EXPRESSION OF GATA3 IN INVASIVE DUCTAL CARCINOMA OF THE BREAST: AN IMMUNOHISTOCHEMICAL CLINICOPATHOLOGICAL STUDY

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Abstract

Background

GATA-binding protein 3 (GATA3) is a lineage-specific transcription factor that plays a critical role in mammary epithelial differentiation and has emerged as a valuable immunohistochemical marker in breast carcinoma. However, its association with clinicopathological characteristics and molecular subtypes remains variable across different populations. The present study evaluated GATA3 expression and its relationship with histopathological parameters, hormone receptor status, HER2 expression, and immunohistochemically defined molecular subtypes in invasive ductal carcinoma of the breast.

Methods

This cross-sectional study included 52 histopathologically confirmed cases of invasive ductal carcinoma, no special type (IDC-NST), treated at a tertiary care teaching hospital. Formalin-fixed, paraffin-embedded tissue sections were subjected to immunohistochemistry for GATA3, ER, PR, and HER2. GATA3 expression was assessed using a semi-quantitative immunoreactivity scoring system and categorized as negative, weak, moderate, or strong. Associations between GATA3 expression and clinicopathological variables were analyzed using the Chi-square test or Fisher's exact test, with $p < 0.05$ considered statistically significant.

Results

GATA3 expression was positive in 27 of 52 cases (51.9%). A significant association was observed between GATA3 expression and histological grade ($p = 0.008$), with higher positivity in Grade II than Grade III tumors. GATA3 expression was also significantly associated with ER positivity ($p = 0.032$) and PR positivity ($p = 0.019$). No significant associations were found with patient age ($p = 0.721$), tumor size ($p = 0.300$), lymphovascular invasion ($p = 0.176$), axillary lymph node status ($p = 0.673$), or HER2 expression ($p = 0.278$). Analysis according to molecular subtype demonstrated a significant association between GATA3 expression and immunohistochemically defined molecular classification ($\chi^2=8.393$, df=3, p=0.038). GATA3 positivity was highest among hormone receptor-positive tumors, whereas triple-negative breast cancers exhibited the lowest expression.

Conclusion

GATA3 expression is significantly associated with lower histological grade, hormone receptor positivity, and hormone receptor-positive molecular subtypes in invasive ductal carcinoma of the breast. These findings support the role of GATA3 as a reliable marker of luminal differentiation and emphasize its diagnostic value in the immunohistochemical evaluation and molecular characterization of breast carcinoma.

Keywords: Breast carcinoma; GATA3; Immunohistochemistry; Estrogen receptor; Progesterone receptor; HER2; Molecular subtype.

1. Introduction

Breast carcinoma is the most frequently diagnosed malignancy among women and remains the leading cause of cancer-related mortality worldwide. According to the Global Cancer Statistics 2024, approximately 2.3 million new cases and nearly 670,000 deaths occur annually, accounting for a substantial proportion of the global cancer burden. Despite advances in screening, molecular diagnostics, and targeted therapies, breast cancer continues to pose a major public health challenge, particularly in low- and middle-income countries where delayed diagnosis and limited access to specialized care contribute to poorer outcomes. In India, breast carcinoma has surpassed cervical cancer as the most common malignancy among women, with an age-standardized incidence rate of approximately 25.8 per 100,000 females, and its incidence continues to increase in both urban and rural populations.[1]

Breast cancer is a biologically heterogeneous disease characterized by distinct molecular subtypes with varying clinical behavior, therapeutic response, and prognosis. The routine assessment of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) has transformed the management of breast carcinoma by enabling molecular classification and guiding targeted treatment strategies. Nevertheless, a subset of tumors demonstrates variable immunophenotypic profiles or loss of conventional biomarkers, highlighting the need for additional diagnostic and prognostic markers that improve tumor characterization and aid clinical decision-making.[2]

GATA-binding protein 3 (GATA3) is a member of the zinc-finger transcription factor family encoded by the GATA3 gene located on chromosome 10p14. It is a key regulator of mammary gland morphogenesis and luminal epithelial cell differentiation, maintaining normal mammary epithelial identity through the regulation of genes involved in cellular proliferation, differentiation, adhesion, and hormonal responsiveness. In normal breast tissue, GATA3 is strongly expressed in luminal epithelial cells and plays an essential role in preserving epithelial differentiation.[3-5]

Immunohistochemical expression of GATA3 has emerged as a valuable biomarker in breast pathology because of its high sensitivity for breast epithelial differentiation. Numerous studies have demonstrated GATA3 positivity in the majority of luminal breast carcinomas, where its expression shows a strong association with ER and PR positivity, lower histological grade, and favorable clinical outcome. Conversely, reduced or absent GATA3 expression has been linked to poorly differentiated tumors, triple-negative breast carcinoma, basal-like molecular subtype, increased tumor aggressiveness, and adverse prognosis. Furthermore, GATA3 has gained importance as a diagnostic marker in identifying metastatic breast carcinoma, particularly in poorly differentiated lesions where the primary site is uncertain.[6-9]

Although the diagnostic and prognostic significance of GATA3 has been extensively investigated in Western populations, data from the Indian population remain relatively limited. Ethnic diversity, differences in tumor biology, and variations in molecular characteristics necessitate region-specific evaluation of this biomarker. Therefore, the present study was undertaken to assess the immunohistochemical expression of GATA3 in invasive breast carcinoma and to determine its association with established clinicopathological parameters and hormone receptor status (ER, PR, and HER2) in patients from a tertiary care center in North India. The findings may further clarify the clinical utility of GATA3 as an adjunctive biomarker for breast cancer diagnosis, molecular characterization, and prognostic assessment.

2. Materials And Methods

Study Design and Setting

A laboratory-based cross-sectional observational study was conducted on 52 histopathologically confirmed cases of invasive ductal carcinoma, no special type (IDC-NST). Formalin-fixed, paraffin-embedded tissue specimens and corresponding clinicopathological data retrieved from pathology records were evaluated for GATA3, ER, PR, and HER2 immunohistochemical expression.

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Study Population

The study included 52 consecutive female patients with histopathologically confirmed invasive breast carcinoma who underwent modified radical mastectomy during the study period. Consecutive sampling was employed to minimize selection bias. Demographic and clinicopathological information were obtained from patients medical records and pathology requisition forms.

Inclusion Criteria: Histopathologically confirmed invasive ductal carcinoma of no special type (IDC-NST). Patients who underwent modified radical mastectomy with complete surgical specimens available for histopathological examination. Cases with adequate formalin-fixed paraffin-embedded tissue for immunohistochemical evaluation.

Exclusion Criteria: Patients who received neoadjuvant chemotherapy, radiotherapy, or hormonal therapy before surgery. Breast tumors other than invasive ductal carcinoma, no special type. Recurrent breast carcinoma. Inadequate or poorly preserved tissue samples unsuitable for immunohistochemical analysis. Cases with incomplete clinicopathological or immunohistochemical data.

Histopathological Evaluation

All mastectomy specimens were fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin, and sectioned at 3–5 μm thickness. Hematoxylin and eosin-stained slides were independently examined by experienced pathologists to confirm the diagnosis of invasive ductal carcinoma, no special type (IDC-NST).

Histological grading was performed according to the Nottingham modification of the Bloom–Richardson grading system by assessing tubule formation, nuclear pleomorphism, and mitotic count. The cumulative score classified tumors into Grade I, Grade II, or Grade III. Axillary lymph nodes retrieved from each specimen were examined microscopically for metastatic involvement.

Immunohistochemical Analysis

Immunohistochemistry (IHC) was performed on representative formalin-fixed paraffin-embedded tissue sections using commercially available monoclonal antibodies against estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and GATA3 according to the manufacturers' recommended protocols. Appropriate positive and negative controls were included in each staining run. Normal breast ductal epithelial cells served as the positive control for GATA3 expression.

Sections measuring 3–5 μm were mounted on poly-L-lysine-coated slides, deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval. Endogenous peroxidase activity was blocked before incubation with the primary antibodies, followed by polymer-based secondary detection. Immunoreactivity was visualized using 3,3′-diaminobenzidine (DAB) chromogen, and sections were counterstained with hematoxylin.

Interpretation of Immunohistochemistry

ER and PR expression were interpreted according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Tumors showing nuclear staining in ≥1% of invasive tumor cells were considered positive.

HER2 expression was evaluated according to the ASCO/CAP recommendations based on complete circumferential membranous staining of invasive tumor cells. Cases with equivocal (2+) staining were interpreted according to institutional reporting protocols.

GATA3 immunoreactivity was assessed exclusively as nuclear staining. The extent of staining (percentage of positive tumor nuclei) and staining intensity were recorded. A composite immunoreactivity score was calculated by multiplying the percentage score by the staining intensity score. Based on the final score, GATA3 expression was categorized into four groups:

Group 1: Negative

Group 2: Weak positive

Group 3: Moderate positive

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Group 4: Strong positive

Outcome Measures

The primary outcome was the pattern of GATA3 expression in invasive ductal carcinoma of the breast. Secondary outcomes included its association with histological grade, lymph node metastasis, and expression of ER, PR, and HER2 receptors.

Molecular subtypes were assigned using immunohistochemical expression of ER, PR, and HER2. As Ki-67 proliferation index was not available, ER+/PR+/HER2− tumors were categorized as Luminal A-like for analytical purposes.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Sri Guru Ram Das Institute of Medical Sciences and Research before commencement of the study. Written informed consent was obtained from all participants prior to enrollment. Patient confidentiality was maintained throughout the study, and all procedures were performed in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, whereas categorical variables were expressed as frequencies and percentages. Associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test whenever expected cell frequencies were less than five. A two-tailed p-value <0.05 was considered statistically significant.

3. Results

A total of 52 histopathologically confirmed cases of invasive ductal carcinoma, no special type (IDC-NST) were included in the study. GATA3 immunohistochemistry demonstrated positive expression in 27 (51.9%) cases and negative expression in 25 (48.1%) cases. Based on the immunoreactivity score, GATA3 expression was categorized as negative, weak, moderate, or strong (Table 1 & Figure 1).

Table 1: Immunohistochemical Scoring System for GATA3 Expression in Breast Carcinoma

GATA 3 group	Immunoreactivity score	Interpretation
1	0-1	Negative
2	2-4	Weak positive
3	5-8	Moderate positive
4	9-12	Strong positive

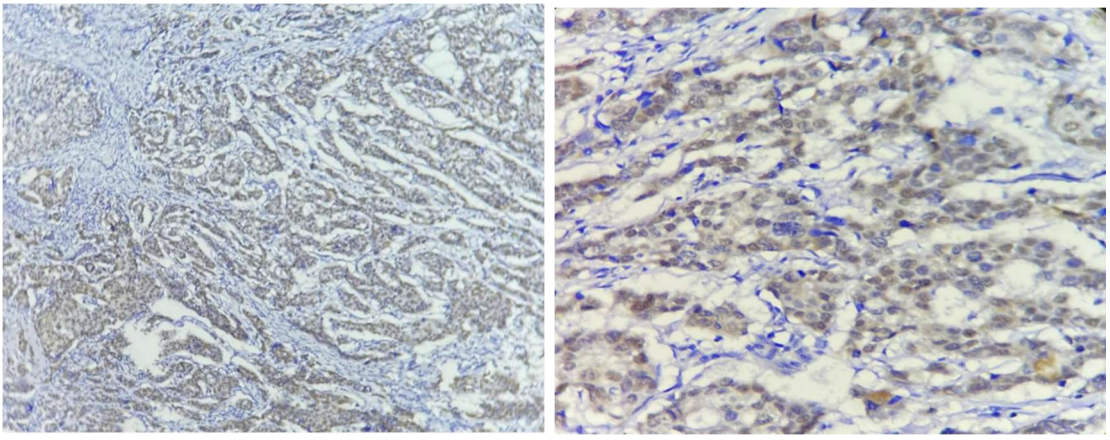

Figure 1. Representative photomicrographs of GATA3 immunohistochemical staining in invasive ductal carcinoma of the breast showing diffuse strong nuclear positivity: 100X and 400X

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magnification.

A statistically significant association was observed between GATA3 expression and histological grade (p = 0.008). GATA3 positivity was more frequent in Grade II tumors (55.6%), whereas Grade III tumors showed a higher proportion of GATA3-negative cases (80.0%).

GATA3 expression was also significantly associated with hormone receptor status. Positive GATA3 expression was observed more frequently in ER-positive tumors (55.6%) than ER-negative tumors (p=0.032). Similarly, PR-positive tumors demonstrated significantly higher GATA3 positivity (76.5%) compared with PR-negative tumors (p=0.019).

No statistically significant association was identified between GATA3 expression and age group (p = 0.721), tumor size (p = 0.300), lymphovascular invasion (p = 0.176), axillary lymph node status (p = 0.673), or HER2 expression (p = 0.278) (Table 2).

Association of GATA3 Expression with Molecular Subtypes

Analysis according to molecular subtype demonstrated a significant association between GATA3 expression and breast cancer phenotype (χ^2=8.393, df=3, p=0.038). GATA3 positivity was most frequently observed in the Luminal A-like subtype (ER+/PR+/HER2−), with 14 of 20 cases (70.0%) showing positive expression, followed by the HER2-enriched subtype (ER−/PR−/HER2+), in which 6 of 10 cases (60.0%) were GATA3 positive. In contrast, the triple-negative (basal-like) subtype (ER−/PR−/HER2−) demonstrated the highest proportion of GATA3-negative tumors (15 of 21 cases; 71.4%). The single case classified as Luminal B (HER2-positive) (ER+/PR+/HER2+) exhibited positive GATA3 expression. Overall, GATA3 expression showed a statistically significant association with the molecular subtype of breast carcinoma (Table 3).

Table 2. Association of GATA3 Expression with Clinicopathological Characteristics and Hormone Receptor Status in Breast Carcinoma (n=52)

Variable	Category	GATA3 Negative n (%) (n=25)	GATA3 Positive n (%) (n=27)	Total n (%) (n=52)	p-value
Histological Grade	Grade II	5 (20.0)	15 (55.6)	20 (38.5)	0.008
	Grade III	20 (80.0)	12 (44.4)	32 (61.5)	
Estrogen Receptor (ER)	Negative	18 (72.0)	12 (44.4)	30 (57.7)	0.032
	Positive	7 (28.0)	15 (55.6)	22 (42.3)	
Progesterone Receptor (PR)	Negative	21 (60.0)	14 (40.0)	35 (67.3)	0.019
	Positive	4 (23.5)	13 (76.5)	17 (32.7)	
Age Group (years)	31–40	4 (16.0)	6 (22.2)	10 (19.2)	0.721
	41–50	5 (20.0)	7 (25.9)	12 (23.1)	
	51–60	5 (20.0)	3 (11.1)	8 (15.4)	
	61–70	7 (28.0)	9 (33.3)	16 (30.8)	
	>70	4 (16.0)	2 (7.4)	6 (11.5)	
Tumor Size	<2 cm	2 (40.0)	3 (60.0)	5 (9.6)	0.300
	2–5 cm	16 (43.2)	21 (56.8)	37 (71.2)	
	>5 cm	7 (70.0)	3 (30.0)	10 (19.2)	
Lymphovascular Invasion	Absent	13 (52.0)	9 (33.3)	22 (42.3)	0.176
	Present	12 (48.0)	18 (66.7)	30 (57.7)	
Axillary Lymph Node Status	N0	12 (54.5)	10 (45.5)	22 (42.3)	0.673
	N1	5 (45.5)	6 (54.5)	11 (21.2)	
	N2	5 (35.7)	9 (64.3)	14 (26.9)	
	N3	3 (60.0)	2 (40.0)	5 (9.6)	
HER2 Status	Negative	20 (52.6)	18 (47.4)	38 (73.1)	0.278

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	Positive	5 (35.7)	9 (64.3)	14 (26.9)	

Abbreviations: GATA3, GATA-binding protein 3; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion. Associations were evaluated using the Chi-square test or Fisher's exact test, as appropriate. A two-tailed $p < 0.05$ was considered statistically significant.

Table 3. Association of GATA3 Expression with Molecular Subtypes of Breast Carcinoma (n = 52)

GATA3 Expression	Luminal B (HER2-positive) (ER+/PR+/HER2+) n (%)	Triple-Negative (Basal-like) (ER−/PR−/HER2−) n (%)	Luminal A-like (ER+/PR+/HER2−) n (%)	HER2-Enriched (ER−/PR−/HER2+) n (%)	Total n (%)
Negative	0 (0.0)	15 (71.4)	6 (30.0)	4 (40.0)	25 (48.1)
Positive	1 (100.0)	6 (28.6)	14 (70.0)	6 (60.0)	27 (51.9)
Total	1 (1.9)	21 (40.4)	20 (38.5)	10 (19.2)	52 (100.0)
$\chi^2 = 8.393$; df = 3; p = 0.038					

Associations between GATA3 expression and molecular subtype were evaluated using the Pearson Chi-square test. A two-tailed $p < 0.05$ was considered statistically significant.

4. Discussion

Breast carcinoma is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide. Despite substantial advances in screening and targeted therapy, the biological heterogeneity of breast cancer continues to present significant diagnostic and therapeutic challenges. In addition to established biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), GATA-binding protein 3 (GATA3) has emerged as an important transcription factor involved in mammary epithelial differentiation, luminal lineage specification, and maintenance of cellular differentiation. Consequently, GATA3 has gained increasing attention as both a diagnostic marker and a potential indicator of tumor biology and prognosis. The present study evaluated the immunohistochemical expression of GATA3 in invasive ductal carcinoma, no special type (IDC-NST), and investigated its association with clinicopathological characteristics, hormone receptor status, and immunohistochemically defined molecular subtypes.

The majority of patients in the present study belonged to the 61–70-year age group, consistent with the increasing incidence of breast carcinoma with advancing age. Sharma et al.[10] similarly reported that most patients presented between 40 and 60 years of age, reflecting the predominance of breast cancer in postmenopausal women. Right-sided breast involvement was more common than left-sided disease, and the upper outer quadrant represented the most frequent tumor location. Comparable findings have been described by Piplani et al.[11] also observed a predominance of right-sided tumors and upper outer quadrant involvement. The higher frequency of tumors in the upper outer quadrant has been attributed to the greater concentration of glandular tissue within this region, making it more susceptible to malignant transformation.

Histological grade remains one of the strongest pathological predictors of tumor aggressiveness and patient outcome. In the present study, Grade III tumors constituted the largest proportion of cases (61.5%), followed by Grade II tumors (38.5%), while Grade I tumors were absent. Similar findings were reported by Piplani et al.[11] whereas Sood et al.[12] observed a predominance of Grade II tumors. Such variations may reflect differences in patient demographics, referral patterns, and disease stage at presentation. A higher proportion of poorly differentiated tumors in the present cohort may indicate delayed clinical presentation, a phenomenon frequently encountered in developing countries.

Hormone receptor analysis demonstrated ER positivity in 42.3%, PR positivity in 32.7%, and HER2

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positivity in 26.9% of tumors. These frequencies are comparable to those reported by Kanwar et al.[13] who documented ER and PR positivity rates of 42% and 32%, respectively. Similarly, HER2 positivity in the present study closely resembles the observations of Shukla et al.[14] and Upadhyay & Prakash,[15] suggesting that the immunophenotypic profile of our cohort is representative of previously published Indian data.

Overall, GATA3 immunoreactivity was detected in 27 of 52 tumors (51.9%). Published studies have reported considerable variability in GATA3 expression, ranging from approximately 40% to over 90%, depending on patient population, antibody clone, scoring criteria, histological subtype, and molecular classification. Suri & Ahluwalia,[16] reported GATA3 positivity in 46.7% of invasive breast carcinomas, whereas Cakir et al.[7] demonstrated positivity in 47% of tumors, with expression being highest among hormone receptor-positive carcinomas. The overall positivity rate observed in the present study therefore lies within the range reported in previous investigations.

No statistically significant association was observed between GATA3 expression and patient age, tumor size, lymphovascular invasion, axillary lymph node status, or HER2 expression. Ismail et al.[17] likewise found no significant relationship between GATA3 expression and patient age. Although GATA3 positivity showed a decreasing trend with increasing tumor size in the present study, the association did not reach statistical significance. In contrast Mehra et al.[5] reported significantly reduced GATA3 expression in larger tumors, suggesting that reduced statistical power related to the relatively small sample size may have limited the detection of similar associations in the present study. Likewise, the absence of significant associations with lymphovascular invasion and nodal metastasis should be interpreted cautiously, as larger cohorts have demonstrated variable results regarding these clinicopathological parameters.

One of the principal findings of the present study was the significant inverse relationship between GATA3 expression and histological grade. GATA3 positivity was significantly more frequent in Grade II tumors than in Grade III tumors ($p=0.008$), indicating preservation of GATA3 expression in relatively well-differentiated carcinomas. These findings corroborate the observations of Mehra et al.[5] and Krings et al.[18] both of whom demonstrated significantly reduced GATA3 expression in poorly differentiated breast carcinomas. From a biological perspective, GATA3 plays a pivotal role in maintaining luminal epithelial differentiation; consequently, progressive loss of GATA3 expression may accompany dedifferentiation, epithelial plasticity, and acquisition of a more aggressive tumor phenotype. The present findings therefore further support GATA3 as a marker of favorable tumor differentiation.

The present study also demonstrated significant associations between GATA3 expression and hormone receptor status. Positive GATA3 expression was significantly more frequent in ER-positive ($p=0.032$) and PR-positive tumors ($p=0.019$), supporting the well-established interaction between GATA3 and luminal differentiation pathways. GATA3 functions as a key transcriptional regulator of mammary epithelial development and participates in a positive regulatory network with ER signaling that promotes maintenance of the luminal phenotype. Similar associations have been reported by other authors,[8,19,20] all demonstrated significantly higher GATA3 expression in hormone receptor-positive breast carcinomas. Collectively, these observations reinforce the biological relationship between GATA3 expression and hormone-responsive breast cancer.

Analysis according to immunohistochemically defined molecular subtypes further revealed a statistically significant association between GATA3 expression and molecular classification ($\chi^2=8.393$, $p=0.038$). The highest GATA3 expression was observed among hormone receptor-positive/HER2-positive (ER+/PR+/HER2+) and hormone receptor-positive/HER2-negative (ER+/PR+/HER2−) tumors, whereas the triple-negative subtype (ER−/PR−/HER2−) exhibited the lowest frequency of GATA3 positivity. These findings are in agreement with those of Shaoxian et al.[21] who reported consistently high GATA3 expression in luminal breast carcinomas, reflecting the close biological relationship between GATA3 and luminal differentiation. Conversely, only 28.6% of triple-negative tumors expressed GATA3 in the

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present study, closely resembling the findings of Byrne et al.[22] who demonstrated GATA3 positivity in approximately one-fifth of triple-negative breast carcinomas. Although GATA3 expression is less frequent in triple-negative breast cancer, its retention in a subset of these tumors remains diagnostically valuable, particularly when distinguishing metastatic breast carcinoma from non-mammary malignancies in conjunction with other breast lineage markers.

The diagnostic utility of GATA3 extends beyond primary breast carcinoma. Owing to its high sensitivity for tumors of mammary origin and its consistent nuclear staining pattern, GATA3 has become an important component of immunohistochemical panels used in the evaluation of metastatic carcinomas of unknown primary site. When interpreted together with ER, PR, mammaglobin, gross cystic disease fluid protein-15 (GCDFP-15), and SOX10, GATA3 substantially improves diagnostic accuracy, particularly in poorly differentiated carcinomas and limited biopsy specimens. Furthermore, preservation of GATA3 expression in many metastatic lesions supports its usefulness even after tumor progression, although reduced expression may occur in high-grade and triple-negative tumors.

Limitations

The present study has certain limitations. The relatively small sample size from a single tertiary care center may have limited the statistical power to detect associations with some clinicopathological variables. Molecular classification was based solely on ER, PR, and HER2 immunohistochemistry because Ki-67 proliferation index and genomic profiling were not available. In addition, survival analysis and long-term follow-up could not be performed, precluding assessment of the prognostic significance of GATA3 expression. Future multicentric studies with larger patient populations, comprehensive molecular characterization, and longitudinal follow-up are warranted to further clarify the prognostic and predictive value of GATA3 in breast carcinoma.

5. Conclusion

The present study demonstrates that GATA3 is a reliable breast-specific immunohistochemical marker expressed in approximately half of invasive ductal carcinomas. Significant associations with lower histological grade, ER positivity, PR positivity, and hormone receptor-positive molecular subtypes indicate that GATA3 is closely linked to luminal differentiation and favorable tumor biology. Although no significant associations were observed with age, tumor size, lymphovascular invasion, nodal status, or HER2 expression, the overall findings support the incorporation of GATA3 into routine immunohistochemical panels for breast carcinoma. Its combined diagnostic and biological relevance makes GATA3 a valuable adjunct for tumor classification, assessment of metastatic lesions, and refinement of clinicopathological evaluation in breast cancer.

Availability of Supporting Data

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that no competing interests.

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