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Clinicopathological Correlation Of Er, Pr And Her 2 Neu In Epithelial Ovarian Tumors

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ABSTRACT

Background: Expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2/neu) may reflect tumor biology and prognostic strata in epithelial ovarian tumors (EOTs). We evaluated their immunohistochemical (IHC) expression and clinicopathological correlations in a North Indian cohort.

Methods: In a five-year study (2010–2015) at SKIMS, 50 consecutive EOTs were analyzed (benign, borderline and malignant). Routine histopathology and IHC for ER, PR and HER2/neu were performed on formalin-fixed paraffin-embedded tissue. Intensity was semi-quantitatively graded (0/1+/2+/3+). For HER2/neu, 1+ was considered negative. Clinicopathological variables included histotype, grade, FIGO stage, nodal status, lymphovascular invasion (LVI), capsular invasion, metastatic status and pre-operative CA-125 where available.

Results: Of 50 EOTs, 8 (16%) were benign, 9 (18%) borderline and 33 (66%) malignant. Among malignant tumors, serous histology predominated (23/33; 69.7%), followed by mucinous (9/33; 27.3%) and clear cell carcinoma (1/33; 3.0%). ER was positive in 30/33 malignant cases, PR in 28/33 and HER2/neu in 5/33; all benign and borderline tumors were HER2/neu-negative. High-grade carcinomas more often showed higher ER and PR expression than low-grade tumors. ER/PR positivity was enriched in cases with adverse features (metastasis, LVI, capsular invasion), while HER2/neu was largely negative across strata. Stage-3 tumors showed higher ER/PR intensity compared with stage-1/2. Elevated CA-125 was more frequent in high-grade than low-grade disease.

Conclusions: In this cohort, ER and PR expression was significantly more frequent and stronger in malignant versus benign/borderline EOTs, and associated with higher grade and advanced stage, whereas HER2/neu overexpression was infrequent and restricted to carcinomas. These findings support potential utility of ER/PR profiling for prognostication and selection for endocrine strategies in ovarian carcinoma, while HER2/neu appears to have limited role in this setting.

Keywords: Ovarian carcinoma, epithelial ovarian tumors, estrogen receptor, progesterone receptor, HER2/neu, immunohistochemistry, prognostic markers

INTRODUCTION

Ovarian carcinoma is not a single entity but a heterogeneous group of diseases, underscoring the need to study specific tumor types and their biology rather than ovarian cancer as a whole[1,2]. Among ovarian neoplasms, common epithelial tumors constitute roughly two-thirds of all ovarian tumors and nearly 90% of ovarian cancers, occurring predominantly in adults with malignancies presenting later in life[3,4]. The WHO classification organizes epithelial tumors serous, mucinous, endometrioid, clear cell, and Brenner by their patterns of differentiation, providing a clinicopathologic framework for evaluation[5].

Hormonal signaling is implicated in ovarian tumorigenesis: estrogens and progesterone act through their receptors (ER and PR), with ER–estradiol interactions driving transcriptional programs (including PR), and PR mediating progesterone-dependent effects[6-8]. Estrogen and its metabolites possess mutagenic properties in ovarian surface epithelial cells, whereas progesterone pathways may exert protective, anti-proliferative, and pro-apoptotic influences[9-11]. Additional oncogenic drivers such as HER-2/neu amplification/overexpression have been reported and may portend poorer survival[12]. Crucially, ER, PR, and HER-2/neu epitopes remain detectable in formalin-fixed, paraffin-embedded tissue, allowing routine immunohistochemical (IHC) assessment and correlation with histology and adjacent tissue context[10,13].

Expression profiles vary by histotype and adverse clinicopathologic features: serous tumors more often express ER/PR and HER-2/neu, while mucinous tumors show low expression; higher ER/PR and HER-2/neu expression aligns with serous histology, advanced stage, higher grade, ascites, and elevated CA-125, supporting estrogen's mitogenic role and offering potential diagnostic and prognostic utility[14-16].

AIMS AND OBJECTIVES:

To find clinicopathological correlation of ER, PR and HER 2 NEU in epithelial ovarian tumors.

MATERIALS AND METHODS

Clinicopathological observational study conducted in the Department of Pathology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, over five years (2010–2015). The cohort comprised a retrospective component (three-and-a-half years) and a prospective component (one-and-a-half years).

Fifty epithelial ovarian tumor (EOT) cases were included spanning benign (n=8), borderline (n=9) and malignant (n=33) categories. Detailed clinical information for each patient was abstracted using a standardized pro-forma; pre-operative CA-125 was recorded wherever available.

Resected specimens were fixed overnight in 10% neutral buffered formalin. After external examination, conventional opening and grossing were performed; size and appearance were recorded, and multiple representative tissue bits were sampled at ~1-cm intervals, placed in labeled stainless-steel cassettes and returned to fixative for 2–4 hours. Blocks were washed three to four times in distilled water and processed through ascending grades of ethanol (50%—1 h; 70%—1 h; 90%—1 h; absolute ethanol—two changes, 2 h each), followed by xylene (two changes, 1 h each) and paraffin embedding at wax melting point. Paraffin blocks were cast using Leuckhart's "L" blocks and sectioned at 3–5 µm on a rotary microtome. Sections were mounted on Mayer's-albumin–coated slides via a warm water bath, dewaxed in a hot-air oven and rehydrated through descending alcohols to water. Routine hematoxylin–eosin staining was performed and slides mounted in DPX. Tumors were classified per WHO criteria. Recorded variables included histologic subtype; grade (for malignant tumors); lymph-node status; lymphovascular invasion; capsular invasion; and pathologic stage as documented in records. IHC for ER, PR and HER-2/neu was performed on formalin-fixed, paraffin-embedded sections in all malignant (n=33), all borderline (n=9) and eight randomly selected benign EOTs. Staining localization was assessed (nuclear for ER/PR; membranous for HER-2/neu), and intensity was graded semi-quantitatively. For HER-2/neu, 1+ staining was considered negative; stronger (≥2+) membranous staining was recorded as positive.

Data were tabulated as counts and percentages. Marker expression was correlated with histotype, grade, nodal status, lymphovascular invasion, capsular invasion, metastatic status, stage, and pre-operative CA-125 where available. Selected comparisons are summarized with p-values where applicable.

RESULTS AND OBSERVATIONS

Table 1: Association of Grade with Intensity of ER

Grade		**1+**	**2+**	**Negative**	**Total**
High		9	11	0	20
Low		6	4	3	13
Total		15	15	3	33
PR					
Grade	**1+**	**2+**	**3+**	**Negative**	**Total**
High	6	9	4	1	20
Low	7	2	0	4	13
Total	13	11	4	5	33
Her-2-Neu					
Grade		**1+**	**2+**	**Negative**	**Total**
High		7	4	9	20
Low		1	1	11	13
Total		8	5	20	33

Among high-grade tumors (n=20), ER staining was uniformly positive (9 with 1+ and 11 with 2+; 100%). In low-grade tumors (n=13), ER was positive in 10 cases (6 with 1+ and 4 with 2+) and negative in 3 (76.9% positive). PR was positive in 95% of high-grade tumors (6 with 1+, 9 with 2+, 4 with 3+) versus 69.2% in low-grade tumors (7 with 1+, 2 with 2+; 4 negative). HER-2/neu positivity was more frequent in high-grade tumors (55%; 7 with 1+, 4 with 2+) than in low-grade tumors (15.4%; 1 with 1+, 1 with 2+), where negativity predominated (11/13). Higher histologic grade is associated with stronger receptor expression especially a shift toward higher-intensity PR and greater HER-2/neu positivity while ER remains frequently positive across grades but shows more negatives in low grade.

Table 2: Relation between Metastasis and intensity of ER, PR and HER-2-Neu			
Intensity		**Metastasis**	
		Negative	Positive
ER	1+	5	10
	2+	7	8
	N	2	1
PR	1+	9	4
	2+	2	9
	3+	1	3
	N	2	3
HER-2-Neu	1+	1	6
	2+	2	3
	N	11	10

ER was positive in most cases regardless of metastatic status (94.7% in metastasis-positive vs 85.7% in metastasis-negative), with a slight tilt toward 1+ among metastasis-positive cases (10 vs 5). For PR, overall positivity was similar (84.2% with metastasis vs 85.7% without), but higher-intensity staining (2+/3+) was much more common when metastasis was present (63.2% vs 21.4%). HER-2/neu positivity nearly doubled with metastasis (47.4% vs 21.4%). Metastatic disease is characterized by a clear shift toward stronger PR staining and higher HER-2/neu positivity, whereas ER is broadly positive in both groups and is less discriminatory for metastasis.

Table 3: Correlation of ER, PR and HER-2-Neu with Lymph Nodal Status, Lymphovascular Invasion Status and Capsular Invasion Status							
Intensity		**Lymph Node Status**		**Lymphovascular Invasion Status**		**Capsular Invasion Status**	
		Negative	**Positive**	**Negative**	**Positive**	**Negative**	**Positive**
ER	1+	11	4	6	9	9	6
	2+	10	5	5	10	7	8
	N	3	0	1	2	3	0
PR	1+	10	3	6	7	8	5
	2+	6	5	3	8	4	7
	3+	3	1	1	3	2	2
	N	5	0	2	3	5	0
Her-2-Neu	1+	3	4	1	6	3	4
	2+	3	2	2	3	2	3
	N	18	3	9	12	14	7

ER was positive in 100% of node-positive and capsular-invasion–positive tumors (LN+: 4 with 1+, 5 with 2+; Caps+: 6 with 1+, 8 with 2+). Among node-negative and capsular-invasion–negative tumors, ER positivity remained high but slightly lower (LN– 87.5%, Caps– 84.2%), with more negatives in the latter groups. LVI status showed similar overall positivity (LVI– 91.7%; LVI+ 90.5%) with a modest shift toward 2+ in LVI-positive cases. PR was positive in 100% of node-positive and capsular-invasion–positive tumors and showed a higher share of strong intensities (2+/3+: LN+ 66.7%, Caps+ 64.3%) compared with node-negative (37.5%) and capsular-negative (31.6%) tumors. With LVI, overall positivity was comparable (LVI+ 85.7% vs LVI– 83.3%), but higher-intensity staining was again more frequent with LVI (52.4% vs 33.3%). HER-2/neu positivity was enriched in adverse groups—66.7% in node-positive vs 25.0% in node-negative, 42.9% in LVI-positive vs 25.0% in LVI-negative, and 50.0% with capsular invasion vs 26.3% without. Adverse pathological features (nodal spread, LVI, capsular invasion) cluster with stronger PR expression and higher HER-2/neu positivity. ER remains widely expressed, but intensity trends slightly higher with nodal and capsular invasion.

Table 4: Correlation of Stage with ER, PR and HER-2-Neu				
		Stage -1	**Stage-2**	**Stage-3**
ER	**1+**	**7**	**3**	**5**
	2+	3	2	10
	N	3	0	0
PR	**1+**	8	0	5

	2+	1	2	8
	3+	0	2	2
	N	4	1	0
HER-2-Neu	**1+**	0	3	4
	2+	0	0	5
	N	13	2	6

ER positivity increased from 76.9% in stage 1 (7 with 1+, 3 with 2+) to 100% in stages 2 and 3, with a marked rise in 2+ staining at stage 3 (10/15, 66.7%). PR positivity also rose with stage (69.2% in stage 1; 80.0% in stage 2; 100% in stage 3), accompanied by a shift from predominantly 1+ at stage 1 to mainly 2+/3+ in stages 2–3 (stage 2: 80% 2+/3+; stage 3: 66.7% 2+/3+). HER-2/neu was absent in stage 1 (0/13) but present in 60% of both stage-2 and stage-3 tumors (stage 2: 3 with 1+; stage 3: 4 with 1+, 5 with 2+).

Advancing stage is associated with universal ER positivity, increasing PR intensity, and the emergence/maintenance of HER-2/neu positivity (absent at stage 1, present in ~60% from stage 2 onward), all of which align with a more aggressive clinicopathologic profile.

DISCUSSION

In this 5-year series of 50 epithelial ovarian neoplasms, malignant tumors predominated (66%), with serous histology forming the largest malignant subset and mucinous tumors next in frequency an overall pattern that mirrors prior Indian and international series[1,17-21]. The age distribution, with peaks in the fourth to fifth decades for borderline and malignant categories, is likewise consistent with earlier observations[17]. Across histotypes, ER and PR were more frequently expressed in serous than in mucinous tumors, aligning with reports that steroid-receptor positivity is characteristically higher in serous epithelium[21,22,23]. HER-2/neu was absent in benign and borderline lesions and present only in a small subset of malignant tumors, concordant with literature noting negligible expression in benign disease and relative enrichment within malignant serous tumors[15]. Grade correlated with receptor patterns. High-grade carcinomas showed universal ER positivity and a shift toward higher-intensity PR staining compared with low-grade tumors; HER-2/neu was more often detected in high-grade than in low-grade disease but remained infrequent overall. These trends support the biologic link between hormonal signaling and aggressive morphology and agree with studies documenting greater ER/PR expression and some HER-2/neu overexpression in higher-grade disease[15,24,25]. At the same time, heterogeneity in the literature persists, with several series reporting weak or absent associations between grade and receptor status[12,26,27].

Stage-wise, ER and PR positivity increased with advancing FIGO stage, with stage-3 tumors showing universal ER positivity and a clear shift toward 2+/3+ PR intensity; HER-2/neu was absent in stage-1 and stage-2 disease and appeared in roughly one-third of stage-3 tumors. These observations echo prior reports that receptor positivity particularly ER tends to rise with stage[23,28,15]. Adverse clinicopathologic features clustered with stronger hormone-receptor signals. Metastatic, node-positive, lymphovascular-invasion–positive, and capsular-invasion–positive tumors exhibited higher-intensity PR staining, while ER remained broadly positive across categories. HER-2/neu positivity was low overall and showed modest enrichment with nodal and capsular invasion but not with LVI, and was similar between metastatic and non-metastatic groups findings that partially align with the association of HER-2/neu with aggressive biology reported in some ovarian cancer series[12] and with the broader pattern of ER/PR association with adverse features[15].

Finally, higher CA-125 levels in high-grade tumors and predominantly normal levels in low-grade tumors in this cohort are directionally consistent with studies that link adverse histopathology with elevated serologic tumor markers[15]. Collectively, these data reinforce the clinicopathologic relevance of ER and PR in epithelial ovarian tumors in this population and suggest limited but situational value for HER-2/neu, with the caveat that scoring conventions (e.g., counting 1+ HER-2/neu as negative) and cohort composition can influence cross-study comparisons[12,26,27].

CONCLUSION

Immunohistochemical evaluation of estrogen and progesterone receptors should be incorporated into routine reporting of epithelial ovarian tumors to assist prognostic stratification and to identify candidates who may benefit from endocrine therapy in appropriate clinical contexts. By contrast, HER-2/neu lacks consistent clinicopathologic association in this cohort and, on current evidence, should not be used as a routine prognostic or predictive marker in our setting. Future work should standardize scoring thresholds and correlate receptor status with treatment response and survival in larger, multi-center cohorts to refine therapeutic decision-making.

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