



A diagnostic strategy for breast calcifications based on a long-term follow-up of 615 lesions

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Abstract

Purpose To clarify the long-term outcomes of breast calcifications after stereotactic vacuum-assisted breast biopsy (SVAB) and to develop strategy after SVAB.

Methods Subject comprised 594 patients with 615 calcifications who underwent SVAB. 371 (60.3%) lesions were diagnosed as benign, 38 (6.2%) as indeterminate, and 206 (33.5%) as malignant. We retrospectively reviewed post-biopsy courses of non-malignant lesions which were followed. A histopathological review was performed for false negatives to clarify the reasons.

Results Of the 308 patients with benign lesions, with a median follow-up time of 55.8 months, re-biopsy was performed for 11 (3.6%) due to changes of imaging, and 4 (1.3%) were diagnosed as breast cancer. Of the 36 patients with indeterminate lesion, re-biopsy was performed for 16 (44.4%), and 8 (22.2%) were diagnosed as breast cancer, while 20 (55.6%) showed no changes in imaging with a median follow-up time of 91.7 months without re-biopsy. Weak atypism of intraductal carcinoma may cause a false-negative diagnosis in SVAB for breast calcifications.

Conclusions When SVAB results in non-malignant, patients may be followed by annual screening, while re-biopsy needs to be performed for the patients with a discordant result of SVAB and with changes in an imaging finding during a follow-up.

Keywords Breast cancer · Calcifications · Mammography · Stereotactic vacuum-assisted breast biopsy

Introduction

Breast calcifications in mammography screening may indicate early breast cancer and are generally diagnosed by stereotactic vacuum-assisted breast biopsy (SVAB). SVAB is widely used to reach a histopathological diagnosis and permit the classification of lesions as follows: normal tissue (B1), benign (B2), uncertain malignant potential (B3), suspicious (B4), and malignant (B5) [1].

In 2003, one interdisciplinary consensus on the use and technique of SVAB stated that follow-up mammography needs to be conducted 3–9 months after SVAB at the same institution at which the original SVAB procedure was performed [2]. Therefore, follow-up mammography was performed 6 months after SVAB at many institutions. However, several studies with short- and mid-term follow-ups suggested that a 6-month follow-up examination after SVAB is unnecessary for B1 and B2 concordant lesions [3–5]. Calcifications diagnosed as B3 by SVAB are mostly flat epithelial atypia (FEA) and atypical

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intraductal hyperplasia (ADH). Their upgrade rates have been reported and whether surgical biopsy needs to be performed has been discussed. In 2016, the first international consensus for B3 lesions was reported [6]. According to the consensus, surveillance is acceptable for FEA, whereas surgical biopsy needs to be performed for ADH.

The practical guidelines after SVAB for B1–3 lesions need to be based on evidence from their long-term outcomes. However, to the best of our knowledge, the long-term outcomes of breast calcifications and subsequent breast cancer remain unclear. The present study aimed to investigate the long-term outcomes of non-palpable calcifications diagnosed as non-malignant by SVAB and develop a practical diagnostic strategy.

Patients and methods

This retrospective study was approved by the Institutional Review Board of our hospital.

Patients and lesions

Subjects consisted of 594 patients with 615 breast calcifications on mammography who underwent SVAB at our hospital between January 2006 and December 2007. SVAB was performed at 1 site for 573 patients, and at 2 sites for 21 patients (9 unilateral, 12 bilateral). The mean age of the 594 patients was 49.4 years (range 24–86 years) when SVAB was performed. Forty-two patients had a history of breast cancer and 7 of them had ipsilateral breast cancer.

Two breast surgeons described mammography findings in a mammography report. Both had training in mammography reports at The Japan Central Organization on Quality Assurance of Breast Cancer Screening. Before SVAB, a radiologist checked the report. In the present study, we reviewed the mammography reports. Of the 615 lesions, 60 (9.8%) were classified as Breast Imaging-Reporting and Data System (BIRADS) 3, 540 (87.8%) as BIRADS 4, and 15 (2.4%) as BIRADS 5. The diameter of the calcification area on mammography was a minimum of 2 mm and maximum of 100 mm (mean, 26.8 mm; standard deviation, 19.5 mm).

A follow-up was generally recommended for patients with BIRADS 3 calcifications. However, we recommended SVAB when the patient was at high risk of breast cancer or when the doctor in charge suspected a slight increase in calcifications. When a patient was introduced to our hospital for SVAB by affiliated hospitals, we performed SVAB even if calcifications were BIRADS 3 lesions.

Biopsy procedures

A radiologist skilled in breast biopsies performed the SVAB procedure on a digital prone biopsy table using 11-gauge probes (ST Mammotome®; Devicor Medical Japan, Tokyo, Japan). The number of specimens collected from each lesion was 2–5 in 353 (57.4%) cases, 6–10 in 216 (35.1%), and 11–22 in 46 (7.5%). And the median number of specimens collected from each lesion was 5 (range 2–22). In all cases, specimen radiographs were obtained to confirm that at least one specimen had calcifications before SVAB was completed. No severe complications were recorded. The SVAB results were compared according to the BIRADS category (Table 1).

Pathological diagnoses

Two pathologists who specialized in breast disease initially classified pathological diagnoses in 2006. In the diagnosis of breast disease, one pathologist had 20 years of experience, and the other had 10 years of experience. They classified B1 and B2 as ‘benign’, B3 as ‘indeterminate’, and B5 as ‘malignant’ [1]. The B3 report included FEA, mucocele-like tumors (MLT), atypical intraductal proliferation (AIP), and atypical lobular hyperplasia (ALH). In the present study, we reviewed the pathological reports. Among the 615 lesions, 4 (0.7%) were considered to be inadequate samples for a histopathological diagnosis because there were few ducts with atypical epithelia or no epithelia due to healing in SVAB specimens; these lesions were diagnosed as malignant by re-biopsy. As a result, 371 (60.3%) lesions were diagnosed as benign, 38 (6.2%) as indeterminate, and 206 (33.5%) as malignant (Fig. 1).

In cases in which breast cancer was diagnosed at the biopsy site after SVAB, SVAB and surgical specimens were reviewed by three authors to establish whether SVAB had collected some breast cancer tissue.

Table 1 Comparison of stereotactic vacuum-assisted breast biopsy results by BIRADS classification

BIRADS	3	4	5
Total case number	60	540	15
Initial histological diagnosis			
Benign (B1, B2)	47 (0)	324 (4)	0 (0)
Indeterminate (B3)	4 (1)	33 (6)	1 (1)
Inadequate amount (B4)	0 (0)	2 (2)	2 (2)
Malignant (B5)	9	181	12
False-negative rate (%)	2.0	3.3	100

Numbers in parentheses indicate false-negative cases
BIRADS Breast Imaging Reporting and Data System

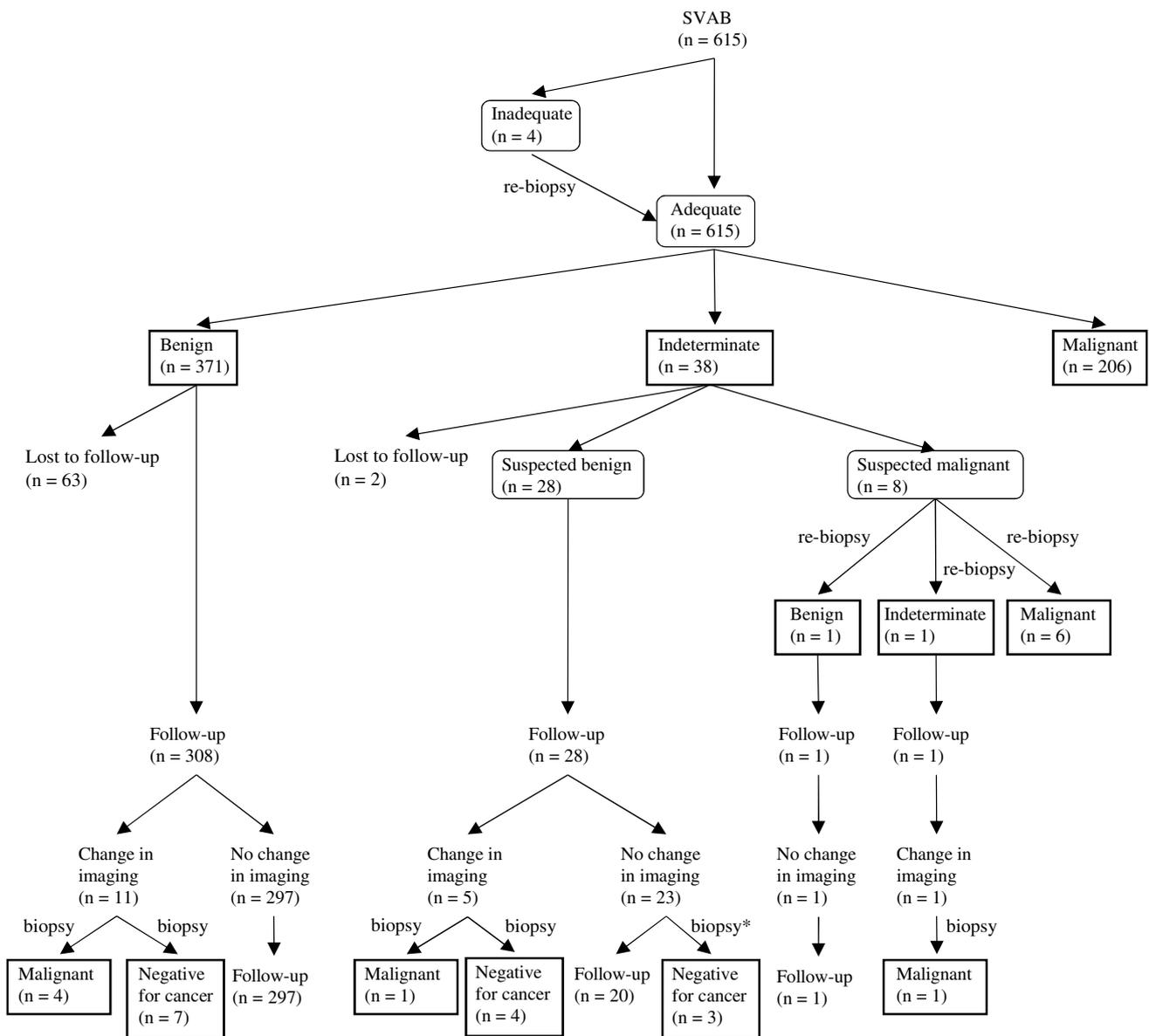


Fig. 1 Post-biopsy outcomes of 594 patients with 615 calcifications. Asterisk One patient underwent biopsy due to the patient’s request, while 2 underwent mastectomies because breast cancer was diagnosed in another area of the ipsilateral breast

Collecting the outcome data

In the present study, we examined the outcomes in the patients after SVAB. All the patients who hoped to be followed at our institution were followed 6 months after SVAB by mammography, ultrasound and examination. Then, the patients with benign and indeterminate lesions were followed annually and every 6 months, respectively, by mammography, ultrasound and examination. We reviewed electronic medical record including reports of imaging examinations.

Results

Post-biopsy course of benign lesions on SVAB

After SVAB, 63 (17.0%) patients with benign lesions were lost to the follow-up, and 308 (83.0%) were followed up. The median observation time was 71.5 months (range 5.6–119.3 months).

Of the 308 patients, re-biopsy was performed in 11 (3.6%) because of changes in the imaging results, and subsequently resulted in malignant diagnoses in 4 (1.3%), an

indeterminate diagnosis in 1 (0.3%), and benign diagnoses in 6 (1.9%) (Fig. 1). The median time from the initial benign SVAB to the diagnosis of breast cancer was 55.8 months (range 26.9–98.7 months). All 4 patients with breast cancer showed no changes in calcifications on mammography. Two patients were examined regularly, and ultrasonography revealed a small tumor and enlarged and grouped small cysts at the biopsy site. They were diagnosed with ductal carcinoma in situ (DCIS) (Table 2, Cases 8 and 9). In contrast, the other 2 patients were not examined regularly, and visited after detecting a lump at the biopsy sites in their breasts. They were diagnosed with invasive ductal carcinoma (IDC). The images and histologies of these cases are shown in Fig. 2. We reviewed SVAB and surgical specimens, and confirmed that SVAB specimens contained intraductal carcinoma in 3 out of the 4 cases. However, due to their weak atypism, they were initially diagnosed as benign. In the remaining case, calcifications were observed in adenosis adjacent to cancer in surgical specimens (Table 2, Case 9).

Post-biopsy course of indeterminate lesions on SVAB

Among the 38 patients with indeterminate lesions, 2 (5.3%) were lost to the follow-up, and 36 (94.7%) underwent a follow-up or re-biopsy at our hospital. The median observation time was 68.3 months (range 1.3–110.6 months).

Eight cases were suspected to be malignant based on either imaging or pathological findings, and re-biopsy was subsequently performed: 6 cases were diagnosed as malignant, 1 as indeterminate, and 1 as benign (Fig. 1). Six out of the 8 cases showed enhancement on contrast-enhanced MRI. However, 2 cases did not show enhancement on contrast-enhanced MRI even though they were diagnosed as malignant (Table 2, Cases 1 and 2). In the repetitively indeterminate case, a hypoechoic area detected by ultrasonography 51 months after the initial SVAB indicated malignancy following ultrasonography-guided biopsy (Table 2, Case 10). Therefore, 7 (87.5%) of the 8 cases were diagnosed as breast cancer. The median time from the initial SVAB to the diagnosis of breast cancer was 3.9 months (range 1.3–55.0 months).

The remaining 28 cases were suspected to be benign based on imaging and pathological results, and were subjected to follow-ups involving mammography, ultrasonography, and examinations every 6 months after SVAB. Re-biopsy was performed on 5 (17.9%) cases with changes in imaging findings: 1 (3.6%) was diagnosed as malignant, 1 as indeterminate, and 3 as benign (Fig. 1). Additionally, 1 patient underwent re-biopsy at the patient's request, and 2 patients underwent mastectomies because breast cancer was diagnosed in another area of the ipsilateral breast. However, there was no malignancy at their biopsy sites (Fig. 1). A total

of 20 (55.6%) lesions were followed up by imaging without re-biopsy, and no significant changes were observed in the images obtained (Fig. 1). The median observation time was 91.7 months (range 12.6–115.2 months). The images and histology of 1 case are shown in Fig. 3.

Of the 8 patients diagnosed with malignant lesions, 7 underwent surgery in our hospital: 1 was diagnosed with IDC and 6 with DCIS. The IDC case had minimal invasion (Table 2, Case 1). Among the 6 DCIS cases, 4 were classified as grade 1 with nuclear atypia and without comedo necrosis, and 2 were classified as grade 2 with nuclear atypia. Comedo necrosis was observed in 1 case (Table 2, Case 7). A retrospective review recognized all the histological changes in the SVAB specimen as indicative of intraductal carcinoma. However, difficulties were associated with diagnosing malignant lesions due to weak atypism.

Post-biopsy diagnosis of malignant lesions on SVAB

Surgery was performed on 173 out of the 206 malignant lesions at our hospital. Of the 173 cases, 123 (71.1%) were diagnosed as DCIS, 48 (27.7%) as IDC, and 2 (1.2%) as Paget's disease. There was no lymphatic metastasis in any of the cases examined.

Discussion

As far as we know, this study is the first report to clarify the long-term outcomes of breast calcifications after SVAB and the pathological causes of false negatives. SVAB is widespread as an accurate way to diagnose breast calcifications. The false negatives of SVAB may occur when calcifications are absent in SVAB specimens or when the areas of lesions with weak atypia have been sampled due to tumor heterogeneity [7–10]. Therefore, the false-negative rate due to weak atypia needs to be elucidated with long-term follow-up outcomes. The present study consisted of 615 calcifications only, and the median observation period for B1 and B2 lesions was 71.5 months. Compared to the study of Jackman et al., the present study involved the longest follow-up outcomes of breast calcifications after SVAB with the largest number of cases [11]. Among 413 lesions that were initially diagnosed as non-malignant, 16 (3.9%) were diagnosed as false negative. In addition, 5 (31.3%) of the 16 cases were diagnosed as false negatives at a later stage.

A histopathological review clarified three reasons for the false negatives by SVAB for calcifications. First, when an inadequate tissue for a diagnosis is sampled by SVAB, it may be misdiagnosed as benign. Even if a specimen radiograph shows calcifications, in a case that intraductal carcinoma disappears due to 'healing' and only calcifications remain, the lesion may be misdiagnosed as benign. 'Healing' is a

Table 2 Clinicopathological characteristics of 12 breast cancer cases initially diagnosed as nonmalignant by SVAB

Case	1	2	3	4	5	6	7	8	9	10	11	12
Time from SVAB to diagnosis of breast cancer (m)	1.3	1.8	2.0	3.9	4.0	5.6	11.2	26.9	54.9	55.0	56.6	98.7
Age at SVAB (y)	60	55	48	49	45	46	51	50	40	51	37	61
BIRADS	4	4	5	4	3	4	4	4	4	4	4	4
Calcification diameter (mm)	16	63	55	39	38	42	45	14	20	22	47	39
Ultrasonography findings before SVAB	No finding	No finding	Hypochoic areas with hyperchoic spots	Tumor	No finding	No finding	No finding	No finding	Grouped small cysts	No finding	Small cysts	No finding
Contrast-enhanced MRI	Not enhanced	Not enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced	Enhanced
Number of specimens per lesion	6	7	5	3	5	6	5	5	7	3	4	4
Initial diagnosis of SVAB	Indeterminate	Indeterminate	Indeterminate	Indeterminate	Indeterminate	Indeterminate	Indeterminate	Indeterminate	Benign	Indeterminate	Benign	Benign
Histology of SVAB	FEA and AIP	FEA	MLT	MLT	FEA	FEA	FEA and AIP	Mastopathy	Normal breast tissue	FEA	Small cysts	Mastopathy
Final diagnosis	IDC ^a	DCIS	DCIS	DCIS	DCIS	NA	DCIS	DCIS	DCIS	DCIS	IDC	IDC
Comedo necrosis	Absent	Absent	Absent	Absent	Absent	NA	Present	Absent	Absent	Absent	Absent	Absent
Nuclear atypia grade	2	1	1	1	1	NA	2	1	1	2	1	2

MRI magnetic resonance imaging, SVAB stereotactic vacuum-assisted breast biopsy, BIRADS Breast Imaging Reporting and Data System, FEA flat epithelial atypia, AIP atypical intraductal proliferation, MLT mucocoele-like tumor, DCIS ductal carcinoma in situ, IDC invasive ductal carcinoma, NA not available

^aMinimal invasion

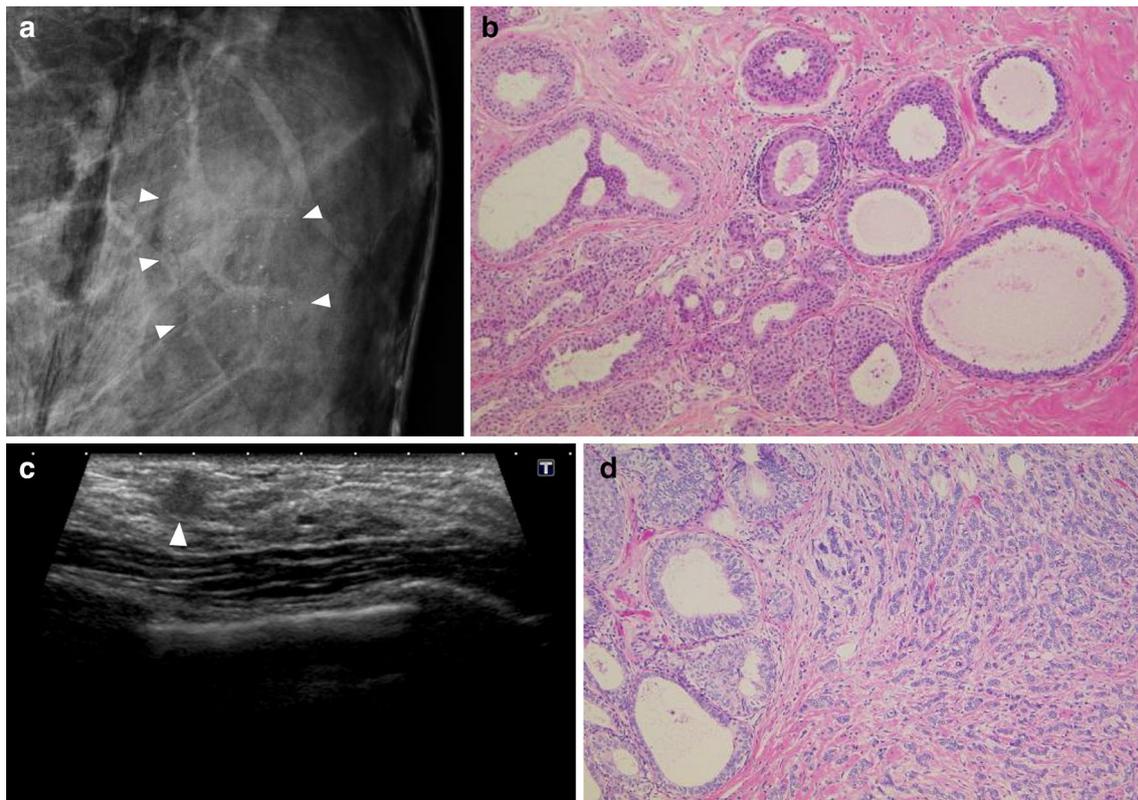


Fig. 2 Images and histology of a case initially diagnosed as benign by stereotactic vacuum-assisted breast biopsy (SVAB), but eventually diagnosed as invasive ductal carcinoma (IDC). **a** Enlarged mediolateral oblique mammography of the left breast before SVAB. Segmental amorphous calcifications were observed (arrowheads) and assigned as Breast Imaging-Reporting and Data System (BIRADS) 4. **b** Hematoxylin & eosin (H&E) staining of the SVAB specimen, with

medium magnification. Secretory calcifications were observed in the normal duct and diagnosed as benign. **c** Ultrasonography 55 months post-SVAB. A 7-mm hypoechoic mass was detected at the biopsy site (arrowhead). **d** H&E staining of the surgical specimen. The specimen was diagnosed as invasive ductal carcinoma with 5-mm invasion on the surgical specimen. Histological changes in the SVAB specimen were similar to intraductal carcinoma in the surgical specimen

histological finding indicating that cancer cells have disappeared. It is reportedly observed in intraductal carcinomas, such as comedo- and solid-type carcinomas [12]. When ‘healing’ is recognized or suspected, re-biopsy needs to be performed. Second, when calcifications exist in benign lesions in close proximity to the cancer, which is not identified on mammography, the sampling of calcifications by SVAB may lead to a false-negative result. Third, when low-grade intraductal carcinoma is sampled by SVAB, it may be diagnosed as benign. An annual screening is appropriate to follow-up for such lesions, since they progress slowly over a long period. When imaging changes are observed at the biopsy site, biopsy needs to be performed regardless of the finding and timing.

The post-biopsy courses of the present study that three steps after SVAB are important as a diagnostic strategy for calcifications. The first step is the evaluation of the SVAB specimen. When SVAB specimens are inadequate for a diagnosis, re-biopsy needs to be performed. The second step is the comprehensive evaluation of radiopathological

results. The cases shown in Figs. 2, 3 were both BIRADS 4 calcifications, and the histology of SVAB was very similar, while only 1 case showed imaging changes and was diagnosed as breast cancer. Contrast-enhanced MRI may contribute to this evaluation for B3 lesions to decide to perform a re-biopsy. However, prospective studies are needed to clarify the long-term prognosis of B3 lesions, while also considering the possibility of an ‘over-diagnosis’. Until then, clinicians need to examine individual patients in collaboration with imaging specialists and pathologists and select the optimal approach. The third step is re-biopsy when imaging findings change during the follow-up. Supplemental ultrasonography is reported to be useful for detecting early breast cancer especially in dense breasts [13, 14].

This study has some limitations. It was retrospective, with some cases being lost to the follow-up, and was performed at a single institution. In 2006 and 2007, SVAB was performed in fewer hospitals, and some patients visited our hospital for SVAB. After SVAB, they were

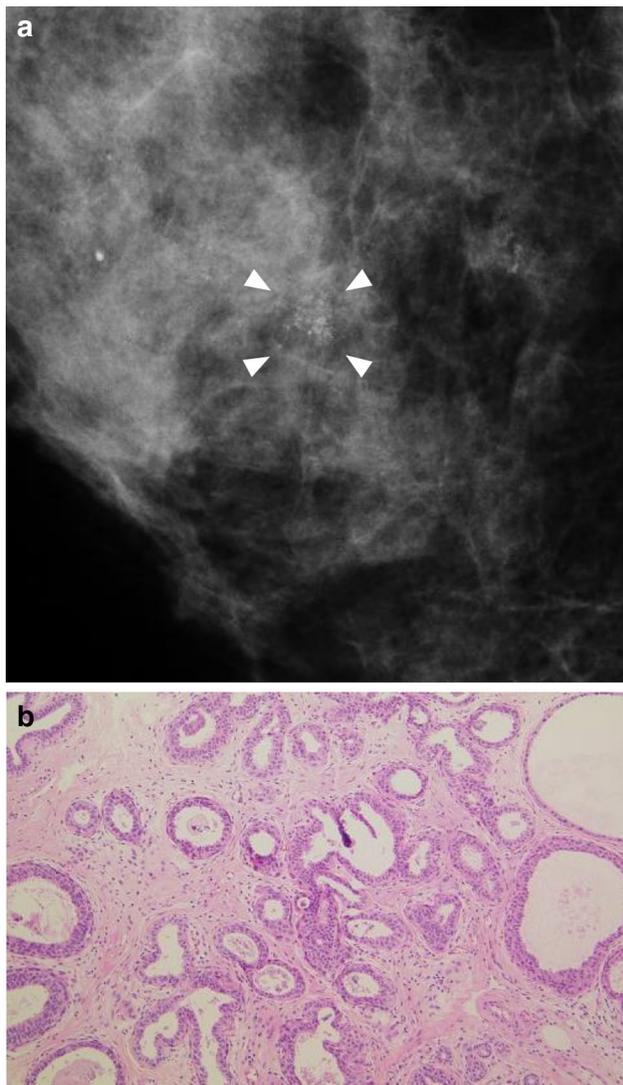


Fig. 3 Image and histology of a case diagnosed as indeterminate by stereotactic vacuum-assisted breast biopsy (SVAB) and followed up without additional biopsy. **a** Enlarged craniocaudal mammography of the right breast before SVAB. Grouped amorphous calcifications were observed (arrowheads) and assigned as Breast Imaging-Reporting and Data System (BIRADS) 4. **(b)** Hematoxylin & eosin staining of the SVAB specimen, with medium magnification. Secretory calcifications were observed in flat epithelial atypia (FEA), which was indeterminate. No changes were observed in images 97.4 months after SVAB

followed up at the affiliated institutions and visited our hospital when they needed a detailed examination.

In conclusion, this study reported the long-term follow-up data of breast calcifications after SVAB and revealed three necessary steps as a diagnostic strategy after SVAB. When SVAB results in non-malignancy, these three steps may contribute to an accurate diagnosis.

Compliance with ethical standards

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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