Clinicopathological Factors Associated with Remnant or Regrowth of Benign Breast Tumor after Previous Vacuum-Assisted Core Biopsy

Won Gong Choo, Chang Wan Jeon, Dong Won Ryu

Department of Surgery, Kosin University Gospel Hospital, Busan, Korea

Purpose: We sometimes encounter remnant or regrowth of benign breast tumors diagnosed as Breast Imaging-Reporting and Data System (BI-RADS) C4 in follow-up breast ultrasound after previous vacuum-assisted core biopsy (VACB). We aimed to evaluate the factors that influence remnant or regrowth tumors at post-VACB site or adjacent tissue. **Methods:** From January 2010 to December 2015, we analyzed 647 cases on follow-up. Patients were divided into two groups; group A was defined as patients without recurrent masses on breast ultrasonography during the follow-up period, and group B was defined as those with recurrent masses diagnosed as more than BI-RADS C4 on ultrasonography. **Results:** Fibrocystic changes, proliferative disease without atypia, intraductal papilloma, apocrine cell change, atypical ductal hyperplasia, sclerosing adenosis, and radial scars were observed in 89.5% (n=579), 15.9% (n=103), 15.3% (n=99), 5.3% (n=34), 5.7% (n=37), 7.6% (n=49), and 6.3% (n=41) of patients, respectively. During the follow-up period, 85 patients were diagnosed as group B. Group B was significantly associated with proliferative diseases without atypia, sclerosing adenosis, and microcalcifications compared to group A ($p=0.008$, $p=0.007$, and $p=0.001$, respectively). After adjustment for confounding variables, group B was more significantly associated with proliferative breast diseases than group A (hazard ratio [HR], 0.558; 95% confidence interval [CI], 0.343–0.907; $p=0.018$). Furthermore, group B was more significantly associated with intraductal papilloma (HR, 0.571; 95% CI, 0.342–0.953; $p=0.032$). **Conclusion:** Previously diagnosed proliferative diseases without atypia or microcalcification at first VACB were significantly associated with recurrent breast tumor. Intraductal papilloma was also significantly associated with tumor regrowth.

Key Words: Intraductal papilloma, Recurrence

INTRODUCTION

Vacuum-assisted core biopsy (VACB) is a minimally invasive method used in the diagnosis and treatment of focal breast lesions [1]. Various advantages of VACB have made it a commonly used procedure to diagnose breast lesions. VACB allows removal of multiple tissue samples at a single attempt in a relatively short time, and the patient is able to patients are discharged from the hospital soon [2]. VACB is primarily a diagnostic method for focal breast lesions. Focal lesions in the breast requiring histopathological examination are the primary indications for this procedure [3]. In some cases, VACB can be used therapeutically. It is not used to treat malignant lesions because the samples obtained in this procedure are fragmented, which make it impossible to precisely establish the margin of the removed tissue [4]. However,

for treating small benign lesions, VACB is currently used as a minimally invasive alternative to open surgical biopsy [5]. Benign breast disease (BBD) is a heterogeneous condition consisting of many histological entities, including ductal proliferation with or without atypia, fibroadenomas, and intraductal papillomas [6]. Some of these lesions are thought to represent progressive changes in the stepwise sequence of histological changes leading to the development of breast cancer. Specifically, it has been hypothesized that nonatypical proliferative forms of BBD, proliferative diseases with atypia, and *in situ* cancer represent successive steps preceding the development of invasive breast carcinoma [7]. We have occasionally encountered tumor regrowth in sites where VACB was previously performed or in adjacent tissues. Hence, we aimed to evaluate the factors that influence tumor regrowth at post-biopsy sites or at adjacent tissues.

Correspondence: Dong Won Ryu

Department of Surgery, Kosin University Gospel Hospital, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6462, Fax: +82-51-246-6093, E-mail: lovebreast@naver.com

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METHODS

Patients

The medical records and pathological reports of 647 patients from

therapeutic Mammotome (Ehicon, Cincinnati, USA) biopsies performed in the Department of Surgery of Kosin University Hospital from January 2010 to December 2015 were reviewed. The patients were divided into two groups; group A was defined as those without recurrent masses on breast ultrasonography during the follow-up periods, and group B was defined as those with recurrent masses diagnosed as more than Breast Imaging-Reporting and Data System (BI-RADS) C4 on ultrasonography. We aimed to compare the clinicopathological features, treatment strategies, and clinical outcomes of post-VACB with and without recurrent masses on breast ultrasonography and to determine their prognostic factors. All VACB and surgical excisions were performed by the same experienced surgeons. A pathologist examined the samples in the laboratory of Kosin University Hospital. The patients with histopathological diagnosis of benign lesions were followed up with clinical and ultrasound examinations after 3, 6, and 12 months. All women with atypical ductal hyperplasia (ADH), ductal carcinoma *in situ*, or invasive cancer were qualified for surgical excision. The median follow-up time was 11 months (range, 4–38 months). The exclusion criteria were as follows: (1) patients who refused to give informed consent for undergoing VACB; (2) those who were allergic to local anesthetics; and (3) those with active skin infections on the breast. The inclusion criterion was cases diagnosed as BI-RADS category 5. This study was approved by the Institutional Review Board of the Kosin University (IRB number: 201509-BR-013).

Procedure

Breast ultrasonographic examinations were performed using a Siemens ACUSON S2000 US system (Siemens Medical Solutions, Mountain View, USA) with a linear probe (9L4; Siemens Medical Solutions). A single surgeon performed the biopsies under local anesthesia. A small skin incision (4 mm) was made and the probe was positioned into the lesion by ultrasound-guidance. The acquisition of tissue was performed in different ways and from different angles, as needed. The number of samples varied according to the size of the lesion. Finally, hemostasis was achieved by performing manual compression for 10 minutes. The patients were instructed to inform the radiologist or visit the hospital in case they developed any complications after the procedure. Criteria for making a diagnosis of benign lesions included specific findings such as fibroadenoma, papilloma, phyllodes tumors, as well as nonspecific findings such as fibrosis and

fibrocystic changes. For patients who met the aforementioned criteria, they were advised to undergo mammographic or ultrasonographic follow-up in 6 months. In situations of discordance between imaging and histologic findings, surgery was proposed.

Statistical analyses

Groups were compared with chi-square test or Fisher exact test, as appropriate. Statistical tests were performed using SPSS 12.0 statistical software package for Windows (SPSS Inc., Chicago, USA). The chi-square test was used to evaluate correlation between pathologic benign diseases and clinicopathological parameters in all cases. A p -value < 0.05 was considered as statistically significant. A Cox regression analysis was used to compute the risk of BI-RADS C4 in breast ultrasonography during the follow-up period. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined.

RESULTS

A total of 647 women who underwent VACB were identified from the patient report of Kosin University Hospital. In this cohort, the median age at diagnosis was 56 years (range, 20–95 years), and 36% of patients were aged 50 and over. Patients' demographics and BBD data are presented in Table 1. A majority of patients (86.7%) had a normal body mass index (BMI). Among them, 562 patients (86.9%) were categorized as group A (post-VACB without recurrence). Group A was more likely to have proliferative lesions without atypia, sclerosing adenosis, and microcalcification. According to the post-VACB pathology report, most BBDs were heterogeneous. Fibrocystic changes were found in 579 tumors (89.5%), intraductal papillomas in 99 tumors (15.3%), proliferative lesions in 103 tumors (15.9%), sclerosing adenosis in 49 tumors (7.6%), radial scars in 41 tumors (6.3%), apocrine metaplasia in 34 tumors (5.3%), and ADH in 37 tumors (5.7%). Reoperation was done in 37 patients with ADH due to safety concerns about surgical margins. Furthermore, patients were followed up for 6 months intervals. During the follow-up periods, 85 patients were diagnosed as group B, and biopsies were taken. According to the second pathology reports, fibrocystic diseases were found in 77 (90.6%), intraductal papillomas in 19 (22.4%), proliferative diseases without atypia in 22 (25.9%), sclerosing adenosis in 13 (15.3%), radial scars in two (2.3%), and apocrine metaplasia in six (7.0%) tumors (Table 2). For analysis

Table 1. Patient and tumor characteristics (n=647)

Characteristic	Group A (n = 562) No. (%)	Group B (n = 85) No. (%)	Total (n = 647) No. (%)	p-value
Age (yr)*	45.7	43.9		0.191
Age of menarche (yr)*	15.0	14.8		0.757
Status of marriage				0.902
Married	414 (73.7)	61 (71.8)	475 (73.4)	
Not married	76 (13.5)	13 (15.3)	89 (13.8)	
Missed	72 (12.8)	11 (12.9)	83 (12.8)	
Total	562 (86.9)	85 (13.1)	647 (100)	
Age of marriage (yr)*	25.7	25.6		0.976
Age of menopause (yr)*	48.6	46.2		0.005
Family history of breast cancer				0.029
Positive	24 (4.3)	2 (2.4)	26 (4)	
Negative	220 (39.1)	22 (25.9)	242 (37.4)	
Unknown	318 (56.6)	61 (71.8)	379 (58.6)	
Body mass index (kg/m ²)				0.789
Normal	364 (64.8)	55 (64.7)	419 (64.8)	
High	36 (6.4)	7 (8.2)	43 (6.6)	
Unknown	162 (26.8)	23 (27.1)	185 (28.6)	
Fibrocystic change				0.449
Positive	502 (89.3)	77 (90.6)	579 (89.5)	
Negative	60 (10.7)	8 (9.4)	68 (10.5)	
Atypical ductal hyperplasia				0.356
Positive	31 (5.5)	6 (7.1)	37 (5.7)	
Negative	531 (94.5)	79 (92.9)	610 (94.3)	
Intraductal papilloma				0.144
Positive	80 (14.2)	19 (22.4)	99 (15.3)	
Negative	482 (85.8)	66 (77.6)	548 (84.7)	
Proliferative diseases without atypia				0.008
Positive	81 (14.4)	22 (25.9)	103 (15.9)	
Negative	481 (85.6)	63 (74.1)	544 (84.1)	
Sclerosing adenosis				0.007
Positive	36 (6.4)	13 (15.3)	49 (7.6)	
Negative	526 (93.6)	72 (84.7)	598 (92.4)	
Radial scars				0.074
Positive	39 (6.9)	2 (2.4)	41 (6.3)	
Negative	523 (93.1)	83 (97.6)	606 (93.7)	
Calcification				< 0.001
Positive	20 (3.6)	15 (17.6)	35 (5.4)	
Negative	542 (96.4)	70 (82.4)	612 (94.6)	
Apocrine metaplasia				0.281
Positive	28 (5.0)	6 (7.1)	34 (5.3)	
Negative	534 (95.0)	79 (92.9)	613 (94.7)	

Group A = those without recurrent mass in breast ultrasonography during follow up periods after vacuum-assisted core biopsy (VACB); group B = those with recurrent mass diagnosed as more than scores of Breast Imaging-Reporting and Data System C4 in breast ultrasonography after VACB.

*Mean.

Table 2. Histopathologic results of core needle biopsy about group B

	Total (n = 85) No. (%)
Fibrocystic change	
Positive	77 (90.6)
Negative	8 (9.4)
Intraductal papilloma	
Positive	19 (22.4)
Negative	66 (77.6)
Sclerosing adenosis	
Positive	13 (15.3)
Negative	72 (84.7)
Radial scars	
Positive	2 (2.3)
Negative	83 (97.7)
Apocrine metaplasia	
Positive	6 (7.0)
Negative	79 (93.0)

Group B = those with recurrent mass diagnosed as more than scores of Breast Imaging-Reporting and Data System C4 in breast ultrasonography after vacuum-assisted core biopsy.

Table 3. Clinicopathological variables for 1-year recurrence-free survival rate in univariate analysis

	HR (95 % CI)	p-value
BMI (kg/m ²)	0.511 (0.219–1.193)	0.286
Fibrocystic change	0.859 (0.414–1.782)	0.683
Atypical ductal hyperplasia	0.657 (0.285–1.511)	0.319
Intraductal papilloma	0.571 (0.342–0.953)	0.032
Proliferative diseases without atypia	0.558 (0.343–0.907)	0.018
Sclerosing adenosis	0.707 (0.391–1.280)	0.253
Radial scars	2.953 (0.726–12.011)	0.130

HR = hazard ratio; CI = confidence interval; BMI = body mass index.

accounting for various confounding factors, group B was significantly associated with proliferative diseases without atypia, sclerosing adenosis, and microcalcification compared to group A ($p = 0.008$, $p = 0.007$, and $p = 0.001$, respectively). After adjustment for confounding variables, group B was associated more with proliferative breast diseases than group A (HR, 0.558; 95% CI, 0.343–0.907; $p = 0.018$). Furthermore, group B was associated with intraductal papilloma (HR, 0.571; 95% CI, 0.342–0.953; $p = 0.032$). However, group B was not associated with high BMI (HR, 0.511; 95% CI, 0.219–1.193; $p = 0.286$) (Table 3).

DISCUSSION

Breast tumors can recur at the original site (called local recurrence).

Local recurrence is usually found on breast ultrasound during a follow-up examination by a health care provider or if a morphologic change is observed. Recurrence is usually found when breast ultrasound is reported as BI-RADS C4 during follow-up. When a local recurrence is observed, it is diagnosed in a similar manner as that used for the diagnosis of the first breast tumor. The tumor is biopsied by the surgeon and examined by the pathologist. Tests are done to ensure that there is no sign of malignancy. In our study, there was no evidence of malignancy on pathology reports. Hence, most cases were diagnosed as BI-RADS C4 on breast ultrasonography during follow-up. Post-VACB scar formation was believed to have influenced the diagnosis of BI-RADS C4 on breast ultrasound. Developments in imaging diagnostics and relatively good availability of devices for performing mammography and ultrasound has increased the detection of breast focal lesions at the preclinical stages [6]. The differential diagnosis of small, impalpable focal lesions suspected of a malignant process is especially difficult [8,9]. Until recently, the gold standard treatment for such cases was an open surgical biopsy. However, the possibility of developing complications, the length of the procedure, high costs, formation of scars, and frequent occurrence of breast deformation have led to a search for less invasive and less expensive methods [10]. VACB proves to be a method that eliminates or to a large extent limits these disadvantages [11]. It is an efficient, minimally invasive, relatively inexpensive procedure with a good cosmetic effect, and has a low complication rate [12]. Similar to minimally invasive techniques used in the treatment of other organs, VACB, in some cases, can be an alternative to a more extended surgical procedure [13]. This procedure is gradually replacing the commonly used procedure: fine needle aspiration biopsy, whose main disadvantage is a high rate of nondiagnostic results (4%–35.4%), as well as false negative findings (2.6%–20%). VACB provides multiple quality samples from a single procedure compared to a traditional core biopsy [14]. The diagnostic accuracy of the Mammotome biopsy is 98% to 100% for breast lumps [15]. Open surgical biopsy yields similar results, but is more invasive and expensive. In our patients, a sufficient number of samples for histopathological examination were obtained in the first biopsy from 647 patients (99.2%) [16]. VACB can have therapeutic value, while being well tolerated and associated with low complication rates compared to surgery [17]. In our study, we entirely removed lesions with a low-risk of malignancy using VACB in imaging examinations with an incision diame-

ter up to 15 mm in 94.5% of women. This is similar to Plantade, who excised entire lesions in 98.1% of his patients [18]. However, if cases are diagnosed as benign lesions by biopsy, and the lesions are classified as BI-RADS 4a, 4b, 5 by imaging examinations, it is necessary to repeat the biopsy or perform open surgical biopsy as there is a high risk that the cancer may not be completely treated [19]. In conclusion, lesions previously diagnosed as proliferative diseases without atypia or microcalcification during the first VACB were significantly associated with recurrent benign breast tumors. Intraductal papilloma was also significantly associated with tumor regrowth. Therefore, close follow-up is needed for such diagnosis on VACB samples.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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