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Original Article

Comparison of The Expression of GATA-3 Protein from The Transcription Factor Family and Pathological Prognostic Parameters in Invasive Ductal Carcinomas of The Breast

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ABSTRACT

Background GATA binding protein 3 (GATA-3) is one of the six transcription factor family members and is important for glandular development in the breast. Its expression becomes important in breast cancer. We aimed to compare GATA-3 immunoreactivity and pathological prognostic factors in patients with invasive ductal carcinoma.

Material and Methods Our study was conducted retrospectively with 300 breast invasive ductal carcinoma patients who were operated on in our hospital between May 2013 and June 2014. Patient reports, slides and blocks in the pathology archive were scanned. GATA-3 immunohistochemical (IHC) staining was evaluated according to the nuclear staining, intensity and percentage. The relationship between clinicopathological prognostic parameters and GATA-3 IHC staining results was investigated.

Results A positive staining was observed in 286 (95.3%) cases. According to the GATA-3 staining intensity and percentage, 210 (70%) cases stained strongly and 246 (82%) stained +4, respectively. There was a significant relationship between GATA-3 immunoreactivity with ER, PR, Cerb-B2, Ki-67, mitotic degree, mitotic count and histological grade.

Conclusions There was a correlation between the high expression of GATA-3 and good prognostic markers. Hormone receptors can be evaluated with Cerb-B2 and Ki-67 and used as prognosis determinants in breast cancers. They can be used to identify both primary and secondary breast tumors.

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Introduction

Breast cancers are the most common malignancies among women and constitute approximately 26% of all cancer cases, and 17.6% of these cases result in death.[1,2] The most important cause of mortality in breast cancers is metastatic progression. Metastasis development is associated with various risk factors such as primary tumour size, histological grade, lymph node involvement, tumour type, and biomarkers.[3] It has been reported that the 5-year survival rate in patients with metastatic breast cancer is below 30%.

One of the most important prognostic indicators in breast cancers is changes in GATA-3 (GATA binding protein 3) transcription factor expression. The decrease in GATA-3 expression has been reported to be associated with aggressive tumour development and low patient survival.[2] GATA-3, a member of the GATA transcription factor family, is a gene that has a regulatory role in the differentiation and specialization of many tissues such as mammary glands, skin, inner ear, central nervous system, and epithelial structures of the kidney.[4] In the mammary glands, it gains importance, especially in the differentiation of luminal cells.[5-7] However, while the loss of expression in the GATA-3 gene region is associated with the development of breast cancer, low expression of this gene region was determined to be related to estrogen receptor (ER) and progesterone receptor (PR) negativity. It is thought that overexpression of GATA-3 contributes to abnormal aromatase expression in breast tumours.[8] In the conducted studies, when the cases in which GATA-3 was expressed high and low were compared, the tumours with a low expression profile indicated poor prognosis. Expression of GATA-3 was observed in 97% of patients with ten years or more survival time.[8,9]

Material and Methods

The research was approved by hospital ethical committee (04 February 2015, No: 2015-02/153). In our study, all incisional biopsy, excisional biopsy, lumpectomy and mastectomy specimens diagnosed with invasive ductal carcinoma in our centre between May 2013 and June 2014 were retrospectively analyzed. The microarray study identified three hundred cases and was included in the study.

Our study used hematoxylin-eosin (HE) stained preparations and paraffin blocks of the 300 patients diagnosed with invasive duct carcinoma. The tumoral area was marked on selected HE-stained slides, and a piece with a 5 mm diameter was removed from the corresponding tumoral area on the paraffin block with a manual tissue microarray device. Subsequently, this area was transferred onto recipient paraffin with 20 holes. At the same time, GATA-3 (–) non-breast control tissue (endomyometrium, cervix, liver) was also embedded in these recipient holes to determine the negative control and starting point. Seventeen paraffin blocks were obtained for a total of 300 patient specimens (depending on tissue quality or other technical reasons), and 3 μm sections were taken on adhesive slides, and GATA-3 (mouse monoclonal antibody, clone/L50-823) immunohistochemical (IHC) staining was applied. GATA-3 IHC study slides were examined under a light microscope. Nuclear staining was considered to be significant. Membranous and cytoplasmic stainings were not evaluated. The positive staining was evaluated according to the intensity of staining as negative/weak/moderate/strong and the staining percentage (*Table 1*).

Table 1. Evaluation score according to the percentage of GATA-3 immunoreactivity.

0	Less than 5% tumor cell nuclei
+1	5-25% tumor cell nuclei
+2	26-50% tumor cell nuclei
+3	51-75% tumor cell nuclei
+4	More than 76% tumor cell nuclei

Clinicopathological prognostic parameters such as the results of GATA-3 immunoreactivity and previous studies of ER, PR, Cerb-B2, Ki-67 IHC, patient's age, tumour size, presence of in situ carcinoma accompanying the tumour, presence of lymphovascular invasion (LVI), axillary lymph node involvement, the histological grade of the tumour and mitotic degree were compared.

Statistical Analysis

Data analysis was performed with SPSS for Windows 11.5 package program. The significance of the difference between the groups in terms of means was evaluated with Student's t-test when the number of independent groups was two. The significance of the difference between groups in terms of median values was examined with the Mann-Whitney U test when the number of independent groups was two. In contrast, the Kruskal-Wallis test analysed the difference between more than two groups. If the results of the Kruskal-Wallis test statistics were significant, the situation(s) causing the difference was determined using Conover's non-parametric multiple comparison test. Pearson's Chi-Square and Fisher's exact or Likelihood ratio tests were used for categorical variables. The results were considered statistically significant with a p-value of <0.05.

Results

Our study was carried out on 300 patient samples diagnosed with breast invasive duct carcinoma. Of all our cases, 286 (95.3%) were GATA-3 positive, and 14 (4.7%) were negative. The related data of GATA-3 immunoreactivity, GATA-3 staining degree, and GATA-3 staining percentages of the cases are shown in Table 2 and Figure 1. All-female patients' ages ranged between 22 and 80, and the mean age was 53.7±12.8 years.

ER positivity was found in 78.3% of the cases, and secondly, PR positivity was found in 56%. The rate of patients with both ER and PR positivity was 54.7%. Cerb-B2 was found to be positive in 26% of all cases. When evaluated in histological grading, most patients (61.3%) had a high grade with Grade 3. In most of our cases (67.7%), the tumour size was 2-5 cm, and the T stage was T2. Distant metastasis (bone, lung, liver, and brain) was found in 4%. 55.7% of the cases had TNM result stage 2 (*Table 3*).

When the mean ages of the patients in both the GATA-3 positive and negative groups were examined, they were found to be similar. The relationship between mean age and GATA-3 staining intensity and the percentage was also not statistically significant. All cases that showed ER and PR positivity were correlated with GATA-3

Table 2. Distribution of cases according to GATA-3 immunoreactivity, staining intensity and percentage.

GATA-3 immunoreactivity	
Negative	14 (4.7%)
Positive	286 (95.3%)
GATA-3 staining intensity	
Negative	14 (4.7%)
Weak	25 (8.8%)
Moderate	51 (17.0%)
Strong	210 (70.0%)
GATA-3 staining intensity	
Negative	14 (4.7%)
1+	0 (0%)
2+	15 (5.0%)
3+	25 (8.3%)
4+	246 (82.0%)

Table 3. Demographic distribution and pathological characteristics of the cases.

Variables	n: 300	Variables	n: 300
Age	53.7±12.8	LN+	138 (46.0%)
ER+	235 (78.3%)	LN+ number	3 (1-31)
PR+	168 (56.0%)	T-stage	
Cerb-B2+	78 (26.0%)	1	67 (22.3%)
Ki-67	25 (1-95)	2	203 (67.7%)
Mitotic count	12 (1-81)	3	25 (8.3%)
DCIS+	195 (65.0%)	4	5 (1.7%)
LVI	67 (22.3%)		
Mitotic degree		N-stage	162 (54.0%)
1	97 (32.3%)	1	72 (24.0%)
2	109 (36.3%)	2	38 (12.7%)
3	94 (31.3%)	3	28 (9.3%)
Histological grade		M-stage	
1	18 (6.0%)	M0	286 (95.3%)
2	98 (32.7%)	M1	14 (4.7%)
3	184 (61.3%)	TNM-stage	
Tumour size		1	48 (16.0%)
≤2 cm	71 (23.7%)	2	167 (55.7%)
2-5 cm	203 (67.7%)	3	71 (23.7%)
>5 cm	26 (8.7%)	4	14 (4.7%)

ER: estrogen receptor, PR: progesterone receptor, DCIS: ductal carcinoma in situ, LVI: lymphovascular invasion, LN: lymph node metastasis.

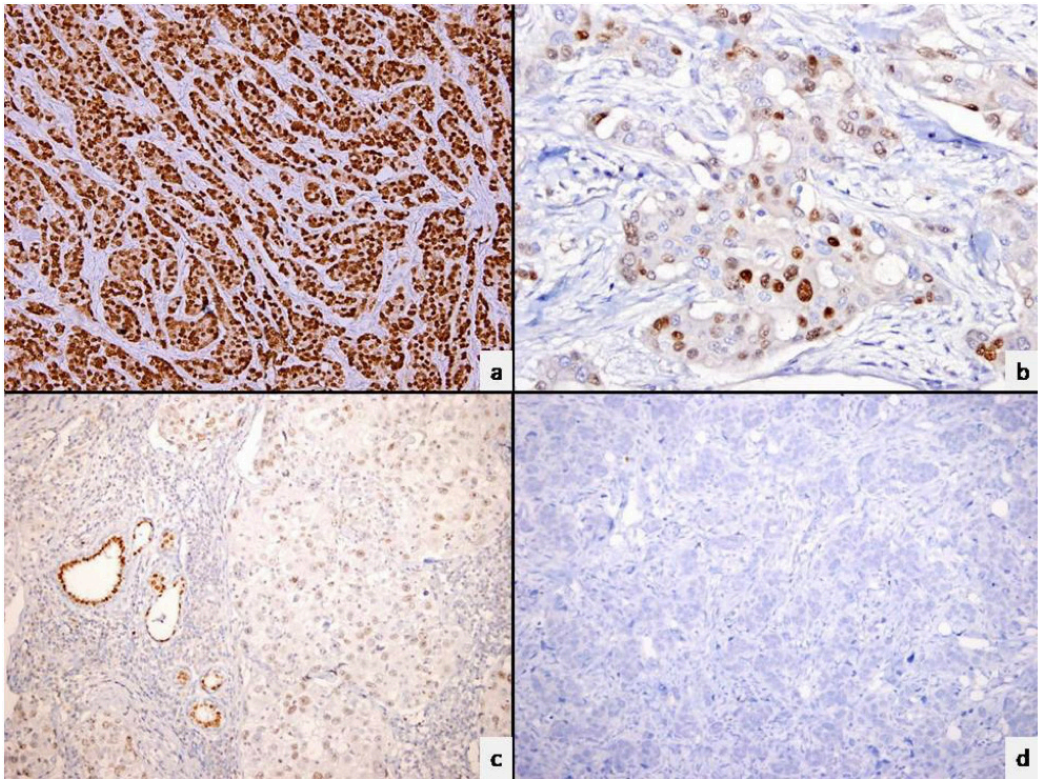

Figure 1. a: GATA-3 immunoreactivity is strong according to staining intensity and +4 according to percentage (GATA-3 IHC, 200x); b: Moderate and +3 GATA-3 immunoreactivity (GATA-3 IHC, 400x); c: The case that GATA-3 immunoreactivity was evaluated as weak and +2 per percentage. Benign glands with strongly stained luminal epithelium are seen on the left side of the figure (GATA-3 IHC, 200x); d: A case with no GATA-3 immunoreactivity (GATA-3 IHC, 200x).

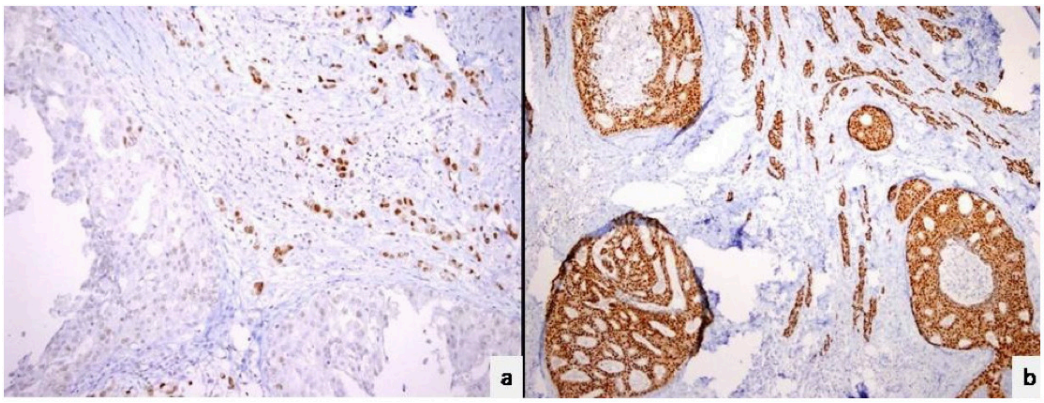

Figure 2. a: In situ carcinoma showing weak GATA-3 immunoreactivity in the sparsely is seen below left part, strong GATA-3 immunoreactivity in the invasive carcinoma area in the upper right part (GATA-3 IHC, 200x); b: Diffuse and strong GATA-3 immunoreactivity in in situ and invasive carcinoma areas (GATA-3 IHC, 20x).

Table 4. Distribution of GATA-3 immunoreactivity of the cases in positive and negative groups.

Variables	Negative (n: 14)	Positive (n: 286)	P-value	Variables	Negative (n: 14)	Positive (n: 286)	P-value
Age	55.5±15.2	53.6±12.7	0.598*	LN	7 (50%)	131 (45.8%)	0.758†
ER+	0 (0%)	235 (82.2%)	<0.001¶	LN– number	3 (1-15)	3 (1-31)	0.613ϕ
PR	0 (0%)	168 (58.7%)	<0.001¶	T stage			0.178ϕ
Cerb-B2+	1 (7.1%)	77 (26.9%)	0.125¶	1	1 (7.15)	66 (23.1%)	
Ki-67	55 (10-95)	25 (1-90)	<0.001¶	2	11 (78.6%)	192 (67.1%)	
Mitotic count	19 (8-81)	12 (1-48)	0.002ϕ	3	2 (14.3%)	23 (8.0%)	
DCIS+	9 (64.3%)	186 (65%)	1.000*	4	0 (0%)	5 (1.7%)	
LVİ	3 (21.4%)	64 (22.4%)	1.000*				
				N-stage			0.859ϕ
Mitotic degree			0.005ϕ	0	7 (50%)	155 54.2%)	
				1	4 (28.6%)	68 (23.8%)	
				2	2 (14.3%)	36 (12.6%)	
				3	1 (7.1%)	27 (9.4%)	
1	1 (7.1%)	96 (33.6%)					
2	4 (28.6%)	105 (36.7%)					
3	9 (64.3%)	85 (29.7%)					
Histological grade			0.003ϕ	M-stage			1.000¶
1	0 (0%)	18 (6.3%)		M0	14 (4.9%)	272 (95.1%)	
2	0 (0%)	98 (34.3%)		M1	0 (0%)	14 (4.9%)	
3	14 (100%)	170 (59.4%)		TNM stage			0.973ϕ
Tumour size			0.118ϕ	1	1 (7.1%)	47 (16.4%)	
<2 cm	1 (7.1%)	70 (24.5%)					
2-5 cm	11 (78.6%)	192 (67.1%)					
>5 cm	2 (14.3%)	24 (8.4%)					

*Student's t test, ¶ Fisher's exact test, † Pearson Chi-Square test, ϕ Mann-Whitney U test.
ER: estrogen receptor, PR: progesterone receptor, DCIS: ductal carcinoma in situ, LVI: lymphovascular invasion, LN: lymph node metastasis.

positivity (p<0.001). Ki-67 positivity was inversely correlated with GATA-3 positivity, which was statistically significantly lower (p<0.001). All the GATA-3 negative groups and 59.4% of the GATA-3 positive group had a histological grade of 3. The mitotic count was lower in the GATA-3 positive group compared to the negative group (p=0.002) (*Table 4*).

Although ductal carcinoma in situ (DCIS) was found in 195 cases, it was observed in only 55 of the IHC slides because the microarray study only consisted of invasive tumoral areas. Weak GATA-3 immunoreactivity was observed in 20% of these cases, and strong GATA-3 immunoreactivity in 80% (*Figure 2*).

Cerb-B2 positive cases were mostly in the weak and moderately stained groups. Ki-67 proliferation index decreased gradually from negative to strong staining (p<0.001). While all of the GATA-3 negative cases had a histological grade of 3, only 55.2% of those with strong and +4 staining had a histological grade of 3. While 64.3% of the GATA-3 negative group had a mitotic degree of 3, those with strong staining with GATA-3 were mostly in groups 1 and 2. The mitotic count decreased gradually from the GATA-3 negative group to the group with strong GATA-3 staining (p<0.001). The mitotic count decreased statistically significantly from the GATA-3 negative group to the 4+ group (mitotic count, 19, 20, 16, 12, respectively). The distribution of GATA-3 immunoreactivity according to the staining percentage and intensity in our cases is shown in Table 5.

GATA-3 staining was observed in all ER+, PR+, and ER+/PR+ groups. Cerb-B2 positive

Table 5. Distribution of the GATA-3 immunoreactivity of the cases in the groups by staining percentage and intensity.

Variables	Negative (n: 14)	Weak (n: 25)	Moderate (n: 51)	Strong (n: 210)	P-value
ER+	0 (0%)	4 (16%)	32 (62.7%)	199 (94.8%)	<0.001*
PR+	0 (0%)	4 (16%)	23 (45.1%)	141 (67.1%)	<0.001*
ER+ and PR+	0 (0%)	3 (12%)	20 (39.2%)	141 (67.1%)	<0.001*
Cerb-B2+	1 (7.1%)	7 (28%)	26 (51%)	44 (21%)	<0.001*
Ki-67	55 (10-95)	40 (10-90)	30 (5-90)	25 (1-90)	<0.001¶
Histological grade					0.002¶
1	0 (0%)	1 (4%)	2 (3.9%)	15 (7.1%)	
2	0 (0%)	6 (24%)	13 (25.5%)	79 (37.6%)	
3	14 (100%)	18 (72%)	36 (70.6%)	116 (55.2%)	
Mitotic count	19 (8-81)	19 (1-45)	14 (3-45)	12 (1-48)	<0.001¶
Mitotic degree					<0.001¶
1	1 (7.1%)	4 (16%)	10 (19.6%)	82 (39%)	
2	4 (28.6%)	7 (28%)	21 (41.2%)	77 (36.7%)	
3	9 (64.3%)	14 (56%)	20 (39.2%)	51 (24.3%)	
Variables	Negative (n: 14)	+2 (n: 15)	+3 (n: 25)	+4 (n: 246)	P-value
ER+	0 (0%)	4 (26.7%)	8 (32%)	223 (90.7%)	<0.001ϕ
PR+	0 (0%)	3 (20%)	6 (24%)	159 (64.6%)	<0.001*
ER+ and PR+	0 (0%)	3 (20%)	5 (20%)	156 (63.4%)	<0.001*
Cerb-B2+	1 (7.1%)	7 (46.7%)	13 (52%)	57 (23.2%)	0.002ϕ
Ki-67	55 (10-95)	60 (20-90)	30 (7-80)	25 (1-90)	<0.001¶
Histological grade					<0.001¶
1	0 (0%)	0 (0%)	1 (4%)	17 (6.9%)	
2	0 (0%)	2 (13.3%)	3 (12%)	93 (37.8%)	
3	14 (100%)	13 (86.7%)	21 (84%)	136 (55.3%)	
Mitotic count	19 (8-81)	20 (10-36)	36 (4-30)	12 (1-48)	<0.001¶
Mitotic degree					<0.001¶
1	1 (7.1%)	0 (0%)	2 (8%)	94 (38.2%)	
2	4 (28.6%)	5 (33.3%)	12 (48%)	88 (35.8%)	
3	9 (64.3%)	10 (66.7%)	11 (44%)	64 (26%)	

* Pearson Chi-Square test, ¶ Kruskal-Wallis test, ϕ Likelihood Ratio test.
ER: estrogen receptor, PR: progesterone receptor.

cases were mostly in the 2+ and 3+ groups. The Ki-67 proliferation index was gradually decreased from negative to +4 staining with respect to the percentage (p<0.001). Similar characteristics were observed when the GATA-3 immunoreactivity was evaluated according to the staining percentage and intensity. There was no significant relationship between age, LVI, metastatic lymph node number, tumour size, T stage, N stage, M stage, TNM final result stage, presence of DCIS, and GATA-3 immunoreactivity.

Discussion

Breast cancer is the most common cancer in women and the second most common cause of cancer-related deaths after lung cancer.[10] The prognosis of the disease is determined according to the patient's age, tumour size, presence of in situ carcinoma accompanying the tumour, LVI, axillary lymph node involvement, and histological grade of the tumour. Also, ER, PR, Cerb-b2, and

Ki-67 IHC studies of pathological specimens affect the treatment and prognosis. Nevertheless, different prognostic data may emerge from patient to patient with the same results. GATA-3, which has come to the fore in recent years as a new immune marker for breast carcinoma, has a high incidence and is one of the six transcription factor family members. It plays an important role in cell death. It is understood that it is a critical determinant of luminal cell differentiation in adult mammary glands.[11] GATA-3 IHC staining was performed on 300 cases in our study, and a positive result was obtained in 95.3% (286/300) of the cases. Wendroth et al.[12] found the rate of GATA-3 immunoreactivity of invasive ductal carcinoma as 92.7% (51/55), Miettinen et al.[13] as 92% (163/178), Clark et al.[14] as 91% (177/186) and Lui et al.[15] as 91% (90/99). These results are similar to our data.

One of the most important risk factors for breast cancer is age. In their study, Voduc et al.[16] found the mean ages as 60 and 58 years in the GATA-3 positive and negative groups, respectively, and reported a linear relationship between GATA-3 and age. However, they stated that the difference was little.[16] In our study, the mean age was 53.7 years, the youngest patient was 22 years old, and the oldest patient was 88 years old. No significant relationship was found with age when GATA-3 was evaluated according to positive/negative staining intensity and staining percentage.

When ER+ breast cancers and ER– breast cancers are compared, it is known that the ER– group is more aggressive and poorly differentiated. In ER+ and ER– breast cancer groups, loss of expression of GATA-3 was observed in the ER– group in many microarray studies and was associated with a poor prognosis.[17,18] In their research, Bong et al.[19] found a rate of 80% of GATA-3 positivity in the ER+ group in breast cancers in Malaysia, similar to our study. They emphasized the significant relationship between ER and GATA-3 positivity.[19] Graham et al.[20] analyzed the ER+ and ER– groups genetically and reported that GATA-3 was overexpressed in the ER+ group. In their study with a series of 305 cases, Mehra et al.[9] evaluated GATA-3 staining in 83 ER+ cases as high and low, and they observed high expression in 38 (45.8%) cases and low expression in 45 (54.2%) cases. They reported that the prognosis of the ER+ and high expression of the GATA-3 group was better, and the recurrence and/or metastasis rate of the ER+ and low expression of the GATA-3 group was high.[9] Fang et al.[21] found a strong relationship between ER and GATA-3 and suggested that GATA-3 can be a clinical marker in response to hormonal therapy. Hosodo et al.[22] reported higher expression of GATA-3 in ER+ premenopausal women compared to postmenopausal women and stated that disease-free survival was longer in these cases. Besides, they said there was a correlation between PR and GATA-3 in premenopausal women.[22] In our study, there were 235 (78.3%) ER+ cases. All of these cases were GATA-3 positive. According to the staining intensity of the cases, 199 (84.6%) were strongly stained, and according to the percentage of staining, 223 (94.9%) were +4. As the GATA-3 staining intensity and the percentage increased, the rate of ER positivity cumulatively increased. In our study, the relationship between ER positivity and GATA-3 expression was found to be significant ($p<0.001$). The results were consistent with the literature.

In our study, the number of ER– cases was 65. No GATA-3 positivity was found in 14 (21.5%) cases. Eleven patients were evaluated as strong, 19 cases as moderate, and 21 as weak staining. Liu et al.[23] found that the expression of GATA-3 was 69% (66/96) in 96 ER– cases and determined that GATA-3 was the most specific marker for the breast. In our study, the expression of GATA-3 was 78.5% (51/65) in the ER– group, which was higher than in Liu et al.'s study.[23] However, unlike our study, their study also included metaplastic carcinomas. Albergaria et al.[24] reported in their study that there was an inverse relationship between GATA-3 and histological grade and GATA-3 and Cerb-B2 in hormone receptor (HR) negative tumours.

PR positivity is important for hormone therapy, even though not as much as ER positivity. In our study, a positive/negative relationship was found between GATA-3 and PR in terms of the percentage and intensity of staining. Like our study, Yoon et al.[8] found a significant association with PR. Besides, they emphasized the relationship between low GATA-3 expression and high tumour grade, large tumour size, and ER negativity.[8]

Histological tumour grade is a prognostic

factor independent of staging. Grade 1 tumours are reported to have better survival.[25] Usary et al.[26] said that high GATA-3 expression correlated with low grade and slow proliferation rate. In our study, 18 (6%) cases were evaluated as histological grade 1, 98 (32.6%) cases as histological grade 2, and 184 (61.6%) cases as histological grade 3. Histological tumour grade was statistically lower in the GATA-3 positive group compared to the GATA-3 negative group (p=0.003). The grade distribution was statistically significant when evaluated according to the intensity and percentage of GATA-3 staining (p=0.002).

The mitotic count has been used alone to predict prognosis for many years. Another parameter used in the histological grading system is the mitotic degree.[27] In our study, the mitotic degree was lower in the GATA-3 positive group than in the negative group (p=0.005). According to the scoring system made according to the mitotic count, 97 (32.3%) cases were evaluated as score 1, 109 (36.4%) cases as score 2, and 94 (31.3%) cases as score 3. It was observed that the average number of mitoses counted at ten high power fields was 12 (min: 1, max: 81). In our study, the mitotic count was lower in the GATA-3 positive group compared to the negative group (p=0.002). The mean number of mitosis was 12 (1-48) in the GATA-3 positive group and 19 (8-81) in the GATA-3 negative group.

Cell proliferation markers (Ki-67) are used to determine the degree of malignancy in breast cancer, a follow-up response to treatment, and determine prognostic features.[28] Usary et al.[26] also found a significant relationship between high GATA-3 expression and low proliferation rate. In our study, the percentage of Ki-67 was lower in the GATA-3 positive group than in the GATA-3 negative group. The mean Ki-67 staining percentage was 25 in the GATA-3 positive group and 55 in the GATA-3 negative group. The relationship between GATA-3 staining percentage and intensity and Ki-67 was statistically significant.

Most studies indicate that HER-2/neu gene amplification and protein overexpression are associated with a poor prognosis, especially in breast cancer.[29] In our study, according to Cerb-B2 (Her2/neu) scoring system, 222 (74%) cases were evaluated as negative and 78 (26%) as positive. There was no significant difference when the GATA-3 positive and negative groups were compared, while a significant difference was observed when the percentage and intensity of staining were compared. Albergaria et al.[24] reported an inverse relationship between GATA-3 and Cerb-b2 in HR-negative tumours.

With the widespread use of cancer screening in recent years, the breast cancer detection rate in the early stages has increased.[30] 55.2% of our cases were TNM stage 2. No significant relationship was found between GATA-3 and positive/negative patients, the percentage and intensity of staining, T stage, lymph node involvement, and distant organ metastasis. In the animal experiment conducted by Yan et al.[31], they investigated GATA-3 in 36 rats with invasive ductal carcinoma. They found the expression of GATA-3 in 21 cases. In the study, the GATA-3 negative group contained 5-6 times more distant metastases than the GATA-3 positive group. In addition, they reported that the disease-free survival time of the GATA-3 positive group was longer.[31] Only 14 (4.7%) of our cases contained distant metastases. This explains that the relationship between GATA-3 and distant metastasis is not statistically significant due to the reduction of distant metastasis with early diagnosis and developing treatment methods. Gonzalez et al.[32] applied GATA-3 IHC to male and female breast cancer cases. Unlike female breast cancers, they did not find the relationship between GATA-3 and ER/PR and distant organ metastasis in male breast cancers statistically significant. Also, in their study, they reported that the GATA-3 immunoreactivity rate was found as 31.6% in male breast cancers and 82.3% in female breast cancers. They did not find a statistically significant relationship between lymph node metastasis and Cerb-B2 in both genders.[32] Mehra et al.[9] reported a significant relationship between low GATA-3 expression and large tumour size, positive lymph node, high grade, ovarian expression of Her-2, and recurrence and metastasis rate. Unlike this study, in our research, we found a significant relationship between GATA-3 and Her-2 when evaluated according to the histological grade and staining percentage. Voduc et al.[16] found an association between GATA-3 and grade 1/2 tumours and tumour size of >5 cm. However, the difference was small. They found no significant relationship with

lymph node metastasis.[16] Hosodo et al.[22] found an inverse relationship between GATA-3 and tumour size and lymph node metastasis in premenopausal women.

LVI is an important step in breast cancer metastasis and is one of the significant causes of mortality and morbidity. LVI detection in the primary tumour is an important marker for metastasis potential.[33] Jacquemier et al.[34] found a relationship between LVI and GATA-3 and reported that it could be used in determining prognosis. In our study, LVI was detected in 20.3% of the cases. However, the relationship with GATA-3 was not significant. This led us to think that more sampling should be done more carefully, especially in high-grade cases with aggressive progression potential. If necessary, IHC should be performed to detect LVI.

There is no publication in the literature investigating the relationship between the presence of in situ carcinoma and GATA-3. However, Asselin-Labat et al.[35] investigated GATA-3 expression in 11 cases with only in situ carcinoma. They reported that GATA-3 positivity was associated with recurrence-free survival in cases with in situ carcinoma.[35] In our study, the in situ component could be evaluated in 55 GATA-3 stained IHC slides. However, no statistically significant correlation was found between GATA-3 and positive/negative staining percentage, intensity, and in situ component.

Mammaglobin and GCDFP-15 positivities are widely used as descriptors in breast cancers. It has been reported that mammaglobin positivity is found in 23-74% of breast cancers, and GCDFP-15 positivity is found in 48-72%.[36] Although the specificity and sensitivity of both IHC markers were reported to be low, GATA-3 immunoreactivity was seen as high as 95.3% in our study. As a result of this study, it was understood that the GATA-3 immune marker is more reliable in identifying breast carcinomas. Having GATA-3 in the immune panel is important and guiding while determining the prognosis in primary breast cancers and investigating the primary metastatic cancers. In their study with 30 male breast cancer cases, Biserni et al.[37] compared GATA-3, NY-BR-1, mammaglobin, and GCDFP-15. They showed that GATA-3 is more sensitive in males breast cancers as well than other immune markers.[37] We could not evaluate this finding because there were no male cases in our study.

Conclusions

There was a correlation between the high expression of GATA-3 and good prognostic markers. In addition, with their high immunoreactivity in breast cancers, HRs, Cerb-B2, and Ki-67 can be evaluated together and used as prognosis determinants. The high incidence of GATA-3 immunoreactivity in most cases suggested that GATA-3 was the most specific and sensitive breast marker ever found. Therefore, it should be used to identify both primary and secondary breast tumours.

Conflict of interest

The authors declare that they have no conflict of interest.

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There are no funding sources to declare.

Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception: LP, OK; Study Design: LP, OK; Supervision: LP, OK; Literature Review: LP; Critical Review: OK; Data Collection and/or Processing: LP; Statistical Analysis and/or Data Interpretation: LP, OK; Manuscript preparing: LP.

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