Galactography Combined with Sonogalactography for Improving the Evaluation of Pathological Nipple Discharge

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Featured Application: The combination of galactography and sonogalactography improves the diagnostic efficiency of ductal lesions of patients with pathological nipple discharge.

Abstract: Diagnosing patients with pathological nipple discharge (PND) is controversial, and therefore a standardized diagnosis algorithm is needed. The objective of this study was to investigate the usefulness of galactography (GL) combined with sonogalactography (SGL) for the evaluation of PND patients. A retrospective study was conducted of 51 patients with PND who were evaluated with GL and SGL. The findings from the galactograms of the patients in this study were assigned to different categories of the Galactogram Image Classification System. Additionally, the sensitivity, specificity, and the positive predictive values and negative predictive values of the GL and SGL tests were calculated, considering the gold standard of pathology diagnosis. The results obtained show that GL combined with SGL improved the diagnostic efficiency of ductal lesions, especially for borderline and malignant lesions. Papilloma was diagnosed in 19 cases, and ductal carcinoma in situ in 8 patients. Conclusions: To the best of our knowledge, this is the first study in which the combination of GL and SGL improves the diagnostic efficiency of ductal lesions of patients with PND. A diagnosis algorithm is recommended for women with PND.

Keywords: breast; pathological nipple discharge; galactography; sonogalactography

1. Introduction

Nipple secretions are an important clinical problem that causes discomfort and anxiety for many women [1–3]. Pathological nipple discharge (PND) is defined as a unilateral spontaneous secretion that can be sanguineous, serous, or mucinous [4–6]. Although most of the PNDs are caused by benign lesions, approximately 3–20% of the cases are due to mammary carcinoma [1,6–9]. The evaluation and diagnosis of PND is fundamental for the early detection of carcinoma. However, the evaluation of the cause behind PND is difficult for both clinicians and radiologists.

The selection of type of image in the management of PND varies among radiologists, which can result in unnecessary diagnostic tests [10]. Nevertheless, a conventional study of the image through a mammography (MMG) and ultrasonography is recommended [1,9,11,12]. If the result is negative, the galactography (GL) has been considered the best procedure for the evaluation of PND, as it allows identifying the ductal anomalies and their location, and is used as a guide for surgical excision [3–5,7,8,13,14]. However, GL is still debated, as establishing a differential diagnosis between benign and malignant diagnoses is considered

difficult [5–7,14]. Thus, the Galactogram Image Classification System (GICS) was reported, and GL was defined as a useful procedure for differentiating benign lesions from malignant ones [15]. However, various studies [16–18] have pointed out that magnetic resonance imaging (MRI) is a more useful diagnostic tool for the evaluation of PND. However, its use is only recommended for selected patients, for example, when the GL technique fails, or when the results from the image tests are not conclusive, especially for the planning of surgery [11,12,19].

In a recent study [20], it was shown that the second-look ultrasonography (US) performed 5–30 days after a GL was a powerful diagnostic tool for the detection of lesions in PND patients. We believe that the US test performed after a GL, which we have named sonogalactography (SGL), can improve the evaluation of the duct system shown in the galactograms, as the injection of the contrast dye in the secretory duct allow us to improve the selective visualization of the problem duct. The objective of the present study was to investigate the value of a GL combined with a SGL for the evaluation of women with PND.

2. Patients and Methods

2.1. Patients

A retrospective study was conducted between January 2012 and September 2020 with women with PND who were referred to our breast care unit at our hospital and were evaluated with a GL. Before the GL, all the women were tested with a MMG and a US. The findings from the MMG and US were categorized using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) [21]. The inclusion criteria were: women with PND and a finding from the MMG and US indicating probably benign or suspicion for malignancy (BI-RADS 3 and 4). The study was approved by the Institutional Review Board. In all the cases, the procedure was explained to the patients in detail, and an informed consent was obtained from them.

2.2. Galactography

Before the GL, an anesthetic cream was applied to the areola/nipple area for about 40–60 min [22]. Next, a coaxial GL technique was performed, as previously described [23]. A 24 G catheter was inserted into the secretory duct (Figure 1). The studies were conducted with a digital mammography system (Lorad Selenia, Hologic Inc., Bedford, MA, USA). Craniocaudal and mediolateral mammograms were obtained after the injection with the contrast dye. All the galactograms were reviewed in agreement by 2 radiologists with experience in breast imaging. The localization of the abnormalities detected in the galactograms were determined as retro-periareolar, central, peripheral, retro-peripheral, retro-central, or central-peripheral. The findings detected in the galactograms of the patients in this study were categorized according to the Galactogram Image Classification System (GICS). The GICS 1 and 2 categories were considered as a negative test, and the GICS categories 3, 4, and 5 as positive.

2.3. Sonogalactography

After the GL, the patients were taken to the echography room with the catheter still inserted in the secretory duct with a cap to avoid the loss of the contrast dye (Figure 2). The US tests were performed with an Acuson S2000 US system (Siemens, Erlangen, Germany) equipped with an 18L6HD transducer. The duct system shown in the galactograms were evaluated selectively. The catheter could be removed if it made the examination difficult. It is important to consider that the SGL must be performed with the minimum compression from the transducer to achieve the best visualization of the duct system. The findings observed in the SGL were included in the following groups: 1. Normal; 2. Benign, 3. Papilloma; 4. Papillomatosis; 5. Suspected malignancy: (a) intraductal micronodular pattern or solid isoechoic or hypoechoic without duct dilation; (b) abnormalities in the duct wall; thickening of the duct wall or duct wall not well defined. The 1 and 2 groups were considered as a negative test, and the groups 3, 4, and 5 as positive. A US-guided core

needle biopsy (CNB) was performed in all the patients. Additionally, in the cases included in the SGL/GL groups papilloma/GICS 3, papillomatosis/GICS 4, and suspicion for malignancy/GICS 5, a microdochectomy was performed. For these patients, a pre-surgical localization was performed with a US-guided wire insertion.

Figure 1. Galactography technique. The picture shows a catheter inserted in the secretory duct.
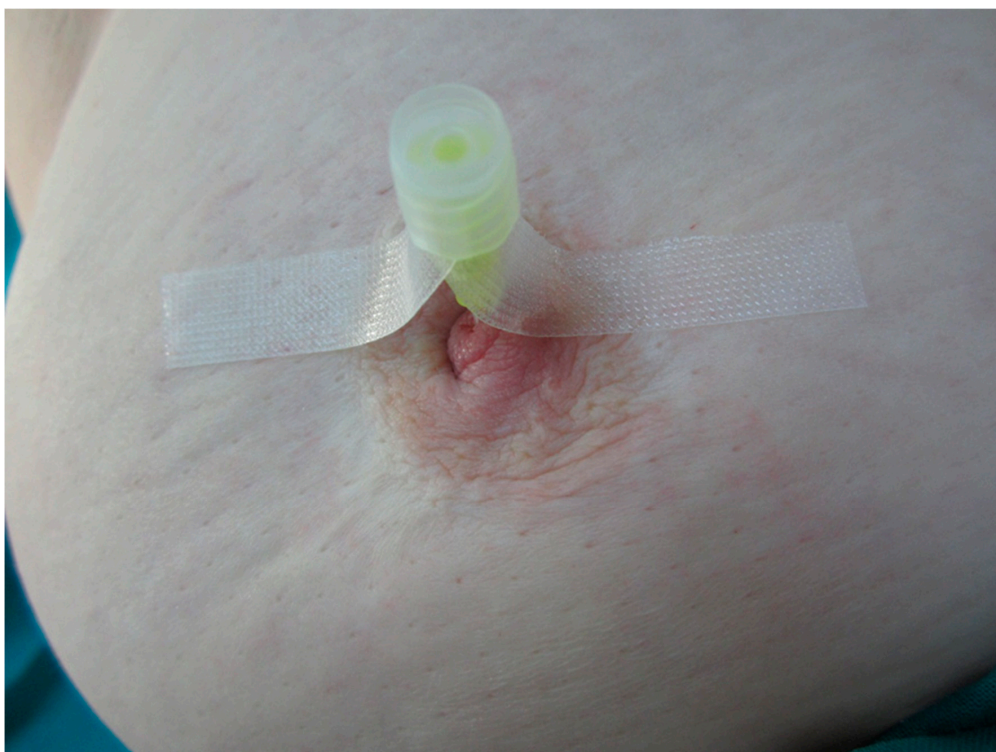
Figure 2. Catheter with cap and fixed with tape.

2.4. Data Collection

The clinical histories of the patients were reviewed, and the following parameters were recorded: age, family and/or personal history of breast cancer, type of nipple secretion, MMG exam, MMG density patterns, US exam, microdochectomy, mastectomy, and histopathological findings. As for the MMG density patterns, the Breast Imaging Reporting and Data System (BIRADS) was utilized: Type A, breasts that are almost entirely fatty; Type B, breasts with scattered areas of fibroglandular density; Type C, breasts that are heterogeneously dense; and Type D, extremely dense breasts [21]. The data from the histopathology were reviewed by two pathologists with experience in breast pathology, and the lesions were classified into the following categories: (a) duct ectasia; (b) fibrocystic changes; (c) usual duct hyperplasia; (d) atypical duct hyperplasia; (e) solitary intraductal papilloma; (f) papillomatosis; and (g) duct carcinoma in situ (DCIS). As a standard reference, the clinical and image monitoring >2 years were used of patients with benign findings, and the pathological diagnosis was categorized into three groups: 1. Benign: ductal ectasia, fibrocystic changes, and usual duct hyperplasia; 2. Borderline: solitary intraductal papilloma, papillomatosis, and atypical duct hyperplasia.

2.5. Statistical Analysis

The statistical analysis was performed with the statistical software package SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, New York, NY, USA: IBM Corp.). For the descriptive analysis of the sample, the mean and standard deviation was calculated for the quantitative variables, and frequencies and percentages for the qualitative variables. The normality of the data was evaluated with the Kolmogorov–Smirnov test. To determine the relationship between the image tests, the demographic and clinical variables, and the histopathological results, the differences in means were utilized for the quantitative variables (ANOVA and Student's t test), and the differences of proportions (Chi-square χ^2, replaced by Fischer's exact test for cells with n < 5 cases) for the categorical variables. Lastly, the sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV) were calculated for the galactography, sonogalactography tests, considering the pathology diagnosis results as the gold standard. For this, the results of the tests were categorized in two ways: (a) borderline and malignant, and (b) malignant. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Demographic and Clinical Characteristics of the Participants

The mean age of the 51 women included in the study (Figure 3) was 52.89 (SD − 11.44) years old. Most of the patients, 25 cases (49%), had sanguineous secretions (Table 1). Three patients had a family history of breast cancer, and one case had a personal history of breast cancer. As for the relationship with the density pattern observed in the MMG, the most frequent was type C (15 cases, 29.4%).

3.2. Pathological Diagnosis

The histopathological findings of the CNB were benign in 48 cases (94.1%): duct ectasia (*n* = 3), fibrocystic condition (*n* = 9), and ductal hyperplasia (*n* = 4); and borderline in 3 cases (5.9%): papillary lesion (*n* = 2), and ductal hyperplasia with atypia (*n* = 1). As for the pathological diagnosis, of the 40 patients who were subjected to a microdochectomy, the results were the following: benign in 5 cases (12.5%): ductal ectasia (*n* = 4), and fibrocystic condition (*n* = 1); borderline in 27 cases (67.5%): papilloma (*n* = 19), papillomatosis (*n* = 6), and ductal hyperplasia with atypia (*n* = 2); malignant in 8 cases (20%), which corresponded to a CDIS 8. A mastectomy was performed on 3 patients.
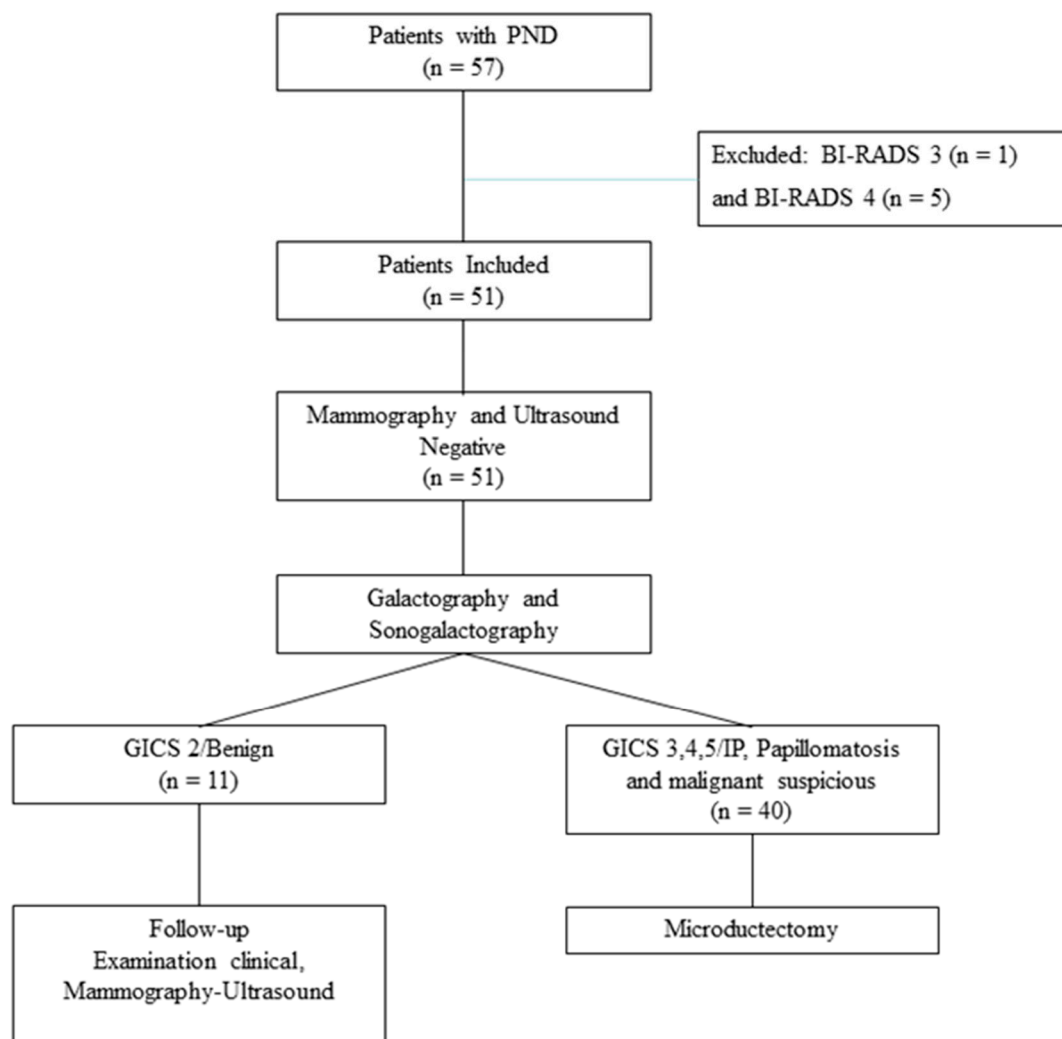
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┌─────────────────────────────┐
│      Patients with PND       │
│         (n = 57)             │
└─────────────────────────────┘
              │                    ┌────────────────────────────────┐
              ├────────────────────│ Excluded: BI-RADS 3 (n = 1)    │
              │                    │ and BI-RADS 4 (n = 5)          │
              │                    └────────────────────────────────┘
┌─────────────────────────────┐
│      Patients Included       │
│         (n = 51)             │
└─────────────────────────────┘
              │
┌─────────────────────────────┐
│  Mammography and Ultrasound  │
│          Negative            │
│         (n = 51)             │
└─────────────────────────────┘
              │
┌─────────────────────────────┐
│     Galactography and        │
│     Sonogalactography        │
└─────────────────────────────┘
        /                    \
┌──────────────────┐   ┌──────────────────────────────┐
│  GICS 2/Benign   │   │ GICS 3,4,5/IP, Papillomatosis │
│    (n = 11)      │   │   and malignant suspicious    │
└──────────────────┘   │         (n = 40)              │
        │              └──────────────────────────────┘
┌──────────────────┐               │
│    Follow-up      │   ┌──────────────────────────────┐
│ Examination clinical,│ │       Microductectomy         │
│ Mammography-Ultrasound│└──────────────────────────────┘
└──────────────────┘
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Figure 3. Flow diagram of the patients in this study.

Table 1. Demographic and clinical characteristics.

Variables	Total	Benign	Borderline	Malignant	p
Age, M (DE)	52.56 (11.44)	50.69 (11.71)	53.93 (10.29)	52.50 (15.23)	0.68
Secretion, *n* (%)					0.16
Sanguineous	25 (49)	8 (32)	13 (52)	4 (16)	
Serous	22 (43.1)	8 (36.4)	10 (45.5)	4 (18.2)	
Mucinous	4 (7.9)	0 (0)	4 (100)	0 (0)	
Family history, *n* (%)					0.73
Yes	3 (5.9)	1 (33.3)	2 (66.7)	0 (0)	
No	48 (94.1)	15 (31.3)	25 (52.1)	8 (16.7)	
Personal history, *n* (%)					0.64
Yes	1 (2)	0 (0)	1 (100)	0 (0)	
No	50 (98)	16 (32)	26 (52)	8 (16)	
Density Pattern, *n* (%)					0.31
Type A	12 (23.5)	1 (8.3)	9 (75)	2 (16.7)	
Type B	13 (25.5)	3 (23.1)	8 (61.5)	2 (15.4)	
Type C	15 (29.4)	7 (46.7)	5 (33.3)	3 (20)	
Type D	11 (21.6)	5 (45.5)	5 (45.5)	1 (9.1)	

3.3. Correlation of the Imaging Tests with the Pathological Diagnosis

Of the 51 women, 40 were identified with positive findings with a GL (5 benign lesions, and 35 with borderline lesions + malignant in the anatomical pathological diagnosis). On the other hand, 35 patients were identified with positive findings after a sonogalactography (all of them with borderline + malignant lesions in the pathological diagnosis). The associations between the imaging tests according to the pathological diagnosis are shown in Table 2, with statistically significant results for GL (χ^2 = 30.68; p = 0.000) and for SGL (χ^2 = 51; p = 0.000). The localization of the more frequent lesions were retro-periareolar, retro-central, and central. The density pattern with the greatest percentage of borderline and malignant lesions were type A and B. The mean follow-up performed with the 11 women who were not subjected to surgery, due to the findings observed in the GL and the SGL, were benign, with a value of 59.82 (SD = 19.57).

Table 2. Association between the results of the imaging tests and pathological anatomy.

Variables	Total	Benign	Borderline + Malignant	p
Secretion, n (%)				0.35
Sanguineous	25 (49)	8 (32)	17 (68)	
Serous	22 (43.1)	8 (36.4)	14 (63.6)	
Mucinous	4 (7.9)	0 (0)	4 (100)	
Density Pattern, n (%)				0.11
Type A	12 (23.5)	1 (8.3)	11 (91.7)	
Type B	13 (25.5)	3 (23.1)	10 (76.9)	
Type C	15 (29.4)	7 (46.7)	8 (53.3)	
Type D	11 (21.6)	5 (45.5)	6 (54.5)	
Conventional echography, n (%)				0.72
Negative	40 (78.4)	12 (30)	28 (70)	
Benign	11 (21.6)	4 (36.4)	7 (63.6)	
Galactography, n (%)				<0.001
Negative	11 (21.6)	11 (100)	0 (0)	
Positive	40 (78.4)	5 (12.5)	35 (87.5)	
SonoGalactography, n (%)				<0.001
Negative	16 (31.4)	16 (100)	0 (0)	
Positive	35 (68.6)	0 (0)	35 (100)	
Localization, n (%)				0.29
Retro-periareolar	12 (23.5)	2 (16.7)	10 (83.3)	
Central	12 (23.5)	4 (33.3)	8 (66.7)	
Peripheral	0 (0)	0 (0)	0 (0)	
Retro-peripheral	6 (11.8)	2 (33.3)	4 (66.7)	
Retro-central	17 (33.3)	8 (47.1)	9 (52.9)	
Central-peripheral	4 (7.8)	0 (0)	4 (100)	
Microdochectomy, n (%)				<0.001
Yes	40 (78.4)	5 (12.5)	35 (87.5)	
No	11 (21.6)	11 (100)	0 (0)	
Mastectomy, n (%)				0.54
Yes	3 (5.9)	0 (0)	3 (100)	
No	48 (94.1)	16 (33.3)	32 (66.7)	
Follow-up (months)⊕, M (SD)	59.82 (19.57)	59.82 (19.57)	-	-

3.4. Diagnostic Efficiency of the Galactography and the Sonogalactography

Table 3 shows the diagnostic efficiency of GL and SGL to detect "borderline and malignant lesions", and only malignant lesions. The use of SGL after the GL showed a greater diagnostic efficiency, with a diagnostic precision of 100%, sensitivity of 100%, a specificity of 100%, and NPV/PPV of 100% for the detection of borderline and malignant lesions. However, for the detection of malignant lesions, the SGL and the GL seemed to have the same diagnostic efficiency.

**Table 3.** Diagnostic efficiency of the galactography and the sonogalactography.

	Borderline + Malignant				
	Acc % (95% CI)	Se % (95% CI)	Sp % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Galactography	90.2 (77.8–96.3)	100 (87.7–100)	68.75 (41.5–87.9)	87.5 (72.4–95.3)	100 (67.9–100)
Sonogalactography	100 (91.3–100)	100 (87.7–100)	100 (75.9–100)	100 (87.7–100)	100 (75.9–100)
	Malignant				
	Acc % (95% CI)	Se % (95% CI)	Sp % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Galactography	96.08 (85.4–99.3)	100 (59.8–100)	95.35 (82.9–99.2)	80 (44.2–96.5)	100 (89.3–100)
Sonogalactography	96.08 (85.4–99.3)	100 (59.8–100)	95.35 (82.9–99.2)	80 (44.2–96.5)	100 (89.3–100)

PPV: positive predictive value, NPV: negative predictive value; Acc: accuracy; Se: sensitivity; Sp: specificity.

4. Discussion

As far as we know, this is the first time that a SGL after a GL has been utilized for the evaluation of PND patients. The results obtained provide evidence that SGL combined with GL improves diagnostic efficiency, especially of borderline and malignant lesions. These findings are fundamental for establishing the differential diagnosis between benign, borderline, and malignant lesions.

The physical examination was negative in all the patients in the present study, and the cytology of the nipple discharge was negative in the two cases where it was performed. The physical examination, MMG, and US, are the first-line methods for evaluating PND. Considering the various types of imaging methods utilized for the management of women with PND, it is fundamental to establish standardized diagnosis algorithms for better efficiency [9,10,20,24]. In this sense, when the conventional image examination (MMG and US) is negative, the GL is considered a fundamental procedure for the diagnosis of PND, as it provides precise information for the localization of the lesions, and it is used as a guide for the planning of surgery [5,8–10,20]. Likewise, the GL is a simple, cheap, and fast technique which takes about 15 min [8,9,20,25]. Likewise, the GICS classification system [15] is a useful tool for differentiating between benign and malignant lesions. In addition, with the application of an anesthetic cream in the areola-nipple area, the patients tolerate the procedure well [22]. In the cases of extravasation or failure of the technique, repeating the GL is recommended again after one or two weeks. Despite all the advantages of GL, it is an underutilized technique. We believe, in agreement with other authors [8,9,20,25], that GL is not an obsolete technique and should be utilized as a second-line diagnostic procedure in PND. In addition, it is important to perform a SGL after the GL so that the intraductal lesions without ductal ectasia can be evaluated, which in the DCIS cases are very small (<3 mm) and cannot be observed with conventional imaging methods. In the present study, the findings that were most frequently observed in the GL were filiform ducts with microdefects (Figures 4 and 5), which in the SGL corresponded to micronodules and badly-defined duct walls. In these cases, it is important to take into account the identification of the problem duct, which can be observed with the contrast dye as anechoic, and could have an aspect of small hyperechoic foci or with a hyperechoic continuous intraductal content. Based on our experience, the SGL is a complementary test to the GL which allows for the precise localization of small intraductal lesions as well as their characterization. In this way, the differentiation between benign, borderline, and malignant lesions can be improved.
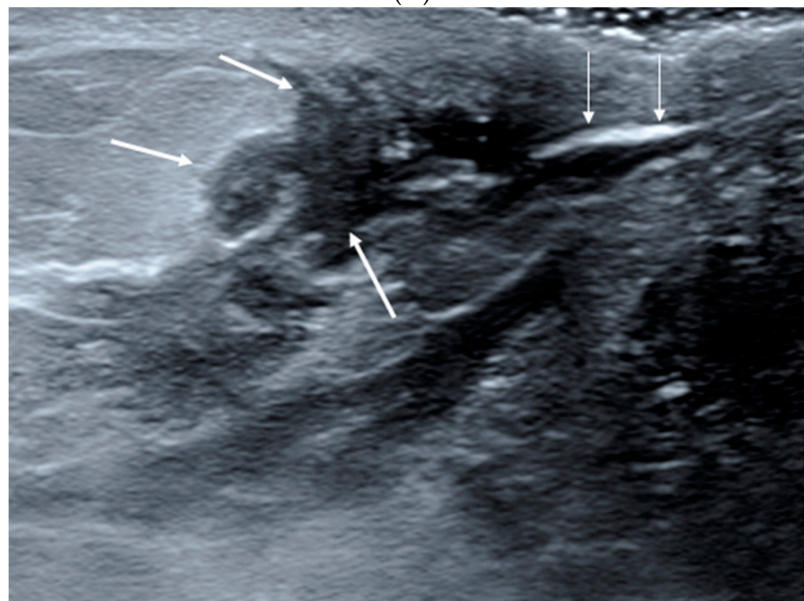
(**A**)

(**B**)
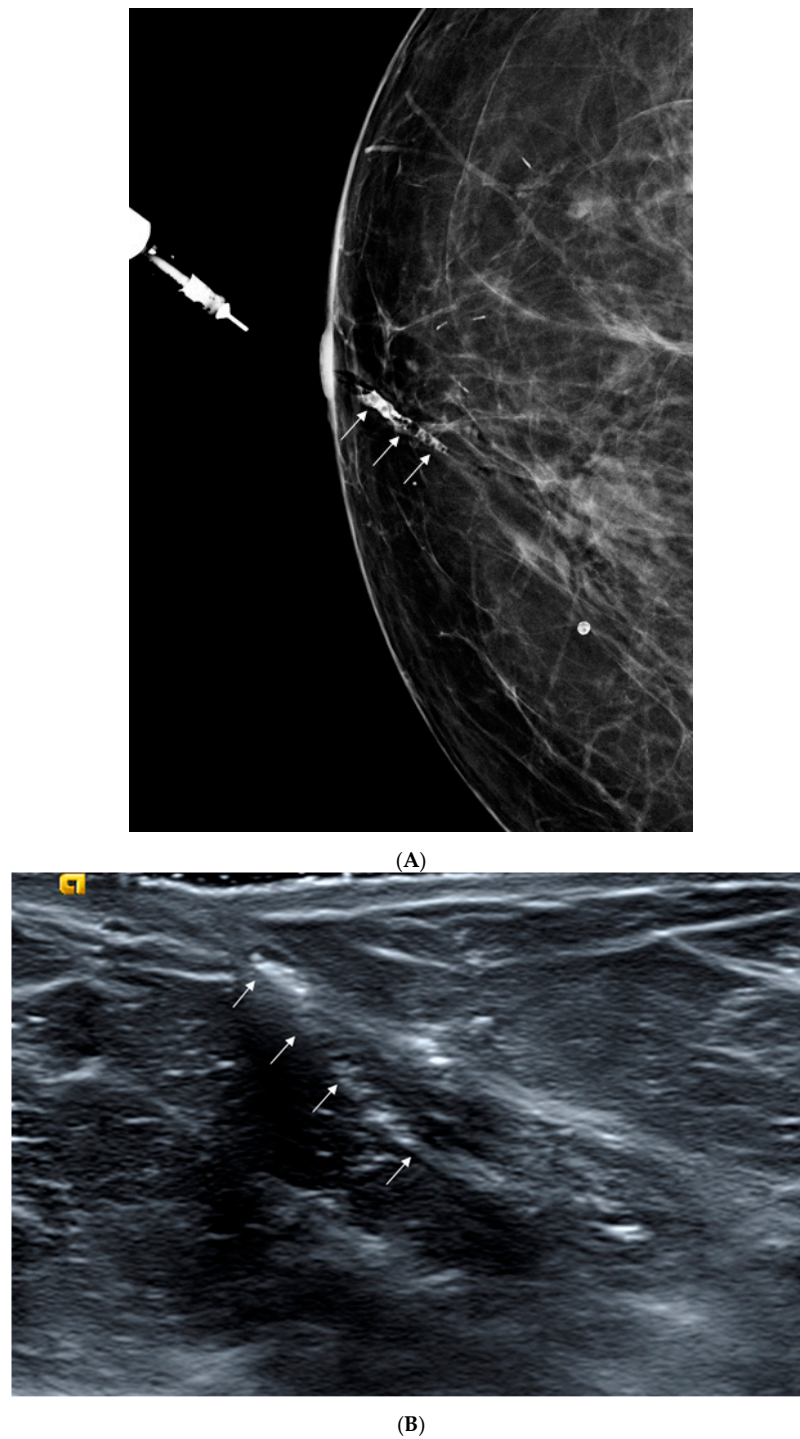
Figure 4. A 79-year-old woman with a pathological diagnosis of ductal carcinoma in situ. (**A**) Magnified galactogram which shows obstruction in the duct and microdefects with a moth-eaten appearance (arrows), which was included in the Galactogram Image Classification System (GICS) 5 category: high suspicion of malignancy. (**B**) Magnified sonogram showing a micronodular pattern and badly-defined duct wall (arrows), with hyperechoic foci which correspond to the contrast dye injected.
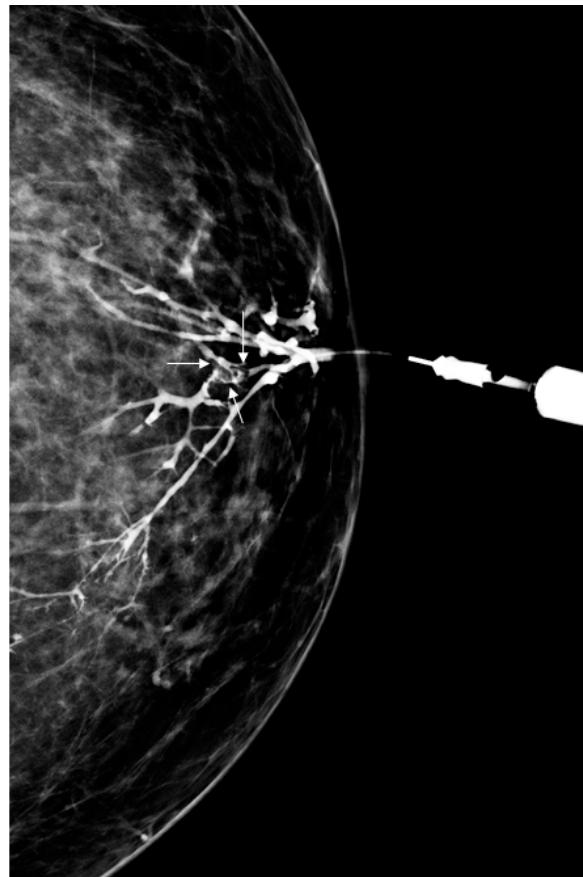
(**A**)

(**B**)

Figure 5. A 58-year-old woman with a pathological diagnosis of ductal carcinoma in situ. (**A**) Magnified galactogram which shows microdefects with a moth-eaten appearance (arrows), which was included in the GICS 5 category: high suspicion of malignance. (**B**) Sonogram showing a solid hyperechoic pattern with badly-defined duct wall (thick arrows), and intraductal hyperechoic content (thin arrows), which correspond to the contrast dye injected.

As for the GL, inconveniences were also found, as it is a minimally invasive technique, the procedure takes some time, there could be a failure in the canalization of the secretory duct, and it does not allow for differentiating between benign and malignant lesions [3,6,7,17]. In addition, many studies [16–18] point out that MRI is superior to the GL for the evaluation of PND. However, MRI is more expensive than the GL, and the examination time is even longer [9]. Likewise, MRI cannot be utilized with women who suffer from claustrophobia and its contraindications must be considered, such as metallic implants, allergy to the contrast dye, or renal insufficiency. Lastly, it should be pointed out that MRI is not included among the recommendations for the evaluation of PND patients [1,11,12]. Additionally, mammary ductoscopy is a technology that allows for the direct visualization and biopsy examination of the mammary ductal abnormalities [26,27]. Furthermore, recent studies [28,29] have reported that digital breast tomosynthesis-GL may become an important diagnostic step for managing PND.

In a recent study [20], the diagnostic potential of a second-look US after a GL for borderline and malignant lesions was evidenced. In the present study, the SGL combined with the GL improved the diagnostic efficiency, especially with borderline and malignant lesions. In addition, the SGL allows performing the CNB. In this study, the histopathological results of the CNB did not correlate with the final pathological diagnosis, perhaps because the intraductal lesions were very small. Additionally, it has been reported that the papillary neoplasia diagnosis of the breast can be challenging, especially if only the equipment for a CNB is available [30]. Therefore, the collaboration between clinicians, radiologists, and pathologists is of great importance for optimizing the efficiency of diagnosis.

Our study also had limitations, as it is a retrospective study and the sample was small. In addition, experience is required for the interpretation of the findings from the GL and the SGL as well. The galactograms were categorized with the GICS, which has been reported to have a good to very good inter- and intra-observer agreement [31]. It should also be taken into account that the SGL is an operator-dependent examination. Nevertheless, we consider that in this study, the combination of GL with SGL was fundamental for the diagnosis of PND. We thus recommend the diagnostic algorithm described in the present study for the management of PND patients.

5. Conclusions

According to our knowledge, this is the first time that a SGL has been utilized after a GL for the evaluation of PND patients. The results obtained showed that the SGL combined with the GL improved the diagnosis of PND, especially for the borderline and malignant lesions. An algorithm for the management of PND is also recommended. Future studies are needed for optimizing the management of PND patients.

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Institutional Review Board Statement: Diagnostic examination is systematically protocolized at this Center and the study is a retrospective review of the examinations performed.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used in this study are found in the medical records of the patients examined. Require a specific authorization for review.

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