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Original Paper

The diagnosis of non-malignant papillary lesions of the breast: comparison of ultrasound-guided automated gun biopsy and vacuum-assisted removal

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AIM: To compare the histological upgrade rate of ultrasound (US)-guided vacuum-assisted removal (VAR) and US-14 G-automated core needle biopsy (ACNB) in the diagnosis of papillary breast lesions.

MATERIALS AND METHODS: Two hundred and seventy-one biopsies of 230 papillary lesions were examined, which underwent subsequent surgical excision or long-term follow-up after US-ACNB ($n = 206$) or US-VAR ($n = 65$). The false-negative and atypical papilloma underestimation rate were compared between the ACNB and VAR groups. Patient and lesion characteristics were collected. The histological upgrade rates of the diagnosis were estimated and compared.

RESULTS: Out of 271 papillary lesions, 195 (80.0%) were benign, 21 (7.7%) were atypical, and 55 (20.3%) were malignant. There were no false negatives or underestimated atypical papillomas in the VAR group. However, in the ACNB group, the false-negative rate was 7.6% (12 of 157 benign papillomas, 95% CI; 4.4–12.9%, $p = 0.039$) and the atypical papilloma underestimation rate was 33% (five of 15 atypical papillomas, 95% CI; 15.2–58.3%, $p = 0.135$). The histological upgrade rates of the diagnosis for papillary breast lesions were 0% for the VAR (0 of 66) group and 10.2% for the ACNB (21 of 206) group before adjusting for the population ($p = 0.003$).

CONCLUSIONS: ACNB was associated with significantly higher false-negative and histological upgrade rates of diagnosis for papillary breast lesions than VAR.

Introduction

Papillary lesions of the breast encompass such a wide spectrum of lesions that it can be difficult to differentiate between a benign papillary lesion and a papillary carcinoma upon histological evaluation.[1–3] A papilloma can display focal proliferation of a mildly atypical, monotonous cell population identical to non-comedo ductal carcinoma *in situ* (DCIS). According to the size of such epithelial proliferation, it can be considered an atypical papilloma in cases ≤3 mm, while it can be considered papilloma with DCIS in cases >3 mm in size.[4] Although a percutaneous breast biopsy is a highly reliable method for the diagnosis of breast lesions, several investigators have suggested that subsequent surgical excision is recommended for percutaneously identified papillary lesions.[5–7]

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A previous report suggested that benign papillary lesions diagnosed by ultrasound (US)-guided vacuum-assisted removal (VAR) do not need to be surgically excised for accurate diagnosis.[8] However, the study population only included benign papillary lesions upon US-VAR, and did not compare the diagnostic accuracy between US-VAR and US-14 G automated core needle biopsy (ACNB). In the present study the performance of US-VAR and US-ACNB in the diagnosis of papillary breast lesions was evaluated and compared.

Materials and methods

The institution's review board approved this research study and waived the requirement for informed consent because it was a retrospective study.

Patients

The pathology database of 7462 consecutive percutaneous core biopsies of 7048 consecutive breast lesions performed at our institution between February 2000 and December 2006 was reviewed. Among these, 424 papillary lesions (6%, 424 of 7048) had been diagnosed using US-ACNB. Of 424 papillary lesions, 150 lesions (35.3%) were excluded because they lacked subsequent surgical excision or long-term imaging follow-up for at least 2 years. The remaining 274 papillary lesions were in 232 patients who underwent subsequent surgical excision or long-term imaging follow-up for at least 2 years. Three lesions that were diagnosed by vacuum-assisted biopsy were excluded because the biopsy was performed to sample the lesions, not to remove them. The remaining 271 papillary lesions in 230 patients were used to compare the US-ACNB ($n = 206$) and VAR methods ($n = 65$). Of the 65 VAR cases, VAR was the initial biopsy method in 36, and in remaining 29, VAR was performed after initial ACNB when a diagnosis of a papillary lesion was obtained. The VAR procedure for all 65 lesions was prospectively intended to remove a sonographically visible mass.

Before 2003, US-ACNB was used to diagnose any sonographically visible papillary lesion in our institution. If determined to be benign by US-ACNB, the lesions were surgically excised or followed-up with imaging examinations, depending on the imaging and clinical findings. Although surgical excision was recommended first, a follow-up study could be considered as an alternative method in papillary lesions with no symptoms and a low probability of malignancy as a final assessment according to Breast Imaging Reporting and Data System (BI-RADS), such as category 3 or category 4a. Since January 2003, US-VAR has been recommended as an alternative to surgical excision for benign papillary lesions diagnosed at US-ACNB. However, for papillary lesions with a subareolar location or with nipple discharge, surgical excision was preferred. In addition, when a lesion was suspected of being a papillary lesion based on imaging findings, such as an intraductal mass accompanied by adjacent ductal dilatation, US-VAR was performed as the initial diagnostic method. However, the biopsy method was selected based on the preferences of the patient and of the radiologist who performed the biopsy taking into consideration the conditions of medical insurance support and the cosmetic interests of the patient. Surgical excision was recommended for atypical papillomas at US-ACNB or US-VAR.

For the histological diagnosis of benign papilloma, proliferation of ductal epithelium with fibrovascular core formation, presence of myoepithelial cells, and absence of pleomorphism or cellular monotony were required. Papillary proliferations with focal cytological or architectural atypical, focal absence of myoepithelial cells, and monotonous epithelial proliferation were defined as atypical papilloma. The diagnosis of papillary carcinoma was reserved for cases with atypical monotonous epithelial cells and without myoepithelial cells.[9]

US-guided ACNB and VAR

US-guided core needle biopsies were performed using a free-hand technique, guided by 7.5- or 12-MHz linear array transducers (HDI 5000 or 3000, Philips-Advanced Technology Laboratories, Bothell, WA, USA; Logic 9, GE Medical systems, Milwaukee, WI, USA) in each procedure. All procedures were performed in an outpatient setting using local anesthesia with the patient in the supine position. US-ACNB was performed using an automated gun (Pro-Mag 2.2, Manan Medical Products, Northbrook, IL, USA) and a 14 G Tru-cut needle with a 22 mm throw (SACN™ Biopsy Needle, Medical Device Technologies, Gainesville, FL, USA). They were performed by one of the 13 radiologists who specialized in interpreting breast images and performing percutaneous breast biopsy under sonographic guidance. According to the standard protocol, four or five core samples per lesion were routinely obtained.

At our institution, percutaneous, sonographically-guided vacuum-assisted core biopsies of breast lesions have been performed with the Mammotome system (Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA) since February 2002. The probe (11 or 8 G) was selected based on the size of the lesion.[8] The probe was inserted into the breast through a small skin incision and was guided into a biopsy position under direct ultrasound visualization (HDI 5000, Philips-Advanced Technology Laboratories) after the administration of local anesthesia. A vacuum-assisted core biopsy was used for biopsy only or lesion removal at our institution. All the cases included in the study were performed for lesion removal. For VAR, multiple core samples were taken until the mass was completely removed, as determined by real-time sonography of the biopsy site. The details of the ACNB and VAR procedure are described in previous reports.[8,10]

Data analysis

The clinical, pathological, and imaging findings from the 271 lesions in 230 patients were reviewed, including subsequent excisions and follow-up imaging studies. Follow-up imaging studies included annual mammograms and biannual sonograms for the first 2 years, followed by annual sonograms. Final diagnosis was replaced by a pathological diagnosis at follow-up, which was made based on

a larger tissue sampling or long-term follow-up imaging studies for at least 2 years. Even if the lesions were found to be benign or no evidence of residual disease was found after the surgery performed after VAR, the final disease was considered to be atypical or carcinoma if the histopathology of the VAR specimen was atypical or carcinoma.

False negative, underestimation, and histological upgrade

The percentages of false-negative diagnoses and underestimation were compared between the ACNB and VAR groups. Lesions were considered false negatives when they were benign on the core biopsy, including ACNB and VAR, but were later found to be carcinoma at surgery or subsequent VAR.[11] Atypical underestimated lesions were those diagnosed as atypical papilloma by a core biopsy but were found to be carcinoma at surgery. The histological upgrade rate, including the false negative and underestimated lesion, was also compared between the ACNB and VAR groups. Lesions diagnosed as benign papillomas by ANCB or VAR but diagnosed as atypical papillomas after surgery or subsequent VAR were also considered histologically upgraded[11] Statistical comparisons were performed using the chi-square test or Fisher's exact test for the above rates. Exact confidence intervals (CI) were calculated according to the formula given by Berry.[12]

Clinical and imaging characteristics

Patient demographic factors, diagnostic findings, and lesion characteristics were reviewed. Demographic factors included patient's age, symptoms (palpability or nipple discharge), and risk factors (family cancer history, personal cancer history, high-risk factor history, such as papilloma or atypical ductal hyperplasia, and multiplicity of papillary lesions). Lesion characteristics and diagnostic findings included lesion size, distance from nipple, the abnormality on mammogram, the number of specimens, and final assessment based on BI-RADS.[13] The abnormality on the mammogram included the mass, focal asymmetry or distortion, and microcalcifications. However, typical benign-looking calcifications were not considered abnormal. The above characteristics were compared between the ACNB and VAR groups. Statistical comparisons were performed using the *t*-test for parametric variables and chi-square test or Fisher's exact test for nonparametric variables. Statistical significance was assigned to *p*-values less than 0.05.

A chi-square test was undertaken to determine whether the histological upgrade rate was different between the two groups. The data were processed with statistical software (SAS system for Windows, version 9.1, SAS Institute, Cary, NC, USA).

Table 1
Histological findings according to tissue acquisition method in 271 papillary lesions

	Tissue acquisition method	
	ACNB	VAR
Papilloma	146	48
Multiple papilloma	7	3
Sclerosing papilloma	2	1
Other benign papillary lesions	2	1
Atypical papilloma	15	7
Carcinoma	34	5
Total	206	65

ACNB, automated core-needle biopsy; VAR, vacuum-assisted removal.

Results

Table 1 lists the pathological findings from US-ACNB and US-VAR. Among the 271 papillary lesions, there were 38 malignancies (13%) with ACNB in 34 lesions and VAR in four lesions (Fig 1), which were diagnosed by an initial percutaneous biopsy. They underwent surgical treatment and all were malignant. The other 146 of the 172 lesions with ACNB, including 15 atypical papillomas, underwent subsequent surgical excision. The remaining 26 ACNB lesions (12.6% of 206 lesions) were followed-up with an imaging study for at least 2 years (range 24–72 months; median 36 months). In the VAR group, an 11 G directional vacuum biopsy device was used for 44 lesions, and an 8 G was used for the remaining 21 lesions. Ten of 61 papillary lesions in

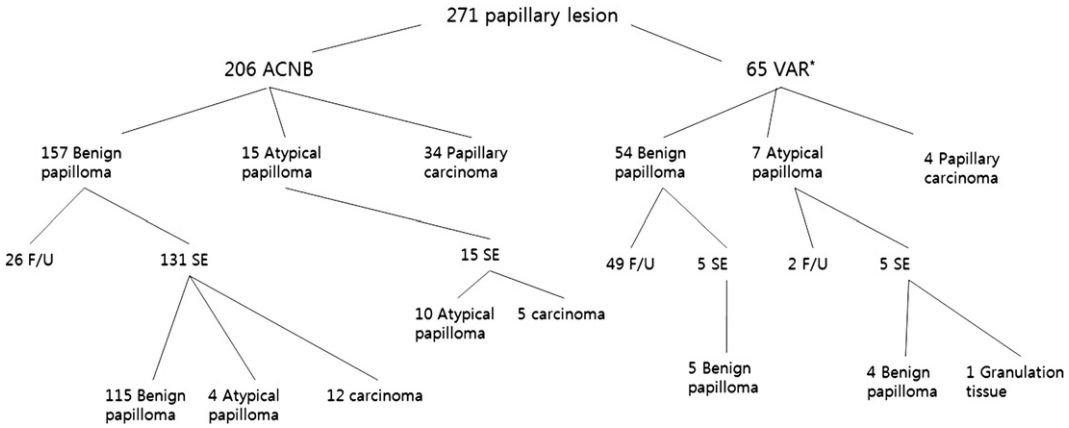

Figure 1 Diagram of diagnosis and management of 271 papillary lesions. ACNB, automated core-needle biopsy; VAR, vacuum-assisted removal; SE, surgical excision.

the VAR group (excluding four papillary carcinomas) underwent surgical excision. The remaining 51 lesions were followed by mammography and ultrasonography (24–48 months; median 32 months). Two atypical papillomas after VAR were followed in patients who refused subsequent excision, although subsequent excisions were recommended. Finally, out of 271 papillary lesions, 195 (80%) were benign, 21 (7.7%) were atypical, and 55 (20.3%) were malignant (Table 2).

False negative lesions after ACNB and VAR

Among 157 benign papillary lesions in the ACNB group, carcinoma was found in 12 lesions, producing a false-negative rate of 7.6% (95% CI, 4.4–12.9%).

There was no carcinoma at the follow-up histopathological diagnosis among the 54 benign papillary lesions in the VAR group. A false negative accounted for 0% (0 of 54 benign papillomas; 95% CI, 0.0–6.6%). Significantly more false-negative results were found in the US-ACNB group than in the US-VAR group ($p = 0.039$).

Atypical papilloma underestimation after ACNB and VAR

Among 15 atypical papillomas in the ACNB group, carcinoma was found in five lesions, showing that 33.3% (95% CI, 15.2–58.3%) of the lesions were underestimated as atypical papilloma. The VAR group had five atypical papillomas. However, subsequent excision ($n = 5$) revealed no residual atypical component and a long-term follow-up imaging study ($n = 2$) showed no residual. Therefore, the percentage of atypical papilloma underestimation was also 0% (zero of seven; 95% CI, 0–35.4%). However, no significant difference was found in terms of the underestimation percentage between the two groups ($p = 0.135$).

Histological upgrade of ACNB and VAR specimens

Of the 172 benign or atypical papillary lesions in the ACNB group, 17 were upgraded to carcinoma from a benign or atypical papillary lesion, and four were upgraded from benign to atypical papilloma at the follow-up pathological diagnosis. Histological upgrade was found in 10.2% (21 of 206 papillary lesions; 95% CI, 6.8–15.1%) at the follow-up histopathological diagnosis: eight intraductal carcinomas, two DCIS arising papillomas, four papillary carcinomas, two invasive ductal carcinomas, one invasive low-grade carcinoma from a sclerosing papilloma, and four atypical papillomas. There was no histological upgrade of papillary lesions treated with VAR (0 of 65 lesions; 95% CI, 0–5.6%). The frequency of histological upgrade was significantly higher in the US-ACNB group than the US-VAR group ($p = 0.003$).

Patient and lesion characteristics

For the patient and lesion characteristics in the cases with benign papilloma at the core needle biopsy, the ACNBs and VARs presented significant differences in terms of the prevalence of palpability, mammographic abnormality, maximal lesion size, and the number of specimens in the core needle biopsy ($p < 0.05$; Table 3). There was no significant difference in patient age, risk factors, the distance from nipple, and the final assessment. In cases with atypical papilloma, only the number of specimens showed a statistically significant difference between the ACNBs and VARs (Table 4).

Discussion

Papillary lesions of the breast include a broad spectrum of lesions ranging from papilloma to papillary carcinoma.[1–3] Although a percutaneous breast biopsy is a highly reliable method for the diagnosis of breast lesions, it is difficult to

Table 2
Follow-up histopathological diagnosis and histopathological results of ACNB and VAR in 271papillary lesions

Histological results at ACNB and VAR		Follow-up histopathological diagnosis considering surgical pathology and follow-up study		
		Carcinoma	Atypical papilloma	Benign papilloma
ACNB	Papillary carcinoma	34	0	0
	Atypical papilloma	5	10	0
	Benign papilloma	12	4	141
VAR	Papillary carcinoma	4	0	0
	Atypical papilloma	0	7	0
	Benign papilloma	0	0	54

ACNB, automated core-needle biopsy; VAR, vacuum-assisted removal.

Table 3
Patient and lesion characteristics of 210 benign papillomas: ACNB and VAR

Characteristics	ACNB ($n = 157$)	VAR ($n = 54$)	p-value (ACNB versus VAR)
Patient age			0.146
Mean ± SD	46.5 ± 9.4	44.3 ± 10.1	
Age range (years)	19–79	19–64	
Symptom	65	4	
Palpable	49	2	<0.001
Discharge	18	2	0.111
Risk factor	44	18	
Family history	3	2	0.604
Cancer history	13	1	0.123
High-risk history	7	3	0.718
Multiplicity	29	16	0.122
Mammographic abnormality			<0.001
Yes	75	11	
No	82	43	
Maximal lesion size (mm)			0.001
Mean ± SD	11.3 ± 6.3	8.4 ± 3.6	
Range	3–55	3–27	
Distance from nipple (cm)			0.522
Mean ± SD	1.8 ± 1.1	1.7 ± 1.0	
Range	0–7	1–5	
Final assessment			0.056
Category 3	29	17	
Category 4	128	37	
Number of specimens			<0.001
Mean	4.5 ± 0.4	12.7 ± 6.4	
Range	3–6	6–40	

ACNB, automated core-needle biopsy; VAR, vacuum-assisted removal.

differentiate between a benign papillary lesion and a papillary carcinoma upon histological evaluation of the fragmented material obtained by core needle biopsy specimens. Furthermore, possible sampling errors may prevent the right diagnosis.[1,3] Therefore, subsequent surgical excision is recommended for percutaneously identified papillary lesions despite a long-standing debate regarding patient management.[5–7,14–17] In the present study, the false-negative rate of 7.6% and histological upgrade rate to atypia or malignancy of 10.2% was seen when papillary breast lesions were diagnosed after US-14 G-ACNB, which supported subsequent larger tissue sampling rather than imaging follow-up as an appropriate management for benign papilloma after US-14 G-ACNB.

In the present study, the percentages of false-negative rates, atypical papilloma underestimation, and histological upgrades between US-VAR and US-14 G-ACNB in the diagnosis of papillary lesions were compared. False-negative rates and histological upgrades were found less often in US-VAR lesions than in US-14 G-ACNB lesions, which supports the findings of a previous study that the diagnosis of benign papillary lesions with US-VAR is accurate enough, requiring no subsequent surgical excision for diagnosis.[8] Several reports on papillary lesions biopsied under US guidance[6–9,16,18–25] were reviewed and among these 13 previous reports, only five investigations and two recent papers included more than 20 papillary lesions biopsied under US guidance.[7,8,19,20,23–25] Moreover, results of US-guided vacuum-assisted biopsy for papillary lesions are rarely reported,[8,23–25] and outcomes of US-VAR for papillary lesions are also limited.[8,23,24] The results of the present study are consistent with those recently reported on US-guided vacuum-assisted biopsy and VAR, which showed a higher diagnostic accuracy for the diagnosis of papillary lesions than US-14 G-ACNB.[8,23–25] Moreover, the present study population was the largest for both US-14 G-ACNB and US-VAR of papillary lesions, and was the first to find a significant difference in the histological upgrade rate between US-14 G-ACNB and US-VAR ($p < 0.05$). Moreover, the cases with VAR in the present study were performed not simply for the diagnosis but also for lesion removal. Therefore, an attempt was made to completely remove the lesion during the procedure, not just sample it. The present results could not be generalized to that for US-vacuum-assisted biopsy for sampling and not uncertain whether histological upgrade will develop after US-vacuum-assisted biopsy for sampling.

In the present study histological upgrade, false-negative rates, and underestimation were assessed from the outcomes of ACNB and VAR. Histological upgrade included final carcinoma showing benign or atypical papilloma at biopsy and atypical papilloma showing benign papilloma at the biopsy. Several previous studies have reported not only the percentage of the follow-up pathological diagnosis of carcinoma, which were presented as benign papilloma at the core needle biopsy, but also the percentage of final atypical papilloma showing as benign papilloma at the core needle biopsy.[4,6,26,27] This is because atypical papilloma must be considered as a precursor lesion rather than a marker of a generalized increase in breast cancer risk.[28] Such high-risk lesions should be excised. Moreover, the diagnosis of a high-risk lesion, such as atypical papilloma, at surgery may alter patient management, leading to more intensive surveillance. Therefore, the accurate diagnosis of a high-risk lesion is also important for the percutaneous biopsy. From this point of view, US-VAR is an accurate diagnostic tool for papillary lesions of the breast.

The present study was limited by a high exclusion rate (35.3%, 150 of 424); however, 19–35% of papillary lesions were excluded due to insufficient follow-up data in other studies.[6,16,17,21,22,26,29] Moreover, in two of the studies that included cases with a follow-up less than 2 years,[9,30] the mean follow-up was 14.7 and 19 months. This could mean that half of the cases without a surgical excision in these studies were followed for less than 2 years. The present study only included cases with a follow-up period of more than 2 years and the median follow-up period of the cases was about 3 years. Despite this exclusion rate, the present study had the largest series of papillary lesions at a single-type image (US or stereotaxis)-guided biopsy.[5–7,9,16–23,26,31–35] The present study is also limited by a lack of subsequent surgical histopathological diagnosis in 28.4% (77 of 271 lesions) of the study population. As most upgrades of papillary lesions are to low-grade DCIS, it is not clear if a 2-year follow-up is sufficient to evaluate the rate of malignancy. However, previous studies for papillary lesions also included a variable range (0–67.4%) of cases with imaging follow-up.[5–7,9,16–23,26,30–35] From the present results, it could not be guaranteed that carcinoma would not

Table 4
Patient and lesion characteristics of 22 atypical papillomas: ACNB and VAR

Characteristics	ACNB ($n = 15$)	VAR ($n = 7$)	p-value (ACNB versus VAR)
Patient age			0.111
Mean ± SD	46.4 ± 7.2	39.3 ± 5.3	
Age range	27–49	30–46	
Symptom	7	2	
Palpable	5	2	1.000
Discharge	2	0	1.000
Risk factor	5	3	
Family history	0	1	0.318
Cancer history	1	0	1.000
High-risk history	1	1	1.000
Multiplicity	4	2	1.000
Mammographic abnormality			0.361
Yes	6	5	
No	9	2	
Maximal lesion size (mm)			0.995
Mean ± SD	15.6 ± 11.6	15.6 ± 6.3	
Range	5–30	7–27	
Distance from nipple (cm)			0.422
Mean ± SD	1.7 ± 1.3	1.3 ± 0.8	
Range	1–5	1–3	
Final assessment			0.680
Category 3	1	1	
Category 4	13	6	
Category 5	1	0	
Number of specimen			<0.001
Mean	4.5 ± 0.4	14.6 ± 6.1	
Range	3–6	9–25	

ACNB, automated core-needle biopsy; VAR, vacuum-assisted removal.

develop at the site of a papillary lesion (or atypia) with US-VAR. Nevertheless, a follow-up study could be suggested as acceptable management for benign papilloma after US-VAR, because the false-negative rate and histological upgrade for the diagnosis of a papillary lesion with US-VAR are lower than the 2% frequency of cancer in lesions interpreted as probably benign (BI-RADS category 3). From the present results, the upgrade rate after US-VAR would not be as high as that after US-ACNB. This information could be helpful for management and explanation to patients with papillary lesions. However, further study is needed with long-term follow-up or surgical pathology. Third, the number of carcinomas in the VAR group is low with only four cases. Although studying the histological upgrade to carcinoma in VAR cannot be sufficient in this population, the pretest possibility of upgrade for the VAR group is significantly lower than that for the ACNB group.

In conclusion, ACNB was associated with higher false-negative rates and histological upgrades of diagnosis for papillary breast lesions than VAR. For benign papillary lesions that were removed by US-VAR, a surgical excision may not be mandatory for accurate diagnosis.

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