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Assessment of Breast Specimens With or Without Calcifications in Diagnosing Malignant and Atypia for Mammographic Breast Microcalcifications Without Mass

A STARD-Compliant Diagnostic Accuracy Article

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Abstract: Presence of microcalcifications within the specimens frequently signifies a successful attempt of stereotactic vacuum-assisted breast biopsy (VABB) in obtaining a pathologic diagnosis of the breast microcalcifications. In this study, the authors aimed to assess and compare the accuracy and consistency of calcified or noncalcified specimens obtained from same sites of sampling on isolated microcalcifications without mass in diagnosing high-risk and malignant lesions. To the best of our knowledge, an individual case-based prospective comparison has not been reported.

With the approval from institutional review board of our hospital (Chang Gung Memorial Hospital), the authors retrospectively reviewed all clinical cases of stereotactic VABBs on isolated breast microcalcifications without mass from our database. The authors included those having either surgery performed or had clinical follow-up of at least 3 years for analysis. All the obtained specimens with or without calcification were identified using specimen radiographs and separately submitted for pathologic evaluation. The concordance of diagnosis was assessed for both atypia and malignant lesions.

A total of 390 stereotactic VABB procedures (1206 calcified and 1456 noncalcified specimens) were collected and reviewed. The consistent rates between calcified and noncalcified specimens were low for atypia and malignant microcalcifications (44.44% in flat epithelial atypia, 46.51% in atypical ductal hyperplasia, 55.73% in ductal carcinoma in situ, and 71.42% in invasive ductal carcinoma). The discordance in VABB diagnoses indicated that 41.33% of malignant lesions would be misdiagnosed by noncalcified specimens. Furthermore, calcified specimens showed higher diagnostic accuracy of breast cancer as compared with the noncalcified specimens (91.54% versus 69.49%, respectively). The evaluation of both noncalcified specimens and calcified specimens did not show improvement of diagnostic accuracy as compared with evaluating calcified specimens alone (91.54% versus 91.54%, respectively).

Editor: Uma Sundram.

Received: May 26, 2015; revised: August 17, 2015; accepted: September 23, 2015.

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The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001832

The high prevalence of diagnostic discordance between the calcified and noncalcified specimens indicated the higher value of calcified specimens in diagnosing atypia and malignant microcalcifications. Noncalcified specimens did not provide additional diagnostic benefit from this study. The separation of calcified and noncalcified specimens may facilitate more focused interpretation from pathologists among the large number of specimens.

(*Medicine* 94(42):e1832)

Abbreviations: ACR = American College of Radiology, ADH = atypical ductal hyperplasia, BI-RADS = Breast Imaging Reporting and Data System, DCIS = ductal carcinoma in situ, FEA = flat epithelial atypia, IDC = invasive ductal carcinoma, NHSBSP = National Health Service Breast Screening Programme, VABB = vacuum-assisted needle breast biopsy.

INTRODUCTION

Minimally invasive percutaneous core needle biopsy is a cost-effective and reliable alternative to surgical biopsy for tissue sampling of suspicious breast lesions in both screening and clinical diagnostic contexts.¹⁻⁸ Breast biopsy is recommended for lesions with suspicious malignancy, classified as Breast Imaging Reporting and Data System for any lesion with malignant probabilities between 2% to 95%.⁹ Stereotactic vacuum-assisted needle breast biopsy (VABB) has been the standard for diagnosis of suspicious malignant breast microcalcifications, particularly in cases without associated mass.

As compared with the other available tissue sampling methods, VABB can accurately retrieve subtle or small microcalcifications and facilitate diagnosis of early breast cancer or high-risk breast lesions before they can be palpated. Currently, use of VABB over a targeted area enables retrieval of breast tissue both with and without calcifications; however, the presence or absence of calcifications may result in different pathologic diagnoses, despite being obtained from the same area. The aim of this study is to assess and compare the accuracy and consistency of calcified or noncalcified specimens obtained from same sites of sampling on isolate microcalcifications without mass in diagnosing high-risk and malignant lesions.

METHODS

From January 2008 to January 2010, we conducted a retrospective search for all clinical cases of stereotactic VABBs on isolated breast microcalcifications without mass from our database. Institutional Review Board of Chang Gung Memorial Hospital approved our study and waived the need for written

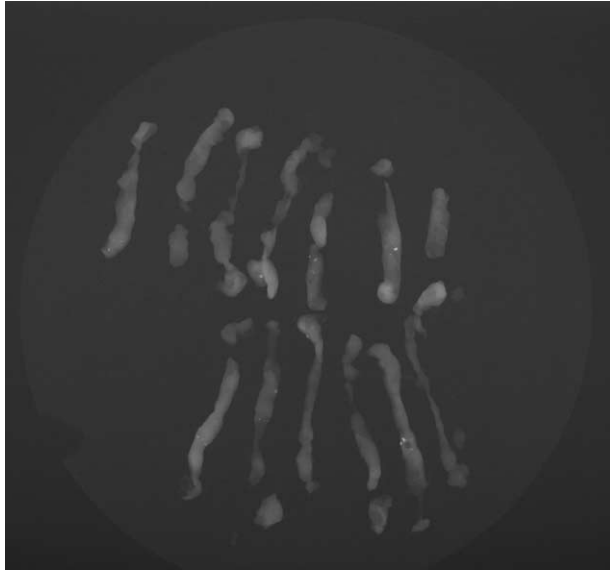


FIGURE 1. Specimen radiograph showing several pieces of specimens obtained by the stereotactic vacuum-assisted needle breast biopsy with presence of multiple isolated microcalcifications.

informed consent. Procedures were included for review if all of the following criteria were met: stereotactic VABBs were performed; absence of associated breast mass based on the findings by physical examination, mammography, and breast sonography; both specimens with (calcified specimens) and without calcifications (noncalcified specimens) have obtained by VABB from same sites of biopsy; either surgery or clinical follow-up of at least 3 years have performed. The presence or absence of calcifications was confirmed by using specimen radiographs after retrieval (Fig. 1), and the calcified and noncalcified specimens were separated and individually submitted for histologic diagnosis.

Before the biopsy procedure, all patients had been well explained and signed their agreement for the VABB procedure, and all VABB procedures were performed for clinical diagnostic purpose. Using mammography with an add-on biopsy unit (Lorad, Danbury, CT), the biopsy was performed using 10-gauge vacuum-assisted needles (Bard Vacora, Covington, CA) with the patient in either a sitting or lateral lying position depending on feasibility of localizing the microcalcifications. After localizing the target, microcalcification within the biopsy window, VABB was performed over the targeted area with 6 sampling retrievals routinely conducted with the multidirectional biopsy notch at different clock allocations. Additional retrieval around the target sites depended on the sufficiency of excised microcalcifications on the specimen mammography. The number of biopsy specimens ranged from 6 to 12 in the current case series.

Pathologists specializing on breast pathology were responsible for the histopathologic diagnosis. The calcified and noncalcified specimens were individually diagnosed, thus independent diagnoses were obtained for each specimen. The pathologic diagnoses were reviewed and evaluated for their consistency. Diagnosis consistency was defined as the case having an identical histopathologic diagnosis from both calcified and noncalcified specimens.

Histopathologic classifications were categorized from individual cases as benign, atypia, or malignant lesions for

comparison of consistency in both calcified and noncalcified specimens. All the patients had clinical follow-up for at least 3 years. Malignant lesions included invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS). The atypia lesions consisted of atypical ductal hyperplasia (ADH) or flat epithelial atypia (FEA). Lesions that were not categorized as histologically malignant or high-risk lesions were classified as benign.

Diagnostic performance was assessed using the standards specified by the National Health Service Breast Screening Programme publication number 50.¹⁰ Accuracy was defined as the number of malignant or suspicious lesions diagnosed by needle biopsy expressed as a percentage of the total number of surgically proven malignant cases.

RESULTS

A total of 390 consecutive stereotactic VABB procedures on female patients aged 30 to 66 years (49.40 ± 7.53 years) were included in the analysis. The demographic information of the patients receiving the VABB procedures was summarized in Table 1. Of 1206 calcified and 1456 noncalcified specimens, the VABB results documented 191 (48.97%) benign lesions, 124 (31.79%) atypia lesions (81 FEA + 43 ADH), and 75 (19.23%) malignant lesions (61 DCIS + 14 IDC). The calcified and noncalcified specimens obtained the same histologic diagnoses in 36 of 81 FEAs (44.44%), 20 of 43 ADHs (46.51%), 34 of 61 DCISs (55.73%), and 10 of 14 IDCs (71.42%) (Table 2). There was no statistic difference between the atypia and cancer lesions. The discordance of diagnoses indicated 41.33% (44 of 75 patients of VABB-diagnosed malignant lesions) would be misdiagnosed by noncalcified specimens.

The prevalence of breast malignancies by VABB was 19.23% (75 of 390 patients). A total of 79 patients underwent surgery, consisting of 54 patients with VABB diagnoses of malignancies (46 DCIS + 8 IDC), 21 patients with high-risk lesions (14 ADH + 7 FEA), and 4 patients with benign breast diseases. The types of surgeries performed included 4 excision biopsies, 32 partial mastectomies, 10 simple mastectomies, and

TABLE 1. Summary of the Demographic Data of the 390 Vacuum-Assisted Breast Biopsy Procedures

Category	Values (n = 390)
Age (years)	49.40 ± 7.53*
Reason for Mammography	
Cancer screening	155 (39.7%)
Clinical referral	235 (60.3%)
Sex	
Female	390 (100%)
Male	0 (0%)
Side of Breast Procedure	
Left	207 (53.1%)
Right	183 (46.9%)
Contralateral Breast Cancer	
Yes	38 (9.7%)
No	352 (90.3%)
Family History of Breast Cancer	
Yes	39 (10%)
No	351 (90%)

* Denotes value in mean value ± standard deviation.

TABLE 2. Diagnostic Consistencies of the Vacuum-Assisted Breast Biopsy Specimens With or Without Calcification in High-Risk and Malignant Lesions

No. of Procedures	199		Consistency
	1106 Calcified Specimens	1054 Noncalcified Specimens	
Diagnoses			
FEA	81	36	44.44%
ADH	43	20	46.51%
DCIS	61	34	55.73%
IDC	14	10	71.42%

ADH = atypical ductal hyperplasia, DCIS = ductal carcinomas in situ, FEA = flat epithelial atypia, IDC = invasive ductal cancer. $P = 0.701$ by Pearson χ^2 test.

33 modified radical mastectomies. Among the 54 cases of VABB-diagnosed malignant lesions (46 DCIS and 8 IDC) with surgery, 41 of the 46 DCIS cases (89.13%) retained the same diagnosis, in which 5 DCIS (10.86 %) were upgraded to IDC after surgery. Twenty-one atypia lesions subsequently received surgical excision, and 5 cases of ADH (23.8 %) were upgraded to DCIS. The other nonoperated patients of benign or high-risk lesions did not reveal cancer during the time of follow-up. The flow diagram was demonstrated as Figure 2.

Using the above-mentioned definitions, the accuracy of cancer diagnosis from the specimens containing microcalcifications was 91.52% (54 of 59 operated proven cancers) and was only 69.49% (41 of 59 cancers) for specimens without calcifications, resulting 22.03% lower accuracy. The evaluation of both noncalcified specimens and calcified specimens did not show improvement of diagnostic accuracy as compared with evaluating calcified specimens alone (91.54% versus 91.54%, respectively).

DISCUSSION

Breast calcifications are common mammography findings in screening or clinical examinations. Although microcalcifications may be associated with benign processes, precancerous lesions, or cancerous lesions,¹¹ histopathologic diagnoses are often necessary to confirm their natures, and image-guided percutaneous core needle biopsy of detectable breast lesions is a feasible method for obtaining specimens. A previous review of 4035 biopsies reported that the diagnostic accuracy of image-guided core needle biopsy was 90.8% for masses, 91.9% for isolated microcalcifications, and 62.2% for parenchymal distortion.¹² We have used stereotactic mammographic-guided biopsy for isolated microcalcifications identifiable mass in this study, according to the recommendations by American College of Radiology Breast Imaging Reporting and Data System.¹¹ Other literatures also supported the use of stereotactic mammographic-guided biopsy over sonographic-guided biopsy for isolated microcalcifications without mass, in which only 35.3% of mammographic microcalcifications were detectable (including masses or microcalcifications) by repeated sonographic target examinations.¹³ Another study reported that approximately 23% of patients of calcifications without other mammographic abnormalities could be detected by sonography; however, sonographic-guided core needle biopsy or needle localization may be optional for biopsy in other patients with detectable masses.¹⁴

As for the type of biopsy needles, VABB has an additional benefit of obtaining larger areas of specimens than point sampling using the spring-loaded technique, thus resulting in a higher probability of successful calcification retrieval.^{15,16} The retrieval of suspicious microcalcifications has been proven to facilitate histopathologic diagnosis because the retrieved microcalcifications are likely to represent markers of comedo necrosis from intraductal cancers on microscopy, and the presence or absence of microcalcifications in the core specimens may influence the outcome of a biopsy. A retrospective study revisiting the specimens reported a higher probability of cancer diagnosis from core specimens with calcifications than those without (84% versus 71%, respectively), and the diagnosis of cancer was more likely to be missed in core specimens without

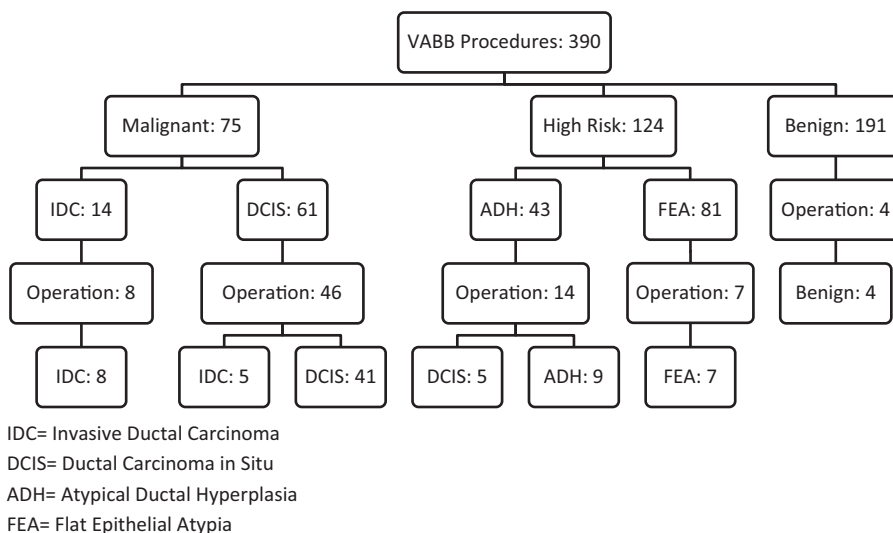


FIGURE 2. Flow diagram summarizing the total number of vacuum-assisted needle breast biopsy procedures, the number of surgeries performed in each category and the final surgical results.

microcalcifications (11% versus 1%).¹⁷ Our study compared the calcified and noncalcified specimens obtained from the same biopsy site, and the accuracy of calcified specimens was higher than that of noncalcified specimens (91.54% versus 69.49%). To the best of our knowledge, a prospective study with separated submission of calcified and noncalcified specimens was not reported before.

Diagnosis of cancer is vital for immediate disease control. High-risk breast lesions are often diagnosed by VABB of isolated microcalcifications; however, the management of such diseases is controversial.¹⁸ Atypical epithelial hyperplasia, such as ADH and FEA, are considered to be premalignant but not pathologically equivalent to malignancy; therefore, it is uncertain whether follow-up or subsequent surgical biopsy has a better prognosis. Although physicians may prefer surgical excision for high-risk lesions to avoid the risks of cancer transformation or biopsy underestimation, some of the patients, however, may choose to have follow-up because of a reluctance to undergo surgery. Therefore, we analyzed our patients with a follow-up of more than 3 years.

Underestimation of biopsy-diagnosed high-risk lesions after surgery has been reported. The underestimation rates have been reported to be 14% for FEA¹⁹ and 10.3% for ADH.²⁰ Although sampling adequacy was improved by VABB, the contributory factors of underestimation can be because of subtle histopathologic differences among atypia lesions and DCIS. We believe that the results in our study also showed similar reasoning, in which specimens in IDC generally have larger areas of cancer involvements, thus it will be more feasible to diagnose IDC from either calcified or noncalcified specimens. On the contrary, the difference between DCIS and atypia lesions are subtle, thus accurate VABB diagnosis can be better achieved from calcified than noncalcified specimens. Furthermore, recent studies involving epithelial atypia, including FEA or ADH, revealed an association with malignancy.²¹ Widespread mammographic screening would result in the detection of more isolated microcalcifications, and stereotactic core needle biopsy allows diagnosis of more high-risk lesions. Previous literatures revealed a 4- to 5-fold increased risk of cancer development with ADH,^{22,23} and a reported cancer rate of approximately 3% in FEA.²⁴ Nevertheless, early diagnosis of an atypia lesion provides timely warning of possible future cancer development.

As an effort to compare calcified and noncalcified specimens in the same case, we have adapted the practice of separating calcified from noncalcified specimens using specimen radiographs for independent histologic diagnoses since 2008. As reported in our study, we have observed an inconsistency of the diagnoses obtained from calcified and noncalcified specimens. We found a higher proportion of diagnostic consistency between calcified and noncalcified specimens by VAB in IDC, but lower for atypia lesions and DCIS. In addition, the results of our study also showed that the evaluation of both noncalcified specimens and calcified specimens did not show improvement of diagnostic accuracy as compared with evaluating calcified specimens alone. We believe that the radiographic identification and separate submission of calcified and noncalcified specimens may facilitate more focused interpretation from pathologists among the large number of specimens.

LIMITATIONS

Our study was limited by the small patient population, and the data were retrospectively collected in a single institution. In addition, not all the VABB-diagnosed high-risk lesions or

cancers received surgery in clinical practice; thus we have only included the cases with at least 3-year clinical follow-up.

CONCLUSIONS

The high prevalence of diagnostic discordance between the calcified and noncalcified specimens indicated the higher value of calcified specimens in diagnosing atypia and malignant microcalcifications. Noncalcified specimens did not provide additional benefit in diagnosing such cancers or high-risk lesions from this study. The separation of calcified and noncalcified specimens may facilitate more focused interpretation from pathologists among the large number of specimens.

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