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Original Research Article

GATA 3 Expression in Locally Advanced Breast Cancer and its Association with Prognostic Markers

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ABSTRACT

Background

Breast cancer is the most common cancer in Indian women, with a mortality rate of 12.7 per 100,000 women and an age adjusted incidence of up to 25.8 per 100,000 women. The breast cancer projection for India in 2020 predicts a potential occurrence of up to 1,797,900 cases. (1) Breast cancer incidence peaks in the 40–50 years age group in Indian women. Most of these cancers are HER2 positive and ER/PR negative, or triple negative, with poor prognosis.(2)In developing nations, the majority of breast cancer cases are detected at an advanced stage, and 50% of patients undergoing certain treatments have locally advanced breast cancer (3) The current methods of treatment consist of surgery, radiotherapy, chemotherapy, and hormonal therapy. Hormone treatment is determined by the tumor tissue's hormone receptor (ER, PR) status.

The objective of this study is to establish a relationship between expression of conventional hormone receptors and HER-2/neu status and GATA 3 expression. this study also aims to find associations if any between GATA 3 expression and AJCC 8th edition prognostic staging.

Methods

This prospective study included 30 locally advanced breast cancer patients admitted to KR Hospital Mysuru (Mysore) from September 2022 to March 2024. Age, gender, lump duration, parity, and clinical stage were recorded, BIRADS score, pathological type, stage, grade, ER, PR, and HER2/Neu status were determined. The AJCC 8th edition breast carcinoma staging guidelines were used for clinical, pathological, and prognostic staging. Postoperative histopathological Parafin blocks were stained with GATA 3 on microarray slides. Data was tabulated and coded in Microsoft® Excel before IBM® SPSS ver18.0 statistical analysis.

Results
This study examined 30 clinical/pathological locally advanced breast cancer cases, focusing on GATA 3 expression and its relationship with prognostic factors and hormone receptors. The majority of patients were women (96.7%). They were 46–60 years old and 37% had clinical stage 3B. 86% had invasive ductal carcinoma and 84% were moderately to poorly differentiated. About 50% of patients were HER2 positive, while 80% were ER and PR positive.

GATA 3 expression was measured using immunohistochemistry, resulting in a mean score of 17.4 ± 12.048. ER-positive tumors had significantly higher GATA 3 scores (19.8 ± 11.4) compared to ER-negative tumors (5.2 ± 7.3), with a significant correlation ($p = 0.012$). GATA 3 predicted ER status with 76.7% accuracy and 75% to 99.8% sensitivity. The relationship between GATA 3 positivity and PR status was not significant ($p = 0.141$). A significant correlation ($p=0.011$) showed higher GATA 3 scores for PR-positive. GATA 3 scores were higher in HER2-positive tumors (22.1 ± 10.6) compared to HER2-negative tumors (13.3 ± 12.5), but the correlation was weaker ($p = 0.044$). The GATA 3 scores did not vary with clinical or pathological stages, suggesting they may not be reliable indicators. Further research is needed on these findings.

Conclusion
The study demonstrates that GATA 3 expression is significantly associated with ER and PR status, making it a valuable marker for these receptors. However, GATA 3's role in predicting clinical or pathological stages is less clear, as it does not show strong correlations with these prognostic factors. The high sensitivity of GATA 3 for ER status suggests it could be a useful tool in identifying ER-positive tumors. The findings also highlight the need for further research to explore the potential role of GATA 3 in HER2-positive tumors and its overall utility in breast cancer prognosis

Key words: Breast cancer, GATA 3, ER, PR, HER 2, Prognostic scoring.

INTRODUCTION

Breast cancer is the most prevalent cancer among Indian women, with a mortality rate of 12.7 per 100,000 and an age-adjusted incidence of 25.8 per 100,000. In 2020, India was expected to have 1,797,900 breast cancer cases.[1] The incidence peaks between ages 40 and 50, with HER2-positive, ER/PR-negative, or triple-negative cancers having poor prognoses.[2] In developing countries, many cases are advanced at diagnosis, with 50% of patients having locally advanced cancer[3]

Before 1990, lung cancer was the leading cause of cancer in women in India, followed by breast cancer. However, lifestyle changes have made breast cancer the most common cancer in Indian women.[4]

Estrogen and progesterone, key endocrine regulators, impact mammary gland pathology. Estrogen receptor α (ERα) is essential for ductal elongation during puberty, while progesterone receptor (PR) and ERβ are involved in lobular differentiation. ERα-positive cancers generally have a better prognosis, with over 90% of lobular cancers being ER-positive. The significance of ERβ is less clear.[5]

PR is a heterodimer of A and B subunits. High PR levels are inversely related to tumor size and grade. Positive samples have PR or ER in 1% to 100% of tumor nuclei. The sample is negative for ER or PR if tumor cell nuclei have immunoreactivity of 1% or less.[5,6]

HER2, also referred to as neu or c-erbB-2, is a protooncogene that produces a 185-kDa EGFR family tyrosine kinase glycoprotein. Due to gene amplification, it is overexpressed in approximately 30% of cases of breast cancer. Of these cases, 20–30% are infiltrating breast carcinomas and 60% are ductal carcinomas in situ.[7]

GATA 3

The six transcription factors that make up the GATA family are highly conserved and bind the DNA sequence (A/T)GATA(A/G) through two zinc-finger domains that share the consensus sequence CX2CX17CX2C.[8]

GATA Subtype	Role
GATA-1, GATA-2 and GATA-3	specification of hematopoietic cell fates,
GATA-4, GATA-5 and GATA-6	Specification of endodermal tissues, including heart and lung.
GATA-3	T-cell and Th2 differentiation,
GATA-4	in cardiac and gastric epithelial differentiation,
GATA-6	in lung epithelial differentiation

Table 1: GATA 3 Subtype and Role

Mammary epithelium has high levels of luminal cell-specific GATA 3, which is needed for differentiation. Breast cancer causes luminal cells to lose GATA 3 and become stem cells.[9-10] Microarray research shows GATA 3 predicts breast cancer prognosis reliably and independently. Low GATA-3 expression was associated with higher histologic grade, positive lymph nodes, larger tumor size, ER and PR-negative status, and HER2 overexpression. A meta-analysis of microarray data showed that GATA-3 was a better prognostic factor than ER status.[11-12] GATA 3 positivity is noted in Breast cancer, urothelial cancer, malignancies of skin like squamous cell carcinoma, malignant mesothelioma, Pancreatic adenocarcinoma, endodermal sinus tumor, choriocarcinoma, paragangliomas. [13]

Breast cancer, in situ lesions, and hyperplastic tissue expressed GATA3 significantly more than normal breast tissue. Low GATA3 expression increases tumor grade. Low GATA3 expression predicted disease-related death in all patients, including estrogen receptor-positive and low-grade subgroups. Furthermore, low GATA3 expression was linked to larger tumors and estrogen and progesterone receptor negativity.[14-15] GATA3 levels predict breast cancer patients' outcomes. This has been confirmed in multiple populations. GATA3 is useful for metastatic breast cancer, especially triple-negative and metaplastic carcinomas, which lack mammary-specific markers. Finally, GATA3 staining may distinguish metaplastic carcinoma from malignant phyllodes tumors. [16]

The prognostic staging protocol was developed by the AJCC committee for the eighth edition. This incorporates biomarkers into the TNM staging system and demonstrates how different biomarkers and pathologic stage, may impact survival The biomarkers are: tumor grade, hormone receptor status, and HER2 In certain subgroups, the staging system also incorporates multigene panel status [17]

			ER+, PR+, HER2+	ER+, PR+, HER2-	ER+/PR-, HER2+	ER-/PR+, HER2+	ER-, PR-, HER2+	ER+, PR-, HER2-	ER-, PR+, HER2-	ER-, PR-, HER2-	Anatomic stage
TisN0	M0	G1-3	0	0	0	0	0	0	0	()	0
T1N0		G1	IA	IA	IA	IA	IA	IA	IA	IB	IA
T0N1mi		G2	IA	IA	IA	IA	IA	IA	IA	IB	IA
T1N1mi		G3	IA	IA	IA	IA	IA	IA	IB	IB	IA
T0N1		G1	IB	IB	IIA	IIA	IIA	IIA	IIA	IIA	IIA
T1N1		G2	IB	IB	IIA	IIA	IIA	IIA	IIA	IIB	IIA
T2N0		G3	IB	IIA	IIA	IIA	IIA	IIB	IIB	IIB	IIA
T2N1		G1	IB	IIA	IIA	IIA	IIB	IIB	IIB	IIB	IIB

T3N0		G2	IB	IIA	IIA	IIA	IIB	IIB	IIB	IIIB	IIB
		G3	IB	IIB	IIB	IIB	IIB	IIIA	IIIA	IIIB	IIB
T0N2		G1	IIA	IIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
T1N2		G2	IIA	IIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
T2N2 T3N1											

Table 2: Clinical prognostic Index

			ER+, PR+, HER 2+	ER+, PR+, HER 2-	ER+/PR-, HER 2+	ER-/PR+, HER 2+	ER-, PR-, HER 2+	ER+, PR-, HER 2-	ER-, PR+, HER 2-	ER-, PR-, HER 2-	Anatomic stage
TisN0	M0	G1-3	0	0	0	0	0	0	0	0	0
TIN0		G1	IA	IA	IA	IA	IA	IA	IA	IA	IA
T0N1 mi		G2	IA	IA	IA	IA	IA	IA	IA	IB	IA
TIN1 mi		G3	IA	IA	IA	IA	IA	IA	IA	IB	IA
T0NI		GI	IA	IA	IB	IB	IIA	IB	IB	IIA	IIA
TIN1		G2	IA	IA	IB	IB	IIA	IIA	IIA	IIA	IIA
T2N0		G3	IA	IB	IIA	IIA	IIA	IIA	IIA	IIA	IIA
		G1	IA	IA	IIB	IIB	IIB	IIB	IIB	IIB	IIB
T2N1 T3N0		G2	IB	IB	IIB	IIB	IIB	IIB	IIB	IIB	IIB
		G3	IB	IIA	IIB	IIB	IIB	IIB	IIB	IIIA	IIB
T0N2		G1	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA
TIN2		G2	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
T2N2 T3N1 T3N2		G3	IIA	IIB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIC	IIIA
T4N0		G1	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
T4N1		G2	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIB
T4N2 AnyN3		G3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC	IIIB
Any	M1	Any	IV	IV	IV	IV	IV	IV	IV	IV	IV

Table 3: Pathological prognostic Index

AIM

To Determine the association of GATA 3 and various Prognostic indicators

OBJECTIVE

1. To assess the clinical profile, hormone receptor status, histopathology of breast cancer cases
2. To assess the GATA 3 expression of breast cancer cases
3. To assess the correlation between GATA 3 expression with clinical, radiological parameters
4. To assess the correlation between GATA 3 expression with histopathology, hormone receptor, HER2 status & prognostic staging.

MATERIALS AND METHODS

The Current Prospective study was conducted in the Department of General Surgery, Mysore Medical College And Research Institute, Mysuru from September 2022 to March 2024. 30 Patients with Locally Advanced Breast Cancer were recruited into this study after prior consent.

Inclusion Criteria

Age >18 years, Patient willing to give informed consent, clinically diagnosed case of breast cancer.

Exclusion Criteria

Surgery for breast lesion in the ipsilateral breast, Inflammatory breast cancer, Soft tissue tumors of breast other than carcinoma breast like sarcomas, phylloides, Benign breast disease.

Source of Data

After a thorough clinical history and examination, age, gender, lump duration, parity, and clinical stage were recorded. After routine breast cancer workup and modified radical mastectomy, BIRADS score, pathological type, stage, grade, ER, PR, and HER2/Neu status were determined.

The AJCC 8th edition breast carcinoma staging guidelines were used for clinical, pathological, and prognostic staging. Postoperative histopathological Parafin blocks were stained with GATA 3 on microarray slides. We immunostained tissue microarrays. IHC slides were scored semiquantitatively for expression. Percentage of nuclear positive cells times expression intensity (weak=1, moderate=2, strong=3) gave score. Good scores were over 10.

Statistical Analysis

Data was tabulated and coded in Microsoft® Excel before IBM® SPSS ver18.0 statistical analysis. A descriptive statistic was frequency, percentage, and percentile. We tested significance using Kruskal Wallis, Mann Whitney, and chi square tests, with a p value <0.05 considered significant.

RESULTS

One male patient was among 30 patients, but 96.7% were female. Most patients were between 46 and 60, suggesting locally advanced breast cancer is common in this age group. Most had parity scores of 2, ranging from nulliparous to multiparous. This suggests that many patients have had two pregnancies. A high likelihood of malignancy was indicated by 93.3% of patients having a BIRADS score of ≥ 4. The disease phenotype was more aggressive, as 84% were moderately too poorly differentiated.

In 80% of patients, ER and PR were positive, while nearly half had HER 2. Pathological and Clinical stages were converted to prognostic staging, upgrading/downgrading them. The most common clinical and prognostic stage was 3A. A positive GATA 3 IHC staining score is 10. One third of the tumors in this study scored less than 10, while two thirds scored more than 10.A mean GATA 3 score of 17.4 ± 12.048 was observed.

Figure 1: High GATA 3 expression on Microscopy

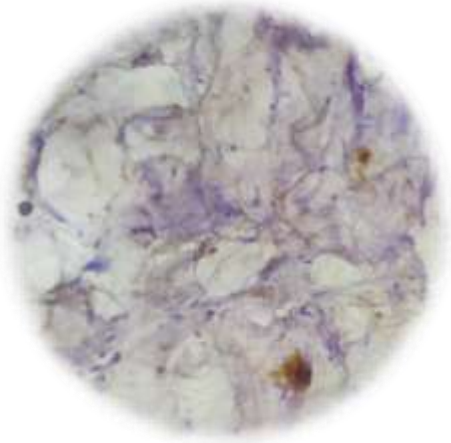
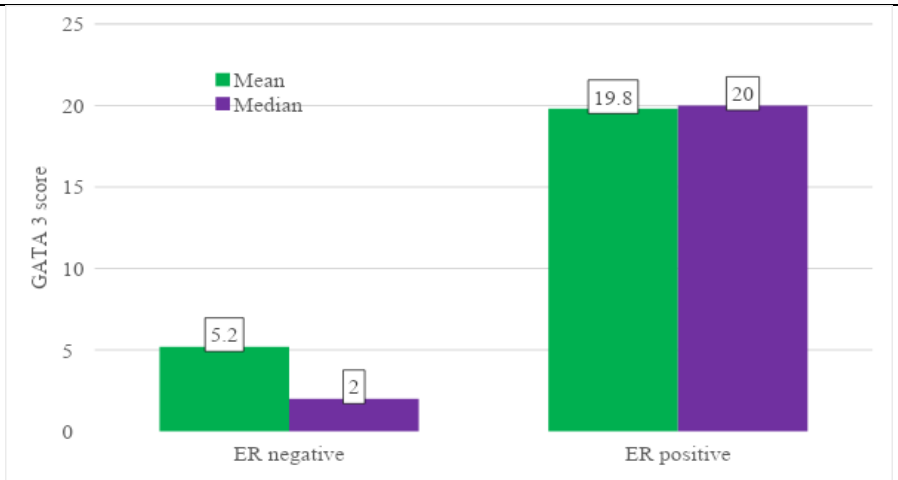


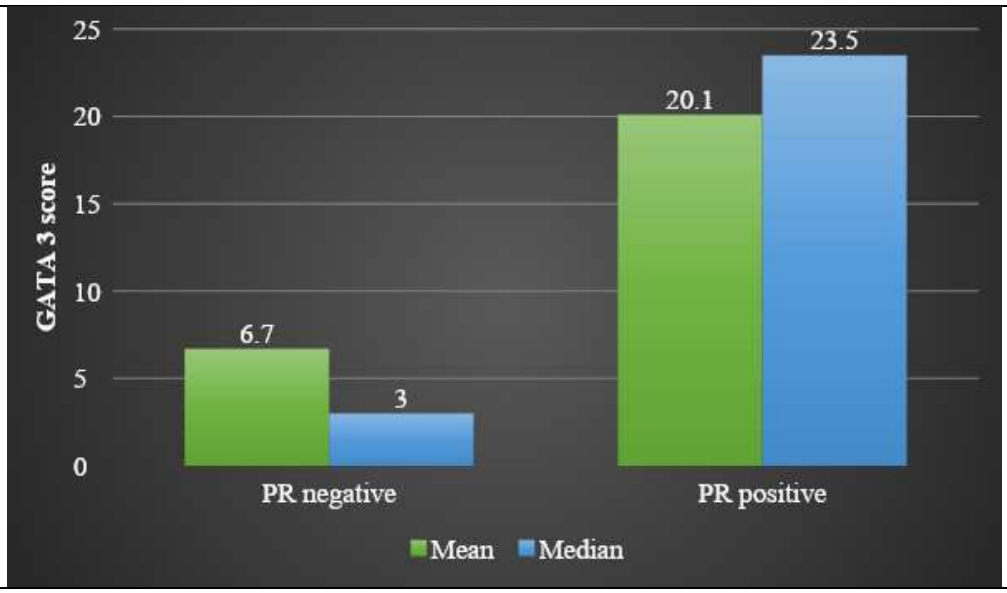
Figure 2: No GATA 3 expression on Microscopy

ER Status and GATA 3 scoring were compared. ER negative tumors had a mean GATA 3 score of 5.2 ± 7.3. ER positive tumors had a higher mean GATA 3 value of 19.8 ± 11.4. ER negative tumors had a median GATA 3 score of 2 versus 30 for ER positive tumors. Mann Whitney test showed 0.012 p value for ER and GATA 3 comparison.



Graph 1: Comparison of GATA 3 score with ER status among study subjects

Tumors that were PR-negative had a mean GATA 3 score of 6.7 ± 7.4. PR-positive tumors had a higher mean GATA 3 value of 20.1 ± 11.6. PR-negative tumors had a median GATA 3 score of 3, while PR-positive tumors had 23.5. The Mann Whitney test showed a 0.011 p value for PR and GATA 3.



Graph-2: Comparison of GATA 3 score with PR status among study subjects

The Mann Whitney test showed a significant difference between HER2 and GATA 3 (p = 0.044). Comparing GATA 3 scores to clinical TNM stage showed a decreasing trend from 22 in stage 1 to 15.9 in stage 4, but a significant p value was not found. 80% of GATA 3-negative tumors were ER-negative. The majority (75%) of GATA 3 positive tumors were ER positive. Chi square test p-value was 0.031, indicating statistical significance. Compared to ER status, GATA 3 is 75% to 99.8% sensitive.The positive predictive value is 65.4%–84.1% and the negative predictive value is 33.9%–96.9%. 76.7% accuracy Predicting ER status.

GATA 3 categories	**ER status**		**Total**
	Negative	**Positive**	
Score ≤10	4	1	5
	80.0%	20.0%	100.0%
Score ≥11	6	19	25
	24.0%	76.0%	100.0%
p-value	0.031		

Table 4: Comparison of GATA 3 categories with ER status among study subjects

Most GATA 3 negative tumors (66.7%) were PR negative, while 75% of GATA 3 positive tumors were PR positive. The Chi square test showed no associations with a p-value of 0.141. GATA 3 negative tumors were equally HER 2 negative/positive. No trends were observed when GATA 3 was compared to clinical and pathologoical prognostic indices, with chi square test p values of 0.118 and 0.828.

DISCUSSION

Mammary epithelium has high levels of luminal cell-specific GATA 3, which is needed for differentiation. Breast cancer causes luminal cells to lose GATA 3 and become stem cells. [8-10, 18] In line with multiple studies, breast tumors with reduced GATA3 expression exhibited a significantly worse prognosis. Patients with GATA3 mutations have a more favourable prognosis than those with high GATA3 expression. A meta-analysis of the microarray data showed that GATA-3 was a more useful prognostic factor than traditional variables like ER status[19-20] GATA3 mutation status is linked to several clinicopathological features and overall survival only in ER-positive breast cancer. [21-23]

30 cases of clinical/pathological locally advanced breast cancer were assessed in this study. The study concentrated on the expression of GATA 3 and its correlation with other prognostic factors, incorporating a diverse array of data points from clinical history, Examination of the patient and Investigations like Radiology, histopathology, and immunohistochemistry (IHC) staining.

HER2 positivity was detected in nearly half of the patients, while ER and PR positivity were observed in 80% of patients.

Low GATA3 expression predicted disease-related death in all patients and estrogen receptor–positive or low-grade subgroups.[14] GATA3 positivity has been investigated previously to be associated to ER positivity. [11,24] Certain studies also suggest GATA-3 positive tumors were more likely to exhibit ER+, PR+, and non-triple-negative phenotypes, as well as grade 1 or 2 tumors.[25] GATA-3 is likely to regulate genes that are essential for the hormone-responsive breast cancer phenotype in conjunction with ER. well as grade 1 or 2 tumors. The expression GATA 3 in this study was evaluated using IHC, with a scoring system that classified a score of 10 or higher as positive. A GATA 3 score of ≤10 was present in approximately one-third of tumors, while two-thirds had a score of >10. The mean GATA 3 score was 17.4 ± 12.048, which indicates a substantial level of GATA 3 expression in breast

In ER Positive Tumor mean GATA 3 scores are higher (19.8 ± 11.4) than those of ER Negative Tumors (5.2 ± 7.3). The difference was statistically significant ($p = 0.012$) by the Mann Whitney test, suggesting a robust correlation between increased GATA 3 expression and ER positivity. GATA 3 demonstrated a high degree of sensitivity (75% to 99.8%) in predicting ER status, with an accuracy of 76.7%. This implies that GATA 3 is an effective indicator of ER status. The chi-square test revealed a significant association ($p = 0.031$), thereby confirming that ER positivity is strongly correlated with GATA 3 positivity.

Progesterone receptor has a role in ERα expression and significantly affects disease prognosis[26,27]. A study conducted on African American women with breast tumors demonstrated a statistically significant association between GATA3 expression and the luminal subtype, ER-positivity, PR-positivity, and lower grade. [27] In this study. The chi-square test did not reveal a significant association ($p = 0.141$) between GATA 3 Postivity and PR status, indicating that GATA 3 positivity cannot predict PR status with significant sensitivity, specificity, accuracy. But PR-positive tumors exhibit significantly higher mean GATA 3 scores (20.1 ± 11.6) than PR-negative tumors (6.7 ± 7.4). The difference was statistically significant ($p = 0.011$), suggesting a correlation between increased GATA 3 expression scores and PR positivity.

HER2 Positive Tumor: Mean GATA 3 scores were higher (22.1 ± 10.6) than those of HER2 Negative Tumors (13.3 ± 12.5). The association is less pronounced than that of ER and PR, even though the difference was significant ($p = 0.044$). The GATA 3 scores did not exhibit a significant trend across various clinical stages ($p = 0.937$). This implies that the clinical stage progression may not be well correlated with GATA 3 scoring. Further studies with a larger sample size might be able to ascertain definitive association between GATA 3 and HER 2 status

There was no discernible trend in the GATA 3 scores across various pathological stages. This suggests that GATA 3 may not be a reliable indicator of the pathological stage. No significant associations were observed with clinical and pathological prognostic indices (p-values of 0.118 and 0.828, respectively), indicating that GATA 3 may not be a reliable predictor for these indices.

LIMITATIONS

A small sample size may limit the generalizability of this study and our ability to make significant associations. Single-Center Study: The study was conducted at Mysore Medical College and Research Institute, which may limit patient diversity and generalizability. Selection bias: Only locally advanced breast cancer patients were studied. The findings may not apply to early-stage or metastatic breast cancer due to this narrow focus. No long-term patient outcomes data is provided in the study. It is difficult to determine how GATA 3 expression affects long-term prognosis or survival without this information.

CONCLUSION

The study demonstrates that GATA 3 status is significantly associated with ER and PR status, making it a valuable marker for these receptors and GATA 3 score is significantly associated with ER status. However, GATA 3's role in predicting clinical or pathological stages is less clear, as it does not show strong correlations with these prognostic factors. The high sensitivity of GATA 3 for ER status suggests it could be a useful tool in identifying ER-positive tumors. The findings also highlight the need for further research to explore the potential role of GATA 3 in HER2-positive tumors and its overall utility in breast cancer prognosis.

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