Breast lesions excised via Vacuum-Assisted System: Could We Get Any Clues for B3 Lesions Before Excision Biopsy?

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Research article

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Abstract

Background: The purpose of this study was to determine the validity of the ultrasound features as well as patient characteristics assigned to B3 (uncertain malignant potential) breast lesions before vacuum-assisted excision biopsy (VAEB).

Methods: This study population consisted of 2245 women with breast-nodular abnormalities, which were conducted ultrasound-guided VAEB (US-VAEB). Patient's clinical and anamnestic data and lesion-related ultrasonic feature variables of B3 were compared with those of benign or malignant cases, using histopathological results as a benchmark.

Results: The proportions of benign, B3 and malignant breast lesions were 88.5%, 8.2% and 3.4% respectively. B3 high frequent occurred in BI-RADS-US grade 3 (7.7%), grade 4 (9.3%), grade 4a (11.3%) and grade 4b (9.1%). The overall malignancy underestimation rate of B3 cases was 4.4% (8/183). The more common malignancy underestimation of B3 subtypes were PL/ADH 50% (1/2), ADH 23.1% (3/13), and CSL/RS 16.7% (1/6). And the highly frequent recurrence rates of B3 subtypes were ADH 10% (1/10), PL 4.9% (4/82), and PT 8.6% (6/70). Multivariate binary logistic regression analyses (B3 *vs* benign) showed that non-menopausal patients (95% CI 1.628-8.616, $P = 0.002$), single (95% CI 1.370-2.650, $P = 0.000$) or abundant blood supply (95% CI 1.745-4.150, $P = 0.000$) nodules via ultrasound examination were significant risk factors for B3 occurrences. Moreover, patients elder than 50 years (95% CI 3.178-19.816, $P = 0.000$), unclear margin (95% CI 3.571-14.119, $P = 0.000$) or microcalcification (95% CI 4.010-30.733, $P = 0.000$) nodules were significantly associated with higher risks of malignant potentials (B3 *vs* malignant).

Conclusion: The results of this study indicate that ultrasound findings and patients' characteristics could provide valuable information for distinguishing B3 cases from benign or malignant cases before VAEB.

Background

Over the last decades, incidence rates of breast cancers in women have been significantly rising. Moreover, breast cancer is the most frequently diagnosed cancer and is also the leading cause of death from cancer in the world as well as in China [1, 2]. For the reasons, breast changes are the principal cause of anxiety in patients who consult physicians in outpatient [3]. In addition to history and physical examination, diagnostic imaging is often utilized by physicians to evaluate the malignant potentials of the breast abnormalities.

Since the initial release of the BI-RADS lexicon for ultrasound (BI-RADS-US) in 2003 [4], together with the rapid development of technique, ultrasound is getting more used for breast screening, especially in Asian women with dense breasts [5]. Compare to mammography, ultrasound examination is a portable, real-time, non-invasive, non-radiative, inexpensive, and highly reproducible method, and well accepted by patients [5–7]. BI-RADS-US is confirmed to be feasible to offer typical features for benign or malignant breast lesions [8, 9]. Therefore, BI-RADS-US is often recognized as the qualified indication of biopsy or

surgical excision for breast lesions [10]. Currently, US-VAEB tends to be regarded as the best diagnostic way to differentiate benign from malignant breast changes seen at imaging and is popular in China [11, 12]. VAEB could replace core needle biopsy and open surgical biopsy for diagnoses of breast diseases and treatment of benign breast lesions [13, 14]. It has several advantages, including the ability to get more samples for a more reliable histological diagnosis, the ability to complete removal of the breast lesion, and performance under the real-time guidance of ultrasound [15]. The biopsy diagnoses can be usually categorized as normal/benign, B3 (uncertain malignant potential), or malignant [16, 17]. BI-RADS-US features of typical benign or malignant breast lesions are well concordance with the histological results of biopsies, which could help physicians/patients make choices easier before excision biopsy. However, B3 lesion is usually regarded as a post-VAEB histological diagnosis because few studies are referring to imaging features specifically assigned to B3 before VAEB. Therefore, the diagnosis of B3 is much more challenging in clinical practice. It is reported that the approximate proportions of each biopsy results are normal/benign 70%-98.89%, B3 < 10%, malignant < 2%, respectively [18–20]. The data indicate that most breast changes need not excision biopsy. However, in clinical practice, to some extent, the trend of VAEB is to avoid malignancy underestimation of B3, which is subjective and depends on doctors' individual experience. With increasing concern about over-diagnosis and over-treatment through breast screening, it is regarded as a time to consider the possibility of B3 diagnosis before VAEB. Could we get any clues for B3 preoperatively?

This study aims to evaluate and compare the common features of ultrasound findings as well as patient characteristics of B3 cases to those of normal or malignant cases based on histopathological results.

Methods

Study design and patient population

The Institute Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University granted permission for this retrospective study.

A total of 2245 cases with breast nodules were performed US-VAEB in our institute, from June 2014 to December 2018. The inclusion criteria were as follows: (1) All patients included in the study group were women with a US-detectable breast lesion. (2) Availability of clinical and anamnestic data of patients, and ultrasound imaging reporting and data system lexicon for breast lesions before US-VAEB; (3) First time of US-VAEB. (4) Availability of histopathological report. (5) All cases were imaging followed up for at least 12 months after US-VAEB. No follow-up cases were excluded.

Data analysis

The SPSS 25.0 software package was used for all statistical calculations. Chi-square test / Fisher's exact test was utilized to compare the differences of ultrasonic features of B3 lesions before US-VAEB and clinical and anamnestic data of the patients with those of benign or malignant cases. Univariate and

multivariate binary logistic regression analyses were used to find independent predictive risk factors for B3 or malignant occurrences. The result with *P* value < 0.05 was considered statistically significant.

Results

Study population description

Our database included 2245 women who had recent-onset US-detectable breast findings. The mean age was 37.5 years (range 12–79 years). The most frequent complaint of patients was palpable nodules (86.8%). The less frequent complaints were pain (4.1%) and nipple discharge (1.2%), respectively. And 7.9% of cases are asymptomatic, which were image findings. The average maximum diameter of the lesions was 13.2 mm (range 2–75 mm). All patients were addressed to undergo US-VAEB for the first time at our institute. The median duration of imaging follow-up post-US-VAEB was 24.7 months (range 12.0–60.0 months).

The clinicopathologic characteristics of the cases are summarized in Table 1.

Table 1
The distributions of benign, B3 or malignant breast lesions according to BI-RADS-US

BI-RADS category	Benign	Rate (%)	B3	Rate (%)	Malignant	Rate (%)
0	3	60	2	40	0	0
2	138	97.9	3	2.1	0	0
3	1568	90.4	134	7.7	33	1.9
4	31	72.1	4	9.3	8	18.6
4a	204	82.2	28	11.3	16	6.5
4b	28	63.6	4	9.1	12	27.3
4c	14	66.7	0	0	7	33.3
5	0	0	0	0	8	100

BI-RADS the Breast Imaging Reporting and Data System, *US* ultrasound

BI-RADS-US category assessment based on histopathological results of VAEB

Post-US-VAEB histopathological diagnoses confirmed that there were benign, B3, and malignant breast lesions as 1986 (88.5%), 183 (8.2%), and 76 (3.4%), respectively. Malignant lesions account for the minimum amounts of VAEB cases, and the overwhelming majority of VAEB cases are nonmalignant disorders that are unnecessary biopsy, which is consistent with previous reports [21, 22]. Afterward, we subclassified the lesions according to their BI-RADS-US category assessment. The incidences of B3 and

malignant breast lesions in each grade of BI-RADS were listed in Table 1. Notably, the prevalent range for B3 was from BI-RADS 3 to BI-RADS 4b. And they were rarely diagnosed in BI-RADS 4c or BI-RADS 5. On the other hand, the malignant lesions were mainly distributed in the range from BI-RADS 4b to 5, which are compatible with the literature [23].

Malignancy underestimation rate and recurrence rate of B3

Initially, there was a total of 183 cases of B3 lesions proved by US-VAEB. The histopathological results of B3 subtypes were listed in Table 2. Meanwhile, one case of atypical ductal hyperplasia (ADH) which could not be excluded from the possibility of ductal carcinoma in situ (DCIS) was finally confirmed to be invasive breast cancer by open surgery (OS). 1 case of a complex of sclerosing lesions and radial scars (CSL/RS) which was discordant with image finding was confirmed to be invasive breast cancer through OS. 1 case of a complex of papillary lesions and atypical hyperplasia (PL/ADH) which had a high risk of malignant potential was received OS subsequently and verified to be intraductal carcinoma with lobular carcinoma[24]. Besides, 5 cases were followed up after VAEB, and found recurrences at the sites of operation, which were demonstrated as malignancies via OS, including 2 cases of ADH confirmed to be DCIS and invasive ductal carcinoma respectively, 2 cases of PL confirmed to be DCIS and invasive ductal carcinoma, 1 case of phyllodes tumors (PT) diagnosed as invasive breast cancer. In general, the risk of malignancy underestimation in the B3 group of biopsy-proven was 4.4% (8/183). The individual malignancy underestimation rates of B3 subtypes were displayed in Table 2. It is noteworthy that the more underrated B3 subtypes for malignancies were PL/ADH 50% (1/2), ADH 23.1% (3/13), and CSL/RS 16.7% (1/6). The results are in line with the reports [24, 25]. Although the malignancy underestimation rate of B3 is limited, multidisciplinary communication and imaging follow-up are necessary so as not to miss malignant potential [26].

Table 2
The underestimation of B3 lesions

B3 subtype	Number	Underestimation	Rate (%)
ADH	13	3	23.1
FEA	4	0	0
LN	3	0	0
PL	84	2	2.4
PL/ADH	2	1	50
PT	71	1	1.4
CSL/RS	6	1	16.7

ADH atypical ductal hyperplasia; *FEA* flat epithelial atypia; *LN* classical lobular neoplasia; *PL* papillary lesions; *PL/ADH* complex of papillary lesions and atypical hyperplasia; *PT* phyllodes tumors; *CSL/RS* complex of sclerosing lesions and radial scars

After the period of follow-up, the recurrence rates of B3 subtypes were summarized in Table 3. We noticed that the highly frequent recurrences of B3 subtypes were ADH 10% (1/10), PT 8.6% (6/70), and PL 4.9% (4/82). The recurrence rates of the later two subtypes are concordant with the literature [29, 30]. Whether the higher recurrence rate of ADH was due to its fewer cases needs further observation.

Table 3
The recurrences of B3 lesions

B3 subtype	Number	Recurrence	Rate (%)
ADH	10	1	10
FEA	4	0	0
LN	3	0	0
PL	82	4	4.9
PL/ADH	1	0	0
PT	70	6	8.6
CSL/RS	5	0	0

ADH atypical ductal hyperplasia; *FEA* flat epithelial atypia; *LN* classical lobular neoplasia; *PL* papillary lesions; *PL/ADH* complex of papillary lesions and atypical hyperplasia; *PT* phyllodes tumors; *CSL/RS* complex of sclerosing lesions and radial scars

Overall consideration of both the incidence of B3 lesion and its malignancy underestimation rate, only a minority of B3 lesions should be subjected to VAEB. Combining B3 lesion's malignancy underestimation rate with its recurrence rate, we recommend OS for ADH, PL/ADH, and PT subtypes, which is similar to those of reports [27–29].

The specific ultrasonic features and patients' characters of B3 comparing to those of benign or malignant cases

In clinical practice, uncertain malignant potentials are the most frequent causes which disturb both patients and physicians. To a certain extent, this could explain why most of the biopsy cases are nonmalignant breast disorders. One question is presented here that could we get any clues for B3 changes before the excision biopsy? Therefore, we analyzed the differences between the ultrasonic features of B3 lesions before VAEB and their associated patients' characteristics and those of benign or malignant cases by Chi-square test / Fisher's exact test. To our best knowledge, it's the first time that we noticed that among B3 cases, the incidences of non-menopausal patients ($P = 0.002$), single ($P = 0.000$) or blood supply abundant nodules ($P = 0.000$) examined by ultrasound were significantly increased, compared to those of benign cases. Also, the incidence of the irregular shape of nodules in B3 cases tended to be higher than that of benign cases ($P = 0.080$) (Table 4). In the meantime, we compared B3 with malignant cases and found that the incidences of patients elder than 50 years ($P = 0.000$), non-reproductive age ($P = 0.000$) and menopause ($P = 0.000$), and nodules with irregular shape ($P = 0.000$),

uncircumscribed margin ($P = 0.000$), abundant blood supply ($P = 0.002$) or microcalcification ($P = 0.000$) in ultrasound findings were significantly increased in malignant cases (Table 4). Furthermore, univariate and multivariate binary logistic regression analyses (B3 *vs* benign) showed that non-menopausal patients, single or abundant blood supply nodules were significant risk factors for B3 occurrences [Table 5]. While B3 compared to malignant, univariate binary logistic regression analyses showed that patients elder than 50 years, and unclear margin, abundant blood supply or microcalcification nodules were closely associated with malignancies. Moreover, multivariate logistic regression analyses demonstrated that patients elder than 50 years, unclear margin or microcalcification nodules were significant risk factors for malignant potential [Table 6]. On these grounds, we reviewed the 8 malignancy underestimation cases in the B3 group and found that 6 out of them were elder than 50 years, and 5 out of them presented with uncircumscribed nodules, which were well covered by the malignant risk factors.

Table 4
Comparison between characters of B3 and those of benign or malignant cases

	Benign	B3	χ^2	*P*	B3	Malignant	χ^2	*P*
Age								
≤ 50	1809	165	2.081	0.149	165	56	34.583	0.000
> 50	177	10			10	28		
Reproductive age								
Yes	1148	97	0.372	0.542	97	25	15.006	0.000
No	838	78			78	59		
Menopause								
No	1767	169	9.955	0.002	169	58	39.706	0.000
Yes	219	6			6	26		
Multifocality								
Unifocal	454	65	17.979	0.000	65	35	0.490	0.555
Multifocal	1532	110			110	49		
Shape								
Regular	1786	150	3.064	0.080	150	48	25.733	0.000
Irregular	200	25			25	36		
Margin								
Circumscribed	1611	145	0.319	0.572	145	29	60.137	0.000
Not circumscribed	375	30			30	55		
Microcalcification								
Absent	1864	168	1.316	0.572	168	56	41.785	0.000
present	122	7			7	28		
Vascularity								
Absent/scarce	1847	142	30.870	0.000	142	53	9.937	0.002
Abundant	139	33			33	31		

Table 5
Binary logistic regression analyses between characters of benign cases and those of B3

	Univariate		Multivariate	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Menopause				
Yes	3.491 (1.528, 7.976)	0.003	3.745 (1.628, 8.616)	0.002
No				
Multifocality				
Multifocal	1.994 (1.442, 2.757)	0.000	1.905 (1.370, 2.650)	0.000
Unifocal				
Shape				
Regular	1.488 (0.951, 2.329)	0.082	1.259 (0.788, 2.014)	0.336
Irregular				
Vascularity				
Absent/scarce	3.088 (2.037, 4.682)	0.000	2.691 (1.745, 4.150)	0.000
Abundant				

95% CI 95% confidence interval, *OR* odds ratio

Table 6
Binary logistic regression analyses between characters of B3 cases and those of malignancies

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age				
≤ 50	8.25 (3.770, 18.053)	0.000	7.936 (3.178, 19.816)	0.000
> 50				
Margin				
Circumscribed	9.167(5.044, 16.659)	0.000	7.101 (3.571, 14.119)	0.000
Not circumscribed				
Microcalcification				
Absent	12.000 (4.969, 28.981)	0.000	11.101 (4.010, 30.733)	0.000
present				
Vascularity				
Absent/scarce	2.517(1.405, 4.509)	0.001	1.711 (0.808, 3.623)	0.161
Abundant				
95% CI 95% confidence interval, *OR* odds ratio				

Discussion

B3 lesions are borderline with either benign or malignant breast disorders. Women with these lesions are often suffering from psychological torture because of an increased risk of finding concomitant cancer, or evolution toward in situ or invasive cancer over a long time [24, 30]. The patients that underwent a breast biopsy claimed that they also have experienced biopsy-related stress even if the results were nonmalignant [31].

While concern about over-diagnosis and over-treatment through breast screening is on the increase, it must be considered the strategies to manage breast abnormalities because the approaches differences are not trivial and could translate into possibly thousands of patients undergoing unnecessary biopsies or an equal number with delays in diagnoses of malignancies [26].

Our data showed that the overwhelming majority of histopathological results of 2245 VAEB cases were benign breast disorders (88.5%), and only a small proportion (3.4%) was malignancies. The results are consistent with the literature [11, 18–20]. It shows that criteria should be more strict to avoid unnecessary VAEB procedures for the patient's clinical and economic benefit unless there is a specific request from the

patient. Our data showed that 8.2% of 2245 VAEB cases were proved to be B3 lesions. The overall malignancy underestimation rate for this clinical dilemma was 4.4%. The data suggested that excision biopsies are not needed for most of these borderline changes as well. Furthermore, we noticed that B3 high frequent occurred in the range from BI-RADS-US 3 to BI-RADS-US 4b, which is partly consistent with the reports [31, 32]. And the data showed that the most underrated B3 subtypes for malignancies were PL/ADH (50%), ADH (23.1%), and CSL/RS (16.7%), respectively. Moreover, the most frequent recurrence rates of B3 subtypes were ADH (10%), PT (8.6%), and PL (4.9%). These are compatible with the previous study [33]. Taking into account B3 subtypes' malignancy underestimation rates and recurrence rates, we suppose that ADH, PL, or ADH/PL should be resorted to OS.

At present, several studies refer to B3 ultrasonic features but they all are either lack statistical analyses or categorizing B3 into normal lesions for analyses [15, 21, 34]. Therefore, the data could hardly help to identify B3 from benign or malignant breast changes before VAEB. For the first time, we found that the incidences of non-menopausal patients, single or blood supply abundant nodules were significantly increased in B3 cases compared to those of benign cases. Besides these, the incidence of nodules with irregular shape in B3 cases tended to be higher than that of normal cases ($P = 0.080$). Then, multivariate logistic regression analyses showed that non-menopausal women, single or blood supply abundant nodules were significant risk factors for B3 cases. It suggested that normal cases accompanying by one or more of the above risk factors should be aware of B3 occurrences. On the other hand, compared to B3 cases, the incidences of patients elder than 50 years, non-reproductive age and menopause, and irregular shape, uncircumscribed margin, abundant blood supply or microcalcification nodules were significantly increased in malignant cases. Subsequently, multivariate logistic regression analyses showed that patients elder than 50 years, unclear margin or microcalcification nodules were significant risk factors for malignant potential. We reviewed the 8 underestimated cases in this cohort and found that they presented with at least one or more malignant risk factors. It suggested that if B3 cases presented with one or more of the above malignant risk factors should be considered OS to avoid malignancy underestimation. These results provide valuable targeted evidence in clinical practice to assess the probability of B3 diagnosis before VAEB which should not only be managed within the confines of excision biopsy but also benefit from fit surveillance.

Study limitations

The first limitation is the small cohort of B3 cases and the retrospective nature of the study. Another limitation is that there is a lack of ultrasonic features of B3 subtypes and their associated patients' characteristics which allow more accurate comparisons between B3 and benign or malignant cases. Hence, further studies are required in these regards.

Conclusions

The vast majority of VAEB cases were benign breast changes. B3 represented a small part of VAEB cases. The normal cases accompanying by one or more factors of non-menopausal patients, single or abundant

blood supply nodules, which distributed in the range of BI-RADS-US 3-4b, were significantly associated with the risk of B3 occurrences. For these cases, caution is advised by clinical and imaging follow-up. OS should be recommended for ADH, PL/ADH, and PT due to their higher malignancy underestimation rates and/or recurrence rates. B3 cases presented with one or more factors of elder than 50 years, unclear margin or microcalcification nodules were remarkably related to malignant potential. For these cases, OS should be recommended as well. If confirmed on larger series and prospectively validated, the results could help to improve strategies to identify B3 from benign or malignant breast abnormalities before VAEB and reduce the incidence of unnecessary interventions, which would not only relieve the patients' stress level but also save on health care costs.

Abbreviations

B3: uncertain malignant potential; VAEB: vacuum-assisted excision biopsy; US: ultrasound; DCIS: ductal carcinoma in situ; ADH: atypical ductal hyperplasia; FEA: flat epithelial atypia; LN: classical lobular neoplasia; PL: papillary lesions; PT: phyllodes tumors; CSL: complex sclerosing lesions; RS: radial scars; 95% CI: 95% confidence interval; OR: odds ratio;

Declarations

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Not applicable.

Authors' Contributions

Wenjian Wang conceived the original idea, supervised the project, and wrote the draft. Liang Zheng, Fufu Zheng, and Zhaomin Xing collected the data, performed the statistical analysis, and wrote the results. Yuanhui Lai, Jie Li, Yunjian Zhang, Yongxin Li and Hongbiao Xu performed VAEB and collected the data. All authors discussed the results and contributed to the final article.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

The study was approved by the Institute Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University granted permission for this retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no potential conflicts of interest disclosed.

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