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Original Article

Pathology Section

Evaluation of Androgen Receptor in Various Molecular Subtypes of Carcinoma Breast and its Relationship with Clinicopathological Parameters: A Retrospective Study

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ABSTRACT

Introduction: Endocrine therapies targeting Oestrogen Receptor (ER) are the cornerstone for majority of Breast Cancer (BC) patients. However, 25%-30% of breast tumours that do not express ER are non-responsive to existing endocrine therapies. The study of Androgen Receptor (AR) has emerged as a useful marker to refine further the classification of BC subtypes. Anti-androgens therapies are considered to markedly enhance the treatment options and to be the first targeted therapy in hormone receptor negative BCs.

Aim: To evaluate the AR status in various molecular subtypes of BC and to know the relation of AR status with tumour grade, Ki-67 index and Lymph Node (LN) metastasis.

Materials and Methods: This retrospective observational study was carried in tertiary care centre in Government Medical College Nagpur, Maharashtra, India, over a period of two years (from September 2013 to August 2015) and included 40 histopathology-proven cases of Infiltrating Duct Carcinoma -No Special Type (IDC-NST) of breast. Tissue Micro Array (TMA) block prepared from all the pooled cases were processed for panel of Immunohistochemical (IHC) markers such as ER, Progesterone Receptor (PR), AR, Human Epidermal Growth Factor Receptor 2 (Her2/neu) and Ki-67.

Results: The AR expression was observed in 52% (21/40) of BC, independent of ER status. AR expression was 9/25 (36%) in ER negative BC, 75% in Her2 only and 28% in triple negative group. The luminal subtype was classified depending on AR status and compared with respect to tumour grade, Ki-67 index and LN status, revealed that AR negative cohort had low tumour grade, lower Ki-67 index and low risk of LN metastasis. Similarly, Triple Negative Breast Carcinoma (TNBC) with AR negative status, when analysed revealed higher tumour grade and higher mitotic index while LN metastasis was noted in few cases.

Conclusion: The study findings can provide evidence that for ER-negative BC drugs targeting AR and AR-regulated signalling cascade may be the potential therapies and can emerge as a useful marker for further refinement of BC molecular subtypes particularly in hormone receptor negative BCs.

Keywords: Triple negative breast cancer, Hormone receptor negative breast cancer, Molecular phenotypes of carcinoma breast

INTRODUCTION

The receptor for androgen expressed in BC is fascinating given that tumour is predominantly oestrogen-dependent. However, the heterogeneity of disease explains why not all BC express ERs and therefore respond to anti-oestrogen therapy [1,2]. The AR is emerging as a new marker and a new therapeutic target in treatment of patients of carcinoma breast. Circulating androgens are detected at physiological conditions in females, and their levels are different during life. However, the role of genome or expression of ARs in relation to BC is not well known [2]. Researches were undertaken to understand whether ARs interfere with ER and/or Progesterone (PR) activities. It is therefore a therapeutic target and the availability of selective AR inhibitors already approved for prostate cancer treatment has created a possibility of their use in AR-positive BC. However, AR appears to have different functions according to the BC subtype, like ER-positive or triple negative. Luminal BC has been reported to be positive for AR expression with higher level in Luminal A and lower in Luminal B tumours with respect to Her2 enriched and Triple-Negative Breast Cancer (TNBC) [3-6]. The above observations seems controversial as some researchers described role of AR in predicting the response rate and Overall Survival (OS) under hormonal treatment while some authors reported no association between AR expression and Disease Free Survival (DFS) in ER-positive tumours. In the same works, ER status contributes as independent prognostic marker for DFS [7,8]. However, for Cochrane DR et al., AR seemed to be an independent prognostic marker if hormone receptors are expressed [9], while for Vera Badillo FE et al., its prognostic role is considered to be independent from the expression of hormonal receptors [10]. Thus, AR appeared as wolf or lamb on the basis of BC subset in which it was evaluated. Kraby MR et al., demonstrated that AR was an independent predictor of good prognosis in BC, particularly in grade three and Luminal A tumours [11]. It was apparent that in ER-negative BC, AR acted in a more analogous way as compared to BCs that were ER-positive. In this category, receptor promoted cell proliferation and tumour spread by acting at different levels. This evidence favoured AR as a potential therapeutic target exploitable for TNBC group and provides new treatment options [12].

With this background, the present study was conducted to evaluate the AR status in BC patients and its various molecular subtypes. The study also aimed to assess the relation of AR status to tumour grade, Ki-67 labelling index and LN status in different molecular subtypes of BC.

MATERIALS AND METHODS

This retrospective observational study was carried in Government Medical College, Nagpur, Maharashtra, India, from September 2013 to August 2015 (over a period of two years). Total 40 cases were included which belonged to the archived material of TMA that were histopathologicallly proven as IDC-NST patients. The clearance from the Institutional Ethical Committee was not obtained for this study as was a retrospective analysis. The archived

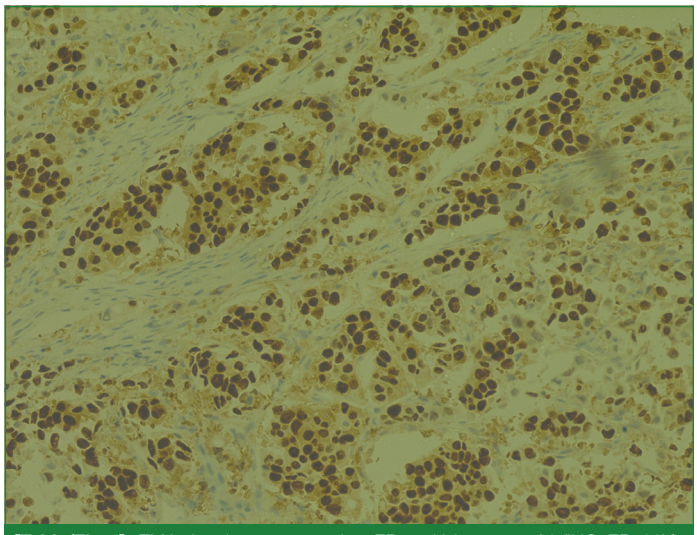
material belonged to patients who had not received preoperative chemotherapy or radiotherapy. The specimen received was of lumpectomy/mastectomy that was immediately and adequately fixed in 10% buffered formalin for 12-48 hours to avoid cold ischaemia time (<1 hour). The tissues were further processed in automated tissue processor machine and the sections were stained with Haematoxylin and Eosin (H&E). The histological grading was done as per Nottingham Modification of Bloom-Richardson method (MBR) [13]. The counting of mitotic figures were done towards the invasive tumour margin in most mitotically active region 10 High Power Field (HPF) (40X) using Nikon microscope (field diameter 0.44 mm) [13]. The paraffin embedded tissue blocks having tumour checked with H&E stained slides were selected for IHC by TMA method. Amongst the randomly selected different tumour grades of 40 carcinoma breast cases of IDC-NST, IHC by TMA was performed. The procedure was done in private accredited pathology laboratory. The expenses incurred for which were bore by investigators and no financial assistance was taken from anyone else. Three tissue cores were selected from each paraffin block (each case) of size of 1 mm each and were spaced 2 mm away from one other. Single recipient block prepared was then subjected to various IHC markers such as ER, PR, AR, Her2/neu and Ki-67. The reporting on stained slides for each marker is done with help of spreadsheet in excel format to identify exact location of each case (tissue). The scoring for ER, PR, AR, Her2/neu was done as per American Society of Clinical Oncology and College of American Pathologist guidelines (ASCO/CAP) guidelines. The average of three scores was considered for analysis [14]. The Allred score was used for interpretation of ER and PR staining [14], while AR was scored as positive when more than or equal to 1% cells showed nuclear staining [6]. The interpretation of HER2/neu, was performed as per ASCO/CAP guidelines [14]. The score of 0 and 1+ were considered negative for HER2/neu expression. Tumours with score of 2+ or 3+ were considered as positive for Her2 overexpression. (2+, scored as positive for statistical calculation) [15]. The interpretation of Ki-67 staining was as per recommendations from international Ki-67 in BC working group, nuclear staining was considered positive. Scoring involved counting of at least 500 malignant invasive cells and expressed as percentage of positively stained cells among total number of invasive cells in the given area [16]. The IHC study was carried out using polymer labelling technique on i6000 Biogenex Automated IHC Staining System. The antibodies used were: ER-clone 6f 11 Leica; PR- clone pa 0312 Leica; AR- clone SP107 Cell Marque; Ki-67- clone MIB 1- Dako; Her2- clone CB 11-Biogenex and CK 5/6- clone D5/16B4 –Dako.

STATISTICAL ANALYSIS

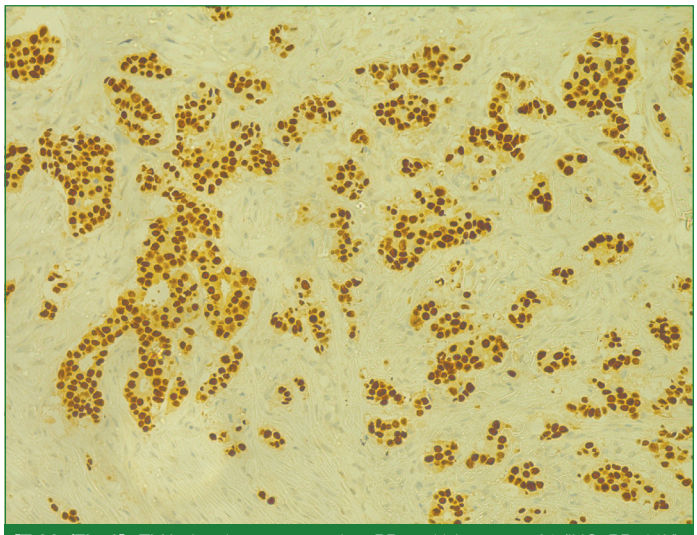
The $p<0.05$ was considered significant. Association of molecular classes, AR status with histological (MBR) grading, LN metastasis and Ki-67 index was assessed. Statistical software STATA Version 13.0 was used for statistical analysis.

RESULTS

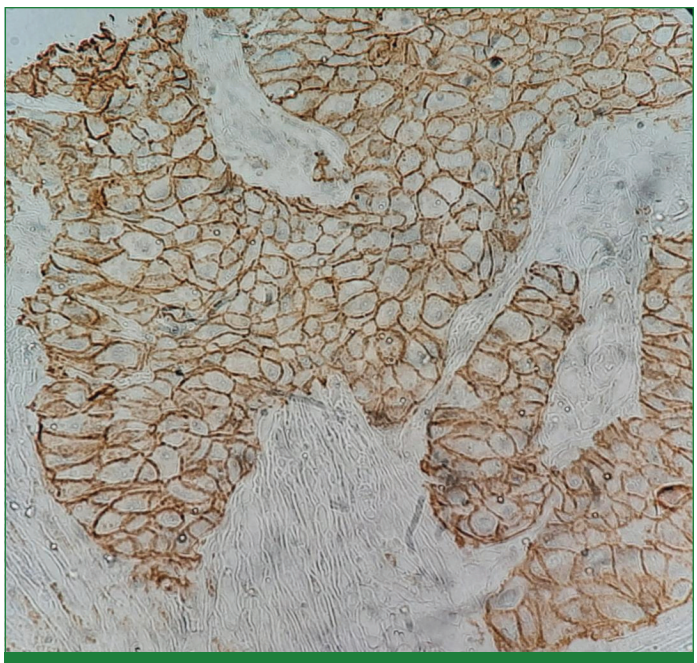
The present retrospective, observational study included total 40 female patients of invasive duct carcinoma breast which were classified depending on expression of ER [Table/Fig-1], PR [Table/Fig-2], HER2/neu [Table/Fig-3] and Ki-67 labelling index (in [Table/Fig-4]) to various molecular subtypes. Luminal A were 9 (22%) amongst which 6 showed AR expression while 3 (7%) were Luminal B, all of which were AR-positive [Table/Fig-5]. The triple positive group consisted of three cases; all of them expressed ARs. The HER2/neu enriched cohort consisted of 4 (10%) cases amongst which three revealed AR expression, while triple negative phenotype comprised of maximum 21 (52%) patients, 6 of which were AR positive. Out of total 40 cases, 21 (52%) showed androgen expression [Table/Fig-6]. Amongst ER-positive cohort which included luminal types and triple positive (ER/PR/HER2/neu +ve), the androgen expression was noticed in 12 out 15 (80%) cases. The tumour grade revealed maximum cases in high grade (II and III) category while 13 cases belonged to low tumour grade (grade I). Out of total 21 AR-positive cases; 8 (38%) belonged to low tumour grade while out of total 19 AR-negative cases, 5 (27%) had lower tumour grade [Table/Fig-7].



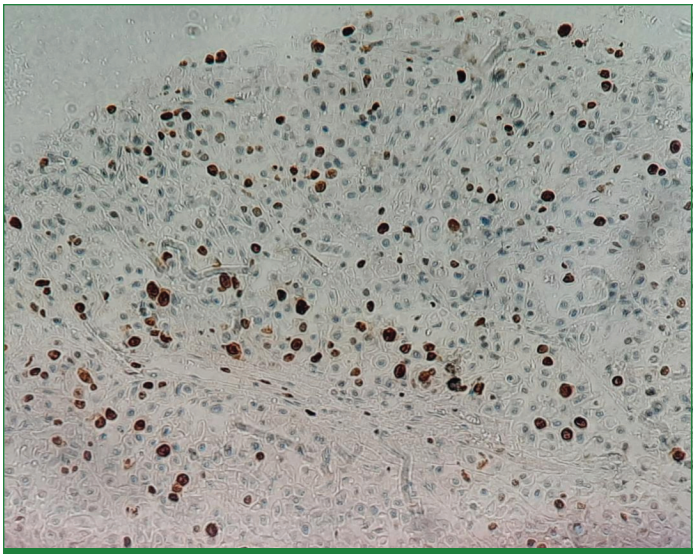
[Table/Fig-1]: TMA showing strong nuclear ER positivity score of 8 (IHC, ER: 20X).



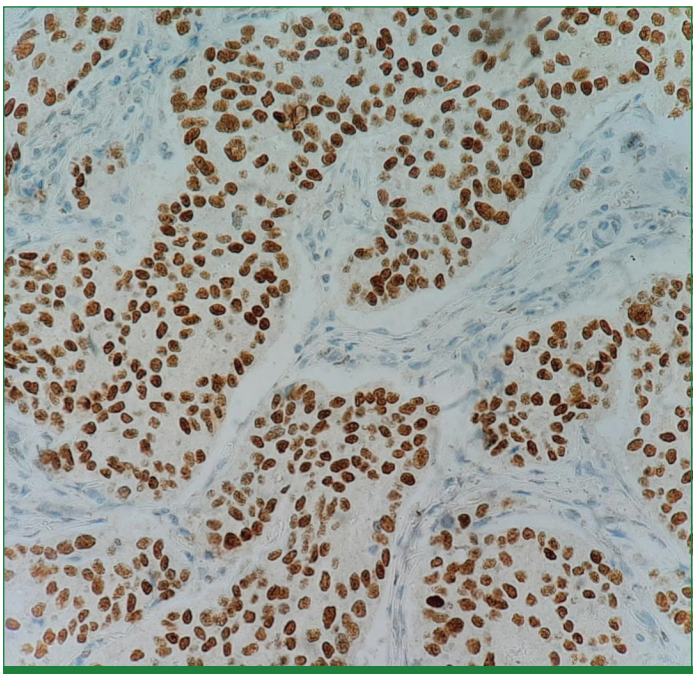
[Table/Fig-2]: TMA showing strong nuclear PR positivity score of 8 (IHC, PR: 20X).



[Table/Fig-3]: TMA showing dense, uniform, membranous expression in >10% of tumour cells (3+ positivity; IHC, Her2/neu: 40X).



[Table/Fig-4]: The TMA showing nuclear positivity in >10% of tumour cells (IHC, Ki-67: 20X).



[Table/Fig-5]: Strong nuclear AR positivity approx. 90% (IHC, AR: 20X).

Molecular types	No.	Androgen receptor expression	
		Positive	Negative
Luminal A: {ER/PR +, HER2/neu -} (Ki-67<10)	9	6 (67%)	3
Luminal B: {ER/PR +, HER2/neu -} (Ki-67 >10)	3	3 (100%)	0
Triple positive {HER2/neu+ (ER/PR ±)}	3	3 (100%)	0
HER2/neu enriched	4	3 (75%)	1
Triple negative: {HER2/neu- (ER/PR -)}	21	6 (28%)	15
Total	40	21 (52%)	19 (48%)

[Table/Fig-6]: Androgen receptor expression and molecular subtypes of Breast Carcinoma (BC).

	No.	Low grade	High grade	p-value (<0.05)
AR-positive	21	8 (38%)	13 (62%)	NS (0.5106)
AR-negative	19	5 (27%)	14 (73%)	
Total	40	13	27	

[Table/Fig-7]: Tumour grade and comparison with androgen receptor status in Breast Carcinoma (BC).
Level of significance (<0.05), Test of significance is Fisher's-exact test

The mitotic activity measured as Ki-67 index when subgrouped into two classes; it was found that, low Ki-67 index (<10%) was seen in 24/40 (60%), while high Ki-67 value (>10%) was noted in 16/40 (40%) of tumours. Amongst 21 AR-positive BC, low Ki-67 index was noted in 12 (58%) patients, while in AR-negative group, low Ki-67 index was found in 12 (63%) cases [Table/Fig-8].

	No.	Ki-67 index <10	Ki-67 index >10	p-value (<0.05)
AR-positive	21	12 (58%)	9 (42%)	NS (0.7553)
AR-negative	19	12 (63%)	7 (37%)	
Total	40	24	16	

[Table/Fig-8]: Ki-67 labelling index with respective androgen status in Breast Carcinoma (BC).
Level of significance (<0.05); Test of significance Fisher's-exact test

The LN metastasis was evident in 30 out of total 40 cases (75%). Amongst which 16 (76%) were AR-positive. Amongst the 10 cases that did not show evidence of LN metastasis, five (24%) were androgen positive [Table/Fig-9]. When the tumour grade was assigned to molecular classes; total 12 cases belonged to luminal types out of which 9 showed AR expression. Out of these 9, six (67%) had lower tumour grade. The three cases which were negative for AR, also had lower tumour grade, 7 patients had Ki-67 labelling index below 10; while all three amongst AR-negative had Ki-67 index below 10. The LN metastasis was noted in 4 (44%) amongst 9, AR positive cases, while 1 (33%) out of 3 AR negative had LN metastasis [Table/Fig-10].

	No.	LN positive	LN negative	p-value (<0.05)
AR positive	21	16 (76%)	05 (24%)	NS (1.000)
AR negative	19	14 (73%)	05 (27%)	
Total	40	30	10	

[Table/Fig-9]: Lymph Node (LN) metastasis in Breast Carcinoma (BC) comparison with Androgen Receptor (AR).
Level of significance (<0.05); Test of significance Fisher's-exact test

Luminal type BC	No.	Tumour grade LG	Tumour grade HG	Lymph node		Ki-67 index	
				Positive	Negative	<10	>10
AR positive	9	6 (67%)	3 (33%)	4 (44%)	5 (56%)	7 (77%)	2 (23%)
AR negative	3	3 (100%)	0	1 (33%)	2 (67%)	3 (100%)	0
Total	12	9	3	5	7	10	2

[Table/Fig-10]: Luminal BC: AR status with respect to tumour grade, Ki-67 index and LN metastasis.

The total cases in triple negative cohort were 21, out of which six (28%) were AR-positive and 15 (72%) were AR-negative. Amongst six AR-positive patients, two (33%) displayed low-grade morphology, 4 (66%) had Ki-67 labelling index below 10 and four (66%) showed LN metastasis. Out of total 15 AR negative cases, two (13%) were low-grade, 8 (53%) had Ki-67 LI below 10 and four (26%) revealed LN metastasis [Table/Fig-11].

Triple-negative BC (TNBC)		LG	HG	LN status		Ki-67 index	
				Positive	Negative	<10	>10
AR-positive	6	2 (33%)	4 (66%)	4 (66%)	2 (34%)	4 (66%)	2 (33%)
AR-negative	15	2 (13%)	13 (87%)	4 (26%)	11 (74%)	8 (53%)	7 (47%)
Total	21	4	17	8	13	13	9

[Table/Fig-11]: Triple-negative BC: AR status with respect to tumour grade, Ki-67 index and LN metastasis.

DISCUSSION

Expression of ARs is seen in two types of mammary epithelial cells. Most uniformly and diffusely it is expressed in metaplastic apocrine cells that are a component of fibrocystic disease. The majority of these apocrine cells lack expression of ER and PR [17]. AR is also exhibited in 5% to 30% of luminal epithelial cells, where it is commonly co-expressed with ER/PR. Tumours arising from these two different cell types may share expression of AR but are morphologically

distinct [18]. In addition, responses to target AR therapeutically can differ based on the origin of a tumour in apocrine vs luminal cells. The AR as a prognostic or predictive biomarker in subset of BC patients is said to be controversial [19]. The AR expression in approx 70% to 90% of primary BCs, a frequency which is comparable or higher than either ER or PR [8,11,20]. The androgen expression among BC in present study population was 52% (21/40). The AR-positive and negative group when compared in current study; 38% of AR-positive displayed low grade morphology, 58% revealed low Ki-67 index and 76% had LN metastasis while amongst AR negative group, 27% had low grade morphology, 63% showed low Ki-67 index and 73% revealed evidence of LN metastasis. However, the difference was not statistically significant. Significant variability exists in reported literature regarding the frequency of AR expression in TNBC that ranges from 6.6% to 75% [21-23].

The triple-negative cohort in present study showed 28% (6/21) positivity for AR. This heterogeneity can be explained primarily due to variability among the reported studies in terms of sample included and the cut-off applied for AR positivity (≥1% or >10%). The other reasons for variability could be source of primary antibody, methodology of testing among different studies so also the confounding effects of patient selection in prospective studies. In the largest meta-analysis consisted of systematic reviews of 7693 BCs, AR was expressed in 74.8% of ER-positive and 31.8% in ER-negative tumours [11]. The growing evidence suggests that AR-positive TNBC may respond to therapeutic agents targeting ARs, are more common in older patients and have higher propensity for LN Metastases (LNM) [17]. The AR-positive TNBC constitute a BC subtype having unique features that can be responsive to treatment with alternative targeted therapies. The triple-negative, AR-positive cohort, this study displayed low grade morphology, majority had Ki-67 index below 10 and about 66% cases revealed evidence of LN metastasis comparable with other studies [24,25]. The AR negative TNBC in present study on other hand revealed high grade morphology in 87%, higher mitotic count in 40% and LN metastasis in lower number of patients. A number of studies have shown that in TNBC tumours, expression of AR is a favourable prognostic factor and associated with a lower clinical stage, lower histologic grade, and lower mitotic score [25,26].

In one of the largest systematic reviews of 19 studies, that included 7693 BCs, AR expression was 74.8% in ER-positive tumours and 31.8% in ER-negative tumours [11]. Patients with ER and AR-positive tumour have a better outcome than those with ER-positive and AR-negative disease [27]. This can be ascribed to competition between androgen and ER at the level of Oestrogen Response Elements (EREs) and therefore impairment of ER-dependent gene transcription [12]. Some researchers underlined the fact that in ER-positive BC, AR could compete with ER-dependent transcription for binding to same sites or facilitate ER binding to DNA. So, also ARs do compete with ER and PR-positive BC [28]. The AR/ER ratio has been reported to impact prognosis and response to anti-oestrogen endocrine therapy. Cochrane and colleagues stated that AR/ER ratio plays an important role to predict the response to tamoxifen [10]. In the study by Bronte G et al., in primary BC or matched metastases of advanced BC, AR was considered as a predictor of efficacy of first-line endocrine therapy [6]. The AR expression did not appear useful to predict the efficacy of endocrine therapy in advanced BC, whereas Ki-67 and PR exert a greater impact on its efficacy [29]. Several analyses based on unselected BC cohorts had shown that AR to be related to ER and PR expression and also be a marker of low-grade, well-differentiated disease [30-33].

In a study done by Rakha EA et al., and Sutton LM et al., they have shown that, absence of AR expression is associated with a higher risk for disease recurrence and distant metastasis in LN -positive TNBC [34,35]. In current study, ER-positive cohort showed 80% AR positivity. The AR-positive ER group revealed disease with low-grade morphology. However, there is little difference of Ki-67 index (58% vs 63%) and LN metastasis (76% vs 73%) between AR-positive and AR-negative ER-positive group, (63% showed low in present study). The luminal type of BC constitutes 30% cases (12/40), of which 9/12 (75%) showed AR positivity. In this subtype, 67% revealed low tumour grade, 77% showed lower Ki-67 index and 44% had LN metastasis. Among AR-negative luminal types, all cases showed low grade histology, low Ki-67 index and lower percentage of LN metastasis. Androgens like testosterone and dihydrotestosterone can behave indirectly as prohormones of estradiol, or act directly by binding to AR [35]. The circulating androgen after binding to AR, leads to translocation of receptor to the nucleus, tether with target genes, and cause transcriptional activation [36]. Studies also have shown that androgen signalling pathway has a critical role to play in the development of normal and malignant breast tissue. The animal model experimentation implicates that androgen signalling is important in the progression of BC [37].

Limitation(s)

Large study samples may be required to exactly assess the role of AR and its biological behaviour in carcinoma breast in this population.

CONCLUSION(S)

This present study allows characterisation of IHC subgroups in patients with BC in Central India, using a recently updated classification. It also permits assessment of subgroup distribution in relation to AR expression and parameters like tumour grade, Ki-67 index and LN metastasis. The standardisation of scoring methods can provide AR as an easily detectable marker in BC. It is required to determine the AR status on all molecular types of BC particularly TNBC amongst different populations with the possibility to treat patients of low economical status with anti-AR compounds considering its cost effectiveness.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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