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Relationships between androgen receptor expression and clinicopathological parameters in male breast cancer

INTRODUCTION: *Most patients with male breast cancer (MBC) express the androgen receptor (AR). AR expression in these tumors may have both prognostic and predictive values because its presence indicates the potential benefits of an anti-androgen therapeutic approach. The present study aimed to investigate the relationship between AR expression and clinicopathological parameters in MBC.*
MATERIAL AND METHODS: *The data of 35 patients who received a histological diagnosis of MBC at the pathology department of our hospital between January 2007 and December 2017 were retrospectively reviewed. The patients' demographic data, follow-up records and pathology reports were recorded. AR expression status and its relationship with clinicopathological parameters were evaluated. The chi-square test was used to compare independent groups. Univariate survival analyses were performed using the Kaplan–Meier survival procedure. A p value of ≤0.05 was considered statistically significant.*
RESULTS: *There was no significant relationship between AR expression and AJCC stage (p=0.585), pathologic stage (p=0.696), histologic grade (p=0.685), lymph-node status (p=0.685), survival rate (p=1.000), age(p=1.000), lymphovascular invasion (p=0.700), perineural invasion(p=1.000), skin invasion (p=1.000), nipple involvement(p=1.000), DCIS presence(p=1.000), ER positivity(p=1.000), PR positivity (p=0.218), Her2 expression (p=0.523), Ki67 index (p=0.685), Luminal A group (p=0.700), Luminal B group (p=0.691), triple negative group (p=1.000).*
CONCLUSION: *Further investigation of the relation between AR expression and clinicopathological parameters of patients with MBC might yield important information and lead to the development of additional treatment options.*

KEY WORDS: Androgen receptor, AR expression, breast cancer, Male Breast cancer, Prognosis, Receptor status

Introduction

Male breast cancer (MBC) is a relatively rare entity when compared with female breast cancer. Currently, MBC accounts for 1% of all breast cancers, although its incidence is increasing steadily [1-4]. Although MBC appears to behave more aggressively than female breast cancer, the characteristic features of this entity remain unclear. MBC generally affects elderly men and develops more frequently in men with underlying medical conditions that lead to a high estrogen/androgen ratio, such as Klinefelter's syndrome, Cowden syndrome, testicular disorders, obesity, or liver diseases. Similar to female breast cancer, MBC is associated with mutations in BRCA1 and BRCA2. This malignancy is also associated with genetic changes in PALB2, CYP17, CHEK2, RAD51B, and the gene encoding the androgen receptor (AR) [2-6]. Family history, alcohol consumption, absence of physical activity, birth order, and occupational exposure (e.g., exhaust emissions, magnetic fields, and heat) have also been identified as potential risk factors for MBC [2-6].

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No special type- (NST-) invasive carcinoma, formerly invasive ductal carcinoma, is the most common type of MBC [1-7], and steroid hormone receptors have been identified as contributors to this tumor development and progression. Several studies have demonstrated high rates of estrogen receptor (ER) and progesterone receptor (PR) positivity [8,9] as well as AR positivity in MBC [10-12]. AR is expressed in the normal human mammary gland predominantly in cells within the epithelial layers of the mammary gland and ducts [13,14]. Androgens play a dual role in the mammary gland and have been implicated both in normal breast physiology and breast cancer pathologies [15].

The vast majority of MBCs express both ER and AR; therefore, the underlying biology is fully dependent on endocrine stimulation. Consequently, AR expression in these tumors may have both prognostic and predictive values because its presence indicates the potential benefits of an anti-androgen therapeutic approach [16]. Unlike ER, the clinical importance of AR and the underlying molecular mechanism have not been as thoroughly investigated despite the frequent expression of AR reported in breast cancer. Therefore, the significance of AR as an independent predictor of clinical outcomes remains controversial [17-19]. In this context, the present study aimed to investigate the relationship between AR expression and clinicopathological parameters in MBC.

Materials and Methods

Study Subjects

We retrospectively reviewed the data of 35 patients who received a histological diagnosis of MBC at the Pathology Department of Şişli Hamidiye Etfal Training and Research Hospital between January 2007 and December 2017. Patients without follow-up and those receiving neoadjuvant therapy were excluded from the study. The patients' demographic data, hospital records (applied adjuvant treatment, local recurrence, and follow-up examination notes), and pathology reports (histological diagnosis, tumor size, stage lymph node involvement, and hormone receptor status) were recorded. Patients with missing follow-up details were not included in the study. This retrospective study protocol was approved by the institutional review board and ethics committee of the University of Health Science. All surgical procedures applied to patients in this study were performed by the surgical team, and all medical treatments and follow-up examinations were performed at the oncology clinic.

Histopathology and Immunohistochemistry

Tumor tissue samples were fixed in 10% neutral-buffered formalin and embedded in paraffin, and tissue sections were cut from these embedded blocks at a thickness of 3 μm. The most representative tumor areas of these paraffin-embedded tissue samples were identified from hematoxylin and eosin (HE)-stained slides, and these areas were then subjected to immunohistochemical staining. The histological classifications of the tissues according to the World Health Organization criteria [20] and the histologic grades according to the modified Bloom and Richardson score (tubule formation, nuclear grade and mitotic activity index) were recorded.

All immunohistochemical stains were performed with appropriate positive and negative controls. Normal mouse serum was substituted for the primary antibody as a negative control. Human hyperplastic prostate tissue was used as a positive control for AR. Normal breast ducts were used as internal positive controls for ER/PR. A case known to be positive by immunohistochemical staining and in situ hybridization examination was used as a positive control for human epidermal growth factor receptor-2 (HER2). Immunohistochemistry (IHC) was performed using a Bond-Max autostainer (Leica BOND-MAX Fully automated IHC & ISH; Leica Microsystems, Wetzlar, Germany) with the Bond polymer refine detec-

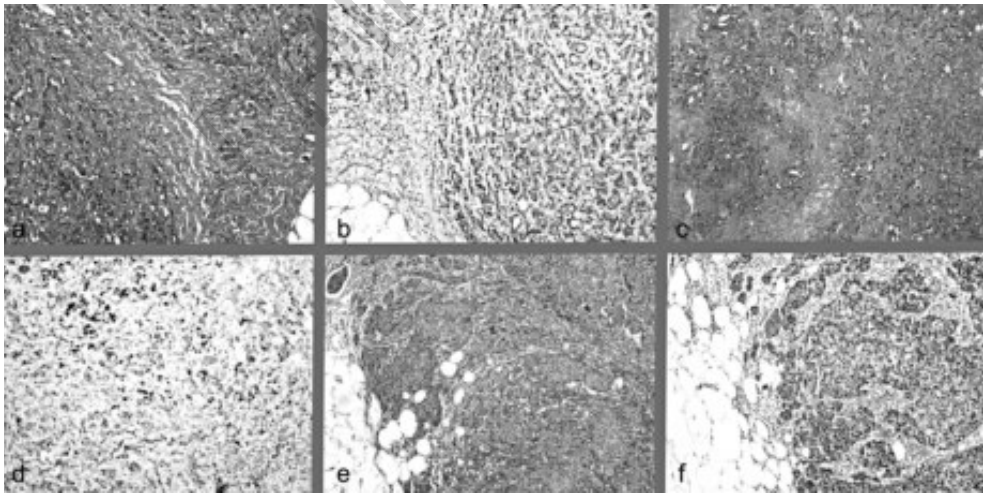


Fig. 1: Tumor tissue observed in routine HE preparations and their AR IHC response. a) Invasive carcinoma, NST, grade II, male breast, HE, ×100 b) Invasive carcinoma, NST, grade II, male breast, AR (–, negative) IHC, ×100 c) Invasive carcinoma, NST, grade II, male breast, HE, ×40 d) Invasive carcinoma, NST, grade II, male breast, AR(++/+++, positive) IHC, ×100 e) Invasive carcinoma, NST, grade III, male breast, HE, ×100 f) Invasive carcinoma, NST, grade III, male breast, AR(+++/+++, positive) IHC, ×100.

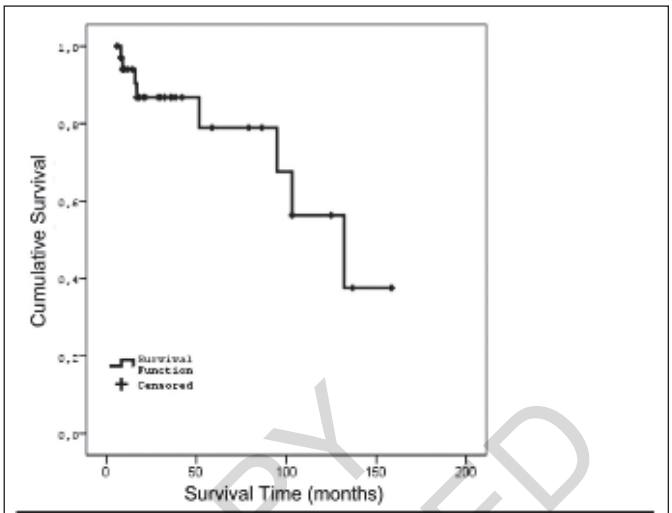
tion kit (Leica Microsystems, DS9800) and the following antibodies:ER Clone 6F11 (Novocastra, Wetzlar, Germany), PR Clone 16 (Novocastra), HER-2 Clone SP3 (Thermo Fisher Scientific, Waltham, MA, USA), Ki67 Clone MIB-I (Dako, Carpinteria, CA, USA) and AR Clone 2F12 (Novocastra).

The HE and IHC slides were reviewed and scored by two experienced observers (Ucak R and Tanık C; breast pathologists) to confirm the diagnoses and characterize the tumors. Biomarker positivity was defined as nuclear ER, PR, AR, Ki67 staining, and HER2 membrane reactivity. ER and PR positivity was defined if ≥1% of cells exhibited nuclear staining, as recommended in the American Society of Clinical Oncology/College of American Pathologists guidelines [21]. In this study, similar to previous studies, AR positivity was defined as nuclear staining in ≥1% of cells [22-24]. In some studies, the cut-off value was 10% [25,26]. Therefore, we also included negative cases with no immune reaction as well as those with weak intensity and <10% of tumor cells. AR expression was compared with other parameters in three groups depending on the severity and percentage of nuclear immunoreactivity: negative (–,+/+++), defined as non-staining or weak nuclear staining in <10% of tumor cells; 2-positive (++/+++), defined as weak-to-moderate nuclear staining in 10%–50% of cells; and 3-positive (+++/+++), defined as intense nuclear staining in >50% of cells (Fig. 1).

The Ki-67 proliferative index was determined from an average of at least 1000 cells in dense areas of the tumor periphery, and the values are expressed as the percentage of positive cells per total cells. The St.Gallen consensus recommends a Ki-67 proliferative index cut-off value of 14%, this value remains subjective and no overall consensus has been reached [27]. Although the latest St Gallen consensus recommends a value of 20% for Ki67, there is controversy due to interlaboratory differences and difficulty in standardization [28]. For this reason, in our study, we determined those who were above the average Ki67 value (which is 23%) as cases with high Ki67 index and included them in the Luminal B group. HER2 immunohistochemistry was assessed according to the ASCO/CAP 2018 protocol and was defined as positive, or 3+, when strong/complete membrane staining was observed in 10% of cells (amplification) [28]. In the negative group, cases without staining or weakly incomplete staining (scores of 0 and 1) were included. The cases that had more than 10% of tumor cells that were weak–moderate and were complete stained (score 2) to the immunohistochemically indeterminate group.

Furthermore, we evaluated them via FISH (Leica Kreatech HER2 FISH analysis) and investigated Her2 amplification.

The molecular subtypes of tumors were determined using immunohistochemical definitions. The following categories were used: i) Luminal A, ER positive, PR ≥ 20%, Ki-67 index < 23%, and HER2 negative; ii) Luminal B, ER positive, PR < 20%, and/or Ki67 index > 23%, and/or HER2 positive); iii) HER2 rich, ER and PR negative (0%), and HER2 positive; and iv) triple negative/basal-like and ER, PR, and HER2 negative [29]. The normal-like group, which was previously described but was a controversial subgroup (29), was ignored. The average value of 23% was considered as the Ki67 value.



		Median (95% confidence interval)
Survival time (months)		132 (76.9–187.1)
Survival rates	1 year	94.0%
	3 years	86.8%
	5 years	78.9%
	10 years	56.4%

Fig. 2: Kaplan–Meier survival curve.

Statistical Analysis

All results were analyzed using SPSS version 15.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as means ± standard deviations (SD) or as minimums and maximums. Categorical variables are presented as absolute values and percentages. The chi-square test was used to compare independent groups. A Monte Carlo simulation was applied when conditions were not met for the chi-squared test. Univariate survival analyses were performed using the Kaplan–Meier survival procedure. A p value of ≤0.05 was considered statistically significant.

Results

Clinicopathological Data

At diagnosis, the 35 patients with MBC had a mean age of 64.0 ± 11.3 years (range: 42–84 years), and 31 were aged ≥50 years. Surgery was the primary treatment

modality, and the following adjuvant therapies were administered: postoperative radiotherapy (n = 24, 68.5%), chemotherapy (n = 26, 74.2%), and hormonotherapy (n = 34, 97.1%). In some patients, multimodal treatment was performed in an adjuvant setting.

Nearly all the patients (n = 34) were diagnosed with invasive carcinoma NST, whereas the remaining one patient was diagnosed with invasive lobular carcinoma. The primary tumor was accompanied by DCIS in 13 (37.1%) patients. The tumor size (pathologic stage) was <2 cm (pT1) in 9 (25.71%) patients, 2–5 cm (pT2) in 23 (65.71%) patients, and >5 cm (pT3) in 3 (8.57%) patients. The tumor stage distribution was as follows: stage 1 in 8 (22.85%) patients; stage 2 in 18 (51.42%) patients, and stage 3 in 9 (25.71%) patients. Overall, 20, 16, 12, and 9 patients presented with lymphovascular invasion, perineural invasion, skin invasion, and nipple involvement, respectively. Lymph node metastasis was observed in 24 (68.57%) patients. One patient each presented with a multicentric tumor or multifocal tumor. The tumor grade distribution was as follows: grade 2 in 24 (68.57%) patients and grade 3 in 11 (31.42%) patients (Table I). The median survival was 132 (76.9-187.1) months. The survivals for 1,3, 5 and 10 years were 94%, 86.8%, 78.9% and 56.4%, respectively. 8 patients (22.85%) had died. 6 of them died from their breast cancer with systemic metastasis, 1 from local recurrence and 1 from non-cancer related reason.

TABLE I - *Demographic characteristics of the patients.*

Age, years [Mean ± SD (Min–Max)]		64.0 ± 11.3 (42–84)
Age [n (%)]	50	4 (11.4)
	>50	31 (88.6)
Type	Ductal	34 (97.1)
	Lobular	1 (2.9)
Tumor diameter, cm [Mean ± SD (Min–Max)]		2.7 ± 1.5 (1-8)
	<2	9 (25.7)
	2–5	23 (65.7)
	>5	3 (8.6)
Tumor stage	I	8 (22.9)
	II	18 (51.4)
	III	9 (25.7)
Multicentricity [n (%)]	Positive	1 (2.9)
	Negative	34 (97.1)
Multifocality [n (%)]	Positive	1 (2.9)
	Negative	34 (97.1)
Histological grade [n (%)]	2	24 (68.6)
	3	11 (31.4)
ER [n (%)]	Positive	34 (97.1)
	Negative	1 (2.9)
PR[n (%)]	Positive	31 (88.6)
	Negative	4 (11.4)
HER2 [n (%)]	Positive	5 (14.3)
	Negative	30 (85.7)
Ki 67 [Mean ± SD (Min–Max)]	23.3 ± 18.3 (3-75)	
Ki67 [n (%)]	<23%	21 (60.0)
	>23%	14 (40.0)
Luminal A [n (%)]	16 (45.7)	
Luminal B [n (%)]	18 (51.4)	
Triple-negative/basal-like [n (%)]	1 (2.9)	
HER2 rich	0 (0)	
Lymph node status [n (%)]	Negative	11 (31.4)
	Positive	24 (68.6)
AR [n (%)]		27 (77.1)
Lymphovascular invasion [n(%)]		20 (57.1)
Perineural invasion [n (%)]		16 (45.7)
Skin invasion [n (%)]		12 (34.3)
Nipple invasion [n (%)]		9 (25.7)
In situ [n (%)]		13 (37.1)
Status of the patient [n (%)]	Alive	27 (77.1)
	Deceased	8 (22.9)

ER: Estrogen receptor, PR: Progesterone receptor, AR: Androgen receptor, SD: Standard deviation.

TABLE II - *Comparison of AR status and clinicopathological parameters.*

		AR				
		Positive		Negative		
		n	%	n	%	P
Age, years	<50	3	11.1	1	12.5	1.000
	>50	24	88.9	7	87.5	
Tumor diameter, cm	<2	6	22.2	3	37.5	0.696
	2–5	18	66.7	5	62.5	
	>5	3	11.1	0	0.0	
AJCC stage	1	6	22.2	2	25.0	0.585
	2	15	55.6	3	37.5	
	3	6	22.2	3	37.5	
Multicentricity		1	3.7	0	0.0	1.000
Multifocality		1	3.7	0	0.0	1.000
Histological grade [n(%)]	2	19	70.4	5	62.5	0.685
	3	8	29.6	3	37.5	
Lymph node status	Positive	19	70.4	5	62.5	0.685
	Negative	8	29.6	3	37.5	
Lymphovascular invasion		16	59.3	4	50.0	0.700
Perineural invasion		12	44.4	4	50.0	1.000
Skin involvement		9	33.3	3	37.5	1.000
Nipple involvement		7	25.9	2	25.0	1.000
In situ		10	37.0	3	37.5	1.000
Status of the patient	Exitus	6	22.2	2	25.0	1.000

AR: Androgen receptor, AJCC: American Joint Committee on Cancer

TABLE III - *Comparison of AR status and immunohistochemical parameters.*

		AR				
		Positive		Negative		
		n	%	n	%	P
ER	Positive	26	96.3	8	100	1.000
	Negative	1	3.7	0	0.0	
PR	Positive	25	96.2	6	75.0	0.218
	Negative	2	7.4	2	25.0	
HER2	Positive	3	7.7	2	14.3	0.523
	Negative	24	92.3	6	85.7	
Ki67 index	<23%	17	37.0	4	50.0	0.685
	>23%	10	63.0	4	50.0	
Luminal A		13	48.1	3	37.5	0.700
Luminal B		13	48.1	5	62.5	0.691
Triple negative/Basal-like		1	3.7	0	0.0	1.000

ER: Estrogen receptor, PR: Progesterone receptor, AR: Androgen receptor.

Immunohistochemical Data

Among the MBC specimens, 25 (71.4%) exhibited moderate AR protein expression in the cell nuclei. No, weak, 2-positive and 3-positive AR staining was observed in 8, 2, 12, and 13 patients, respectively. ER was expressed in 34 (97.1%) patients, while PR expression was observed in 31 (88.6%) patients. There were 5 cases with HER2 immunohistochemical positivity or FISH method amplification. The mean Ki67 score was 23.3% ± 18.3%. In 14 cases, the Ki67 ratio was above this value, whereas in 21 cases, it was below 23%. Based on the immunohistochemical data, 16, 18, and 1 patient were classified as Luminal A, Luminal B, and triple negative, respectively. Next, the clinicopathological parameters were compared between groups of patients stratified by AR expression status. No statistically significant differences in the general characteristics and survival rates were observed between the different AR expression groups (Table II). We next compared the immunohistochemical values and molecular groups with respect to AR status. Similarly, we observed no statistically significant differences between AR-positive and AR-negative patients in terms of ER, PR, and HER2 positivity, the Ki67 index and molecular groups (Table III). We further compared the clinicopathological parameters (survival rates, hormone receptor positivity, HER2 positivity, Ki-67 index and molecular groups) between groups stratified according to AR expression intensity but did not observe any statistically significant inter-group differences (Tables IV, V).

Table IV - *Comparison of AR expression intensity with clinicopathological parameters.*

		AR						
		3-Positive		2-Positive		Negative + 1-positive		
		n	%	n	%	n	%	P
Age, years	<50	0	0.0	3	23.1	1	10.0	0.242
	>50	12	100	10	76.9	9	90.0	
Tumor diameter, cm	<2	2	16.7	4	30.8	3	30.0	0.929
	2–5	9	75.0	8	61.5	6	60.0	
	>5	1	8.3	1	7.7	1	10.0	
AJCC stage	1	3	25.0	3	23.1	2	20.0	0.974
	2	7	58.3	6	46.2	5	50.0	
	3	2	16.7	4	30.8	3	30.0	
Multicentricity		0	0.0	1	7.7	0	0.0	1.000
Multifocality		0	0.0	1	7.7	0	0.0	1.000
Histological grade [n (%)]	2	8	66.7	10	76.9	6	60.0	0.737
	3	4	33.3	3	23.1	4	40.0	
Lymph node st.	Positive	9	75.0	9	69.2	6	60.0	0.819
	Negative	3	25.0	4	30.8	4	40.0	
Lymphovascular invasion		7	58.3	8	61.5	5	50.0	0.853
Perineural invasion		3	25.0	7	53.8	6	60.0	0.198
Skin involvement		5	41.7	3	23.1	4	40.0	0.668
Nipple involvement		4	33.3	2	15.4	3	30.0	0.622
In situ		4	33.3	5	38.5	4	40.0	1.000

AR: Androgen receptor, AJCC: American Joint Committee on Cancer

Table V - *Comparison of AR expression intensity with immunohistochemical parameters.*

		AR						
		3-Positive		2-Positive		Negative + 1-positive		
		n	%	n	%	n	%	P
ER	Positive	12	92.3	12	100	10	100	1.000
	Negative	1	7.7	0	0.0	0	0.0	
PR	Positive	12	92.3	12	100	7	70.0	0.084
	Negative	1	7.7	0	0.0	3	30.0	
HER2	Positive	0	0.0	2	16.7	3	30.0	0.105
	Negative	13	100	10	83.3	7	70.0	
Ki67 index	<22%	7	46.2	8	33.3	6	40.0	0.911
	>22%	6	53.8	4	66.7	4	60.0	
Luminal A		6	46.2	6	50.0	4	40.0	0.895
Luminal B		6	46.2	6	50.0	6	60.0	0.799
Triple-negative		1	7.7	0	0.0	0	0.0	1.000

ER:Estrogen receptor, PR:Progesterone receptor, AR:Androgen receptor

Discussion

MBC is rare, usually diagnosed at an advanced stage, and is often associated with poor prognosis [1-7]. There are few studies with good follow-up periods and a large number of cases. Therefore, standardizing clinical and pathological parameters, hormone receptors (AR, ER, PR), and Her2 as well as Ki67 evaluation becomes difficult [5].

In this study of MBC, our observation that nearly 90% of the patients were older than 50 years was consistent with an earlier finding that this malignancy most commonly arises in older men [5]. One case was invasive lobular carcinoma, whereas all others were invasive carcinoma, NST. These findings correlated with those of previous studies that showed that the vast majority of MBCs (> 80%) were NST followed by lobular carcinoma [2,3,7,30]. However, some studies identified papillary tumors as the second most common type, in contrast to our findings [31].

We note that our study focused on AR expression, which is a common feature of MBC. Despite many studies of AR positivity, its importance in MBC remains unclear. Previous reports have cited AR expression rates of 34%–95% in immunohistochemistry studies of MBC [2,10,11,22,32-34], consistent with the rate of 71.4% detected in our study. We note, however, that we did not observe any significant relationships between AR status and various clinicopathological parameters. Our findings were consistent with an earlier study of a Chinese population, which also found no relationships of AR status with age, tumor size, or lymph node status [24].

Most MBCs are positive for the ER and PR [2,30,31,35,36]. For example, in a large series of 2537 MBC, 90.6% and 81.2% of patients were ER and PR positive, respectively [28]. Our observed ER and PR positivity rates of 97.1% and 88.6 in this study are thus consistent with those in previous reports [9,30,31,36,37-39]. In contrast, HER2 expression is relatively uncommon in MBC [22,23,30]. Only 5 of our patients (14.3%) expressed HER2. In many studies, HER2-enriched cases and triple negative cases are rarely reported or absent altogether [22,23]. In a previous study specific to the Turkish population, the triple negative MBC rate was 5.9% [39]. In our study, only one cases (2.9%) was triple negative, and no cases were HER2-enriched. Our results are thus consistent with the literature.

The molecular subgroup distributions vary widely among reported studies. Some studies have reported Luminal A as the most common subtype, whereas others have reported Luminal B as most common [32,33,40]. Conversely, some studies, have reported high rates of Luminal B disease and lower rates of HER2-enriched disease [22,34]. According to Zhou et al., Luminal A and B are the two major MBC subtypes, and AR is commonly expressed [24]. In our study, Luminal B was the most common subtype, followed by Luminal A and triple negative disease. These differences can be explained by the development of immunohistochemical evaluation and continuous innovations in breast cancer.

In many studies that aimed to contribute toward treatment in male breast cancer, AR expression and clinical and pathological parameters were compared. Pich and colleagues did not observe any correlations among ER, PR, or AR expression with overall survival in patients with MBC [25]. In contrast, Kwiatkowska et al. reported a correlation between AR expression in tumor tissues with shorter survival (74% versus 33% for negative versus positive tumor AR staining) [26]. In this study, BRCA2 mutations and AR expression in tumor tissues have also been proposed as independent negative factors for MBC prognosis [26]. In other words, the role of AR expression as a prognostic factor remains controversial, as some authors reported no association between AR expression and survival, while others reported direct relationships of AR expression with survival and prognostic significance in univariate analyses [1,26,41,42]. In one of these studies, AR-positive patients had significantly lower 5-year overall survival rates and 5-year disease-free survival rates, compared to AR-negative patients, which led the authors to suggest that the former molecular subtype is more aggressive [23]. Some studies have explored the association between AR expression intensity and T-stage, histologic grade, HER2 status, and other sex hormone receptor expression statuses but identified no significant relationship [5,18,23]. Again, the reports of associations between AR expression and clinicopathological parameters in MBC are conflicting. In our study, we conducted separate comparisons of AR expression status and intensity with various clinicopathological parameters but did not identify any statistically significant correlations. Particularly, neither AR expression status nor intensity was correlated with survival, pathologic stage, histological grade, HER2 status, Ki67 index, lymph node metastasis, or other clinicopathological parameters in our study.

Recently, AR status, major molecular classification, and anti-androgen therapy have been identified as potentially important factors in the future management of MBC [5,11]. Some authors suggest a perspective of therapeutic continuity with regard to antiandrogens, especially in the context of AR expression. Such an evaluation would encourage a combined analysis of AR, ER, and PR expressions. Particularly, an AR analysis may lead to the consideration of anti-androgen treatment options in ER-negative patients, as described in a previous study [43,44]. Currently, evaluations of AR expression and options for anti-androgen treatment are available for patients of triple negative breast cancers [45,46]. The observation that AR expression may be present in 87% of MBCs could have important implications for the future study and treatment of this disease [33]. For example, one report provided evidence to suggest that drugs targeting AR and AR-regulated signaling could potentially be used to treat ER-negative breast cancers that overexpress HER2 [47]. In this study, unlike

previous studies, we compared AR expression with some parameters (nipple-skin involvement, multicentricity–multifocality, lymphovascular–perineural invasion, presence of in situ components, and patient age) that we evaluated in breast cancer pathology. However, we did not see any statistically significant difference.

The limitations of the present study were mainly related to its retrospective design and small sample size. The main reason for this was the low incidence of MBC. Furthermore, we had to exclude cases with advanced stage of cancer, short-term survival, and no follow-up from the study. This is already the main problem in MBC studies[5].

In conclusion, we did not identify any significant relationships of AR expression with various clinicopathological parameters in cases of MBC. However, it is possible that a larger-scale investigation of the associations of AR expression with clinicopathological parameters in MBC might yield important information and lead to the development of additional treatment options.

References

1. Anderson WF, Jatoi I, Tse J, Rosenberg PS: *Male breast cancer: A population-based comparison with female breast cancer*. J Clin Oncol, 2010; 28(2):232-39. doi:10.1200/JCO.2009.23.8162

2. Sanguinetti A, Polistena A, D'Ermo G, et al.: *Male breast cancer in the twenty-first century: What's new?* Ann Ital Chir, 2014; 85: 544-50. pii: S0003469X14022143

3. Sperlongano P, Pisaniello D.: *Current management of male breast cancer*. Ann Ital Chir, 2000; 71:2.

4. Privitera A, Ellul E, Giordmaina R, et a: *Androgen receptor and antiandrogen therapy in male breast cancer*. Cancer Lett, 2015; 368(1):20-25. doi:10.1016/j.canlet.2015.07.040

6. Kreiter E, Richardson A, Potter J, Yasui Y: *Breast cancer: Trends in international incidence in men and women*. Br J Cancer, 2014; 110(7):1891-897. doi:10.1038/bjc.2014.66

7. Burga AM, Fadare O, Lininger RA, Tavassoli FA: *Invasive carcinomas of the male breast: A morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases.* Virchows Arch, 2006; 449(5):507-12. doi:10.1007/s00428-006-0305-3

8. Zografos E, Gazouli M, Tsangaris G, Marinos E: *The significance of proteomic biomarkers in male breast cancer*. Cancer Genomics Proteomics, 2016; 13(3):183-90.

9. Nilsson C, Johansson I, Ahlin C, Thorstenson S, Amini RM, Holmqvist M, et al.: *Molecular subtyping of male breast cancer using alternative definitions and its prognostic impact*. Acta Oncol, 2013; 52(1):102-09. doi:10.3109/0284186X.2012.711952

10. Severson TM, Zwart W: *A review of estrogen receptor/androgen receptor genomics in male breast cancer.* Endocr Relat Cancer, 2017; 24(3):R27-R34. doi:10.1530/ERC-16-0225

11. Zhu J, Davis CT, Silberman S, Spector N, Zhang T: *A role for the androgen receptor in the treatment of male breast cancer.* Crit Rev Oncol Hematol, 2016; 98:358-63. doi:10.1016/ j.critrevonc. 2015.11.013

12. Stolnicu S, Moncea D, Dema A, Geambasu S, Moldovan C, Comanescu M, et al.: *Androgen Receptor (AR) Expression in Invasive Male Breast Carcinoma (MBC): An International Multi-Institutional Review of 168 Cases Emphasizing the Potential Use of AR as a Therapeutic Target*. Appl Immunohistochem Mol Morphol. 2017; 25(2):e18-e20. doi:10.1097/PAI.0000000000000376

13. Li S, Han B, Liu G, Li S, Ouellet J, Labrie F, et al.: *Immunocytochemical localization of sex steroid hormone receptors in normal human mammary gland.* J Histochem Cytochem, 2010; 58(6):509-515. doi:10.1369/jhc.2009.954644

14. Yeh S, Hu YC, Wang PH, Xie C, Xu Q, Tsai MY, et al.: *Abnormal mammary gland development and growth retardation in female mice and MCF7 breast cancer cells lacking androgen receptor*. J Exp Med, 2003; 198(12):1899-908. doi:10.1084/jem.20031233

15. Brettes JP, Mathelin C: *Effet dual des androgènes sur la glande mammaire. Dual effects of androgens on mammary gland*. Bull Cancer, 2008; 95(5):495-502. doi:10.1684/bdc.2008.0631

16. Speirs V, Ball G: *Male breast cancer consortium. male versus female breast cancer: A comparative study of 523 matched cases reveals differences behind similarity.* Breast Cancer Res, 2010; 12(Suppl 1):O1. doi:10.1186/bcr2492

17. Lakis S, Kotoula V, Eleftheraki AG, Batistatou A, Bobos M, Koletsa T, et al.: *The androgen receptor as a surrogate marker for molecular apocrine breast cancer* subtyping. Breast, 2014; 23(3):234-43. doi:10.1016/j.breast.2014.02.013

18. Peters KM, Edwards SL, Nair SS, French JD, Bailey PJ, Salkield K, et al.: *Androgen receptor expression predicts breast cancer survival: The role of genetic and epigenetic events.* BMC Cancer, 2012;12:132. Published 2012 Apr 2. doi:10.1186/1471-2407-12-132

19. Kim Y, Jae E, Yoon M: *Influence of androgen receptor expression on the survival outcomes in breast cancer: A meta-analysis.* J Breast Cancer, 2015; 18(2):134-42. doi:10.4048/jbc.2015.18.2.134

20. Lakhani SR, Ellis IO, Schnitt SJ, et al.: *WHO Classification of Tumours of the Bre*ast. 4th ed. France: IARC; 2012.

21. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al.: *American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version*). Arch Pathol Lab Med. ,2010;134(7):e48-e72. doi:10.1043/1543-2165-134.7.e48

22. Sas-Korczynska B, Adamczyk A, Niemiec J, Harazin-Lechowska A, Ambicka A, Jakubowicz J: *Androgen receptor in male breast cancer.* Pol J Pathol, 2015; 66(4):347-52. doi:10.5114/pjp.2015.57065

23. Wenhui Z, Shuo L, Dabei T, Ying P, Zhipeng W, Lei Z, et al.: *Androgen receptor expression in male breast cancer predicts inferior outcome and poor response to tamoxifen treatmen*t. Eur J Endocrinol, 2014; 171(4):527-33. doi:10.1530/EJE-14-0278

24. Zhou R, Yu L, Zhou S, Bi R, Shui R, Yu B, et al.: *Male breast carcinoma: A clinicopathological and immunohistochemical characterization study*. Int J Clin Exp Pathol, 2014; 7(10):6852-861. Published 2014 Sep 15.

25. Pich A, Margaria E, Chiusa L, Candelaresi G, Dal Canton O: *Androgen receptor expression in male breast carcinoma: lack of clinicopathological association*. Br J Cancer, 1999; 79(5-6):959-64. doi:10.1038/sj.bjc.6690153

26. Kwiatkowska E, Teresiak M, Filas V, Karczewska A,

Breborowicz D, Mackiewicz A: *BRCA2 mutations and androgen receptor expression as independent predictors of outcome of male breast cancer patients.* Clin Cancer Res, 2003; 9(12):4452-459.

27. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members: *Strategies for subtypes. Dealing with the diversity of breast cancer: Highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011.* Ann Oncol, 2011; 22(8):1736-747. doi:10.1093/annonc/mdr304

28. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al.: *Human epidermal growth factor receptor 2 testing in breast cancer: american society of clinical oncology/college of american pathologists clinical practice guideline focused update.* Arch Pathol Lab Med, 2018; 142(11):1364-382. doi:10.5858/arpa.2018-0902-SA

29. Tsang JYS, Tse GM: *Molecular Classification of Breast Cancer.* Adv Anat Pathol, 2020; 27(1):27-35. doi:10.1097/PAP.0000000000000232

30. Humphries MP, Sundara Rajan S, Honarpisheh H, Cserni G, Dent J, Fulford L, et al.: *Characterisation of male breast cancer: A descriptive biomarker study from a large patient series.* Sci Rep, 2017; 7:45293. Published 2017 Mar 28. doi:10.1038/srep45293

31. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN: *Breast carcinoma in men: A population-based study.* Cancer. 2004; 101(1):51-57. doi:10.1002/cncr.20312

32. Shaaban AM, Ball GR, Brannan RA, Cserni G, Di Benedetto A, Dent J, et al.: *A comparative biomarker study of 514 matched cases of male and female breast cancer reveals gender-specific biological differences.* Breast Cancer Res Treat, 2012; 133(3):949-58. doi:10.1007/s10549-011-1856-9

33. Wang-Rodriguez J, Cross K, Gallagher S, Djahanban M, Armstrong JM, Wiedner N, et al.: *Male breast carcinoma: Correlation of ER, PR, Ki-67, Her2-Neu, and p53 with treatment and survival, a study of 65 cases.* Mod Pathol, 2002; 15(8):853-61. doi:10.1097/01.MP.0000022251.61944.1D

34. Penault-Llorca F: *Breast Cancer: Essentials for Clinicians. Switzerland (CH): ESMO.* 2017. 12, Prognostic and predictive factors; 64-67.

35. Masci G, Caruso M, Caruso F, Salvini P, Carnaghi C, Giordano L, et al.: *Clinicopathological and immunohistochemical characteristics in male breast cancer: A retrospective case series*. Oncologist, 2015; 20(6):586-92. doi:10.1634/theoncologist.2014-0243

36. Yu XF, Yang HJ, Yu Y, Zou DH, Miao LL: *A Prognostic Analysis of Male Breast Cancer (MBC) Compared with Post-Menopausal Female Breast Cancer (FBC*). PLoS One, 2015; 10(8):e0136670. Published 2015 Aug 27. doi:10.1371/journal.pone.0136670

37. Abreu MH, Afonso N, Abreu PH, Menezes F, Lopes P, Henrique R, et al: *Outcome of non-metastatic male breast cancer: 118 patients*. Med Oncol, 2012; 29(2):554-560. doi:10.1007/s12032-011-9978-9

40. Cardoso F, Bartlett JMS, Slaets L, van Deurzen CHM, van Leeuwen-Stok E, Porter P, et al.: *Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG.* International Male Breast Cancer Program. Ann Oncol, 2018; 29(2):405-17. doi:10.1093/annonc/mdx651

41. Muñoz de Toro MM, Maffini MV, Kass L, Luque EH: *Proliferative activity and steroid hormone receptor status in male breast carcin*oma. J Steroid Biochem Mol Biol, 1998; 67(4):333-39. doi:10.1016/s0960-0760(98)00124-1

42. Song YN, Geng JS, Liu T, Zhong ZB, Liu Y, Xia BS, et al.: *Antiandrogen therapy in metastatic male breast cancer: Results from an updated analysis in an expanded case series*. Breast Cancer Res Treat, 2014; 148(1):73-80. doi:10.1007/s10549-014-3138-9

44. Nahleh Z: *Androgen receptor as a target for the treatment of hormone receptor-negative breast cancer: An unchartered territory*. Future Oncol, 2008; 4(1):15-21. doi:10.2217/14796694.4.1.15

45. Massarweh SA, Choi GL: *Special considerations in the evaluation and management of breast cancer in men*. Curr Probl Cancer, 2016; 40(2-4):163-71. doi:10.1016/j.currproblcancer.2016.09.003

46. Rampurwala M, Wisinski KB, O'Regan R: *Role of the androgen receptor in triple-negative breast cancer*. Clin Adv Hematol Oncol, 2016; 14(3):186-93.

47. Ni M, Chen Y, Lim E, Wimberly H, Bailey ST, Imai Y, et al.: *Targeting androgen receptor in estrogen receptor-negative breast cancer*. Cancer Cell, 2011; 20(1):119-31. doi:10.1016/j.ccr.2011.05.026