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Impact of Non-Calcified Specimen Pathology on the Underestimation of Malignancy for the Incomplete Retrieval of Suspicious Calcifications Diagnosed as Flat Epithelial Atypia or Atypical Ductal Hyperplasia by Stereotactic Vacuum-Assisted Breast Biopsy

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Objective: Stereotactic vacuum-assisted breast biopsy (VABB) is considered a reliable alternative to surgical biopsy for suspicious calcifications. In most cases, the management of flat epithelial atypia (FEA) and atypical ductal hyperplasia (ADH) after VABB with residual calcifications requires surgical excision. This study aimed to evaluate the impact of pathology of non-calcified specimens on the underestimation of malignancy.

Materials and Methods: We retrospectively reviewed 1147 consecutive cases of stereotactic VABB of suspicious calcifications without mass from January 2010 to December 2016 and identified 46 (4.0%) FEA and 52 (4.5%) ADH cases that were surgically excised for the retrieval of residual calcifications. Mammographic features and pathology of the calcified and non-calcified specimens were reviewed.

Results: Seventeen specimens (17.3%) were upgraded to malignancy. Mammographic features associated with the underestimation of malignancy were calcification extent (> 34.5 mm: odds ratio = 6.059, p = 0.026). According to the pathology of calcified versus non-calcified specimens, four risk groups were identified: Group A (ADH vs. high-risk lesions), Group B (ADH vs. non-high-risk lesions), Group C (FEA vs. high-risk lesions), and Group D (FEA vs. non-high-risk lesions). The lowest underestimation rate was observed in Group D (Group A vs. Group B vs. Group C vs. Group D: 35.0% vs. 20.0% vs. 15.0% vs. 3.6%, p = 0.041, respectively).

Conclusion: Considering that the calcification extent and pathology of non-calcified specimens may be beneficial in determining the likelihood of malignancy underestimation, excision after FEA or ADH diagnosis by VABB is required, except for the diagnoses of FEA coexisting without atypia lesions in non-calcified specimens.

Keywords: *Breast disease; Precancerous conditions; Biopsy; Stereotactic techniques*

INTRODUCTION

With the widespread use of screening mammography and improvements in mammographic techniques, more suspicious calcifications are discovered and need to be diagnosed. The current trend is for suspicious calcifications to be diagnosed using a less invasive procedure that replaces excisional biopsy. Stereotactic guidance biopsy for calcifications is a standard diagnostic procedure for lesions that can only be detected by mammography. Currently,

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stereotactic vacuum-assisted breast biopsy (VABB) is considered a reliable alternative to surgical biopsy for diagnosing suspicious breast calcifications (1, 2).

The mammographic appearance of flat epithelial atypia (FEA) is mostly observed as microcalcifications, and the rate of underestimation of malignancy after FEA diagnosis using VABB varies from 0% to 21% (3-7). If FEA is the worst pathological finding diagnosed by VABB for the retrieval of suspicious calcifications and there is no residual calcification after the procedure, close radiologic follow-up is adequate (6, 8-10). Conversely, for lesions with residual calcifications, subsequent surgical excision is advocated.

Similar to FEA, atypical ductal hyperplasia (ADH) mainly presents as calcifications on mammography. The rate of underestimation of malignancy in patients diagnosed with ADH using 11-gauge and 9-gauge VABB varies from 10% to 29% (11-13). Although several studies have suggested that certain subgroups of patients with ADH involving fewer than three foci and microcalcifications can have them completely removed by VABB, which can avoid excisional biopsy (14, 15), for patients with ADH diagnosed by VABB with residual calcifications, surgical excision is recommended.

The application of VABB over a targeted area enables the retrieval of breast tissue both with and without calcifications; therefore, the presence or absence of calcifications may result in different pathological diagnoses. Several studies examined the diagnostic value of calcified and non-calcified specimens and demonstrated that the correct diagnostic rate of calcified specimens was higher than that of non-calcified specimens (16-18). However, Esen et al. (19) reported that 60% of patients with complete retrieval of microcalcifications by stereotactic VABB still had residual disease at surgery. These findings raised questions about the relevance of pathological diagnosis of non-calcified lesions to breast disease itself. We hypothesized that the pathology of non-calcified specimens is associated with the underestimation of malignancy. The primary objectives of this study were to determine the underestimation rates for malignancy in FEA and ADH cases diagnosed by stereotactic VABB on suspicious calcifications with residual calcification and identify specific clinical characteristics, imaging features, and association between calcified and non-calcified specimens, which could be predictors of malignancy. The secondary objective was to identify patients who could avoid surgical excision if the underestimation rate was low.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the electronic medical records in the database of the Department of Radiology at Chang Gung Memorial Hospital collected between January 2010 and December 2016 and identified 1147 consecutive cases of stereotactic VABB on suspicious calcifications without mass-forming lesions. Our department policy is to perform stereotactic biopsy when the lesions had no abnormalities on ultrasound. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No: 201901327B0), and the need for written informed consent was waived. FEA and ADH were each classified according to the criteria adapted by the World Health Organization (20). A single breast pathologist with 15 years of experience reviewed the 1147 stereotactic biopsy results. The inclusion criteria were the presence of residual calcifications after stereotactic VABB was performed, both specimens with and without calcifications were obtained by VABB from the same biopsy sites and were separated and individually submitted for histopathological diagnosis, and subsequent surgical excision was performed (Fig. 1). Finally, 98 patients were identified with a diagnosis of FEA or ADH by stereotactic VABB with residual calcifications followed by surgical excision: 46 and 52 patients had FEA and ADH, respectively, as the most advanced lesion. Clinical data and patient demographics of these cases were collected from the electronic database for analyses.

Mammographic Features

Each suspicious calcification was retrospectively reviewed on a high-resolution digital mammographic screen by one breast radiologist with 22 years of experience. Radiologic findings were classified according to the 5th edition of the Breast Imaging Reporting and Data System (BI-RADS) (21). Morphologically, none of the calcifications in the current case series conformed to either fine linear or fine linear branching shape with diffuse distribution. Therefore, the morphology of calcifications was classified as amorphous, coarse heterogeneous, or fine pleomorphic, and the distribution of calcifications was categorized as grouped, regional, linear, and segmental. Moreover, calcification extent was calculated, and the number of calcifications was recorded and categorized as ≤ 30 or > 30.

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Stereotactic VABB Procedure and Histopathological Diagnosis

All stereotactic VABB procedures were performed using mammography with an add-on stereotactic biopsy unit (Lorad, Danbury, CT, USA), with the patient in either a sitting or lateral position depending on the feasibility of

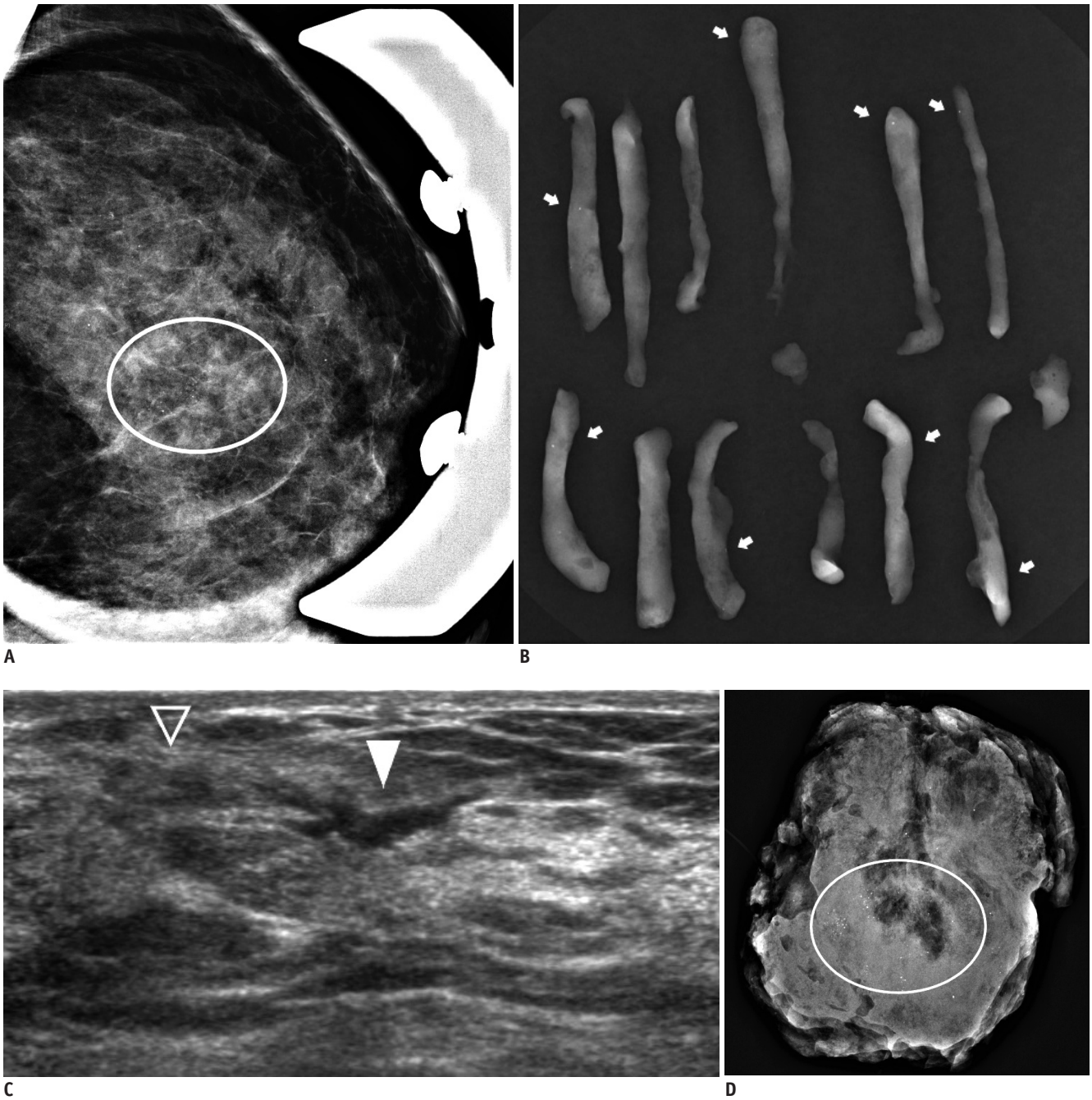

Fig. 1. 48-year-old female patient who underwent screening mammography.
A. Magnified mammogram of left breast reveals suspicious regional amorphous microcalcifications of approximately 24-mm extension (circle). **B.** Specimen mammography reveals several pieces of specimens obtained by stereotactic VABB with presence of multiple isolated microcalcifications (arrows). Pathological diagnoses of calcified-specimens and non-calcified specimens were ADH and adenosis, respectively. **C.** Preoperative ultrasound reveals needle tract (open arrowhead) and hematoma (solid arrowhead) after stereotactic VABB. **D.** Subsequent hematoma-directed ultrasound-guided excision specimen mammography confirms retrieval of residual microcalcifications (circle). Whole specimen is submitted in serial order, and previous biopsy site is identified by histopathology. Calcifications were only observed in ADH. In 20-mm lobular carcinoma *in situ* extent including small invasive lobular carcinoma (< 1 mm), no calcification was not observed. ADH = atypical ductal hyperplasia, VABB = vacuum-assisted breast biopsy

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localizing the calcifications. Biopsy was performed using the vacuum-assisted biopsy devices (Vacora, Bard, Irvine, CA, USA) with 10-gauge needles by two radiologists with 22 and 10 years of experience in breast radiology, respectively. VABB was performed over the target area with six sampling retrievals routinely after localizing the calcifications and was performed with the multidirectional biopsy notch at different clock distributions. Depending on the sufficiency of excised calcifications of the specimen mammography, additional retrieval around the target sites was performed. The calcified and non-calcified specimens were separated based on specimen mammography findings and then individually diagnosed. Independent diagnoses established by pathologists specializing in breast pathology were obtained for each specimen. The percentage of calcification retrieval after stereotactic VABB for calcifications was evaluated using regular mammography, including craniocaudal and true lateral views, and categorized as < 90% and ≥ 90% by the radiologist performing VABB. Histopathological classifications of calcified and non-calcified specimens were categorized from individual cases as non-high-risk lesions, FEA, and ADH. Non-high-risk lesions comprised benign lesions without atypia, and high-risk lesions comprised FEA or ADH.

Risk Group Stratification Based on the Pathology of Calcified Specimens Versus the Pathology of Non-Calcified Specimens

To investigate whether the pathological findings associated with calcified and non-calcified specimens were associated with the underestimation of malignancy, we classified the risk groups (calcified vs. non-calcified) according to different pathological manifestations. Patients were divided into four risk groups: Groups A (ADH vs. high-risk lesions), B (ADH vs. non-high-risk lesions), C (FEA vs. high-risk lesions), and D (FEA vs. non-high-risk lesions).

Subsequent Surgical Excision

To obtain residual calcifications, all 98 patients underwent surgical excision within 2 months after VABB. The surgeon performed hematoma-directed ultrasound-guided excisional procedure. The ultrasonographic transducer was placed in a radial and anti-radial plane over the center of the hematoma from the previous biopsy, and the skin was marked depending on the extent of hematoma followed by excision with a block tissue surrounding the hematoma. The excision specimen was routinely marked with silk stitches for orientation at the boundaries. Specimen mammography was performed to document the presence of calcifications in the excised specimen, and immediate re-excision was performed for the complete retrieval of calcifications in cases where incomplete retrieval was found with specimen mammography. Diagnoses were established by one of four pathologists specializing in breast pathology. Each of the surgical specimens was confirmed to include the previous biopsy site during the pathological examination.

Definition of Underestimation

Underestimation of malignancy was defined when patients had ductal carcinoma *in situ* (DCIS) or invasion breast cancer (IBC) in subsequent surgical excision after FEA or ADH diagnosis by VABB.

Statistical Analyses

To assess the association between documented variables and underestimation of malignancy in patients undergoing stereotactic VABB, categorical variables were compared using Pearson's chi-squared test. The cutoff length for calcification extent was selected to obtain the highest possible Youden index score (sensitivity + specificity-1). The area under the receiver operating characteristic (ROC) curve for calcification extent was calculated. A logistic regression model was used for multivariate analysis. *P* values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical Data and Mammographic Findings

Clinicopathological findings and mammography features are presented in Table 1. The median age of the patients was 50 (27–72) years. The median length of calcification extent was 12 (5–66) mm. To determine the cutoff length for calcification extent that best discriminated malignancy outcomes, we performed ROC curve analyses. The area under the curve was 0.65; we identified 34.5 mm as the cutoff length for calcification extent that minimized the *p* value linking the calcification extent to malignancy outcomes. BI-RADS 4a was the most commonly assessed category of the calcifications on mammography (83.7%, 82/98).

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Table 1. Patients' Clinicopathological Findings and Mammography Features Data

Variables	n (%)
Study period	
2010–2016	98 (100.0)
Age (years), median (IQR)	50.0 (8.0)
Lesion location	
Right breast	50 (51.0)
Left breast	48 (49.0)
Family history of breast cancer	
Yes	5 (5.1)
No	93 (94.9)
Mammographic breast density	
Scattered fibroglandular	11 (11.2)
Heterogeneously dense	65 (66.3)
Extremely dense	22 (22.4)
Calcifications extent (mm), median (IQR)	12.0 (15.0)
Number of calcification specks	
≤ 30	48 (49.0)
> 30	50 (51.0)
Distribution of calcifications	
Grouped	66 (67.3)
Regional	24 (24.5)
Linear or segmental	8 (8.2)
Morphology of calcifications	
Amorphous	70 (71.4)
Pleomorphic	25 (25.5)
Coarse heterogenous	3 (3.1)
BI-RADS category	
4a	82 (83.7)
4b	11 (11.2)
4c	4 (4.1)
5	1 (1.0)
Stereotactic VABB specimens, median (IQR)	9.0 (6.0)
Calcifications retrieval (%)	
< 90	77 (78.6)
≥ 90	21 (21.4)
Diagnosis at stereotactic VABB	
ADH	52 (53.1)
FEA	46 (46.9)
Histology of calcified specimens	
ADH	50 (51.0)
FEA	48 (49.0)
Histology of non-calcified specimens	
ADH	13 (13.3)
FEA	27 (27.6)
Non-high-risk lesions	58 (59.2)
Risk groups* (calcified vs. non-calcified)	
Group A (ADH vs. high-risk lesions)	20 (20.4)
Group B (ADH vs. non-high-risk lesions)	30 (30.6)
Group C (FEA vs. high-risk lesions)	20 (20.4)
Group D (FEA vs. non-high-risk lesions)	28 (28.6)
Final surgical outcome	
Benign	81 (82.7)
Malignancy	17 (17.3)

*Risk group classification according to pathology of calcified specimens (ADH vs. FEA) and pathology of non-calcified specimens (high-risk lesions vs. non-high-risk lesions). ADH = atypical ductal hyperplasia, BI-RADS = Breast Imaging Reporting and Data System, FEA = flat epithelial atypia, IQR = interquartile range, VABB = vacuum-assisted breast biopsy

Stereotactic VABB Results

The median number of specimens obtained per lesion by stereotactic VABB was 9 (6–25); the median numbers of calcified and non-calcified specimens obtained per lesion were 5 (1–16) and 4 (1–16), respectively. Of the 98 patients with FEA or ADH, 21 (21.4%) had a nearly completely removed calcified lesion (≥ 90% calcification removed by VABB); the remaining 77 (78.6%) had < 90% calcification retrieval.

Pathological Findings

The diagnosis of almost all patients (98.0%, 96/98) after VABB was consistent with the pathological diagnosis of calcified specimens. Only two patients diagnosed with ADH had a pathological diagnosis of FEA using calcified specimens but ADH using non-calcified specimens. The diagnosis of 31 patients (31.6%) after VABB was consistent with the pathological diagnosis of non-calcified specimens. Calcified and non-calcified specimens generated the same pathological diagnoses in 18 of 46 FEA (39.1%) and 11 of 52 ADH (21.2%).

Of the 98 patients consecutively diagnosed with FEA or ADH by VABB followed by surgical excision, 14 (14.3%) were upgraded to DCIS and 3 (3.1%) were upgraded to IBC, resulting in a total underestimation rate of 17.3%. The respective underestimation rates were 6.5% for FEA and 26.9 % for ADH.

Factors Associated with the Underestimation of Malignancy

On comparing clinical characteristics, imaging features, and different risk stratifications based on the pathology of calcified and non-calcified specimens between patients with benign outcomes and those with malignancies, we found significant intergroup differences in calcification extent, BI-RADS category, and risk group stratification (Table 2).

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Patients with imaging morphologies of calcification extent > 34.5 mm had a significantly higher underestimation rate (54.5% vs. 12.6%, p = 0.003) than those with a calcification extent ≤ 34.5 mm. Calcifications categorized as a higher BI-RADS category had a higher probability of underestimation rate (BI-RADS 4b + 4c + 5 vs. BI-RADS 4a: 43.8% vs. 12.2%, p = 0.006). In terms of risk group stratification based on pathological results at stereotactic VABB, Group A had the highest underestimation rate (Group A vs. Group B vs. Group C vs. Group D: 35.0% vs. 20.0% vs. 15.0% vs. 3.6%, p = 0.041).

Using multivariate analysis including calcification

Table 2. Correlation of Clinicopathological Findings and Mammography Features with Outcome at Stereotactic VABB

Variables	n	Final Pathology		*P*
		Benign (n = 81)	Malignancy (n = 17)	
Age				0.973
≤ 50 years	58	48 (82.8)	10 (17.2)	
> 50 years	40	33 (82.5)	7 (17.5)	
Lesion location				0.719
Right	50	42 (84.0)	8 (16.0)	
Left	48	39 (81.3)	9 (18.8)	
Family history of breast cancer				0.206
Yes	5	3 (60.0)	2 (40.0)	
No	93	78 (83.9)	15 (16.1)	
Mammographic breast density				0.625
Scattered fibroglandular dense	11	8 (72.7)	3 (27.3)	
Heterogeneously dense	65	55 (84.6)	10 (15.4)	
Extremely dense	22	18 (81.8)	4 (18.2)	
Calcifications extent				0.003
≤ 34.5 mm	87	76 (87.4)	11 (12.6)	
> 34.5 mm	11	5 (45.5)	6 (54.5)	
Number of calcification specks				0.214
≤ 30	48	42 (87.5)	6 (12.5)	
> 30	50	39 (78.0)	11 (22.0)	
Distribution of calcifications				0.212
Grouped	66	57 (86.4)	9 (13.6)	
Regional	24	19 (79.2)	5 (20.8)	
Linear or segmental	8	5 (62.5)	3 (37.5)	
Morphology of calcifications				0.069
Amorphous	70	61 (87.1)	9 (12.9)	
Pleomorphic	25	17 (68.0)	8 (32.0)	
Coarse heterogenous	3	3 (100.0)	0 (0.0)	
BI-RADS category				0.006
4a	82	72 (87.8)	10 (12.2)	
4b + 4c + 5	16	9 (56.3)	7 (43.8)	
VABB specimens, median (IQR)	98	8.0 (6.0)	11.0 (6.0)	0.447
Calcification retrieval				0.110
< 90%	77	61 (79.2)	16 (20.8)	
≥ 90%	21	20 (95.2)	1 (4.8)	
Risk groups* (calcified vs. non-calcified)				0.041
Group A (ADH vs. high-risk lesions)	20	13 (65.0)	7 (35.0)	
Group B (ADH vs. non-high-risk lesions)	30	24 (80.0)	6 (20.0)	
Group C (FEA vs. high-risk lesions)	20	17 (85.0)	3 (15.0)	
Group D (FEA vs. non-high-risk lesions)	28	27 (96.4)	1 (3.6)	

Data are presented as n (%). *Risk groups classification according to pathology of calcified specimens (ADH vs. FEA) and pathology of non-calcified specimens (high-risk lesions vs. non-high-risk lesions).

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extent, BI-RADS category, and risk group stratification, only calcification extent and risk group stratification were identified as independent factors predictive of underestimation in patients with stereotactic VABB diagnosed with FEA or ADH with residual calcifications (Table 3). A calcification extent > 34.5 mm had an odds ratio (OR) of 6.059 with 95% confidence interval (CI) of 1.243–29.541 (p = 0.026). Regarding risk group stratification, using Group D as a reference, Group A had an OR of 12.598 with 95% CI of 1.295–122.601 (p = 0.029), but Groups C and D did not reach statistical significance (p = 0.181 and 0.251, respectively). On comparing clinical characteristics and imaging features between the four groups, significant intergroup differences in clinicopathological findings and mammographic features were not observed (Table 4).

DISCUSSION

The underestimation rates by stereotactic VABB were 6.5% for FEA and 26.9% for ADH, which were comparable to previously published findings (3-7, 11-13). In this study, we assessed the clinical characteristics and imaging features and emphasized the impact of non-calcified specimens in patients diagnosed with FEA or ADH on stereotactic VABB for suspicious calcifications with residual calcifications. The calcification extent and risk group stratification based on the pathology of calcified specimens compared with non-calcified specimens were predictors of underestimation. To the best of our knowledge, no previous studies have focused on the impact of non-calcified specimen pathology on the underestimation of malignancy of FEA and ADH.

The retrieval of suspicious calcifications can facilitate histopathological diagnosis using stereotactic core biopsy. A retrospective study by Margolin et al. (16) reported a higher sensitivity rate of malignancy from calcified core specimens than from non-calcified core specimens (84% vs. 71%) and suggested that pathologists thoroughly evaluate these calcified core specimens with additional levels of sections. Cheung et al. (17) conducted a retrospective study including 390 stereotactic VABB procedures on isolated breast microcalcifications without mass and demonstrated that calcified core specimens showed higher diagnostic accuracy of breast malignancy than non-calcified specimens (91.54 % vs. 69.49%). These results indicate that after biopsy, for lesions that exhibit abnormal calcifications, a calcified specimen is more likely to reflect the most advanced pathological outcome than a non-calcified specimen. The most advanced lesions among patients in this study after VABB were more highly consistent with the histological diagnosis of calcified specimens compared with that of non-calcified specimens (98.0% vs. 31.6%).

For calcified lesions, VABB can achieve larger specimens in higher numbers than core needle biopsy, increasing the diagnostic accuracy rate. However, due to the distribution characteristics of the calcification itself such as being regionally or segmentally distributed or having a large distribution range, it might be difficult for VABB to completely remove all suspicious calcifications. In fact, the diagnosis of high-risk lesions, including FEA and ADH, with incomplete retrieval of suspicious calcifications has always had a certain degree of malignancy underestimation, which is according to the results of this study, which

Table 3. Multivariate Analysis of Selected Characteristics Associated with Malignancy after Stereotactic VABB

Variables	Multivariate		*P*
	Odds Ratio	95% Confidence Interval	
Calcifications extent			
≤ 34.5 mm	1		
> 34.5 mm	6.059	1.243–29.541	0.026
BI-RADS category			
4a	1		
4b + 4c + 5	3.486	0.873–13.924	0.077
Risk groups* (calcified vs. non-calcified)			
Group A (ADH vs. high-risk lesions)	12.598	1.295–122.601	0.029
Group B (ADH vs. non-high-risk lesions)	4.692	0.488–45.074	0.181
Group C (FEA vs. high-risk lesions)	4.213	0.362–48.996	0.251
Group D (FEA vs. non-high-risk lesions)	1		

*Risk groups classification according to pathology of calcified specimens (ADH vs. FEA) and pathology of non-calcified specimens (high-risk lesions vs. non-high-risk lesions).

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Table 4. Differences in Clinicopathological Findings and Mammography Features between Intergroup

Variables	n	Risk Groups* (Calcified vs. Non-Calcified)				*P*
		Group A (n = 20)	Group B (n = 30)	Group C (n = 20)	Group D (n = 28)	
Age						0.413
≤ 50 years	58	12 (60.0)	16 (53.3)	10 (50.0)	20 (71.4)	
> 50 years	40	8 (40.0)	14 (46.7)	10 (50.0)	8 (28.6)	
Lesion location						0.559
Right	50	9 (45.0)	13 (43.3)	12 (60.0)	16 (57.1)	
Left	48	11 (55.0)	17 (56.7)	8 (40.0)	12 (42.9)	
Family history of breast cancer						0.090
Yes	5	0 (0.0)	4 (13.3)	0 (0.0)	1 (3.6)	
No	93	20 (100.0)	26 (86.7)	20 (100.0)	27 (96.4)	
Mammographic breast density						0.866
Scattered fibroglandular dense	11	4 (20.0)	3 (10.0)	2 (10.0)	2 (7.1)	
Heterogeneously dense	65	13 (65.0)	20 (66.7)	13 (65.0)	19 (67.9)	
Extremely dense	22	3 (15.0)	7 (23.3)	5 (25.0)	7 (25.0)	
Calcifications extent						0.489
≤ 34.5 mm	87	17 (85.0)	25 (83.3)	19 (95.0)	26 (92.9)	
> 34.5 mm	11	3 (15.0)	5 (16.7)	1 (5.0)	2 (7.1)	
Number of calcification specks						0.151
≤ 30	48	11 (55.0)	10 (33.3)	13 (65.0)	14 (50.0)	
> 30	50	9 (45.0)	20 (66.7)	7 (35.0)	14 (50.0)	
Distribution of calcifications						0.095
Grouped	66	11 (55.0)	19 (63.3)	17 (85.0)	19 (67.9)	
Regional	24	5 (25.0)	10 (33.3)	1 (5.0)	8 (28.6)	
Linear or segmental	8	4 (20.0)	1 (3.3)	2 (10.0)	1 (3.6)	
Morphology of calcifications						0.378
Amorphous	70	13 (65.0)	23 (76.7)	11 (55.0)	23 (82.1)	
Pleomorphic	25	7 (35.0)	6 (20.0)	8 (40.0)	4 (14.3)	
Coarse heterogenous	3	0 (0.0)	1 (3.3)	1 (5.0)	1 (3.6)	
BI-RADS category						0.490
4a	82	16 (80.0)	24 (80.0)	16 (80.0)	26 (92.9)	
4b + 4c + 5	16	4 (20.0)	6 (20.0)	4 (20.0)	2 (7.1)	
VABB specimens, median (IQR)	98	8.5 (6.0)	11.5 (6.0)	9.5 (6.0)	6.5 (6.0)	
Calcification retrieval						0.872
< 90%	77	15 (75.0)	25 (83.3)	15 (75.0)	22 (78.6)	
≥ 90%	21	5 (25.0)	5 (16.7)	5 (25.0)	6 (21.4)	

Data are presented as n (%). Group A (ADH vs. high-risk lesions); Group B (ADH vs. non-high-risk lesions); Group C (FEA vs. high-risk lesions); Group D (FEA vs. non-high-risk lesions). *Risk group classification according to pathology of calcified specimens (ADH vs. FEA) and pathology of non-calcified specimens (high-risk lesions vs. non-high-risk lesions).

shows a total underestimation rate of 17.3%. Regarding mammographic features, the only predictor of carcinoma was the calcification extent. It is reasonable to expect higher rates of underestimation when sampling is less adequate, which would be more likely in the case of a larger calcification extent or where more residual calcification is present. According to Peña et al. (22) in a series of 399 ADH cases diagnosed by core biopsy followed by surgical excision, patients whose biopsies showed no cell necrosis in combination with either 1 focus of ADH with ≥ 50% removal or 2–3 foci with ≥ 90% removal had an upgraded rate of 4.9% and were defined as a low-risk subgroup. In the current study, although the underestimation rate of malignancy in the nearly complete removal group was lower than that in the incomplete removal group (≥ 90% calcification retrieval vs. < 90% calcification retrieval: 4.8% vs. 20.8%, $p = 0.110$), the difference was insignificant. This may be because the number of subjects in this study was significantly small to be statistically significant. Regarding the calcification extent, a larger lesion size was typically

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associated with the underestimation of malignancy, which was consistent with findings reported by Bedei et al. (23) and Forgeard et al. (24); however, the optimal cutoff length for calcification extent remains unknown. In the present study, we identified 34.5 mm as the cutoff length for calcification extent that best discriminated malignancy outcomes.

It is difficult to distinguish whether the extent of the disease is larger than the extent of its own calcifications from the morphology of the image. Wagoner et al. (25) observed an ADH upgrade rate of 5% (three of 57 cases) when percutaneous biopsy resulted in the complete retrieval of all suspicious calcifications followed by subsequent excision. Schiaffino et al. (26) performed a meta-analysis study including 6458 lesions to estimate the upgrade rate of percutaneously diagnosed pure ADH and found that even if patients with apparent complete lesion removal after biopsy were considered, the pooled upgrade rate was 14%. Most studies emphasized the importance of pathological diagnosis of calcified lesions, but none of them mentioned the association between non-calcified lesions and disease (16-18). In our opinion, taking the pathological diagnosis of non-calcified specimens into consideration is beneficial in determining the extent of the disease. The presence of high-risk lesions in non-calcified tissues suggests that the pathological changes of the overall lesion are larger and may be more advanced. Actually, further stratification of these two factors (including calcified and non-calcified specimen histology) successfully identified that patients with FEA in calcified specimens not accompanied with high-risk lesions in non-calcified specimens were the risk group with the lowest underestimation. Furthermore, only one (3.6%) of the 28 patients belonging to the lowest risk group was diagnosed with DCIS after subsequent excision. It would be acceptable for us to obviate surgery in such scenario. Conversely, patients diagnosed with atypical hyperplasia had the highest underestimation rate of 35% if their non-calcified lesions showed high-risk lesions, and there was still a considerable degree of underestimation (15.0% and 20.0%, respectively) in the other subgroups. Therefore, those lesions in such scenarios should be managed with surgical excision.

Limitations of this study included its retrospective study design and small sample size. Additionally, the hematoma-directed ultrasound-guided procedure used in this study for lesion localization after VABB was different from the current standard needle localization procedure. However, the accuracy of hematoma-directed ultrasound-guided procedure for lesion localization could be confirmed by the retrieval of residual calcifications demonstrated by specimen mammograms and the previous biopsy site confirmed by pathological findings. Furthermore, the extent of FEA and ADH was not measured in the study because the actual volume of calcified and non-calcified tissue removed at stereotactic VABB was not known. Stereotactic VABB as a diagnostic tool for calcifications is mainly aimed at removing the calcifications, and there is usually less non-calcified tissue associated with it. The pathological diagnosis of non-calcified tissues should be considered as a reference factor in diagnosis. Hence, obtaining more non-calcified tissues to avoid underestimation is considered unnecessary. Finally, due to the small number of patients in our series, however, the optimal cutoff length for calcification extent for high-risk patients may need to be revised after inclusion of more cases.

In conclusion, our analyses revealed that larger calcification extent (≥ 34.5 mm) was a predictive factor of the underestimation of malignancy in FEA or ADH cases diagnosed by stereotactic VABB with residual calcifications. Considering the pathology of non-calcified specimens will help set up subsequent diagnostic planning strategies. For patients with FEA or ADH diagnosed by stereotactic VABB with residual calcifications, the results indicate that such findings should warrant subsequent excision, except for the diagnosis of FEA coexisting without atypia lesions in non-calcified specimens.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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