

RESEARCH ARTICLE

Study on the Clinicopathological Characteristics of Adenoid Cystic Carcinoma of the Breast

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Abstract: Adenoid cystic carcinoma of the breast (BACC) is a rare type of invasive ductal breast cancer. The present study aimed to determine the clinicopathological characteristics of BACC in order to determine markers for accurate diagnosis and prognosis. A retrospective analysis of clinicopathological characteristics was conducted in 28 cases of BACC and 30 cases of nonspecific invasive breast cancer which served as the controls. All BACC patients were female, aged from 42 to 63 years. No lymph node metastasis, as well as nerve and lymphovascular invasion, was found in the BACC group. Twenty BACC cases showed classical tubular or cribriform structure, while eight other cases showed tumors of solid variant with obvious atypical cells that were proliferating with frequent mitosis. Epithelial and myoepithelial markers such as cytokeratin 7, CD117, epidermal growth factor receptor, and P63 were expressed in BACC cases. MYB was expressed in 26 BACC cases. Local recurrence happened in two BACC cases who were tested positive for nuclear protein 1 (NUPR1) during a 10 – 84-month follow-up. The expression of MYB and NUPR1 had a significant difference between the two groups ($P < 0.001$). In conclusion, the present study showed that BACC is associated with low invasive characteristics and relatively inert biological behavior on the account of the vast majority of BACC cases which were tested negative for NUPR1. The study also implied that NUPR1 is an indicator of poor prognosis of the tumor. Meanwhile, our study also corroborated the significance of MYB expression for its discriminatory role in BACC diagnosis and differential diagnosis. Therefore, these cases are generally not advocated for chemotherapy, but rather, they are expected to be treated with MYB-targeted therapy.

Keywords: Breast cancer, Adenoid cystic carcinoma, Nuclear protein 1, MYB pathway

Received: January 18, 2022

Accepted: March 16, 2022

Published Online: March 25, 2022

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CITATION

Wang W, Zhao C, Liang Y, *et al.*, 2022, Study on the Clinicopathological Characteristics of Adenoid Cystic Carcinoma of the Breast. *CancerPlus*, 4(1):17–23. DOI: 10.18063/cp.v4i1.256

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1. Introduction

Adenoid cystic carcinoma of the breast (BACC) is a special type of breast cancer. The morphology of BACC is similar to its salivary gland counterpart, but with a low incidence rate, accounting for about 0.1% of all breast cancers^[1]. BACC is cancer with low-grade malignant characteristics. At present, there are no staging and treatment guidelines for BACC. Due to its rarity and atypical morphology, it is very important to explore new diagnostic and prognostic markers for accurate diagnosis and prognosis.

The previous studies have found that BACC has characteristic MYB-NFIB gene fusion

and overexpression of MYB mRNA^[2]. Fluorescence *in situ* hybridization is generally applied for the detection of MYB gene mutations, but this method is time consuming and laborious, whether immunohistochemistry can replace *in situ* hybridization in genetic mutation detection which has become a hot topic for researchers.

Nuclear protein 1 (NUPR1) is a small-molecule nuclear protein that is overexpressed in acute pancreatitis. Later, NUPR1 expression was found to be abnormal in the development of many kinds of tumors^[3], including breast cancer, and was positively related to the malignancy of the tumors. At present, there is no relevant study that investigates the clinicopathological characteristics of BACC which can help pathologist to better understand the disease and design standardized treatment.

This study analyzed the clinicopathological characteristics, including immunohistochemical findings such as NUPR1 and MYB protein expression of BACC patients, to find markers for accurate diagnosis and prognosis.

2. Materials and methods

2.1. Clinical data

From January 2001 to December 2018, there were 28 cases of BACC which accounted for 0.11% of 25450 cases of breast cancer in Affiliated Hospital of Hebei University, Baoding, Hebei, China. Clinical data of these 28 BACC cases were retrospectively analyzed. Thirty cases of nonspecific invasive breast cancer in the same hospital were taken as controls. All BACC patients were female, aged from 42 to 63 years, with the median age at diagnosis of 55 years. All patients presented breast masses. All cases were the first cases and confirmed by three senior pathologists after reviewing the section. Patient consent was obtained where appropriate, according to the protocols approved by the Ethics Committee of the Affiliated Hospital of Hebei University.

2.2. Immunohistochemistry

The resected specimens of the BACC group and the control group were fixed with neutral formalin before embedding in paraffin. The sections which were stained with hematoxylin and eosin were observed under the microscope. Immunostaining was performed using indirect streptavidin-peroxidase system of immunohistochemistry (SP-IHC) method.

Immunohistochemical staining of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), cytokeratin 7 (CK7), CD117, tumor protein p63, CK5/6, and Ki67 was performed. Anti-ER, anti-PR, anti-HER2, anti-CK7, anti-CD117, anti-p63, anti-CK5/6, and anti-Ki67 antibodies were purchased from Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing.

Anti-MYB and anti-NUPR1 antibodies were purchased from the Abcam Company, US, and Kemin Biotechnology Co., Ltd., Shanghai, respectively. The antibodies were categorized as negative control and positive control. Brownish-yellow granules would appear if the resected specimens were tested positive in nuclear staining of ER, PR, P63, and Ki67 and in cytoplasmic staining of CK5/6, CK7, and CD117. The judgment standard of HER2 was based on the guideline stated in the “Breast Cancer HER-2 Testing Guideline”^[4]. The specimens that were positively stained for MYB and NUPR1 would present brownish-yellow granules in the nucleus and cytoplasm.

2.3. Statistical analysis

The statistical analyses in this study were performed using statistical package for social sciences, version 17. $P < 0.05$ was considered statistically significant. The expressions of MYB and NUPR1 in both BACC and control groups were analyzed using Chi-squared test.

3. Results

3.1. Clinicopathological characteristics of BACC

The BACC cases, as described in the present study, were mostly postmenopausal women. All of the BACC patients were treated for painless breast masses. Of 28 cases, three patients had bloody nipple discharge with no other specific symptoms, no previous history of cancer, and a family history of breast cancer. The patients who had low echogenic nodules as detected in ultrasound examination are classified as BI-RADIII-IVB with 10 cases who had breast lump located in the areola area. The masses were located in the left breast in 20 cases and in the right breast in eight cases, 10 of which were located in the areola area. Five patients were diagnosed by coarse needle biopsy before surgical operation, while the rest were diagnosed by intraoperative frozen section examination and immunohistochemistry. There were no statistical differences in age of onset, location and size of lesions, and clinical manifestations between the BACC group and the control group.

3.2. Pathological examination

The gray and pale pink lumps that generally seen were surgically removed. The boundaries between tumor tissue and normal breast tissue were not clear in 20 cases, but clearer in the remaining eight cases. The tumor diameter was 0.5 – 2.8 cm with an average diameter of 1.7 ± 0.5 cm. The tumors were generally hard and no capsule could be seen.

Microscopically, it is similar to adenoid cystic carcinoma of salivary gland. Twenty BACC cases exhibited classic tubular or cribriform structure, and eight cases

were tumors of solid variant showing atypical cells that proliferated under frequent mitosis (**Figure 1**). According to the standard histological classification recommended by Kasami *et al.*,^[5] eight cases were in Grade I, 12 in Grade II, and eight in Grade III. Lymph node metastasis, nerve infiltration, and tumor thrombus in vessels were absent in the BACC cases.

In the control group, the tumor diameter was 0.3 – 5.8 cm, with an average diameter of 2.5 ± 0.7 cm. There was no significant difference in tumor size between the BACC group and control group ($P < 0.05$). No lymph node metastasis was found in the BACC group, and the proportion of lymph node metastasis in the control group was 33.3%.

3.3. Immunohistochemical characteristics

Tumor cells in the BACC group expressed epithelial (CK7 and CD117) and myoepithelial (P63 and CK5/6) markers. Twenty-six cases were identified as triple-negative breast cancer and the remaining two cases were luminal A breast cancer (locally positive for ER, **Figure 2**). The tumors with classic tubular or sieve-like structures (**Figure 3**) had a Ki67 index of 3 – 20%, and the Ki67 index of solid variants was 20 – 30%.

In the control group, the tumor cells expressed CK7 only, and none of them expressed myoepithelial markers and CD117. There were 10 cases of luminal A breast cancer, five cases of luminal B breast cancer, six cases of HER2-positive breast cancer, and nine cases of triple-negative breast cancer. In addition, the Ki67 index of the control group was relatively high.

3.4. Expressions of MYB and NUPR1

The analysis of MYB and NUPR1 expressions in both BACC and control groups are shown in **Table 1**. In the BACC group, 26 cases (92.9%) exhibited positive diffuse nuclear expression of MYB (**Figure 4**), while only two cases exhibited positive expression of NUPR1 (7.1%). In the control group, NUPR1 was highly expressed in 16 cases (53.3%), but no MYB expression was detected. The number of cases which were tested positive for MYB and NUPR1 between control and BACC groups was significantly different ($P < 0.001$), as shown in **Table 1**.

3.5. Treatment and follow-up

Fifteen BACC cases underwent breast-conserving surgery and sentinel node biopsy. Furthermore, five cases underwent a modified radical mastectomy, while eight cases underwent mastectomy and sentinel node biopsy. After the surgical treatment, the surgical margins were found to be negative. No lymph node metastasis was found in all cases. Two BACC cases which were ER-positive were treated with tribenzylamine, and fifteen

patients who underwent breast-conserving surgery were also treated with postoperative radiotherapy. During the follow-up period of 10 – 84 months, all the BACC patients were alive, and only two cases which were tested positive for NUPR1 had local recurrence, but no distant metastasis was found.

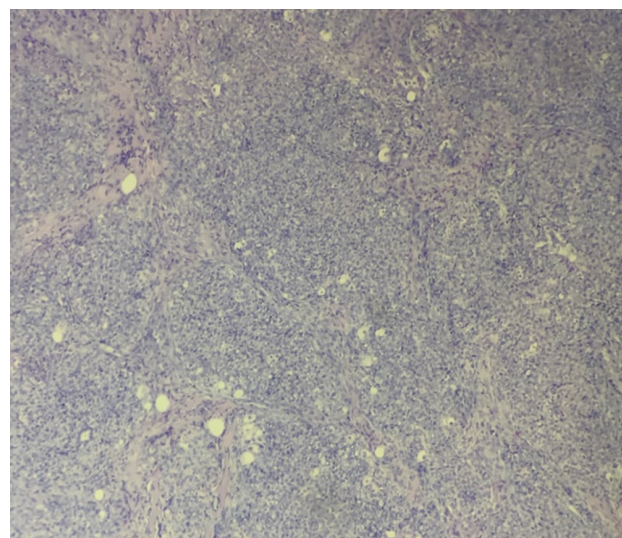


Figure 1. Solid variant of adenoid cystic carcinoma of the breast showing atypical cells that proliferated with accelerated mitosis. The section was stained using hematoxylin and eosin and the image was pictured at $\times 100$.

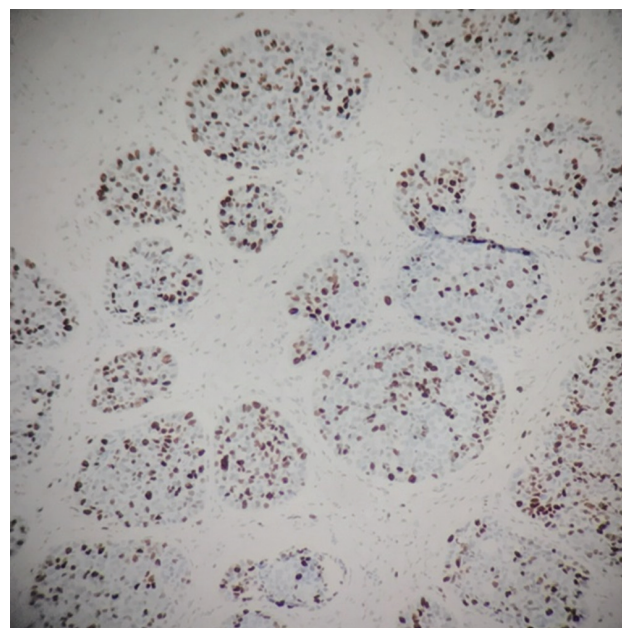


Figure 2. Positive expression of estrogen receptor (ER) in adenoid cystic carcinoma of the breast. The ER was immunostained using streptavidin-alkaline phosphatase labeling system of indirect immunohistochemistry (SP-IHC) method. The image was pictured at $\times 400$.

4. Discussion

In the World Health Organization classification of tumors of the breast (2012), about 75% of invasive breast cancer are not of specific types, and the rest are associated with specific clinical, pathological, and genetic changes. BACC is defined as low-grade tumor with a histologic pattern that resembles that of primary adenoid cystic carcinoma of the salivary gland. Adenoid cystic carcinoma is a common malignant tumor of salivary glands, and BACC is a rare and specific type of cancer with an incidence of 0.1%^[1]. Unlike triple-negative breast cancer, BACC has a very good prognosis. Due to the low incidence and the fact that studies on BACC are scanty, a better understanding of the clinicopathological characteristics of BACC is important for the accurate diagnosis and treatment of the disease.

BACC often occurs in middle-aged and elderly women. The age of onset is similar to other types of breast cancer. Occasionally, it occurs in men. There is no difference in the incidence of BACC in the left and right breasts, and the growth of carcinoma is not quadrant-specific^[6]. About

50% of BACC occur below the areola area and most of them were diagnosed as a breast lump^[6]. In general, BACC does not have specific clinical manifestations and it is occasionally accompanied by pain. In the study, there was no clear correlation between pain and nerve invasion. Three patients with BACC had nipple discharge, which was probably caused by concurrent intraductal papilloma.

It is difficult to distinguish BACC from benign lesions using imaging approach since its findings are not specific. The X-ray scan showed unevenly dense lump with generally clear boundaries, and calcifications are rare. Among them, 10 cases were classified as Grade IVa, 10 cases as Grade IVb, and eight cases as Grade III by Breast Imaging Reporting and Data System. Magnetic resonance imaging (MRI) was not performed before the surgical operation. Besides, ultrasound scan often showed clear boundaries and irregular hypoechoic masses, which estimate tumor size before surgery. However, it is often inaccurate to evaluate tumor size before operative B-mode ultrasound as that may lead to insufficient surgical resection range and lack of surgical resection scope. On the other hand, MRI is more accurate in measuring tumor size and showing BACC as mixed cystic solid mass^[7]; thus, patients who are planning to undergo breast-conserving surgery are recommended to have MRI before surgery, which will help obtain sufficient negative resection margins and reduce recurrence after surgery.

The tumor boundary is relatively clear, along with occasionally seen cystic changes. Some tumors are easily misdiagnosed as benign tumors. The larger tumors which have an average size of 3 cm (0.7 – 12 cm) are more prone to malignancy. The lumps in the BACC group are relatively small, which may be related to the improvement of people’s

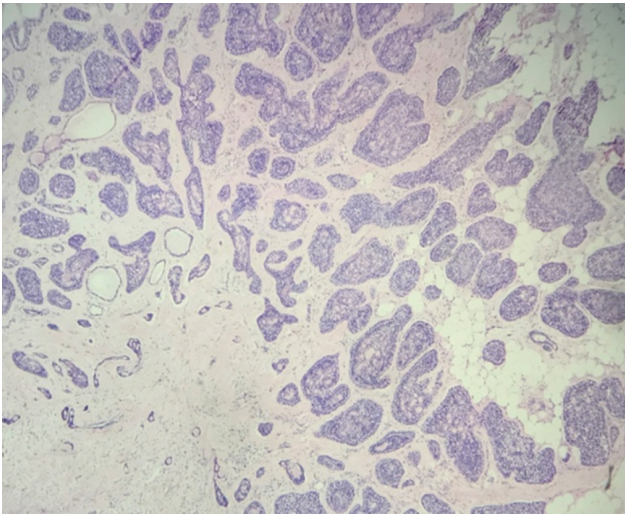


Figure 3. Tubular or sieve-like structures of the adenoid cystic carcinoma of the breast. The section was stained using hematoxylin and eosin and the image was pictured at ×100.

Table 1. Comparison of the number of NUPR1-positive and MYB-positive cases between control and BACC groups

Group	Number of cases (n)	
	NUPR1-positive	MYB-positive
Control	16	0
BACC	2	26
χ^2	14.44	45.37
P	<0.001	<0.001

BACC: Breast adenoid cystic carcinoma, NUPR1: Nuclear protein 1

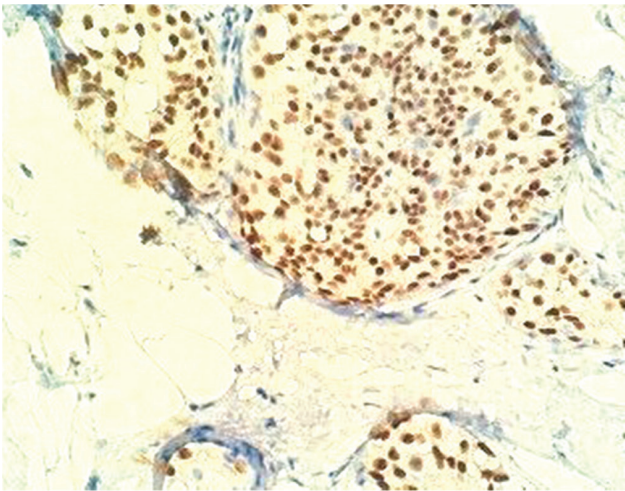


Figure 4. Positive expression of MYB in adenoid cystic carcinoma of the breast. The MYB was immunostained using streptavidin-alkaline phosphatase labeling system of indirect immunohistochemistry (SP-IHC) method. The image was pictured at ×400.

awareness of health examinations. Microscopically, BACC is similar to the adenoid cystic carcinoma of salivary gland, comprising mostly tubular or sieve-like structures, and occasionally solid variants, with prominent basal-like features. Tumor cells can form a true glandular cavity and a pseudoglandular cavity. The true glandular cavity is composed of small cells on the surface of the cavity and contains periodic acid-Schiff-positive mucus. The pseudoglandular cavity is composed of interstitial tissue that surrounds the basal-muscular epithelial cells. Solid variants are rare and difficult to diagnose. In general, solid variants exhibit obvious cellular atypia, mitosis, and occasional squamous metaplasia and adipolysis. In the BACC group, 20 cases were mainly adenoid and tubular structure and eight cases were mainly solid variants which accounted for 28.6% that was higher than that reported in the literature.

Solid variants are associated with high Ki67 index and mitosis, and diagnosis based on morphology is difficult. Histological classification is generally based on the proportion of tumor solid areas. Grade I is assigned to tumor with no solid components, Grade II for tumor with solid components $\leq 30\%$, and Grade III for tumor with solid components $>30\%$. The size of solid variant tumors is generally larger^[6]. Unlike adenoid cystic carcinoma of salivary gland, BACC is unsusceptible to nerve invasion and vascular infiltration is rare.

Most BACC cases are triple-negative breast cancers. In BACC, glandular cells express glandular epithelial markers such as CK7, CD117, CK8/18, and epithelial membrane antigen, while myoepithelial cells express CK5, CK5/6, CK14, CK17, epidermal growth factor receptor, and CD117. Meanwhile, other types of breast cancer often express ER and PR but do not express myoepithelial markers. Specifically, BACC expresses MYB. Due to the complete lack of ER, PR, and HER2, BACC is always classified as a subtype of triple-negative carcinoma. The local expression of ER in two cases of the BACC group suggests that some patients may benefit from hormone therapy. Nevertheless, we believe that increasing the number of cases for observation may lead to different results. Kasami *et al.*^[5] found that myoepithelial-basal cells of BACC often express laminin, fibronectin, basement membrane-related proteins, and Type IV collagen which are involved in cell adhesion, whereas luminal cells express cytokinin, E-cadherin, and β -catenin, which are the cell polarity markers. This may explain why BACC does not easily metastasize.

BACC usually presents as a localized disease (stages pT1/2) with a low frequency of axillary lymph node involvement. Besides, BACC is easily misdiagnosed, especially in the diagnostic procedure involving core needle biopsy and frozen section. Due to its unique

prognostic characteristics, differential diagnosis of BACC from especially the cases with solid structure or tubular structure is important. Solid variant of BACC needs to be differentiated from poorly differentiated nonspecific cancers, such as small cell cancer and anaplastic cancer. Even the sieve structure of BACC needs to be distinguished from the infiltrating cribriform carcinoma and collagenous spherulosis. Infiltrating cribriform carcinoma consists of a single glandular epithelium and has no myoepithelial expression. Collagenous spherulosis has eosinophilic globules that are similar to adenoid cystic carcinoma, but it does not grow infiltratively. There are intact myoepithelial cells around the cribriform structure. Both ER and PR are focal positive in the tumor, while BACC myoepithelium is discontinuous. Thus, it is easy to distinguish them by detecting the expression of ER or PR and CK5/6 or SMA. On the other hand, SRY-Box Transcription Factor 10 (SOX10) played an important role in the differential diagnosis of many tumors as SOX10 was found to be mainly expressed in breast epithelial cells and tumors of salivary gland of epithelial origin^[8]. Triple-negative breast cancer, including BACC, does not express specific markers of breast cancer such as ER, PR, GATA3, and gross cystic disease fluid protein 15. The positive expression rate of SOX10 in triple-negative breast cancer is as high as 71%, but only 5% in luminal breast cancer. Thus, SOX10 can be used as a marker for the differential diagnosis of BACC.

NUPR1 is a stress-related protein that is commonly found in acute pancreatitis. NUPR1 has been found to be related to the occurrence, development, and poor prognosis of a variety of tumors, including pancreatic cancer, oral squamous cell carcinoma, and thyroid cancer. In breast cancer, Ree *et al.*^[9] first found that NUPR1 is related to breast cancer metastasis. This stress-related protein not only participates in the process of cell proliferation mediated by intracellular signal to promoting metastasis but also is related to poor prognosis of breast cancer. Jung *et al.*^[10] found that the changes to 16p11.2 and 17q12 areas of the chromosome in early breast cancer cell lines with metastatic potential were related to the poor prognosis of the tumor. This is because NUPR1 gene is located at 16p11.2 and HER2 is located at 17q12. The prognosis of the tumor became worse if both areas were affected by modifications. Our previous study also found that the expression of NUPR1 was increased in nonspecific invasive breast cancer, which was related to lymph node metastasis and poor prognosis^[11]. Whether NUPR1 is expressed in BACC has never been reported. In this study, we found that the expression of NUPR1 in BACC is very low, which was different from invasive ductal carcinoma (nonspecific type). We speculate that low NUPR1 expression may explain the low invasive characteristics of BACC. Despite that, further study of the relevant mechanism is warranted.

There are few studies investigating the molecular genetics of specific types of breast cancer. Comparative genomic hybridization analysis showed the low incidence of BACC genetic instability, and there was no methylation at the BRCA1 promoter region. Most studies have found that more than 90% of BACC have t(6;9)(q22-23;p23-24) chromosomal translocation which is related to MYB pathway activation. BACC which is negative for MYB-NFIB gene fusions may be related to MYBL1 gene rearrangement or MYB amplification. It is speculated that the change in MYB gene is the key for BACC occurrence^[2,12]. In the past, fluorescence *in situ* hybridization was recommended for the detection of MYB mutations. Recently, Poling *et al.*^[13] reported that the BACC tissues with MYB-NFIB gene fusion showed positive expression of MYB protein, some of the tissues lacked of MYB-NFIB gene fusion and some exhibited MYB gene amplification. Regardless of MYB-NFIB gene fusion or MYB gene amplification, the tissues manifested strong and diffuse nuclear expression of MYB through immunostaining. In view of this, we reported that nearly all BACC cases expressed MYB protein through the use of immunohistochemical method in the present study, which further confirms that strong and diffuse MYB expression using immunohistochemistry is a sensitive and specific diagnostic criterion for BACC. In addition, this detection method is economic and effective. However, the interpretation of weak or focal positive MYB expression needs to be cautious.

Nicola *et al.*^[14] who studied the genetic changes of BACC that coexists with high-grade, invasive cancer, not otherwise specified (NOS) and found that MYB-NFIB gene fusion was present in both cancers, while somatic mutations of EP300, NOTCH1, ERBB2, FGFR1, and KMT2C were found to be associated with high-grade, invasive cancer NOS. Meanwhile, STAG2, KDM6A, and CDK12 mutations only exist in high-grade, invasive cancer NOS, suggesting that clonal evolution or other genetic changes occurred during the transformation from BACC to high-grade, invasive cancer NOS.

Given its low incidence, there is a lack of consensus for the treatment of this rare neoplasm. Most studies have shown that BACC is different from general triple-negative breast cancer as BACC has a good prognosis which is associated with a 10-year survival rate of 90 – 100%, but lymph nodes and distant metastases are rare in BACC. Therefore, mastectomy is recommended for breast cancer that is not cosmetically effective or high-grade cancer. Breast-conserving surgery has a high rate of resection margin at about 42%, and the local recurrence rate in BACC patients is high^[15]. Therefore, it is currently controversial whether chemotherapy is recommended for patients who had underwent breast-conservation surgery. Other studies

have found that solid variant of basal-like BACC, large local tumors, new blood vessels, and PI3K mutations may be the adverse factors for local tumor recurrence and lymph node metastasis^[16,17], and related studies need to be graded to guide the prognosis. Consistent with the findings of Chen *et al.*,^[18] the clinical-pathological stage of BACC, age of onset, tumor size, lymph node metastasis, and overall survival rates in patients with invasive ductal carcinoma of the same histological grade is similar. Although there are many solid variant cases in this group, the prognosis of BACC is better than that of invasive ductal carcinoma if complete tumor resection and post-operative adjuvant treatment were used. In the present study, only two cases of local recurrence were reported. Basal-like BACC is an aggressive variant of BACC. Basal-like BACC is associated with more frequent lymph node involvement and a higher incidence of distant metastasis. It is recommended that all basal-like BACC should be staged. Further research found that ER-positive and HER2-negative BACC have a relatively good prognosis, suggesting that clinicians should consider and select personalized treatment to achieve higher treatment efficacy.

Chemotherapy has been recommended for patients with high-grade cancer accompanied by axillary lymph nodes and distant metastases. Even though local recurrence or distant metastasis could be detected in certain patients during follow-up period, the tumors would still manifest with an inert biological behavior. However, since the relapse and metastasis rates will increase over time, thus it is necessary to follow-up and observe these patients prospectively for a long period of time. Due to MYB mutations in BACC, MYB-targeted therapy should be considered^[19]. Furthermore, MYB/NFIB gene fusion is also expected to be a therapeutic target for advanced BACC.

5. Conclusion

The vast majority of BACC cases which were tested negative for NUPR1 indicate that BACC is associated with low invasive characteristics and relatively inert biological behavior. The study also implied that NUPR1 is indicator of poor prognosis of the BACC, and the expression of MYB in BACC as determined through immunohistochemistry could be a sensitive and specific criterion for BACC diagnosis. In addition, this detection method is cost saving and effective relative to fluorescence *in situ* hybridization. Our study also corroborated the significance of MYB expression for its discriminatory role in BACC diagnosis and differential diagnosis. Therefore, these cases are generally not advocated for chemotherapy, but rather, they are expected to be treated with MYB-targeted therapy.

Acknowledgments

This study was supported by Major Health Projects of

Hebei Provincial Department of Science and Technology (No. 17277752D). The authors would like to thank Dr. Xiao-Chun Wang from the Affiliated Hospital of Hebei University, and Dr. Zhao Yang from Beijing University of Chemical Technology for providing clinical information and assistance in manuscript translation.

Conflicts of interest

The authors declare there are no conflicts of interest regarding the publication of this paper.

Author contributions

W.W. conceived and designed the experiments and wrote the paper. C.Z. performed the experiments. W.W. and Y.L. analyzed the data. J.Z. reviewed drafts of the paper. All authors read and approved the final manuscript.

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