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The Value of Adding Ductography to Ultrasonography for the Evaluation of Pathologic Nipple Discharge in Women with Negative Mammography

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Objective: The optimal imaging approach for evaluating pathological nipple discharge remains unclear. We investigated the value of adding ductography to ultrasound (US) for evaluating pathologic nipple discharge in patients with negative mammography findings.

Materials and Methods: From July 2003 to December 2018, 101 women (mean age, 46.3 ± 12.2 years; range, 23–75 years) with pathologic nipple discharge were evaluated using pre-ductography (initial) US, ductography, and post-ductography US. The imaging findings were reviewed retrospectively. The standard reference was surgery (70 patients) or > 2 years of follow-up with US (31 patients). The diagnostic performances of initial US, ductography, and post-ductography US for detecting malignancy were compared using the McNemar's test or a generalized estimating equation.

Results: In total, 47 papillomas, 30 other benign lesions, seven high-risk lesions, and 17 malignant lesions were identified as underlying causes of pathologic nipple discharge. Only eight of the 17 malignancies were detected on the initial US, while the remaining nine malignancies were detected by ductography. Among the nine malignancies detected by ductography, eight were detected on post-ductography US and could be localized for US-guided intervention. The sensitivities of ductography (94.1% [16/17]) and post-ductography US (94.1% [16/17]) were significantly higher than those of initial US (47.1% [8/17]; $p = 0.027$ and 0.013, respectively). The negative predictive value of post-ductography US (96.9% [31/32]) was significantly higher than that of the initial US (83.3% [45/54]; $p = 0.006$). Specificity was significantly higher for initial US than for ductography and post-ductography US ($p = 0.001$ for all).

Conclusion: The combined use of ductography and US has a high sensitivity for detecting malignancy in patients with pathologic nipple discharge and negative mammography. Ductography findings enable lesion localization on second-look post-ductography US, thus facilitating the selection of optimal treatment plans.

Keywords: *Breast; Ductography; Mammography; Pathologic nipple discharge; Ultrasound*

INTRODUCTION

Pathological nipple discharge (PND), defined as spontaneous uni-orificial nipple discharge, typically requires imaging workup and tissue diagnosis. The most common causes of PND are benign conditions, such as papilloma or duct ectasia, although it indicates underlying malignancy in 5%–23% of the cases [1-3]. Although various diagnostic tools have been employed, it remains controversial whether mammography, ductography, ultrasound (US), or specific

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combinations of multiple modalities represent the optimal radiological examination approach [4,5]. For men or women with PND, aged ≥ 40 years, diagnostic mammography, digital breast tomosynthesis, and US at the initial examination are recommended by the American College of Radiology (ACR) and National Comprehensive Cancer Network (NCCN) [6,7].

Mammography is the first conventional imaging technique for investigating nipple discharge; however, it has low sensitivity and limited accuracy in the detection of small, intraductal, and non-calcified retro-areolar lesions. The reported sensitivity of mammography for nipple discharge ranges from 7%–26% [8]. Thus, many PND cases present with no abnormalities on mammography.

US, as compared to mammography, provides better sensitivity (65%–97% vs. 15%–32%, respectively), but lower specificity (60%–85% vs. 94%–100%, respectively) for detecting intraductal lesions [3,9,10]. US can be employed to investigate retro-areolar ducts with internal content and characterize mass lesions [11-13]. Advances in high-resolution US have led to the proposal to replace ductography with US [9,13-16]. Yoon et al. [13] reported that US detected malignancy in 15% of patients with PND with negative mammography results.

Immediate US-guided biopsy to confirm the etiology has caused a decline in ductography use. However, US has disadvantages such as operator dependency and low reproducibility [2]. Ductography enables the depiction of underlying conditions, localization, definition of the extent and characteristics of ductal morphology, and evaluation of associated microcalcifications [11,17,18]. Without preoperative mapping with ductography, central duct excision may result in incomplete or no removal of the actual abnormal ductal tissue, causing disease underestimation [19]. However, it is an invasive procedure that requires active discharge and use of contrast agents. Comparisons between US and ductography have revealed inconsistent results [9,13,20,21]. Nevertheless, several studies have reported that a combination of US and ductography facilitates lesion localization and characterization [5,10,22-24].

We hypothesized that US and ductography would complement each other and that their combination, which allows for the correlation between ductography and US findings, would be superior to each modality in isolation. Therefore, we investigated the value of adding ductography to US for evaluating PND in patients with negative mammography findings.

MATERIALS AND METHODS

Ethics Approval

This retrospective study was approved by the Institutional Review Board of our institution (IRB No. B-1106-130-102). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Study Population

Between July 2003 and December 2018, US and ductography were routinely performed on 360 women with unilateral single-orifice spontaneous nipple discharge (bloody, serosanguineous, clear, or colorless). Participants who did not undergo surgery or > 2 years of follow-up (n = 110), those without available mammography (n = 46), those with positive mammography (n = 51), or those who did not undergo US before ductography (n = 52) were excluded. Finally, 101 women who underwent US and ductography examinations in addition to mammography were included in the study (Fig. 1).

Imaging Evaluation

Bilateral two-view mammography (craniocaudal and mediolateral oblique views) was performed using dedicated equipment (Selenia Dimensions system, Hologic or a Senographe 2000D full-field digital mammography system, GE Medical Systems). Spot magnification and compression views of the lesions were obtained as required.

Initial US was performed by one of five radiologists (with 18, 14, 12, 8, and 5 years of experience in breast imaging) using 10–12- or 14–16-MHz linear array transducers (HDI 5000, Philips Advanced Technology Laboratories; iU22, Philips Healthcare; or SuperSonic Imagine) in 52 patients. In 49 patients, the initial US was not performed at our institution; however, US images from other institutions were available. Only images obtained within one month before ductography and stored in Digital Imaging and Communication in Medicine files were included. Their quality was checked by consensus between two radiologists with 18 and 14 years of experience.

Ductography was performed by one of the five radiologists using a 31-gauge catheter (sialography needle, Cook Medical). The discharging duct was selected with gentle periareolar pressure under a halogen lamp. A cannula tip was inserted into the discharging orifice, and mammograms were obtained in two projections (craniocaudal and mediolateral oblique views) after slow injection of 0.1–0.5 mL of non-

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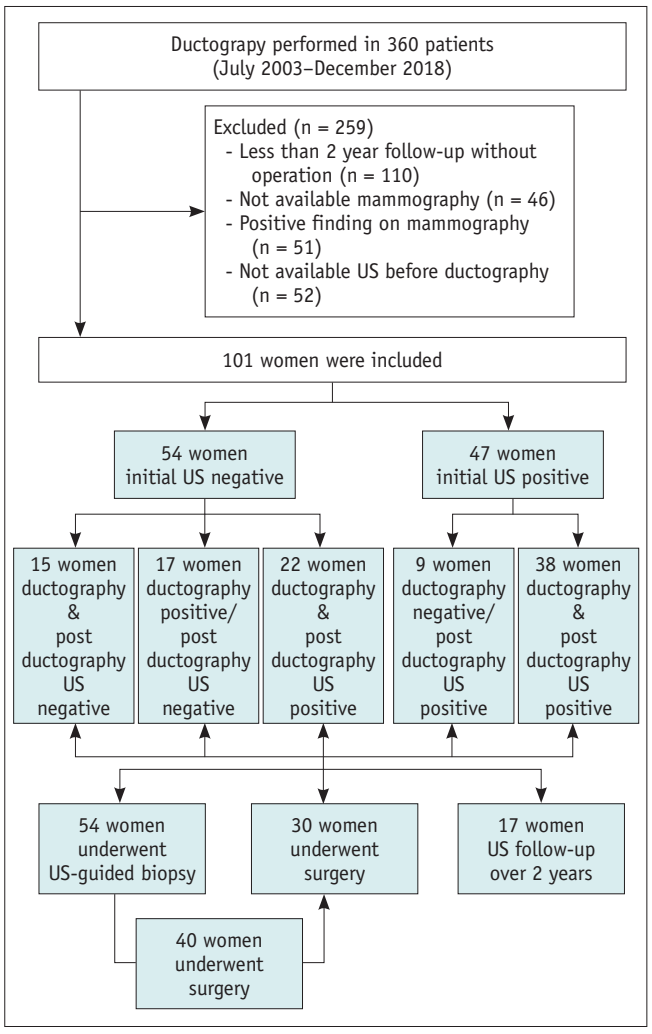

Fig. 1. Flowchart of the study population. US = ultrasound

ionic iodinated contrast material. The process was stopped if the patient reported discomfort or increased pressure.

Patients underwent post-ductography US examination by one of the five radiologists using 10–12- or 14–16-MHz linear array transducers as described above. If possible, post-ductography US was scheduled on the same day as ductography (n = 49); however, it was conducted on different days in 52 patients (mean delay: 8.4 days; range: 1–30 days). The radiologists were aware of the clinical indications from the mammographic and ductography examination results when available. Lesions were interpreted according to the ACR Breast Imaging Reporting and Data System (BI-RADS) [25].

Assessment of Imaging Findings

Two radiologists (with 18 and 14 years of experience), specializing in breast imaging, retrospectively reviewed the ductography and US images in consensus, blinded to the pathological results and recorded features. The US features were recorded using the ACR BI-RADS lexicon [25].

Ductography findings were characterized as dilated duct, filling defect, ductal wall irregularity, or complete ductal obstruction [26]. The most suspicious finding (following the order of suspicious finding: ductal obstruction > irregularity > filling defect > dilated duct) was selected for the classification. US features of ductal changes were characterized as dilated duct only, intraductal mass, mass only (without ductal changes), or mass with an adjacent dilated duct. The correlation between modalities was assessed in terms of lesion location, morphology, size, and distance from the nipple, when abnormalities likely to underlie nipple discharge were detected on both ductography and US.

Pathologic Diagnosis and Follow-Up

When suspicious ductography and US findings were correlated, or if a suspicious US finding (BI-RADS category 4 or 5) was detected, US-guided 14-G core needle biopsy (Stericut®, TSK Laboratory) or 11- or 8-G vacuum-assisted biopsy (Mammotome® system, Devicor Medical Products Inc.) was performed. Patients with confirmed malignant or high-risk lesions underwent surgery after wire localization. Patients with uncorrelated suspicious ductography and US findings underwent a microdochectomy.

Patients with benign lesions discovered via biopsy were advised to undergo US follow-up at 6, 12, 18, and 24 months, and annual mammography examinations, with annual US followed by mammographic evaluations thereafter. Patients without suspicious findings were advised to undergo annual US and mammographic evaluation.

Statistical Analysis

The clinical, pathological, and radiological findings were entered into a spreadsheet (Excel, Microsoft). Final histopathological results from surgical excision, US-guided biopsy, or results from > 2 years of follow-up were used as references. Categorical variables for benign and malignant tumors were compared using the chi-squared or Fisher's exact tests. Continuous variables were compared using Student's *t* tests. The detectability and characteristics of the involved duct under various diagnoses were compared using both the modalities. The BI-RADS final assessment categories were dichotomized as negative for categories 1, 2 and 3 and positive for categories 4 and 5 on US. Filling

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Table 1. Demographics and Lesion Characteristics of 101 Patients with Nipple Discharge and Negative Finding on Mammography

Variable	Total (n = 101)	Benign (n = 84)	Malignant (n = 17)	*P*
Patient age, years	46.3 ± 12.2	45.2 ± 11	55.3 ± 17.6	0.002
Menopausal status				< 0.0001
Premenopausal	73 (72.3)	67(79.8)	6 (35.3)	
Postmenopausal	28 (27.7)	17 (20.2)	11 (64.7)	
Hormone replacement				1
Yes	5 (4.9)	4 (4.8)	1 (5.9)	
No	96 (95.1)	80 (95.2)	16 (94.1)	
Personal history of breast cancer				0.428
Yes	3 (3.0)	2 (2.4)	1 (5.9)	
No	98 (97.0)	82 (97.6)	16 (94.1)	
Family history of breast cancer				1
Yes	5 (5.0)	4 (4.8)	1 (5.9)	
No	96 (95.0)	80 (95.2)	16 (94.1)	
Dense breast tissue				< 0.0001
Yes	78 (77.2)	73 (86.9)	5 (29.4)	
No	23 (22.8)	11 (13.1)	12 (70.6)	
Bloody nipple discharge				0.005
Yes	74 (73.3)	57 (67.9)	17 (100.0)	
No	27 (26.7)	27 (32.1)	0 (0.0)	
Initial US abnormality				0.962
Yes	47 (46.5)	39 (46.4)	8 (47.1)	
No	54 (53.5)	45 (53.6)	9 (52.9)	
Abnormality on ductography				0.066
Yes	77 (76.2)	61 (72.6)	16 (94.1)	
No	24 (23.8)	23 (27.4)	1 (5.9)	
Post-ductography US abnormality				0.011
Yes	69 (68.3)	53 (63.1)	16 (94.1)	
No	32 (31.7)	31(36.9)	1 (5.9)	

The data are presented as the number (percentage) of patients or mean ± standard deviation. US = ultrasound

defects, ductal wall irregularities, and complete obstruction on ductography were considered as positive findings.

The diagnostic performance of initial US, ductography, and post-ductography US was determined by calculating the sensitivity, specificity, positive predictive value, negative predictive value (NPV), and accuracy. McNemar's test or generalized estimating equation was used to estimate the

Table 2. Imaging Findings According to Final Diagnosis

Variable	Benign (n = 84)	Malignant (n = 17)	Total (n = 101)
Initial ultrasonographic finding			
Negative	26 (31.0)	4 (23.5)	30 (29.7)
Dilated duct only	19 (22.6)	5 (29.4)	24 (23.7)
Intraductal mass	23 (27.4)	5 (29.4)	28 (27.7)
Mass only	3 (3.6)	0 (0.0))	3 (3)
Mass with adjacent dilated duct	13 (15.5)	3 (17.7)	16 (15.9)
Ductography finding			
Negative	14 (16.7)	1 (5.9)	15 (14.9)
Dilated duct	7 (8.3)	0 (0.0)	7 (6.9)
Filling defect	29 (34.5)	8 (47.1)	37 (36.6)
Ductal wall irregularity	2 (2.4)	3 (17.7)	5 (5)
Complete obstruction	30 (35.7)	5 (29.4)	35 (34.7)
Failed	2 (2.4)	0 (0.0)	2 (2)
Post-ductography ultrasonographic finding			
Negative	16 (19.1)	0 (0.0)	16 (15.9)
Dilated duct only	15 (17.9)	1 (5.9)	16 (15.8)
Intraductal mass	36 (42.9)	10(58.9)	46 (45.5)
Mass only	3 (3.6)	0 (0.0)	3 (3)
Mass with adjacent dilated duct	14 (16.7)	6 (35.3)	20 (19.8)

The data are presented as the number (percentage) of patients.

Table 3. Comparison of Initial Ultrasound and Ductography Findings

Initial Ultrasound Findings	Ductography Findings					Total
	Normal or Dilated Duct	Filling Defect	Ductal Wall Irregularity	Complete Duct Obstruction	Failed Examination	
All lesions						
Normal or dilated duct	15 (27.8)	18 (33.3)	4 (7.4)	17 (31.5)	0 (0.0)	54 (100)
Intraductal mass	6 (21.4)	10 (35.7)	1 (3.6)	10 (35.7)	1 (3.6)	28 (100)
Mass only	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)	3 (100)
Mass with adjacent dilated duct	1 (6.3)	8 (50.0)	0 (0.0)	6 (37.4)	1 (6.3)	16 (100)
Total	22 (21.8)	37 (36.6)	5 (5.0)	35 (34.7)	2 (2.0)	101 (100)
Malignant lesion						
Normal or dilated duct	0 (0.0)	2 (22.2)	2 (22.2)	5 (55.6)	0 (0.0)	9 (100)
Intraductal mass	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)	0 (0.0)	5 (100)
Mass only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
Mass with adjacent dilated duct	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)
Total	1 (5.9)	8 (47.1)	3 (17.7)	5 (29.4)	0 (0.0)	17 (100)

The data are presented as the number (percentage) of patients.

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differences between the modalities.

All statistical analyses were performed using the STATA software (version 14.0; StataCorp) and MedCalc (MedCalc Software). Statistical significance was set at $p < 0.05$.

RESULTS

Patient and Lesion Characteristics

Of the 101 women, 54 underwent US-guided biopsy after ductography. In 26 women, an initial US lesion was ductography-correlated, and in 20 women, a new ductography lesion was correlated with post-ductography US. The lesions were targeted by biopsy. In eight women, an initial US lesion was not ductography-correlated but was targeted by biopsy. The initial US-guided biopsy results of the 54 lesions are presented in Supplementary Table 1.

Lesion pathology in 70 patients (69.3% [70/101]) was confirmed surgically. Ten of the 101 (9.9%) patients underwent US-guided vacuum-assisted biopsy of lesions, with > 2 years of follow-up (mean, 49.0 months; range, 24–108 months), while 21 (20.8%) with normal findings or US-guided biopsy-confirmed benign lesions were followed-up via US for > 2 years (mean, 36.3 months; range, 24–105 months). Of these patients, 84 and 17 were confirmed

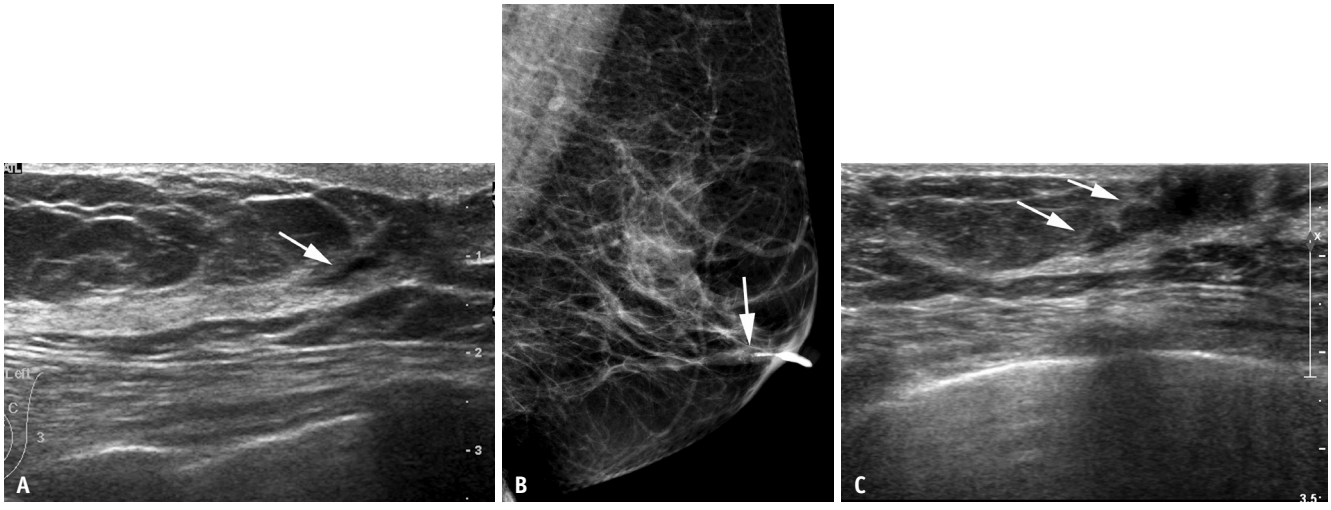

Fig. 2. A 74-year-old woman with bloody nipple discharge.
A. A transverse sonogram depicting a dilated duct (arrow) on initial US. **B.** A mediolateral oblique ductogram (acquired one day after the initial US) demonstrating a completely obstructed duct (arrow). **C.** A transverse sonogram after ductography on the same day (post-ductography US) depicting a 0.7-cm circumscribed, bilobulated hypoechoic mass (arrows) associated with adjacent ductal dilatation. After US-guided localization and excisional biopsy, the lesion was confirmed as a mucinous carcinoma arising in an intraductal solid papillary carcinoma. US = ultrasound

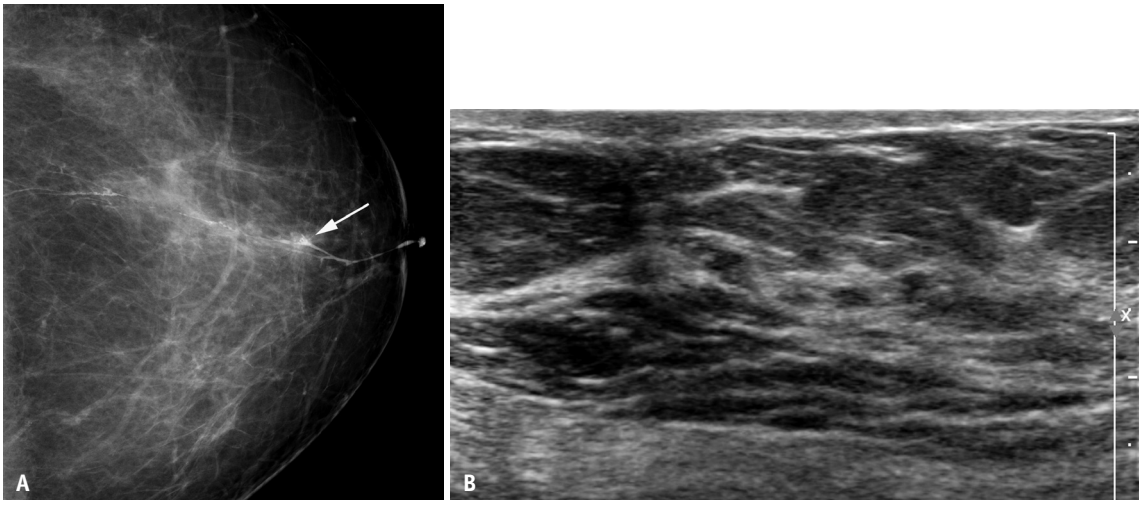

Fig. 3. A 70-year-old woman with a bloody nipple discharge with negative finding on initial US.
A. A craniocaudal ductogram depicting a completely obstructed duct and irregularities (arrow). **B.** A transverse post-ductography US depicting the absence of corresponding abnormalities. A 4.5-cm ductal carcinoma in situ was confirmed after microdochectomy. US = ultrasound

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to have benign and malignant lesions, respectively. The patient and lesion characteristics are summarized in Table 1. The final diagnoses are presented in Supplementary Table 2.

Imaging Findings

Suspicious abnormalities on the initial US were identified in 47 (46.5%) of the 101 patients (Table 2). The lesion extent was 0.3–3.3 cm (mean, 1.0 cm). Most lesions were subareolar (within 1 cm of the nipple, n = 28, 59.6% [28/47]). Other lesion locations were 1–2 cm, 2–3 cm, 3–4 cm, and 4–5 cm from the nipple in eight, six, four, and one patients, respectively. For US only-based analysis, 31, 23, and 47 patients were classified as BI-RADS categories 1, 2, and 4, with four, five, and eight malignant lesions, respectively. The final pathology of the initial US lesions included 30 papillomas, 6 other benign lesions, 3 high-risk lesions, and 8 malignant lesions.

Of the 101 patients, ductography failed in two patients (2%), and a normal/dilated duct appearance was noted in 22 patients (21.8%) (Table 2). Duct abnormalities associated with nipple discharge were successfully visualized by ductography in the remaining of 77 patients (76.2%). The most common lesion site was the lactiferous sinus, noted in 42 patients (41.6%). The mean lesion extent was 1.4 cm (range, 0.2–2.5 cm).

The initial US and ductographic findings are compared in Table 3. Abnormalities were observed via both modalities in 38/101 patients (37.6%), comprising 24 papillomas, 4 other benign lesions, 3 high-risk lesions, and 7 malignant lesions. Among these, 30 lesions showed no additional findings on US, whereas eight showed findings that helped in the selection of the biopsy target (n = 5; four benign, one malignant) or the definition of lesion extent (n = 3; two benign, one malignant). In 39/101 patients (38.6%), abnormalities were detected via ductography only; these included filling defects, ductal wall irregularity, and complete duct obstruction in 18, 4, and 17 patients, respectively (Figs. 2, 3). Diagnoses of ductography-only lesions included 17 papillomas, 9 other benign lesions, 4 high-risk lesions, and 9 malignant lesions. The characteristics of the cancers detected by ductography are presented in Table 4. US revealed abnormalities in 9/101 patients (8.9%) (Fig. 4), whereas ductography was either completely normal (due to incorrect selection of nipple opening), revealed a dilated duct, or failed to visualize the duct in four, three, and two patients, respectively. Abnormalities on US included an intraductal mass in seven

Table 4. Characteristics of Ductography-Only Detected Cancers

Cases (Number)	Age	Symptom	Pathology Result		Pathological Size (cm)	Initial US Finding	Ductography Finding	Post-Ductography (Combined) US Finding	Interval between Initial US and Ductography (Days)
			Pre-op.	Post-op.					
23	70	Bloody nipple discharge	N/A	DCIS	4.5	Negative	Complete duct obstruction	Negative	8
24	63	Bloody nipple discharge	Invasive ductal cancer	Invasive ductal cancer	1.8	Negative	Complete duct obstruction	Mass with adjacent dilated duct	22
26	35	Bloody nipple discharge	DCIS	DCIS	1	Dilated duct	Filling defect	Intraductal mass	23
34	74	Bloody nipple discharge	N/A	Mucinous cancer	1.5	Dilated duct	Complete duct obstruction	Mass with adjacent dilated duct	1
56	74	Bloody nipple discharge	DCIS	DCIS	3.0	Dilated duct	Ductal wall irregularity	Intraductal mass	29
62	60	Bloody nipple discharge	DCIS	DCIS	0.5	Negative	Ductal wall irregularity	Intraductal mass	1
88	70	Bloody nipple discharge	DCIS	DCIS	1	Negative	Ductal wall irregularity	Intraductal mass	1
94	35	Bloody nipple discharge	DCIS	DCIS	1	Negative	Filling defect	Intraductal mass	28
100	61	Bloody nipple discharge	Invasive ductal cancer	Invasive ductal cancer	1	Dilated duct	Complete duct obstruction	Mass with adjacent dilated duct	1

DCIS = ductal carcinoma in situ, op. = operation, US = ultrasound

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patients and a mass with an adjacent dilated duct in two patients. The US-only lesions included six papillomas, two other benign lesions, and one malignant lesion (Fig. 5).

Suspicious abnormalities on post-ductography US were identified in 69/101 patients (68.3%) (Table 2). Among these, 18 intraductal masses and four masses with adjacent

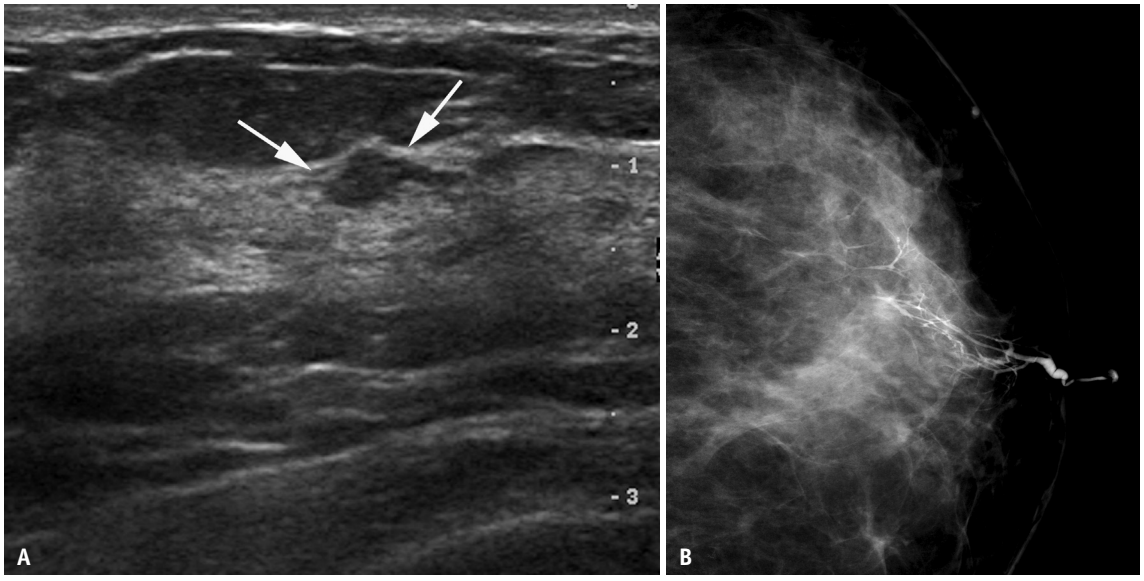

Fig. 4. A 45-year-old woman with bloody nipple discharge.
A. Transverse initial sonogram of the 3 o'clock area of the left breast depicting a 0.5-cm circumscribed oval hypoechoic mass (arrows) with associated prominent ducts. **B.** No ductal abnormality was noted in the left-lower-outer quadrant breast via ductography. The masses were diagnosed as benign papilloma by US-guided vacuum-assisted biopsy and were less prominent on the 27-month follow-up US (not shown). US = ultrasound

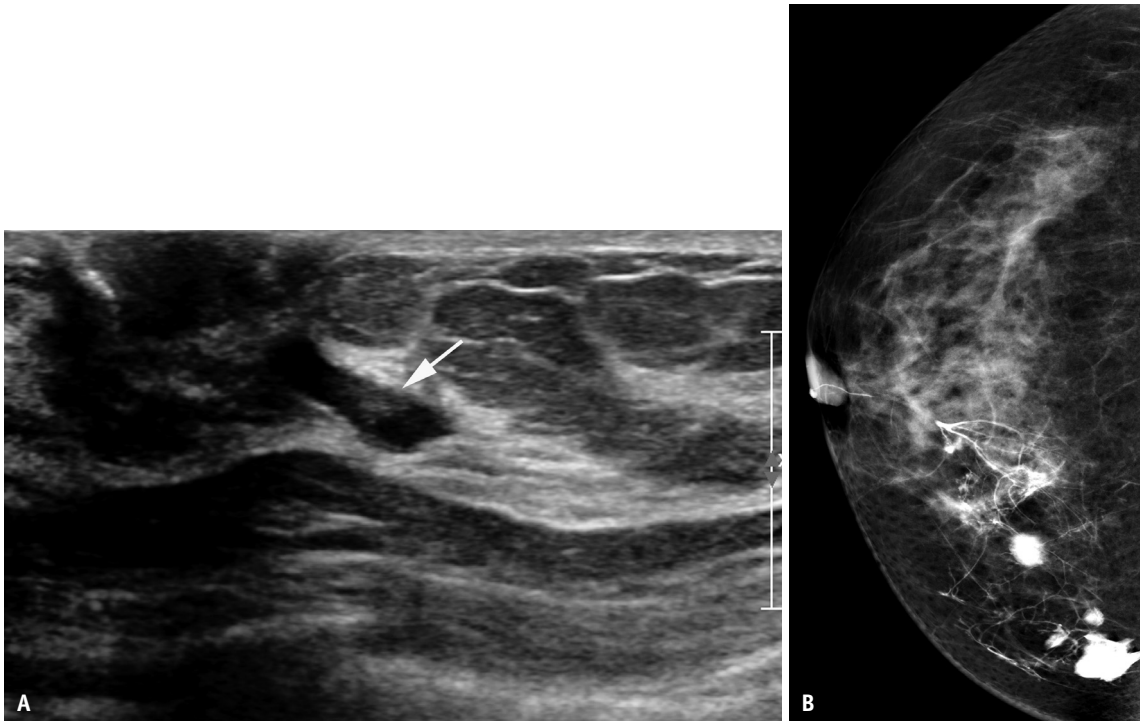

Fig. 5. A 54-year-old woman with bloody nipple discharge.
A. Transverse initial US revealed intraductal mass (arrow) in the 3 o'clock area of the right breast. **B.** No ductal abnormality was noted in the right 3 o'clock area breast on ductography. The masses were diagnosed as intraductal papilloma by US-guided biopsy but were upgraded as intraductal solid papillary carcinoma by US-guided vacuum-assisted biopsy. Subsequent surgery confirmed this as residual intraductal solid papillary carcinoma (ER[+], PR[+], HER2[-], Ki-67[-]). US = ultrasound

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Table 5. Diagnostic Performance of US, Ductogaphy, and Post-Ductography US

Diagnostic Value	US (Initial)	Ductography	US (Post Ductography)	*P**	*P*†	*P*‡
Sensitivity	47.1 [8/17] (23.0–72.2)	94.1 [16/17] (71.3–99.9)	94.1 [16/17] (71.3–99.9)	0.027	0.013	1
Specificity	53.6 [45/84] (42.4–64.5)	27.4 [23/84] (18.2–38.2)	36.9 [31/84] (26.6–48.1)	0.001	0.001	0.153
PPV	17.0 [8/47] (7.6–30.8)	20.8 [16/77] (12.4–31.5)	23.2 [16/69] (13.9–34.9)	0.401	0.110	0.265
NPV	83.3 [45/54] (70.7–92.1)	95.8 [23/24] (78.9–99.9)	96.9 [31/32] (83.8–99.9)	0.054	0.006	0.837
Accuracy	52.5 [53/101] (42.3–62.5)	38.6 [39/101] (29.1–48.8)	46.5 [47/101] (36.5–56.7)	0.061	0.286	0.170

Data are percentage with the raw number of patients in brackets and 95% confidence interval in parentheses. *p value between initial US and ductograph, †p value between initial US and post-ductography US, ‡p value between initial ductography and post-ductography US. NPV = negative-predictive value, PPV = positive-predictive value, US = ultrasound

dilated ducts in 22 patients (21.8%) were newly detected on post-ductography US and corresponded to filling defects, ductal wall irregularity, and complete duct obstruction (7, 4, and 11 lesions, respectively). Twenty-one patients (20.8%) underwent US-guided intervention (biopsy: 20; US-guided localization and excisional biopsy, one). The remaining one patient underwent a direct microdochectomy. The final pathology revealed nine papillomas, four other benign lesions, one high-risk lesion, and eight malignant lesions.

Diagnostic Performance of Initial US, Ductography, and Post-Ductography US

The diagnostic performances of the initial US, ductography, and post-ductography US are summarized in Table 5. Of the 17 malignancies, only eight were detected on the initial US, and nine malignancies were additionally detected via ductography. Of these ductography-detected lesions, eight were detected on post-ductography US and could be localized for US-guided intervention. The sensitivities of ductography (94.1%) and post-ductography US (94.1%) were significantly higher than those of initial US (47.1%; p = 0.027 and 0.013, respectively). The NPV of post-ductography US was significantly higher than that of initial US (96.9% vs. 83.3%, p = 0.006). Specificity was significantly higher for initial US than for ductography and post-ductography US (all p = 0.001). No significant differences were noted between the in-house and other institution's US groups (Supplementary Table 3).

DISCUSSION

We examined the value of adding ductography to US in diagnosing PND in patients with negative mammography findings. This addition facilitated malignancy detection and increased the sensitivity from 47.1% to 94.1% in women with PND. Malignancy not identified via US was detectable via ductography as filling defects, ductal wall irregularity, or complete duct obstruction in approximately 8.9% (9/101) of the patients. The correlation between ductography and US findings enabled the localization of lesions and US-guided intervention for post-ductography US in 21 patients including eight with malignancies. However, for 17 patients without correlating lesions on post-ductography US, microdochectomy was performed, and only one case of ductal carcinoma in situ (DCIS) was found. No malignancy was found in the 15 ductography- and post-ductography US-negative patients.

ACR guidelines recommend mammography or digital breast tomosynthesis as the initial examination for women aged ≥ 40 years [7]. Positive mammography findings in patients with PND include microcalcifications, mass lesions, architectural distortion, asymmetry, and/or solitary dilated ducts [21,27,28]. The benefits of additionally performing ductography for mammography-positive patients remain unclear, although several reports have shown various rates of correlation (80.0% [4/5]–33.4% [2/6]) between ductography and mammography findings for malignant lesions [21,27]. Moreover, ductography has been shown to facilitate preoperative localization of the causative lesion in 36% (13/36) of the cases [29]. Given the low sensitivity (7%–26%) of mammography [8], many cases of PND may not exhibit any abnormalities on mammography. US is recommended as the first-line diagnostic modality for cases of PND, with or without mammography, based on

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the patient's age [7]. The additional use of ductography for US-positive cases is limited. US was shown to be more useful in cases of complete duct obstruction without visualization of the distal portion on ductography [21]. However, ductography allows preoperative determination of the number, location, and extent of the underlying lesions [30]. In the present study, initial US findings correlated with ductography findings for 38 lesions; however, only eight lesions (21.1%) showed additional information that helped in the selection of the biopsy target or definition of the lesion extent. US was advantageous and could identify abnormalities in patients in whom ductography failed or showed negative findings due to the incorrect selection of nipple orifice. The specificity was higher for US than for ductography or post-ductography US because small filling defects or obstructive duct-only lesions were confirmed as papillomas (n = 15) or high-risk lesions (n = 4). Therefore, an initial US workup with mammography is appropriate for patients with PND. However, extremely small or completely intraductal lesions cannot be detected by US [11]. Ductography may be useful when other initial standard imaging evaluations are negative [6,7]. We noted negative findings or findings of dilated ducts on the initial US in 54 patients. After adding ductography, nine additional malignancies were found, which increased the sensitivity from 47.1% to 94.1%. This finding is comparable to the results of Jung et al. [21], who evaluated 46 lesions in 39 patients, including 40 mammography-negative lesions, and reported sensitivity values of 75% and 100% for US and ductography, respectively. Baydoun et al. [27] reported a sensitivity of 86% for both US and ductography, with (n = 92) or without (n = 2) mammography, for 89 mammography-negative patients. They demonstrated that the sensitivity was significantly higher for the combination of imaging modalities than for ductography alone (86% vs. 76%, p = 0.008), suggesting synergistic effects of combining mammography, US, and ductography to determine PND etiology. Istomin et al. [31] reported that the sensitivity of ductography was 77.4% for 146 patients with PND, including 138 patients with normal mammography findings and eight young patients who did not undergo mammography. Blum et al. [23] reported that combining US and ductography increased the sensitivity for intraductal pathology detection compared to either modality alone (91% for combined vs. 73% for ductography vs. 64% for US). The increased sensitivity may be due to a more meticulous examination when searching for intraductal lesions or other pathologies underlying PND while using a combination of modalities than with ductography findings alone. An advantage of using US-ductography correlations is the more accurate localization of the underlying pathology and depiction of both ductal and mass characteristics on US, facilitating the BI-RADS categorization. In this study, in the initial US-negative group, 20.8% of the lesions were detected on post-ductography US by correlation with ductography findings, which enabled lesion localization and US-guided intervention. Finally, eight of the nine (88.9%) malignancies detected by ductography were confirmed by US-guided intervention and reduction surgery.

In this study, 17 (43.6%) of the 39 patients with negative findings on initial US and positive findings on ductography did not exhibit correlating abnormalities on post-ductography US. For patients with inconclusive post-ductography US findings or unsuccessful ductography, MRI might be considered for lesion localization and malignancy exclusion if clinically recommended (Fig. 6) [31].

In the present study, the NPV of ductography was 95.8%, which although non-significant, was higher than that of initial US. Only one DCIS was found in the ductography-negative patients; this case showed an intraductal mass on the initial US. We found no malignancy in the initial US-negative or ductography-negative patients. In this

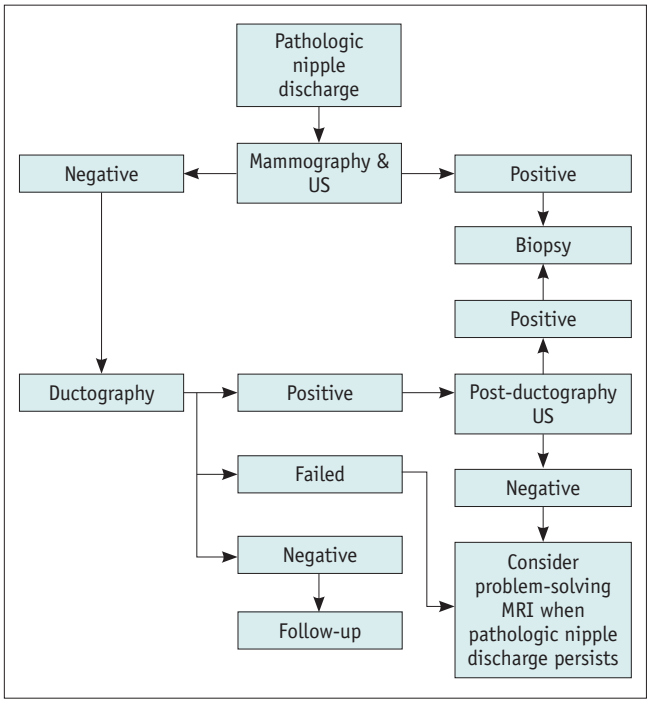

Fig. 6. Proposed breast imaging diagnostic algorithm for the evaluation of pathological nipple discharge. US = ultrasound

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group, post-ductography US showed no additional findings; therefore, patients could be monitored without post-ductography US (Fig. 6). The NPV of post-ductography US was significantly higher than that of the initial US (96.9%), which is comparable to the findings of Kim et al. [24], who reported an NPV of 93.3% for second-look US. In this study, only one case of DCIS was found in a post-ductography US-negative case. This case showed complete obstruction on ductography. In 15 patients with US-negative ductography and post-ductography findings, no malignancy was confirmed.

Our study has several limitations. Given its retrospective nature, a patient selection bias may be present. Furthermore, US and ductography are operator-dependent modalities that are associated with performance bias. Although we confirmed the image quality of the US performed at other institutions by consensus review, 48.5% of the patients were analyzed using initial US images from other institutions. This might have affected the initial US performance. However, there was no significant difference in the diagnostic performance between the in-house and other institution's US groups (Supplementary Table 3). Finally, this study did not include a comparison with MRI. Studies using MRI to detect lesions in patients with PND have reported a high diagnostic performance [1,32]. Nevertheless, routine MRI examinations were clinically unfeasible in our study. In our study, only one DCIS case was diagnosed among 17 patients who underwent microdochectomy. Considering the low malignancy rate in this group, MRI recommendations remain debatable. For MRI, the false-negative rate of non-enhancement of low-grade DCIS or small invasive ductal carcinoma and the high false-positive rate should be considered [8].

In conclusion, the combined use of ductography and US has a high sensitivity for detecting malignancy in patients with PND and negative mammography. Ductography findings enable lesion localization on second-look post-ductography US, thus facilitating the selection of optimal treatment plans.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0850.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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