Advances in Oncopathology Research

ORIGINAL RESEARCH

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Application Value of CK5/6 Combined with GATA-3 in Diagnosis of Breast Cancer

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DOI: https://doi.org/10.62767/aor101.8254

Keywords

Breast cancer

CK5/6

GATA-3

Diagnose

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Received: 20 July 2023

Revised: 17 October 2023

Accepted: 28 October 2023

Published: 11 November 2023

Advances in Oncopathology Research **2025; 1(1): 34-42.**

Abstract

Background: This study explores the application value of CK5/6 combined with GATA-3 in diagnosis of breast cancer. **Methods:** The clinical data of 86 patients with suspected breast cancer admitted to our hospital from August 2022 to May 2023 were retrospectively analyzed. 51 patients with breast cancer confirmed byathological examination were assigned to the breast cancer group, and 35 patients with benign breast lesions were assigned to the benign group. The positive detection rates of CK5/6 and GATA-3 were collected, and the diagnostic results of CK5/6 combined with GATA-3 as well as pathological examination were compared. The diagnostic value of CK5/6 combined with GATA-3 in breast cancer was analyzed by the area under the curve (AUC) for receiver operating characteristic (ROC). **Results:** The positive rates of CK5/6 and GATA-3 in breast cancer group were significantly higher than those in benign group ($p < 0.05$). The co-detection of CK5/6 and GATA-3 were positive in 41 cases, and negative in 45 cases. Among the gold standard (pathological diagnosis) diagnostic results, 51 cases were positive and 35 cases were negative. The concordance index between combined diagnosis and gold standard diagnosis was 0.631. **Conclusion:** CK5/6 combined with GATA-3 may have a good diagnostic value for breast cancer, which can be used as the secondary indicator for the early diagnosis of breast cancer.

1 Introduction

Breast cancer is a tumor disease caused by malignant proliferation of breast glandular epithelial tissues, which is commonly found in women in clinical practice, with the increasing morbidity and mortality in recent years [1-3]. Diagnosing and timely treating breast cancer at an early stage can reduce the risk of distant lymph node metastasis to a certain extent and effectively improve the survival rate of patients, so early detection and diagnosis are pivotal in reducing the mortality and improving the prognosis of breast cancer [4,5]. At present, the gold standard for breast cancer diagnosis is pathological diagnosis, and its pathological examination report often serves as the final reference for the definitive diagnosis of the disease [6,7]. At the same time, increasing studies have shown that the expressions of estrogen receptor (ER) and progesterone receptor (PR) provide a valuable reference to the early diagnosis of breast cancer [8,9]. Therefore, finding more factors that can reflect the changes in the condition of breast cancer is important to improve the accuracy of early breast cancer diagnosis.

Cytokeratin 5/6 (CK5/6) is an important marker for clinical diagnosis of basal-like breast cancer, and its positive expression is a more sensitive and specific indicator of tumor cells [10,11]. Also, the analysis of CK5/6 expression exhibited a great value in clinical practice. The low expression of CK5/6 seems to be closely related to lymphatic invasion in breast cancer [12], while the positive of CK5/6 represents a higher risk of distant metastasis [13,14]. Additionally, CK5/6, combined with other proteins, was also found as the predictive factor for the prognosis of breast cancer patients post neoadjuvant chemotherapy [15,16]. GATA binding protein 3 (GATA-3), as a zinc-binding transcription factor, regulates cell proliferation, differentiation, and development [17]. GATA-3 is an important marker of mammary luminal epithelial cells and widely expressed in breast cancer subtypes [18-20]. As reported, the transcriptional activation of GATA-3 on downstream genes suppresses progression and metastasis of breast cancer [21,22]. Common GATA-3 mutant, especially in ER-positive patients, is implicated in clinicopathological features and expression profile of breast cancer patients [23]. Na et. al suggested GATA-3 as one factor to diagnose of breast cancer metastasis [24].

In this study, the application value of CK5/6 combined with GATA-3 in diagnosis of breast cancer was investigated through comparing the diagnostic results of CK5/6 and GATA-3 co-detection and pathological examination, so as to provide reference and guidance for the clinical diagnosis of breast cancer.

2 Patients and methods

2.1 General data

Clinical data of 86 patients with suspected breast cancer admitted to our hospital from August 2022 to May 2023 were retrospectively analyzed. 51 patients with breast cancer confirmed by pathological examination were assigned to the breast cancer group, and 35 patients with benign breast lesions were assigned to the benign group. There was no statistically significant difference in average age between the two groups of patients ($p > 0.05$), which were shown in Table 1.

Table 1 Comparison of the general data in two groups (mean ± standard deviation).

Groups	Cases	Age (years old)	Average age (years old)
Breast cancer group	51	31-66	47.24 ± 9.40
Benign group	35	32-65	46.89 ± 9.13
t			0.171
p			0.864

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

(1) Patients were diagnosed with breast cancer or benign breast lesions by pathological examination. (2) Patients all underwent a combined diagnosis of CK5/6 and GATA-3. (3) Patients aged 18-70 years. (4) Female patients.

2.2.2 Exclusion criteria

(1) Patients previously developing gynecological diseases. (2) Patients who previously underwent breast surgeries, such as breast augmentation, mastectomy, and minimally invasive surgery. (3) Patients with survival time of not more than 3 months. (4) Patients with other malignant tumors. (5) Patients with dysfunction of heart, liver, and kidneys. (6) Patients with mental disorders and poor treatment compliance. (7) Patients with incomplete clinical data. (8) Pregnant and breastfeeding women.

2.3 Methods

2.3.1 Pathological examination

The color Doppler ultrasound diagnostic system (Shenzhen Talecare TECHNOLOGIES Co., Ltd.) was utilized. Under the guidance of ultrasound image, breast lesion puncture was completed. The patient was in the lateral position, and physical palpation was carried out to clarify the location of the lump. The puncture point was determined with the cooperation of the sonographer. The puncture was performed with a disposable biopsy needle from Bard (USA). A disinfected towel was laid on the puncture site, 2% lidocaine was used for local infiltration anesthesia, and the direction of the puncture needle was at an angle of no more than 45° to the skin, avoiding the important organs and blood vessels. The needle was pushed forward until it entered the internal part of the breast mass, and then it was slightly moved to observe the activity of the mass. The mass moving with the puncture needle suggests the presence of lesions within the mass. The mass was fixed again and ejected, and 3-5 qualified pathological specimens of puncture from each mass were taken (length of glandular tissues $\geqslant$ 8 cm, the way to obtain specimens being clearly showed by color ultrasound). The specimens were put into formaldehyde fixative, dehydrated, embedded, sectioned, and then stained with hematoxylin-eosin (HE). Later, 2 experienced pathologists read the pathological examination results separately at the same time, during which the different opinions were discussed and a unified conclusion was reached. Patients who had no cancer cells according to the pathological results of puncture and those who had no abnormalities of axillary lymph nodes in ultrasonography were subjected to sentinel lymph node biopsy, with methylene blue as the tracer. Pressure dressing was applied 48 h after the end of puncture.

2.3.2 Co-detection of CK5/6 and GATA-3

Immunohistochemical staining of streptavidin-perosidase method was used to detect the positive expression of CK5/6 in above specimens, and the monoclonal antibody (ZA-0683, 1:1000) was obtained from Beijing Zhongshan Golden Bridge Bio-technology Co., Ltd. CK5/6 positivity was manifested by the presence of yellow or brownish yellow particles in the cytoplasm of the tumor, with normal breast tissue as a positive control and adipose tissue as a negative control. Five high magnification fields of view were randomly selected from the specimens ($\times$10). A percentage of positive cells $\geqslant$ 10% indicated that the antibody was positive, and < 10% indicated that the antibody was negative. Immunohistochemistry EnVision method was used to detect the positive expression of GATA-3 in the above specimens, and the GATA-3 antibody (RMA-1067, 1:1000), secondary antibody and the kit were procured from Maxim Biotech Co., Ltd. GATA-3

positivity was manifested as ⩾1% of positive cells under the high magnification view of light microscope.

2.4 Observational indicators

The positive rates of CK5/6 and GATA-3 were collected and compared between the two groups, and combined diagnosis of CK5/6 and GATA-3 was compared with pathological examination in terms of the diagnostic results.

2.5 Statistical methods

SPSS 20.0 was used for statistical analysis, the counting data were represented by examples (%), and comparisons between the two groups were made using X^2 test. Measurement data were expressed as mean ± standard deviation. Independent samples t-test was applied for the comparisons between two groups. The concordance of the results from combined diagnosis and the gold standard diagnosis was calculated. The difference was considered statistically significant at $p < 0.05$.

3 Results

3.1 Pathological results

The results of disease type examination in breast cancer group: 38 cases of invasive ductal carcinoma, 7 cases of papillary carcinoma, 3 cases of squamous cell carcinoma, 2 cases of medullary carcinoma, and 1 case of mucinous carcinoma. The results of staging examination: 25 cases of stage I, 18 cases of stage II, and 8 cases of stage III. The results of disease type examination in benign group: 17 cases of mammary gland fibroma, 12 cases of cystic hyperplasia of breast, and 6 cases of plasma cell mastitis. All results were displayed in Table 2.

3.2 Comparison of CK5/6 and GATA-3 positivity in two groups

The positive rates of CK5/6 and GATA-3 were obviously higher in breast cancer group than in benign group ($p < 0.05$). The results were listed in Table 3.

3.3 Typical pictures

Pathological pictures of CK5/6 and GATA-3 in breast cancer tissues were as follows (Figures 1,2).

Table 2 Pathological results.

Groups	Cases	Disease type (cases)				
		Invasive ductal carcinoma	Papillary carcinoma	Squamous cell carcinoma	Medullary carcinoma	Mucinous carcinoma
Breast cancer group	51	38	7	3	2	1
Benign group	35	-	-	-	-	-

Groups	Cases	Disease type (cases)			Stage (cases)		
		Mammary gland fibroma	Cystic hyperplasia of breast	Plasma cell mastitis	Ⅰ	Ⅱ	Ⅲ
Breast cancer group	51	-	-	-	25	18	8
Benign group	35	17	12	6	-	-	-

Table 3 Comparison of CK5/6 and GATA-3 positivity in two groups [cases (%)].

Groups	Cases	CK5/6	GATA-3
Breast cancer group	51	20 (39.22)	28 (54.09)
Benign group	35	1 (2.86)	2 (5.71)
X^2		14.867	22.108
p		0.000	0.000

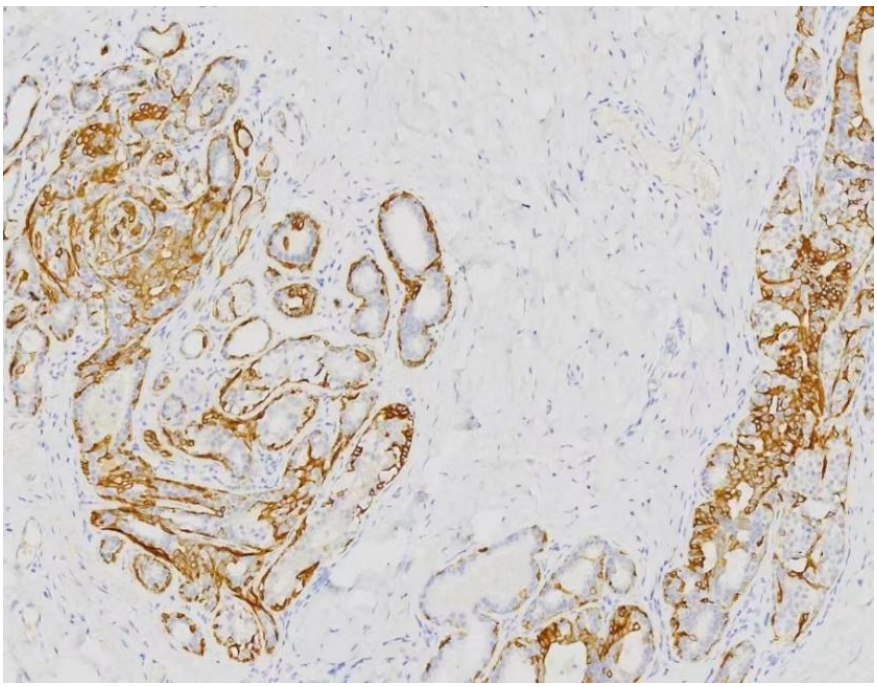

Figure 1 CK5/6 positive expression in breast cancer tissues (×10).

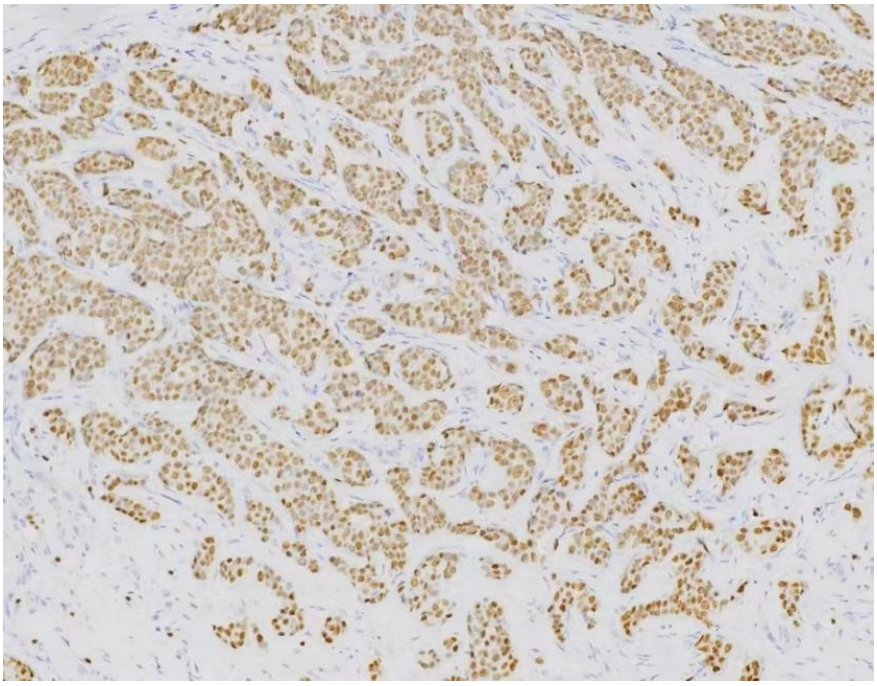

Figure 2 GATA-3 positive expression in breast cancer tissues (×10).

3.4 Comparison of the diagnostic results of CK5/6 and GATA-3 co-detection and pathological examination

The combined diagnosis results were positive in 41 cases, and negative in 45 cases. Among the gold standard diagnostic results, 51 cases were positive and 35 cases were negative. The results were exhibited in Table 4.

3.5 The diagnostic efficiency of CK5/6 combined with GATA-3 for breast cancer

The Kappa value of CK5/6 combined with GATA-3 for breast cancer was 0.631. The results were shown in Table 5.

Table 4 Comparison of the diagnostic results of CK5/6 and GATA-3 co-detection and pathological examination (cases).

Combined diagnosis	Gold standard		Total
	Positive	Negative	
Positive	38	3	41
Negative	13	32	45
Total	51	35	86

Table 5 The diagnostic efficiency of CK5/6 combined with GATA-3 for breast cancer.

Indexes	Sensitivity	Specificity	Kappa value
Combined diagnosis	0.745	0.914	0.631

4 Discussion

In the early stage of breast cancer, glandular epithelial cells will undergo gene mutation and uncontrolled cell proliferation under the action of oncogenic factors, whose histological manifestation is a large number of infantile cancer cells proliferating indefinitely and arranging in a crowded and irregular manner, which will extrude, erode and destroy the surrounding normal tissues, and damage the normal tissue structure of the breasts [8,25]. Therefore, the clinicopathological characteristics of patients can be identified through pathological examination, which is the gold standard for the diagnosis of breast cancer [8,25]. In order to improve the accuracy of early diagnosis of breast cancer and optimize the treatment plan, this study discussed the application value of CK5/6 combined with GATA-3 in the diagnosis of breast cancer. The results showed that CK5/6 combined with GATA-3 might have a better diagnostic value for breast cancer.

In the researches on diagnostic markers for bladder cancer, CK5/6 combined with GATA-3 showed a high auxiliary diagnostic value. The results suggested that this indicator was helpful to identify the patients with basal and lumen tumor characteristics, and could be used as an auxiliary reference indicator for molecular subtypes of chemotherapy patients [26]. In our study, the positive rates of CK5/6 and GATA-3 in breast cancer group were significantly higher than those in benign group. CK5/6, as a member of cytokeratin family and one of the most frequently expressed cytokeratins in basal-like breast cancer, is mainly found in the intermediate filament proteins of the envelope skeleton within the epithelial cells, with extremely high tissue differentiation specificity. It is mainly expressed by the basal cells of the mammary glands, whose positive expression is related to breast cancer proliferation and metastasis. Tumor metastasis and dissemination present organ-specificity, and the higher the specificity, the higher the positive expression of CK5/6 [27,28], consistent with the result of this study, where low positive expression rate of CK5/6 was identified in patients with benign lesions. Additionally, the positive expressions of CK5/6 and epidermal growth factor receptor (EGFR) have mentioned in breast cancer [29]. The correlation between EGFR with tumor cell proliferation, invasion, and metastasis has been proved in many studies [30-32]. Therefore, there is a link between the positive expression of CK5/6 and distant metastasis in breast cancer, which is in line with the results of the present study. Also, high expression of CK5/6 indicates the poor prognosis of breast cancer, which can be used as a potential prognostic marker for breast cancer in combination with other molecular markers, including EGFR [15,33,34]. GATA-3 is a key regulator of breast

morphological changes and ductal epithelial cell differentiation and is mainly expressed in the nucleus and breast cavity surface epithelium, which does not affect the ability of basal stem cells to initiate tumors [35]. GATA-3 has higher frequency and sensitivity in breast cancer patients, and its expression level will change the tumor microenvironment and reduce the tendency of tumor metastasis by reducing the formation of neovascular system [36], in line with the results of this study, where low positive expression rate of GATA-3 was found in patients with benign lesions. In addition to the early diagnostic value, Wang et al. showed that as breast cancer markers, the changes of CK5/6 and GATA-3 are critical for predicting the prognosis and development of breast cancer. Their changes from positive to negative suggest that the prognosis of the disease is improved and the incidence rate is reduced [37,38]. Therefore, CK5/6 combined with GATA-3 has a better diagnostic value for breast cancer.

In addition, in this study, all patients with suspected breast cancer were subjected to pathological examination as well as CK5/6 and GATA-3 co-detection. It was calculated that the concordance between the two diagnostic results was high, indicating that CK5/6 combined with GATA-3 had a good diagnostic value for breast cancer.

Due to the limited review time and number of sample cases in this study, the results are not sufficient to represent the situation of all patients, and the differences in the expressions of CK5/6 and GATA-3 in various subtypes of breast cancer have not been analyzed. The effect of CK5/6 combined with GATA-3 on the diagnosis of breast cancer needs to be further experimented and verified.

In conclusion, CK5/6 combined with GATA-3 may have a good diagnostic value for breast cancer, which can be used as the secondary indicator for the early diagnosis of breast cancer.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, J.C.; Data curation, H.G.; Formal analysis, J.C.; Methodology, H.G.; Writing-original draft, J.C.; Writing-review and editing, H.G. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

Funding

This research received no external funding.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

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