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ORIGINAL ARTICLE

Androgen receptor expression as a prognostic and predictive marker in triple-negative breast cancer patients

Fatma Zakaria, Nehal El-Mashad, Dareen Mohamed *

Departments of Clinical Oncology and Histopathology, Tanta University, Faculty of Medicine, Egypt

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KEYWORDS

Triple-negative breast cancer;
Androgen receptor immuno-histochemistry;
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Abstract *Purpose:* It is clear that triple-negative breast cancer (TNBC) tumors are heterogeneous group, but clinically important sub-sets have begun to emerge. We investigate the immunohistochemical expression of androgen receptor (AR) among those hormonal insensitive groups which have only the option of chemotherapy. Exploiting this knowledge for therapy has been challenging.
Patients & methods: Seventy seven patients with TNBC subtype, treated from January 2009 until February 2011 were evaluated for AR expression where AR-positive expression group (⩾10% nuclear stained cells) was conducted to receive anti-androgen therapy post adjuvant chemotherapy (Bicalutamide "Casodex®") 50 mg, once daily with or without meals at the same time each day, to date. AR expression was correlated with other prognostic factors and survival (disease free survival (DFS) and overall survival (OS)). Cox proportional hazard model was used to assess variables in the multivariate analysis.
Results: The median age in the present study was 35.6 year **(19–63 years)**. The median follow-up period was 24 months **(3–60 months)**. AR-positive expression in the present study was **(21\77) 27.27%** correlated with clinical outcomes, for recurrent event **(*n* = 4, 19.05%)**, **(*P* = 0.000, HR 12.750, CI 95% 3.668–44.318)** and for death event, no body died in AR positive expression group **(*P* = 0.000, HR 0.644, CI 95% 0.533–0.779)**. Improved survival with AR-positive expression group for 2-year and 3-year DFS was 85% and 78% respectively with **(*P* = <0.001, CI 95% 39.17–51.39)** and for OS at 2-year and 3-year was 100% **(*P* = 0.0005)**. In univariate and multivariate analysis, AR positive expression with anti-androgen therapy in TNBC patients in our present study had retained their independent prognostic value for DFS **(*P* = 0.0006, HR 4.659, CI 95% 1.553–13.977)**. Bicalutamide was well-tolerated therapy with no grade 3/4 treatment-related adverse events.
Conclusions: Bicalumide is well tolerated in AR positive TNBC subtype patients and could offer an alternative to cytotoxic chemotherapy in those patients with better OS and DFS.

* Corresponding author.
E-mail addresses: Fatmaz_555@yahoo.com (F. Zakaria), nehalelmashad@yahoo.com (N. El-Mashad).
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1. Introduction

Androgen receptor (AR) positivity has been detected in approximately half of all breast carcinoma cases.[1,2] High (AR) expression in breast cancer has been correlated with a low risk of recurrence and death.[1]

AR has been shown to have prognostic implications in breast carcinoma, and higher AR expression levels have been associated with older age at diagnosis, higher expression of ER or PR, lower nuclear grades, and smaller tumor size.[2,3]

Triple-negative breast cancers (TNBC) were recently divided into further subtypes including a subtype with high AR expression.[4]

Previous studies looking at AR expression in TNBC have demonstrated that AR negativity has been associated with a shorter disease-free interval and overall survival than AR-positive TN cancer. These studies suggest that AR expression could be a useful prognostic marker in TN tumors.[4]

AR is expressed in 60–70% of breast tumors independent of estrogen status, and in 20–32% of TNBC patients. Estrogen and Progesterone and the gene HER-2, these are the three big markers and/or targets in breast cancer. Evidence presented at the AACR Annual Meeting 2013 adds a fourth: androgen receptors.[5]

2. Patients and methods

This Retrospective study was conducted in Clinical Oncology Department and Histopathological Department, Tanta University 2009 until February 2011. The study included 77 consecutively treated patients with TNBC. The established clinical and histo-morphological factors of all patients were assessed. The steroid hormones status including (ER, PR, Her.2, AR and KI-67) was evaluated by immunohistochemistry (IHC).

The aim of this study focused on predictive and prognostic value of AR expression as a hormonal marker in TNBC patients.

2.1. Immunohistochemistry for ER, PR, HER-2, AR and KI-67

For immune-staining, 3–5 mm sections were deparaffinized with 40 min incubation at 60_C and subsequent immersion in xylene, and were rehydrated in solutions of decreasing ethanol. Then specimens were incubated in 0.3% H_2O_2 for 30 min to inhibit activation of endogenous peroxidases. Slides were then washed with phosphate-buffered saline (PBS) and heated in an 830-W microwave oven for at least 15 min in 10 mmol/l sodium citrate buffer (pH 6.0) for antigen retrieval. Sections were incubated with primary antibodies against [mouse monoclonal, androgen receptors (ab9474 1:500 dilution), rabbit monoclonal Estrogen receptor (ab37438 1:25 dilution), rabbit monoclonal Progesterone receptor (ab2765 1:25 dilution), rabbit monoclonal HER-2 receptor (ab134182 1:100 dilution) and Rabbit polyclonal KI-67 (ab15580 1:100 dilution) overnight at 4_C. For the negative control, the primary antibody was replaced with phosphate buffered saline (PBS). Rabbit anti-mouse horseradish peroxidase-conjugated secondary antibody was added followed by incubation for 40 min at room temperature. The color was developed using diaminobenzidine (DAB) as a chromogen. Slides were extensively washed with PBS after each step. Finally they were counter-stained with Mayer's hematoxylin.

The immunostaining results for ER, PR & AR were assessed semiquantitatively and reported as positive if more than 10% of cells have nuclear immunostaining in a tumor. Tumor cells were considered positive for HER2 protein overexpression when more than 10% of the cells showed complete moderate or strong membrane staining. Ki 67 immunostaining was considered positive if there were nuclear staining in more than 10% of the tumor cells.[6]

2.1.1. Study design

Seventy seven TNBC patients were classified into two sub-groups according to AR-expression profile, where AR-positive expression group 21/77 (27.27%) designated to receive anti-androgen therapy post adjuvant traditional chemotherapy, Bicalutamid 50 mg once daily with or without meals at the same time each day still received to date.

At the time of primary treatment, none of the patients had any evidence of distant metastases. After the completion of the primary treatment, our TNBC patients underwent regular follow-up examinations at our department for DFS and OS as regards AR expression profile. All the procedures were in accordance with the ethical standards of our faculty's Ethical committee.

2.1.2. Statistical analysis

Statistical presentation and analysis of the present study were conducted, using Number and percentage for qualitative and tested by chi-square test. We used Kaplan–Meier and Cox regression for survival analysis by SPSS for windows version 18.0 software package (SPSS Inc., Chicago, 11) and P value = $< 0.05\%$. Overall survival (OS) defined the length of time from the date of diagnosis and the patients still alive either free or not. Disease-free survival (DFS) expresses the period after curative treatment (disease eliminated) when no disease can be detected.

3. Results

At the time of the primary treatment, none of the patients had any evidence of distant metastases.

The tumor's, patient's and treatment's characteristics in 77 TNBC patients are presented in Table 1, the median age of the patients was 35.6 years (range, 19–63). Age > 35 years was 50.65%, premenopausal at the presentation was 52.63%, patients had grade III tumors 32.47%, tumor size larger than 2 cm was 27.27%, and patients had invasive ducal carcinoma (IDC) (92.21%). At least one axillary lymph node was positive in 57.14% of patients, and positive mitotic index was 67.53%. In twenty one patients (21/77) 27.27% were positive for AR expression in TNBC patients in the present study. Positive AR immunostaining was inversely correlated with large tumor size ($P = 0.001$), nodal status ($P = 0.007$), high grade ($p = 0.000$) and higher Ki67 ($p = 0.08$). Positive AR expression was associated with age less than 35 years (42.86%), female patients (100%), premenopausal status (42.86%) and no patients had stage III at presentation. For AR negatively expressed tumors in TNBC patients in the present study 51.79% was associated with age < 35, 3 male patients (5.36%), premenopausal status (56.36%). Stage III at

Table 1 Tumor's and treatment's characteristics in 77 TNBC patients.

Patients characteristics		*N*	%
Age	< 35.	38	49.35
	> 35.	39	50.65
Sex	Female	74	96.10
	Male	3	3.90
PS	0	54	70.13
	1	21	27.27
	2	2	2.60
Body mass index	< 25	47	61.04
	> 25	30	38.96
Menopause status	Pre	40	52.63
	Post	36	47.37
Tumor stage	Stage I	11	14.29
	Stage II	43	55.84
	Stage III	23	29.87
T	T1	19	24.68
	T2	37	48.05
	T3	20	25.97
	T4	1	1.30
N	N0	33	42.86
	N1	32	41.56
	N2	12	15.58
Pathological subtypes	Ductal	71	92.21
	Lobular	1	1.30
	Other	5	6.49
Grade	Grade I	7	9.09
	Grade II	45	58.44
	Grade III	25	32.47
CA15.3	Positive	20	25.97
	Negative	57	74.03
Chemotherapy regimens	A/C	32	41.56
	T/A	45	58.44
AR exp	Positive	21	27.27
	Negative	56	72.73
Ki67	Positive	52	67.53
	Negative	25	32.47
Brain	No	58	75.32
	Yes	19	24.68
Bone	No	71	92.21
	Yes	6	7.79
Lung	No	57	74.03
	Yes	20	25.97
Liver	No	71	92.21
	Yes	6	7.79
Local	No	67	87.01
	Yes	10	12.99

presentation was 41.07%, 35.7% presented as T3, N2 in 21.43%, 92.86% presented with IDC histology subtype, GIII in 42.86%, high CA15.3 in 32.14% of patients and 73.21% presented with high KI-67 more than 14%. All patients underwent the radical local treatment, all patients of this study received anthracycline-based chemotherapy regimens A/C (Adriamycin and cyclophosphamide), T/A (Taxol and adriamycin) Table 1

3.1. Follow-up

Local and distant recurrences were 59.74% (n = 46) of patients and 23.38% (n = 18) patients were died in the whole studied population of TNBC (Table 2).

The median follow-up was 24 months (range, 3–60) months. Ten (12.99%) patients experienced local recurrence, 45 (58.44%) patients experienced distant recurrence and 18 (23.38%) patients were died, in the entire study (Table 3). The risk of relapse (local spread) in AR-positive group (n = 1, 4.76%) versus (N = 9, 16.07%) in AR-negative group with p value = 0.15, for distal spread (n = 3, 14.28%) versus (n = 42, 75.00%) for AR-Positive and AR-negative groups respectively, (p = 0.000). AR-expression was positively associated with clinical outcomes for recurrent event (n = 4, 19.05% versus n = 42, 75%), AR-Positive and negative groups respectively (P = 0.000, HR = 12.750, 95 Cl% 3.668, 44.318), for death event nobody died in AR positive group in comparison with (n = 18, 32.9%) for AR-negative group (P = 0.000, HR 0.644, Cl 95% 0.533–0.739) Table 4.

3.2. Survival plots

The median overall-survival (OS) of the entire group was 46.58 months with 5-Year OS 63% (Fig. 1). Median disease-free-survival (DFS) was 22.00 months with 5-year DFS 18% and in the entire group we found a pattern of maximum recurrence and death rates in the first 3 years following the diagnosis and a clear decline after that (Fig. 2).

The median OS, was 35 months for AR-ve group with no death in AR positive group received anti-androgen therapy; 2-year OS was 100% versus 74%, 3-year OS was 100% versus 42% and 5-year OS was 100% versus 42% for AR-positive and AR-negative groups respectively (P = 0.0005) "Fig. 3".

The median DFS was 45.26 months versus 14.00 in AR-positive with anti-androgen therapy and AR-negative groups respectively with (P = 0.000). 2-Year DFS was 85% versus 28%, 3-year DFS was 78% versus 20% and 78% versus 5% at 5-year DFS (p = < 0.001), for AR + positive and AR-negative groups respectively "Fig. 4".

3.3. Univariate and multivariate survival analysis

In the univariate analysis (Table 5), AR expression was positively associated with nodal status, grade, Ki67 and CA 15.3 with significant impact on DFS (P = 0.001, 0.043, < 0.001, 0.003). In the multivariate analysis (Table 6) for DFS, only AR expression group which received anti-androgen therapy, tumor grade and ki-67 proliferation index retained their in-dependent prognostic and predictive values in TNBC patients (P = 0006, HR 4.659, CI 95% 1.553–13.977): for AR expression, (P = 0.000, HR 4.105, CI 95% 2.065–8.159), for tumor grade, and (P = 0.000, HR 0.281, CI 95% 0.119–0.665) for Ki-67.

Table 2 Clinical outcomes in 77 TNBC patients.

Clinical outcomes		*N*	%
DFS event	0	31	40.26
	1	46	59.74
Outcome	Alive	59	76.62
	Died	18	23.38

Table 3 Correlation of different prognostic factors with AR expression (AR + ve versus AR-ve groups).

Prognostic factors		AR therapy						Chi-square	
		Positive		Negative		Total		X^2	*P*-value
		N	%	*N*	%	*N*	%		
Age	< 35	9	42.86	29	51.79	38	49.35	0.488	0.485
	> 35	12	57.14	27	48.21	39	50.65		
Sex	Female	21	100.00	53	94.64	74	96.10	1.956	0.162
	Male	0	0.00	3	5.36	3	3.90		
PS	0	17	80.95	37	66.07	54	70.13	2.513	0.285
	1	4	19.05	17	30.36	21	27.27		
	2	0	0.00	2	3.57	2	2.60		
Body mass index	< 25	9	42.86	38	67.86	47	61.04	3.949	0.047
	> 25	12	57.14	18	32.14	30	38.96		
Menopause status	Pre	9	42.86	31	56.36	40	52.63	1.113	0.291
	Post	12	57.14	24	43.64	36	47.37		
Stage	Stage I	4	19.05	7	12.50	11	14.29	18.103	0.000
	Stage II	17	80.95	26	46.43	43	55.84		
	Stage III	0	0.00	23	41.07	23	29.87		
T	T1	7	33.33	12	21.43	19	24.68	16.147	0.001
	T2	14	66.67	23	41.07	37	48.05		
	T3	0	0.00	20	35.71	20	25.97		
	T4	0	0.00	1	1.79	1	1.30		
N	N0	13	61.90	20	35.71	33	42.86	9.996	0.007
	N1	8	38.10	24	42.86	32	41.56		
	N2	0	0.00	12	21.43	12	15.58		
Path subtypes	Ductal	19	90.48	52	92.86	71	92.21	2.750	0.253
	Lobular	1	4.76	0	0.00	1	1.30		
	Other	1	4.76	4	7.14	5	6.49		
Grade	Grade I	5	23.81	2	3.57	7	9.09	16.177	0.000
	Grade II	15	71.43	30	53.57	45	58.44		
	Grade III	1	4.76	24	42.86	25	32.47		
CA15.3	Positive	2	9.52	18	32.14	20	25.97	4.671	0.031
	Negative	19	90.48	38	67.86	57	74.03		
Chemotherapy regimens	A/C	8	38.9	24	42.86	32	41.56	2.278	0.320
	T/A	13	61.90	32	57.14	45	58.44		
AR exp	Positive	21	100.00	0	0.00	21	27.27	90.237	0.000
	Negative	0	0.00	56	100.00	56	72.73		
Ki67	Positive	11	52.38	41	73.21	52	67.53	2.923	0.087
	Negative	10	47.62	15	26.79	25	32.47		
Brain	No	20	95.24	38	67.86	58	75.32	7.676	0.006
	Yes	1	4.76	18	32.14	19	24.68		
Bone	No	21	100.00	50	89.29	71	92.21	4.008	0.045
	Yes	0	0.00	6	10.71	6	7.79		
Lung	No	20	95.24	37	66.07	57	74.03	8.425	0.004
	Yes	1	4.76	19	33.93	20	25.97		
Liver	No	20	95.24	51	91.07	71	92.21	0.405	0.525
	Yes	1	4.76	5	8.93	6	7.79		
Local	No	20	95.24	47	83.93	67	87.01	2.049	0.152
	Yes	1	4.76	9	16.07	10	12.99		

Table 4 Relation of AR-expression and clinical outcomes.

Clinical outcomes		AR therapy						Chi-square		Odd ratio		
		Positive		Negative		Total						
		N	%	*N*	%	*N*	%	X^2	*P*-value	Odd	*L*	*U*
DFS event	0	17	80.95	14	25.00	31	40.26	20.372	0.000	12.750	3.668	44.318
	1	4	19.05	42	75.00	46	59.74					
Out come	Alive	21	100.00	38	67.86	59	76.62	13.414	0.000	0.644	0.533	0.779
	Died	0	0.00	18	32.14	18	23.38					

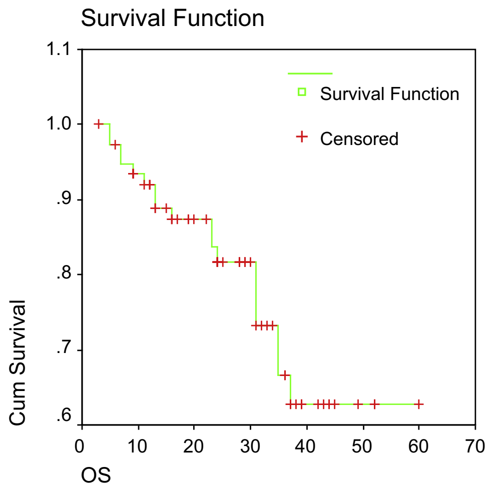

Figure 1 OS in the entire study group Median = 46.58 SE = 2.64.

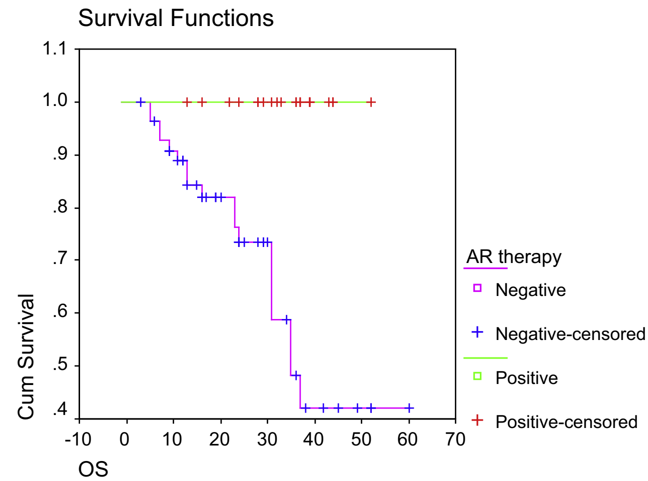

Figure 3 OS in both study groups according to AR-expression (AR + ve and AR-ve).

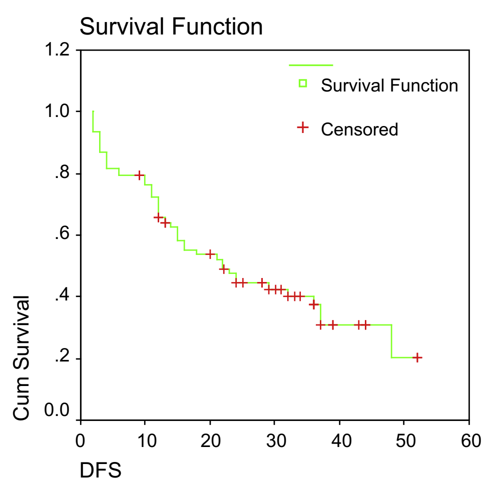

Figure 2 DFS in the entire study group Median = 22.00 SE = 4.39.

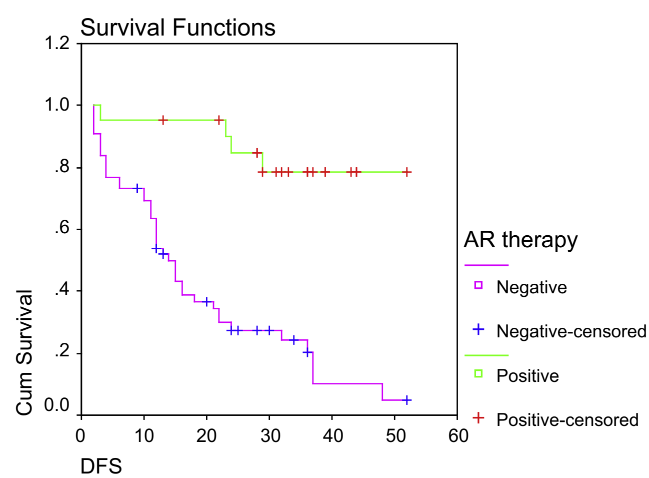

Figure 4 DFS in both study groups according to AR-expression (AR + ve and AR-ve).

Table 5 Univariate analysis of the entire group for our study (77 patients) TNBC of different prognostic factors as regard DFS.

Prognostic factors		2y.	3y.	Median	SE	CI 95%	Log rank test	*P*-value
Age	< 35	0.396	0.346	22.000	6.600	(9.06–34.94)	0.140	0.709
	> 35	0.487	0.411	24.000	7.360	(9.58–38.42)		
Menopause	Pre	0.367	0.275	18.000	6.400	(5.46–30.54)	2.290	0.131
	Post	0.538	0.500	29.000	6.580	(16.11–41.89)		
AR exp	Positive	0.847	0.786	45.260	3.100	(39.17–51.35)	21.710	< 0.001*
	Negative	0.276	0.201	14.000	1.360	(11.34–16.66)		
AR therapy	Positive	0.847	0.786	45.260	3.100	(39.17–51.35)	21.710	< 0.001*
	Negative	0.276	0.201	14.000	1.360	(11.34–16.66)		
Chemotherapy regimens	A/C	0.450	0.360	24.000	10.560	(3.29–44.71)	0.620	0.733
	T/A	0.444	0.377	22.000	4.340	(13.50–30.50)		

Table 6 Multivariate analysis of the entire group for significant prognostic factors as regard DFS.

Prognostic factors	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
AR exp	***1.539***	***0.561***	***7.535***	***0.006***	***4.659***	***1.553***	***13.977***
T	−0.085	0.205	0.173	0.678	0.918	0.615	1.372
N	0.005	0.226	0.000	0.983	1.005	0.645	1.566
Grade	1.412	0.351	16.228	0.000	4.105	2.065	8.159
Ki67	−1.270	0.440	8.333	0.004	0.281	0.119	0.665
CA15.3	−0.018	0.340	0.003	0.957	0.982	0.504	1.912

3.4. Toxicity profile for anti-androgen therapy

As regarded Bicalutamide toxicity profile, no patient presented with grade 3/4 toxicity, only 6\21 patients, 28.57% presented with breast tenderness of fullness and hot flushes ($n = 2$), Feeling sick (nausea) ($n = 3$), weight gain ($n = 1$) and all of them controlled, Bicalutamid still received as hormonal therapy to date among AR-positively expressed subtype in the present study.

3.5. Immunohistochemical results

See Figs. 5a–5d and Figs. 6–8.

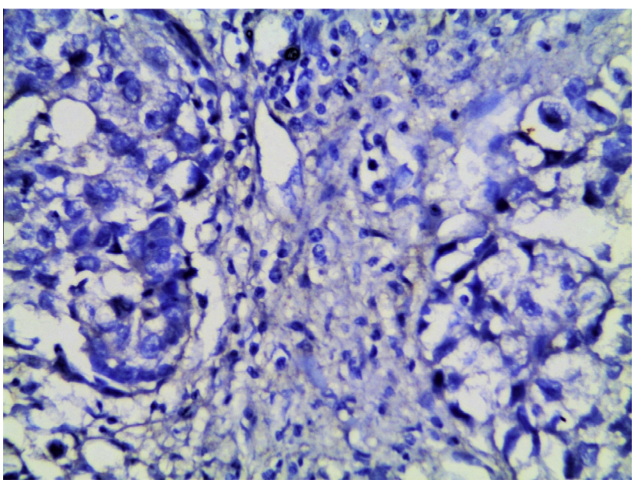

Figure 5a A case of invasive ductal carcinoma grade III showing negative immunohistochemical stain for estrogen receptor [Streptavidin biotin × 400].

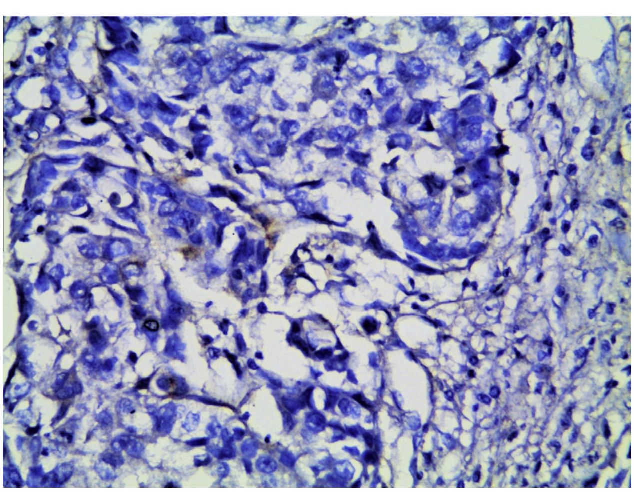

Figure 5b The same case of invasive ductal carcinoma grade III showing negative immunohistochemical stain for progesterone receptor [Streptavidin biotin × 400].

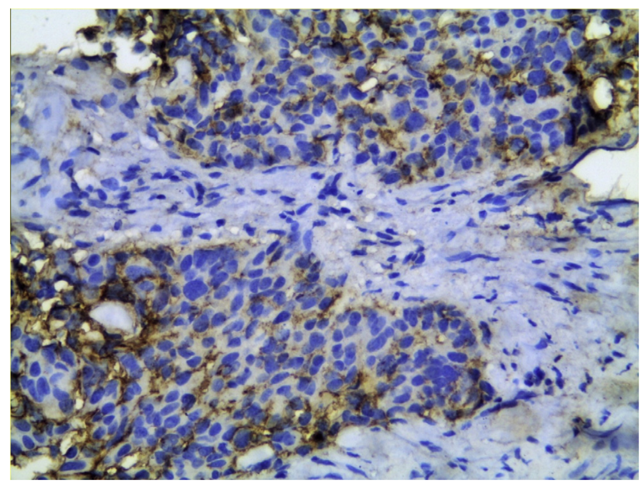

Figure 5c The same case of invasive ductal carcinoma grade III showing negative immunohistochemical stain for HER-2 receptors [Streptavidin biotin × 400].

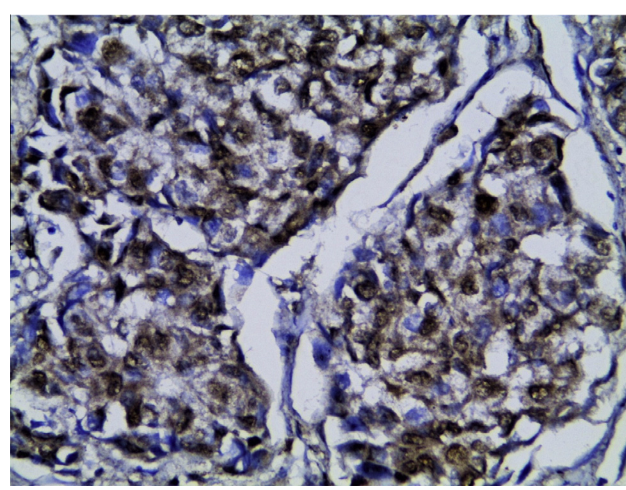

Figure 5d The same case of invasive ductal carcinoma grade III showing positive immunohistochemical stain for androgen receptors in more than 10% of the tumor cells [Streptavidin biotin × 400].

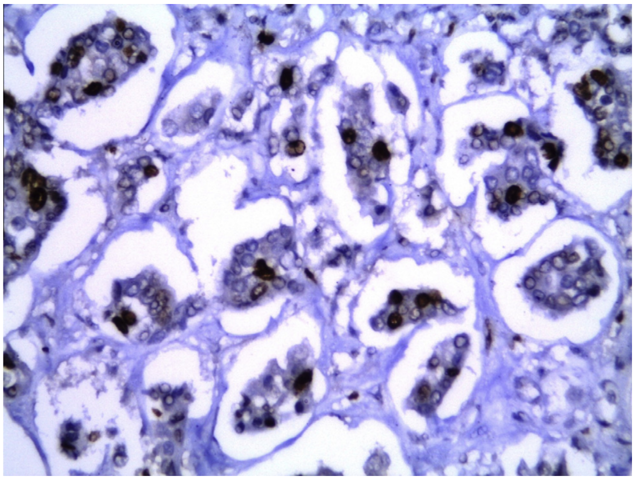

Figure 6 A case of invasive breast carcinoma grade I showing positive immunohistochemical stain for androgen receptors in more than 10% of the tumor cells [Streptavidin biotin × 400].

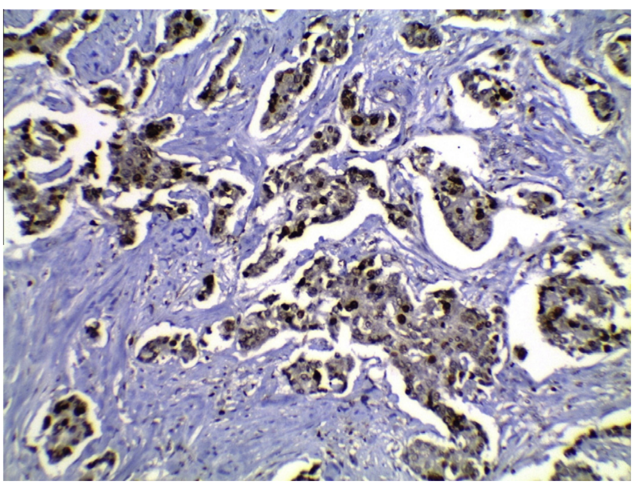

Figure 7 A case of invasive breast carcinoma grade II showing positive immunohistochemical stain for androgen receptors in more than 10% of the tumor cells [Streptavidin biotin × 100].

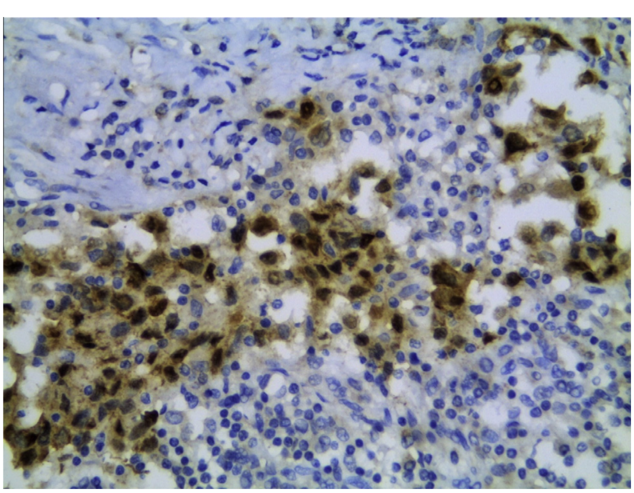

Figure 8 A case of invasive breast carcinoma grade III showing positive immunohistochemical stain for androgen receptors in more than 10% of tumor cells [Streptavidin biotin × 400].

4. Discussion

To date, studies on patients with TNBC have been limited mostly by the small sample sizes and short follow-up times. Our present retrospective study was conducted in 77 TNBC patients treated in the routine clinical practice with the median follow-up time of almost 24 months.

In the study, TNBC patients had relatively large tumors at presentation (more than 2 cm in 27.27% of patients), premenopausal (52.63%), predominant type of tumor was invasive ductal carcinoma (92.21%), poorly differentiated (32.47%), positive ki-67 > 14% (67.53%), almost more than half of patients (57.14%) had positive axillary lymph nodes and twenty-one patients (27.27%) were positive for AR expression at presentation (Table 1). Also, in some previous reports triple-negative tumors were presented in premenopausal young women with poorer clinical outcomes similar to our results, median DFS was 4 years among women who were diagnosed between age 31–40 years compared with 8 years among women diagnosed at age 60 or older (7). TNBC tumors were described as relatively large (> 2 cm) with high rate of node positivity[7–15] similar to our results. Other investigators found that characteristically TNBC exhibits an invasive ductal histology and a high histologic grade, presented with high mitotic index.[16–18] In the population based Carolina Breast Cancer Study (CBCS), basal like breast cancers (defined by triple negative status plus EGFR and/or cytokeratin 5 positivity) were virtually all of ductal or mixed histology 90% and of high grade (84%), whereas TNBC is identified tumor subtype characterized by aggressive behavior and poor prognosis where the majority of triple-negative cases were of high grade and of large tumor size[19–24] similar to our results. TNBC cases are associated with higher expression of ki-67 than non-TNBC and so ki-67 can be used for further classification of TNBC into two subtypes with different response and prognosis.[25–27] Garay et.al.[28] stated that AR was expressed in 10–35% of TNBC patients and also, stated by Richer[5] (5. Traditionally, chemotherapy has been the mainstay of systemic treatment for TNBC, TNBC is highly responsive to primary anthracycline and anthracycline/taxane protocols, however, a high risk of relapse remains[29–31] similar to our study).

AR expression was significantly related to older age at diagnosis, smaller tumor size, well differentiated tumors, lower proliferative index, lack of lymph node metastasis and of ductal type.[8,17,32–38]

TNBC patients with androgen negative have a higher proportion of positive lymph nodes,[3] higher level of pre-operative CA15.3, larger tumor size, higher grade.[19,39,40] It has been documented that AR expression is related to positive prognostic factors.[8,33,38,41]

Correlation between histopathologic grade and the expression of all sex hormone receptors in breast tumors revealed that as tumor grade progressed from 1 to 3 AR-expression decreased from 95% to 76% in ductal carcinoma in situ (DCIS) and 88–47% in invasive carcinoma. In the same analysis, ER expression decreased from 100% to 8% in DCIS and to 9.5% in invasive carcinoma with increasing tumor grade.[28]

In our study as a whole, the median follow-up was 24 months (range, 3–60) where 12.99% of patients experienced local recurrences, 58.44% of patients experienced distal recurrence and 23.38% of patients died. Two-year OS was 82% and

67% for 3-year OS, as regards DFS in the whole study 2-year DFS was 46% and 31% for 3-year DFS. Pattern of metastasis was 25.97%, 24.68%, 7.79% and 7.79% for lung, brain, liver and bone respectively. Other investigators agreed with us where TNBC was reported to have higher rate of recurrences and decreased overall survival.[4,8,27,37,42–44]

Albergaria et al.[10] suggested that there was a significant association of tumor size, histologic grade and lymph node status to high scores of NPI (Nottingham prognostic index) in TNBC. In terms of survival there is a sharp decrease in survival during the first 3–5 years after diagnosis but distant after that time is much less common.[11,23,31,45–48] In a study published by Dent et al.[48] the median time to death was 3.5 years for TNBC compared to 5.7 years for patients with other cancers. In fact, as we can infer by the survival functions, TNBC experienced a severe decrease in their outcomes before 48 months as seen in their overall survival curves.[10,49] The prognosis of women with TNBC is significantly poor, compared to women with other subtypes of breast cancer, and the underlying differences in recurrence and patient mortality rates may be explained in part by different routes of metastatic spread. The current theory points out the suggestion that TNBC metastasizes to axillary bones less frequently than the non-triple negative subset of breast tumors, favoring a hematogenous spread[16,23,45] similar to our results.

Mohamed et al.[19] showed that TNBC is identified tumor subtypes characterized by aggressive behavior and poor prognosis. TN phenotype was associated with high microvessel invasion. The majority of TN cases were of high grade and of large size with biologically heterogeneous group of tumors where expression of basal markers with vascular invasion was 26%, preferable metastatic dissemination sites were visceral like brain, lung and liver and less to the bone (40% lung, 30% brain, 20% liver and 10% bone) in agreement with our results, with 3-year OS with complete pathological remission 94% dropped to 68% in patients with less than complete pathological remission after primary chemotherapy.[11,31,44,47]

In the present study, Androgen receptor-positive expression TNBC tumors which received anti-androgen therapy with tolerable toxicities, showed favorable clinical outcomes in comparison with negatively AR expressed tumors, with 4.76% local spread and 14.28% distal spread. For recurrent event 19.05% and for death event nobody died in AR-positively expressed group of TNBC patients. The median DFS was 45.26 months versus 14.00 months in AR-positive and AR-negative groups respectively, 2-year DFS was 85% versus 28%, 3-year DFS was 78% versus 20% for AR-positive and negative groups, respectively. As regards 2-year OS was 100% versus 74% and 3-year OS was 100% versus 42% for AR positive versus AR-negative groups respectively.

AR-dependent cell cycle progression is a critical regulator of the G1-S transition in prostatic carcinoma, and a similar role may be envisaged in breast cancer.[41] The sensitivity and specificity and likelihood ratio of AR for therapeutic response were higher relatively to other markers, individually and also in combination. AR expression showed inverse correlation with EGFR, and loss of EGFR would lead to suppression of cell growth and consequently would result in better therapeutic response.[41] Because AR ligands can have opposing and paradoxical effects in various breast cancer cell lines expressing AR, applying AR-targeted therapies for breast cancer treatment has been challenging.[28,32,37,49]

Thike et al.[40] suggest that loss of AR in TNBC augurs a worse prognosis and predicts early recurrence in TN and basal like breast cancer. DFS was significant in AR-positive TNBC with trend to improve OS was noted within 5 years of diagnosis, and also, other investigators[28,31,33,50–53] stated a significant correlation between AR expression and DFS and OS, similar to our results in AR expression group which received anti-androgen targeted therapy (Bicalutamide, (casodex) where the prognostic marker give a sufficient level of evidence in this subgroup).[4,28,54–62]

In the present study, the univariate analysis and the multivariate analysis retained the significant prognostic value of AR expression with positive impact on DFS and OS in TNBC patients. This is in agreement with many researchers.[5,28,31,51]

In conclusions, it is apparent that AR inhibition can stabilize disease in TNBC patients. Bicalumide is well tolerated in AR positive patients and could offer an alternative to cytotoxic chemotherapy in those patients. TNBC needs for a paradigm shift in personalized treatment than one size fits all.

Conflict of interest

There was no conflict of interest.

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