-serous epithelial subtype. Our results showed that higher percentage of stage I tumors exhibited ER- (65.0% n=13/20) and PR- (45.0% n=9/20) positive status yet the difference was not statistically significant with stage II and III (p>0.5). In a very recent study, Ajani *et al* demonstrated that there was no significant association between ER expression and FIGO stage in their study[19] similar to what was highlighted in our study and by Kauppila *et al*[20]. In contrast, Burges *et al* reported a significant expression of ER in advanced FIGO stage[21]. The correlation in our study was not significant and was very weakly positive between clinical stages and Allred scores of both ER and PR (r=0.11 and 0.15 respectively, p>0.05). The results are similar with Ajani *et al* who demonstrated a weak positive correlation between ER and PR expressi○on. Pulido *et al* from Mexico and Ayadi *et al* from Tunisia also found positive correlation between ER and PR expression[22,23].

CONCLUSION

Our study showed high expressions of ER and PR in stage I tumors as compared to stages II and III. We suggest that further studies should be conducted on a larger scale to include more number of cases and to include benign and borderline categories for better understanding of association of ER/PR with epithelial ovarian cancer. This will be helpful in improving treatment strategies and survival rates in patients with ER/PR positive EOCs.

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CONFLICT OF INTEREST

We, all the authors, declare that there is no conflict of interest in the designing, data collection and publication of this original research.

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