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ROLE OF ANDROGEN RECEPTOR AS A PROGNOSTIC MARKER IN OVARIAN CANCERS AND ITS RELEVANCE

Oncology

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ABSTRACT

Objective: To study the expression and functional impact of ARs in ovarian cancers and to discuss the implications of AR positivity in High Grade Epithelial Serous Ovarian Cancer(HGSC). **Materials And Methods:** 64 patients undergoing upfront primary surgery for ovarian cancers :18 -75 years of age, between October 2016 -May 2018 (20 months) - patient characteristics, AR expression levels, tumour histology and follow up until October 31, 2018 **in** Gynaecological Oncology Outpatient Department of Amritha Institute of Medical Sciences, Kochi, India. **Main Outcome Measures :** Distribution Of Androgen Receptor Expression Among Ovarian Cancer-Histological subtype. Association Of Androgen Receptor with Surgical Outcome ,Recurrence, Mean Progression Free Survival,) Mean overall Survival, Type 2 (HGSOC) : Stage,Cytoreduction, Recurrence, **Results:** There was no statistical significant survival difference between AR positive and negative groups.AR expression was associated with an improved prognosis which was only clinically significant in high grade serous ovarian cancer although not statistically significant, independent of differentiation grade and clinical stage .It was observed that AR absent subgroup had more recurrences and there was improved overall survival in AR positive subgroup of high grade serous epithelial ovarian cancers. **Conclusion :** This study describes patterns of AR expression in a spectrum of ovarian cancers , no statistical significant association of Androgen receptor positivity in high grade serous cancers with stage, cytoreduction and progression free survival .

KEYWORDS

INTRODUCTION

Androgen receptors (ARs) play a critical role in the development of prostate cancer as there is already historic emphasis. Exploration of the impact of hormonal manipulation of these receptors in pathogenesis and progression of other tumours has not been widely pursued beyond prostate cancer. [1]

Epithelial ovarian cancer (EOC) is the most lethal malignancy of the female reproductive tract. [1] Due to vague symptomatology, majority of the EOC patients are diagnosed in advanced clinical stages with poor survival rates, despite improvements in surgical techniques and the advent of targeted therapeutics. Hence, there is urgent need to identify novel biomarkers of early diagnosis, prognosis and treatment response.

After primary treatment including staging or debulking surgery and platinum-based adjuvant chemotherapy, around half of patients will relapse within 16 months. Thus, effective clinic-pathological biomarkers are urgently required. [4-6]

Jones et al. studied steroid cell ovarian tumours, finding AR immunoreactivity in 64% (9/14) of samples. High AR expression in 18% (28/154) of epithelial ovarian cancer was reported [2]

The AR has been reported to be expressed in up to 95% of EOC diagnosed in women after menopause, when the ratio of androgens: estrogens is high in the ovaries [3] The excessive androgen stimulation of the ovary has been postulated to be a contributing factor and evidence till date suggests that AR levels may be higher in benign compared with malignant ovarian epithelial cells. Previous studies related to the prognostic significance of AR expression in EOC have not been conclusive [1].

Androgen production was also found to be increased in ovarian carcinomas and decreased in response to chemotherapy [5]. Stimulation of the androgen receptor leads to an increase in cell proliferation and a decrease in apoptosis in OSE and ovarian cancer cells [7,8]. The mechanisms by which androgens exert their effects on ovarian cancer cells are still only partially understood but it has been proposed that they act by decreasing expression of transforming growth factor (TGF)–ß receptors [9] and by activating G protein signaling cascades [10]. Androgen receptor expression may be useful as a biomarker to predict sensitivity to anti-androgen therapy [4].

MATERIALS AND METHODS

Sample Size

Based on the reported prevalence of androgen receptor (AR) expression in gynecological malignancies (54%) as described by Muñoz et al. (2014), a minimum sample size of 64 w was estimated at a 95% confidence level with a 20% relative allowable error.

Methodology

This prospective observational study was conducted in the Departments of Gynaecologic Oncology and Pathology at Amrita Institute of Medical Sciences, Kochi, Kerala, from 2016 to 2018, following institutional ethics approval. A total of 64 patients who underwent upfront primary debulking surgery between October 2016 and May 2018 were included. Data were retrieved from the Amrita Hospital Information System and follow-up was completed until October 31, 2018.

Definitions:

- **Optimal cytoreduction (R0):** No macroscopic residual disease or ≤1 cm residual tumor.
- **Platinum sensitivity:** Relapse ≥6 months after completion of platinum-based chemotherapy.
- **Platinum resistance:** Relapse within 6 months of completing chemotherapy or progression during therapy.
- **Progression-free survival (PFS):** Time from primary surgery to recurrence or disease progression.
- **Overall survival (OS):** Time from primary surgery to death or last follow-up.

Patients were reviewed every 3 months for the first two years and every 6 months thereafter. Disease response, progression, and recurrence were assessed per **Gynecologic Cancer Intergroup (GCIG)** criteria, and recurrences were biopsy-confirmed.

Histopathology And Immunohistochemistry:

Tumors were classified according to **WHO criteria (2014)** into low- and high-grade serous carcinomas using a two-tier system. **Androgen receptor (AR)** immunostaining was performed manually (AR-DAKO) following manufacturer protocols. Nuclear staining in >10% of tumor cells, irrespective of intensity, was considered AR-positive. Internal positive and negative controls were included in each run, and all evaluations were performed by an experienced gynecologic pathologist.

Equivocal or mixed morphology cases were resolved using immunohistochemistry (IHC) for diagnostic clarification.

Tumor Classification:
Staging followed **FIGO 2014** criteria. Grades 1–2 were classified as low-grade and grade 3 as high-grade. Tumors were further categorized as:

- **Type I:** Low-grade serous carcinoma (LGSC), low-grade endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, and Brenner tumors.
- **Type II:** High-grade serous carcinoma (HGSC), high-grade endometrioid carcinoma, carcinosarcoma, and undifferentiated carcinoma.

RESULTS:
The association of AR in the study population of 64 cases with different histologic subtype of ovarian cancers where majority of the cases are serous carcinoma; AR also being predominant in serous variety of ovarian cancer. Although outcome is not statistically significance.

Table 1: Distribution Of Androgen Receptor Among Histological Subtype

Histological Subtype (n=64)	Androgen Receptor	
	Present	Absent
SEROUS (n=46)	21(45.7%)	25(54.3%)
MUCINOUS(n=4)	2(50%)	2(50%)
ENDOMETROID(n=7)	3(42.9%)	4(57.1%)
CLEAR(n=5)	0(0%)	5(100%)
CARCINOSARCOMA(n=1)	0(0%)	1(100%)
PPSC(n=1)	0(0%)	1(100%)

61.5% (n=41) are type II ovarian tumours and among them (n=16) 39% are Androgen receptor positive and 61%(n=25) are Androgen receptor negative. However, the difference is not statistically significant with p value=0.72

Table 2: Distribution Of Androgen Receptor Expression Among Ovarian Cancer
(Type I And Type II)

Ovarian Cancer (n=64)	Frequency	AR Present	Percentage
TYPE 1	23	10	38.50
TYPE II	41	16	61.50
TOTAL	64	26	100.00

Early stages (n=9) have 66.7% (n=6) AR positive cases and 31.3%(n=10) advanced stage(n=32) has AR positive cases. The difference is not statistically significant with p value=0.12.

Optimal debulking is done in 27 cases and AR is positive in 37%(n=10) and out of 14 suboptimal debulked cases 42.9% (n=6) AR is positive.

37 cases have taken adjuvant chemotherapy .36 cases are platinum sensitive and one case is platinum resistant.33.3% (n=12) are Androgen positive and 66.7%(24) are androgen negative cases.

Table 3– Mean Overall Survival Estimate Among Androgen Receptor

Androgen Receptor	Mean[a]		95%Confidence Interval		P Value
	Mean Estimate	Std.Error	Lower bound	Upper bound	
Present	26.705	1.770	23.235	30.175	0.98
Absent	26.087	1.537	23.076	29.099	

It is observed that in Table 3 among the 64 ovarian cancer cases , Mean Overall Survival estimate among AR Positive cases is 26.71 and AR absent cases the survival estimate is 26.08.(p value=0.98)

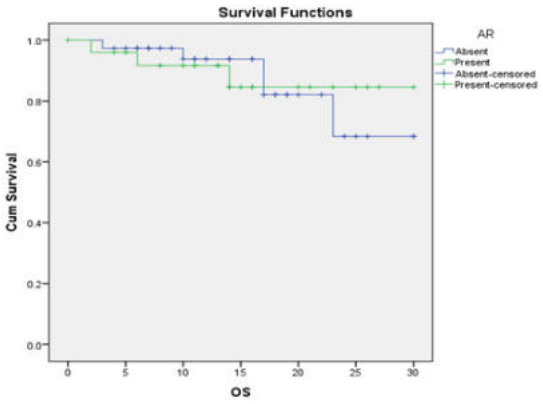

Figure 1-Kaplan Meier Curve By Overall Survival Type

The Follow up mean survival time : 26.3 months[95% CI:23.99-28.62]

There were 8 deaths in total;8 cancer related and 2 women died from other non cancer related deaths.

Table 4 – Mean Progression Free Survival Estimate Among Androgen Receptor

Androgen Receptor	Mean[a]		95%Confidence Interval		pValue
	Mean Estimate	Std.Error	Lower bound	Upper bound	
PRESENT	26.944	1.683	23.645	30.243	0.21
ABSENT	22.579	1.938	18.781	26.377	

Recurrence median survival time :24.25 months[95% CI:21.54-26.96]
It is observed that in Table 4 among 64 cases the Mean Progression Free Survival estimate among AR Positive cases is 26.94 and AR absent cases the survival estimate is 22.58.(p value=0.21)

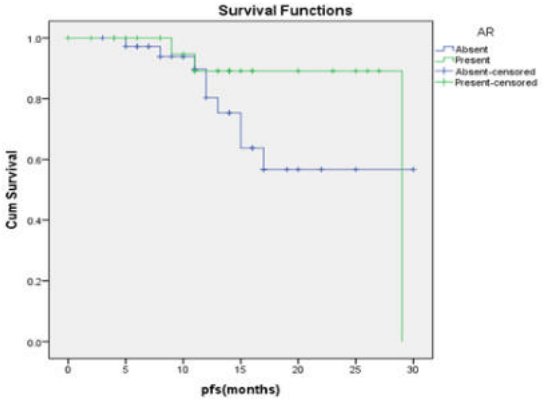

Figure 2– Kaplan Meier Curve By Disease Free Survival Type

Out of 41 Type II High grade ovarian cancer cases; Association expression AR with age <50 years is 53.3% .

Table 5 -Association Of Study Population Type 2 (HGSOC) with Stage

Stage (n=41)	Androgen Receptor		p value
	Present	Absent	
EARLY (n= 9)	6(66.7%)	3(33.3%)	0.12
ADVANCED (n=32)	10(31.3%)	22(68.8%)	

Out of 41 Type II High grade ovarian cancer cases; in table 21 it is observed that the early stages (n=9) have 66.7% (n=6) AR positive cases and 31.3%(n=10) advanced stage(n=32) has AR positive cases (pvalue=0.12.)

Out of 41 Type II High grade ovarian cancer cases; optimal debulking is done in 27 cases and AR is positive in 37%(n=10) and out of 14 suboptimal debulked cases 42.9% (n=6) AR is positive. (p value=0.71) 9 recurrences are there: 22.2%(n=2) recurred cases in type II ovary cases are AR positive and 77.8%(n=7) are AR absent. (p value=0.43)

37 cases have taken adjuvant chemotherapy .36 cases are platinum sensitive and one case is platinum resistant.

33.3% (n=12) are Androgen positive and 66.7%(24) are androgen negative cases. (p value=0.35)

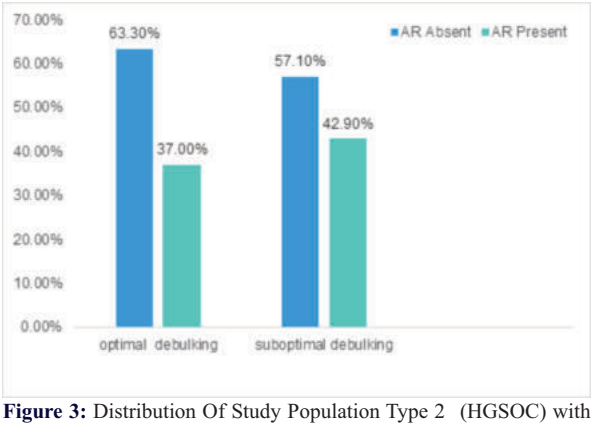

Figure 3: Distribution Of Study Population Type 2 (HGSOC) with Cytoreduction

Table 6- Mean Survival Time In Type 2 Ovarian Cancer

Androgen Receptor	Mean[a]		95%Confidence Interval		pValue
	Mean Estimate	Std.Error	Lower bound	Upper bound	
PRESENT	25.250	2.467	20.414	30.086	0.94
ABSENT	24.372	2.052	20.349	28.395	

Out of 41 Type II High grade ovarian cancer cases , Mean Overall Survival estimate among AR Positive cases is 25.25 and AR absent cases the survival estimate is 24.37.(p value=0.94)

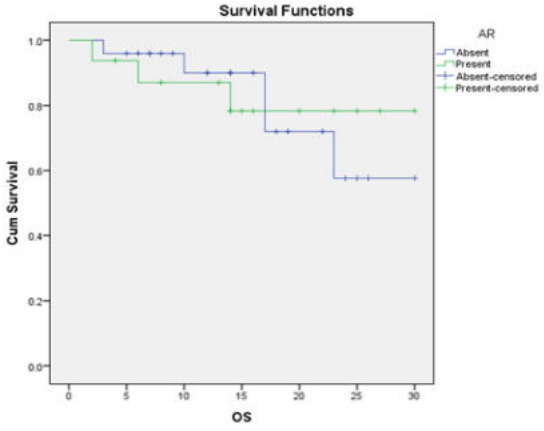

Figure 4: Kaplan Meier Curve By Disease Free Survival Type

Table 7 Mean Survival Time In Type 2 Progression Free Survival Among Androgen Receptor

Androgen Receptor	Mean[a]		95%Confidence Interval		pValue
	Mean Estimate	Std. Error	Lower bound	Upper bound	
PRESENT	27.364	2.206	23.039	31.688	0.14
ABSENT	20.926	2.453	16.118	25.734	

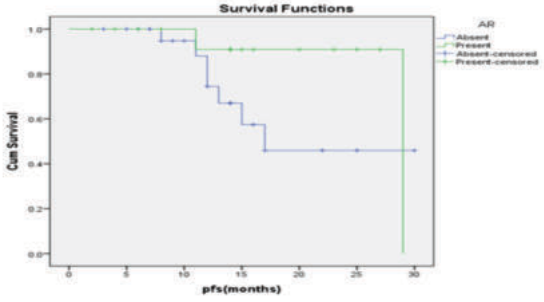

Figure 5: Kaplan Meier Curve By Overall Survival Type

In Type II High grade ovarian cancer,Mean Progression Free Survival estimate among AR Positive cases is 27.37 and AR absent cases the survival estimate is 20.93(p value=0.14)

Sub group analysis out of 64 cases- univariate analysis is made to see the relevance of type II ovarian tumour with age ,FIGO stage ,Cyto reduction, Platinum sensitivity, recurrence and survival statistics and none of them were statistically significant.

DISCUSSION

Lee P et al in 2005 (Expression of progesterone receptor is a favorable prognostic marker in ovarian cancer) is similiar to our study describing a large series of tumors (n = 322), found no association between AR protein expression and clinical outcome [6], however individual histological subtypes were not examined.[16]These findings further highlight the heterogeneity of ovarian cancer, which should not be considered as a single disease, but rather several distinct entities with different clinical behaviours. Nevertheless, as established prognostic parameters, i.e. clinical stage and histological grade, are highly significant indicators of survival, its use for assessment of investigative prognostic markers is justified. [17-19]

AR expression in EOC 18% by jones et al and another study reveals 54.3% in EOC by van Kruchten et al[3].

It is more highly expressed in type II ovarian cancers 39%(n=41/64); ARs were expressed in 45.7% and 50% of all serous and mucinous cases. In this study Sub group analysis is made to see the relevance of type II ovarian tumour with age ,FIGO stage ,Cyto reduction, Platinum sensitivity, recurrence and survival statistics.

The distribution of the six histological subtypes in ovarian carcinoma and their Androgen receptor positivity n=64 - 40.6% is HGSC, 45.7%(n=46/64) are serous; endometroid (n = 7)42.9%; mucinous(n = 4)50% ; clear cell carcinoma (n=5),carcinosarcoma and ppsc (n=1)were androgen receptor positivity is absent. The low grade serous cancers are 43.5%(n=23/64) .Immunostain for AR was observed in the nucleus of carcinoma cells.

Survival analysis revealed that in the entire cohort, there was no significant association between increased AR expression (> 10% nuclear positivity) for progression free survival, over all survival and prognosis. However, in the subgroup of high grade serous carcinomas (n = 41), high AR expression had clinical significant association with a prolonged ovarian cancer specific survival (OCSS) and AR absent tumour for recurrence were significant clinically although not statistically.[2] n a prospective multicenter randomized controlled phase II trial, van Kruchten et al. [12] observed a trend towards AR-positivity associated with decreased overall survival in 121 epithelial ovarian cancer patients, but not reaching statistical significance (P = 0.10). Nevertheless, Lee et al. and Toledo et al. pointed out that AR expression was not associated with survival [15,20]. Conversely, Nodin et al.[1]reported that AR positivity predicted a prolonged disease-specific survival in the serous subtype of epithelial ovarian cancer. The data is supported by two recent studies: one using the TCGA RNA-sequencing data, demonstrated that low AR expression was associated with shorter overall survival in high-grade serous ovarian carcinoma while the other using immunohistochemical staining in 118 serous and endometroid ovarian cancers reported that high level of AR was correlated with improved 5-year progression-free and overall survival[11]. Low AR expression was found to be significantly associated with poor outcome in the subset of serous carcinomas, but not in the full cohort and not statistically significant as the number of sample size is too small and follow up period is short. Results from previous studies related to the prognostic value of AR expression are somewhat divergent and these discrepancies may in part be explained by the use of different methods, or by the number of patient samples analysed [1,12, 13, 14, 15]. The 2-year PFS and OSs were 35.4% and 74.8%, respectively. Several studies have investigated the prognostic impact of hormone receptor expression in ovarian cancer. Androgen receptor expression is associated with an improved prognosis in serous ovarian cancer, independent of differentiation grade and clinical stage[1].

CONCLUSION

Epithelial ovarian cancer is a highly heterogenous disease, biomarker studies must take histological subtypes into consideration. In our study, there is no statistical significant survival difference between AR positive and AR negative groups. Androgen receptor expression was

associated with an improved prognosis which was only clinically significant in high grade serous ovarian cancer although not statistically significant, independent of differentiation grade and clinical stage .It was observed that AR absent subgroup have more recurrences and there was improved overall survival in AR positive subgroup of high grade serous epithelial ovarian cancers which is clinically and not statistically significant. In conclusion findings from the present study, that have to be confirmed in larger trials, highlight the need of assessing the hormonal receptor status in future clinical studies investigating molecular predictors of endocrine therapy responsiveness in HGSOC. Besides, further research is warranted to investigate the contribution of AR in determining the pathogenic role in LGSOC development and progression[9].

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