Original Study

Interventional Ductoscopy as an Alternative for Major Duct Excision or Microdochectomy in Women Suffering Pathologic Nipple Discharge: A Single-center Experience

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Abstract

Ductoscopy is a minimally invasive technique that is currently used to detect, and sometimes remove, lesions that cause pathologic nipple discharge (PND). This study shows that ductoscopy is an alternative for surgery in patients with PND that have negative conventional imagery for breast cancer. Additionally, this study shows that ductoscopy has a high sensitivity, specificity, and negative predictive value for the detection of breast cancer in patients with PND with negative conventional imagery.

Introduction: Pathologic nipple discharge (PND) is, after palpable lumps and pain, the most common breast-related reason for referral to the breast surgeon and is associated with breast cancer. However, with negative mammography and ultrasound, the chance of PND being caused by malignancy is between 5% and 8%. Nevertheless, most patients with PND still undergo surgery in order to rule out malignancy. Ductoscopy is a minimally invasive endoscopic technique that enables direct intraductal visualization. The aim of this study was to evaluate (interventional) ductoscopy as an alternative to surgery in patients with negative conventional imaging. **Materials and Methods:** All patients with PND referred between 2010 and 2017 to our hospital for ductoscopy were retrospectively analyzed. Ductoscopy procedures were performed under local anesthesia in the outpatient clinic. The follow-up period was at least 3 months, and the primary outcome was the number of prevented surgical procedures. Furthermore, we evaluated possible complications after ductoscopy (infection and pain). **Results:** A total of 215 consecutive patients undergoing ductoscopy were analyzed. In 151 (70.2%) patients, ductoscopy was successful. In 102 procedures, an underlying cause for PND was visualized, of which 34 patients could be histologically proven and 82 patients treated. Sixty of the 215 patients were eventually operated, 8 owing to suspicious findings during ductoscopy, 42 owing to persistent PND, and 10 because of recurrent PND. In 7 patients, a malignancy was found (5 of them classified as suspicious at dusctoscopy). No serious side effects were seen. **Conclusion:** Ductoscopy can be safely used as an alternative for surgery in the workup for PND.

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Introduction

Pathologic nipple discharge (PND) is the third most common breast-related complaint, after pain and palpable lumps.[1] PND is defined as unilateral, spontaneous, and bloody or serous discharge, usually arising from a single duct orifice of the nipple. PND is regarded as a possible sign of breast cancer, and it accounts for 3% to 5% of surgical breast clinic referrals.[2-5] However, when ultrasound and mammography are negative, the risk of malignancy is still around 5% to 8%.[6,7] The most common causes of PND are benign: ductal ectasia and intraductal papillomas.[8,9]

Mammography and breast ultrasound are important tools for the detection of breast cancer. However, in the case of PND as the only complaint, they both have limited sensitivity (15% and 56% for mammography and ultrasound, respectively).[10] Magnetic resonance

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imaging (MRI) has shown to be a sensitive tool for the detection of malignancy, but specificity is low. However, detection of small lesions and differentiating them benign from malignant masses remains difficult in using MRI as a diagnostic tool.[11,12] Therefore, the value of MRI is limited in patients with PND, and core needle biopsy or surgical excision is still indicated when MRI shows a suspicious lesion.[13,14]

Because PND is regarded as a possible sign of breast cancer, and standard radiologic imaging often fails to reveal the underlying cause, most women suffering PND undergo surgical procedures, such as microdochectomy or major duct excision, to rule out malignancy.[8,10,11] These surgical procedures are performed under general anesthesia and are associated with scarring, which may result in breastfeeding difficulties in fertile women.[15] Furthermore, malignancy is found in only 5% to 8% of patients.[5-7] This means that around 90% to 95% of these surgical procedures are performed for benign lesions.

Ductoscopy is a minimally invasive micro-endoscopic technique, which makes real-time visualization of the milk ducts of the breast possible. The procedure can be performed under local anesthesia at the outpatient clinic and is currently used as a diagnostic tool in the workup of women suffering from PND without suspicious radiologic findings.[16-22] Previous studies showed the success of ductoscopy in finding the intraductal lesion causing PND before or during duct excision.[23-27] In recent years, a biopsy tool was introduced that can be used through the working channel of the ductoscope, enabling interventional ductoscopy to not only visualize but also remove the lesion underlying PND in a single procedure under local anesthesia.[27,28] Interventional ductoscopy has already been described in a few studies as a safe alternative for classic open surgery in patients with PND,[28,29] but wider implementation requires further validation studies.

In the present study, we describe the experience with interventional ductoscopy as an alternative to surgery in women with PND in a single national referral center in The Netherlands between 2010 and 2017.

Materials and Methods

Patient Selection

This retrospective observational consecutive cohort study included women who presented with unilateral PND between 2010 and 2017 in the University Medical Centre Utrecht (UMCU) in the Netherlands. This included a smaller cohort of 82 patients on whom we reported before.[28] Inclusion criteria were patients with spontaneous PND lasting over at least 3 months. Only the first ductoscopy was included for analysis. Exclusion criteria for analysis were the possible subsequent ductoscopy procedures, radiologic and/or pathologic suspicion of malignancy, or a follow-up period of less than 3 months.

Diagnostic workup of every patient was paramount for this study. Before ductoscopy, patients underwent imaging consisting of ultrasound and/or mammography. Patients received an additional MRI and/or core needle biopsy prior to ductoscopy when there was palpable mass and/or a Breast Imaging Reporting and Data System (BI-RADS) IV. When these additional tests were negative for malignancy (thereby downgrading the initial BI-RADS classification), these patients were eligible for ductoscopy. Either the UMCU (tertiary referring hospital) or the referring hospital performed the diagnostic workup. The ethical committee of the UMCU approved this study and decided that informed consent was not required as data were processed anonymously.

Cannulation

The surgeon performed the ductoscopy in the outpatient setting as described previously.[28] First, the surgeon identified the affected duct by pressing the nipple. Patients that did not have spontaneous PND during ductoscopy received oxytocin nose spray 30 minutes prior to the procedure in order to better locate the affected duct. The next step was to disinfect the areola and the nipple with 70% ethanol. Lidocaine 1% was used for local anesthesia of the nipple. Salivary duct probe (size 0000 to 1; Karl Storz, Tuttlingen, Germany) and an obturator (Polydiagnost, Pfaffenhofen, Germany) widened the lactiferous duct of the nipple. Stretching the nipple outwards was important in order to straighten the milk ducts to facilitate cannulation. Next, a port through which the ductoscope was introduced (SoLex nipple expander; Polydiagnost) was placed into the affected duct.

Ductoscopy

Ductoscopy was performed using a 6000-pixel 0.55-mm optic (LaDuScope T-flex; Polydiagnost) and a Polyshaft (1.15-mm outer diameter, PD-DS-1015; Polydiagnost). The Polyshaft system has 3 channels: 1 for the endoscope, 1 for saline irrigation or additional intraductal anesthetic infusion, and 1 for the endobasket. The ductoscope has a working length of 80 mm, a 0° angle direct view and a field vision of 70°, and is gas-sterilized.

Visualization of the ductal tree started in the lactiferous duct. The surgeon explored the major ducts in an orderly fashion until the ducts became too narrow to pass. Continuous saline irrigation into the ductal tree through the polyshaft is essential to keep the ducts from collapsing. When necessary, additional intraductal anesthesia (bupivacaine) was administered. One of 2 specialized surgeons with an experience of over 10 ductoscopy procedures performed the procedure. Ductoscopy was regarded as successful when a thorough examination of the afflicted ductal tree was possible.

Possible findings during the assessment of the ductal tree are normal duct morphology, polypoid lesions, ductitis, epithelial lesions/damage, etc. When possible, the endobasket facilitated the extraction of the lesion and subsequent histologic examination for diagnosis. When there was no visible intraductal lesion left after ductoscopy, it was defined as complete removal. In case of a visible residual lesion after extraction that was not possible to extract, it was defined as a partial extraction. Reasons to abort the ductoscopy were intolerable pain or perforation of the duct wall hampering further inspection of the underlying ducts.

Complications

Two weeks after ductoscopy, the attending physician contacted patients in order to gather information about pain, infections, or any other possible side effect or complication. A scale of 1 to 3 was used to code the pain (no pain, mild pain, or severe pain).

Follow-up

Patients were at least followed after 2 weeks and 3 months post ductoscopy. Depending on the outcome of the ductoscopy (suspicious findings, persistent PND, and/or patient preference), they were scheduled for surgery or follow-up.

Statistics

First, normality was determined using Kurtosis, in which z-values between −3 and 3 were considered as normally distributed data. Normally distributed continuous data was described by means and standard deviations. In non-continuous not normally distributed data, median and interquartile range were used to describe the data. For categorical values, the χ^2 test or the Fisher exact test (if the expected value in each cell was less than 5) was used to assess differences between groups. Sensitivity and specificity with 95% confidence intervals (CIs) were also assessed. *P* values below .05 were considered to be significant. Statistical analysis of the database was performed using SPSS v.23 (IBM, Armonk, NY).

Results

The flowchart in Figure 1 depicts the patients selected for analysis. Between 2010 and 2017, 244 patients with PND underwent a ductoscopy. Seventeen of these patients underwent multiple ductoscopy procedures, resulting in 261 procedures. This analysis only included the first ductoscopy. One male patient was excluded for further analysis. Twenty-eight patients were lost to follow-up, leaving 215 patients suitable for analysis.

Figure 1 Flowchart Showing all Ductoscopies Performed in Patients With Pathologic Nipple Discharge and Consequent Selection for Analysis

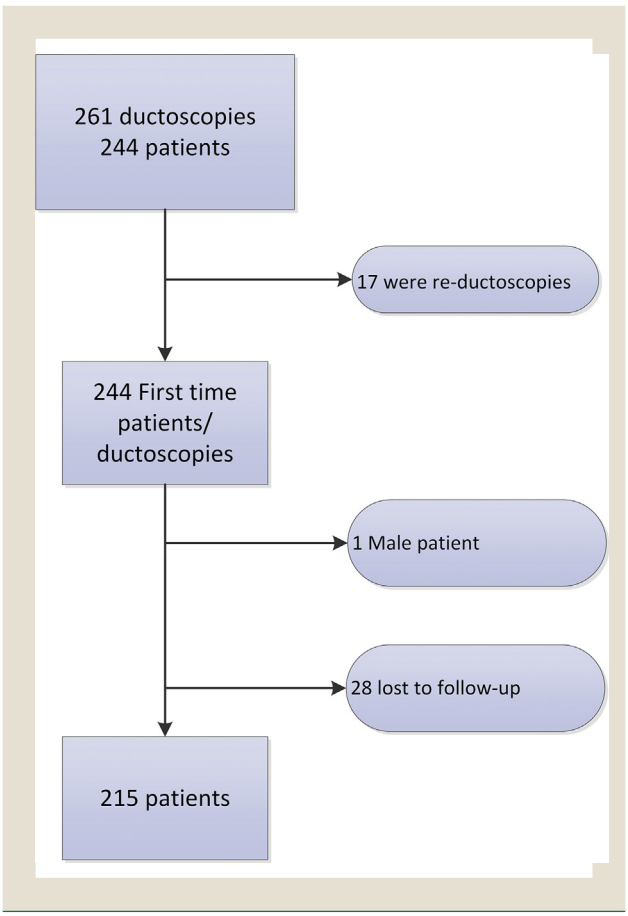


Table 1 shows the baseline characteristics of the 215 patients suitable for analysis. The mean age was 49 years (range, 20-81 years), with a mean follow-up of 14.5 months (range, 3-44 months). Six (2.8%) patients had palpable abnormalities at the time of ductoscopy.

Sixty of the 215 patients had had a biopsy prior to the ductoscopy. Histology revealed that 32 (54.2%) patients had a papilloma, and in 24 (40.7%) patients, normal or benign tissue was diagnosed. Atypical morphology and infection were diagnosed in 1 (1.7%) and 2 (3.4%) patients, respectively.

Cytology of the nipple discharge prior to ductoscopy was performed in 103 patients. In 53 (51.5%) patients, cytology showed no abnormalities or was benign. Papilloma was cytologically diagnosed in 30 (29.1%) patients. Eleven (10.7%) patients showed atypical cells during cytologic examination. Inflammatory cells were seen in 7 (6.8%) patients with examined nipple discharge. In 2 (1.9%) patients, cytologic analysis was not conclusive with no signs of malignancy. Initial BI-RADS classification for ultrasound and mammography can be seen in Table 1.

Ductoscopy

Figure 2 and Table 2 show the results of the ductoscopy procedures. In 151 (70.2%) patients, it was possible to visualize the ductal tree, 149 with full ductoscopy report. Sixty-eight (45.6%) of these 149 successful ductoscopies showed a polypoid lesion, 49 (32.9%) displayed no abnormalities, and 19 (12.7%) depicted flat epithelial lesions. Eight (5.4%) ductoscopies showed suspicious lesions; there was 1 (0.7%) duct ectasia as single finding and the remaining 4 (2.7%) were not otherwise specified than not suspicious for malignancy. Of the 49 attempted basket extractions, 34 biopsies were suitable for histopathologic examination. Thirty-three of these lesions turned out to be papillomas (without atypia) according to pathologic analysis, and 1 was found to be normal ductal tissue. Additionally, none of the 34 patients with basket extraction biopsies suitable for histopathologic analysis developed breast cancer in the future.

Ductoscopy did not succeed in 64 patients, 62 with an available report. The ductoscopy failed because of perforation through the ductal wall, making further inspection impossible in 28 (45.2%) of the 62 patients. Sixteen (25.8%) patients underwent attempted ductoscopy despite a relative contraindication (retracted nipple or previous operation on the mammilla). Too narrow ducts impeded proper visualization of the ductal tree in 14 (22.6%) patients. The ductoscopy failed in the remaining 4 (6.4%), owing to total occlusion of a milk duct because of an obstructive lesion.

Follow-up

Follow-up data were available for all of the 151 successful ductoscopy procedures. After successful ductoscopy, PND stopped in 84 (55.6%) patients. In 7 (4.6%) patients, the PND had already spontaneously stopped at the time of the ductoscopy. The PND did not stop in 60 (39.7%) of the 151 successful ductoscopy procedures.

Table 1 Clinical Data of 215 Patients With PND Undergoing Ductoscopy

	Patients, N = 215 (%)
Age, y (SD)	49.2 (13.6)
Follow-up, mos (SD)	14.1 (11.4)
Affected breast	
Left	106 (49.3)
Right	100 (46.5)
Both	9 (4.2)
Previous pathology	
Papilloma	32 (54.2)
Benign/normal	22 (37.3)
Atypical cells	1 (1.7)
Infectious cells	2 (3.4)
Other	2 (3.4)
Not performed	156
Cytology PND	
Normal/benign	53 (51.5)
Papilloma	30 (29.1)
Atypical cells	11 (10.7)
Infectious cells	7 (6.8)
Other	2 (1.9)
Not performed	122
Ultrasound BI-RADS classification	
BI-RADS I	127 (61.7)
BI-RADS II	73 (35.4)
BI-RADS III	4 (1.9)
BI-RADS IVa	1 (0.5)
Other	1 (0.5)
Not performed	9
Mammography BI-RADS classification	
BI-RADS I	166 (81.8)
BI-RADS II	33 (16.3)
BI-RADS III	1 (0.5)
BI-RADS IVa	2 (1)
Other	1 (0.5)
Not performed	12
MRI BI-RADS classification	
BI-RADS I	21 (56.8)
BI-RADS II	14 (37.8)
BI-RADS III	1 (2.7)
BI-RADS IVa	1 (2.7)
Not performed	178

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; MRI = magnetic resonance imaging; PND = pathologic nipple discharge; SD = standard deviation

Follow-up PND data were available for all of the 64 patients in whom ductoscopy was unsuccessful. Of these patients, 45 (62.7%) still complained of PND. The PND stopped after unsuccessful ductoscopy in 18 (28.1%) patients. In 1 (1.6%) patient, the PND spontaneously resolved before attempted ductoscopy. PND stopped significantly more often in patients with a successful ductoscopy ($P < .001$).

Surgery After Ductoscopy

Figure 3 and Table 2 show the decisions to operate and the outcome respectively. Sixty (27.8%) of 215 patients were operated on after ductoscopy. Forty-two (70.0%) of these 60 patients underwent an operation because of persistent symptoms within a few weeks after ductoscopy. Eight (13.3%) patients had suspicious findings during ductoscopy, and 10 (16.7%) patients underwent an operation owing to recurrent symptoms during follow-up. One (1.7%) patient had a breast amputation after 2 irradical duct excisions showing malignancy. Eight (13.3%) patients underwent a local excision, 24 (40.0%) a central duct excision, and 27 (45.0%) a microdochectomy. From 55 patients, pathology reports were available for evaluation: 4 (7.3%) patients had duct ectasia as the only finding, 7 (12.7%) showed ductal carcinoma in situ (DCIS), 44 (73%) had a benign lesion, of which 28 (51%) were a papilloma without atypia. Patients with a successful ductoscopy were significantly less likely to be operated ($P = .047$).

The reasons not to operate were recorded in all of the 155 patients that were not operated. In 82 (52.9%) of them, the PND symptoms resolved spontaneously after the attempted ductoscopy. The remaining 73 (47.1%) patients were sufficiently reassured that (pre)malignancy was ruled out to abandon surgery despite having mild complaints of PND. They were all offered yearly follow-up with mammography and ultrasound. None of them developed (pre)malignancy during follow-up (mean, 14.4 months; range, 3-44.6 months).

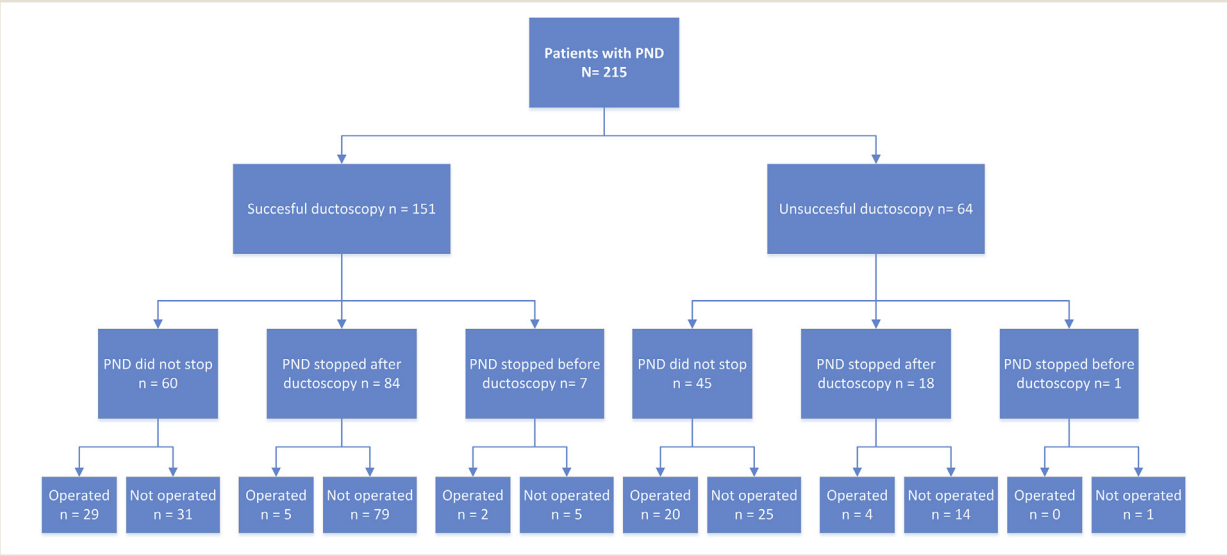
Malignancy in Patients with PND

Eight (3.7%) patients of the 215 with PND and no suspicious radiologic or pathologic findings were diagnosed with (pre)malignancy after surgery (Table 3). Ductoscopy was unsuccessful in 2 (25.0%) of these patients. These patients were operated owing to persistent serious symptoms. Another 3 (37.5%) patients underwent an operation owing to suspicious findings during ductoscopy; pathologic diagnosis revealed DCIS in 2 patients and lobular carcinoma in situ (LCIS) in 1. In 1 (12.5%) patient, ductoscopy images suggested ductitis. Intraductal biopsy possible was not possible, so the patient was operated on when PND persisted after ductoscopy. Pathologic diagnosis after surgery revealed DCIS. One (12.5%) patient did not have suspicious intraductal lesions during ductoscopy, but a suspicious lesion was seen at the duct orifice on the outside of the nipple. This lesion was biopsied, and pathology revealed DCIS. Two (25.0%) patients with DCIS did not have any suspicious findings during ductoscopy. One of these patients underwent duct excision owing to persistent symptoms, and pathology did not reveal (pre)malignancy. However, DCIS was diagnosed in the breast reduction specimen performed for cosmetic reasons 45 months after initial ductoscopy. The other patient without suspicious findings underwent surgery owing to persistent PND.

Sensitivity and Specificity

Summary of the diagnostic value of ductoscopy is summarized in Table 4. Eight (5.3%) of the 151 successful ductoscopies revealed suspicious findings leading to an operation, revealing DCIS in 4 patients and LCIS in 1 patient, with the other 3 patients showing benign lesions. Additionally, 4 of the 6 patients diagnosed with DCIS showed suspicious lesions during ductoscopy. Therefore,

Figure 2 Flowchart Showing the Follow-Up of Patients Undergoing (Attempted) Ductoscopy for PND



Abbreviation: PND = pathologic nipple discharge.

ductoscopy has a sensitivity for detecting malignancy of 71.4% (95% CI, 29.0%-96.3%), a specificity of 97.9% (95% CI, 94.0%-99.6%), and a negative predictive value of 98.6% (95% CI, 95.6%-99.6%).

Complications

Eleven (5.1%) of the 215 patients with PND suitable for analysis experienced severe post procedural pain longer than 1 day, and 21 (9.7%) patients had minor complaints of pain. The remaining 184 (85.2%) did not experience any post procedural pain. There were no significant differences in pain perception between successful and unsuccessful ductoscopy procedures.

Five (2.3%) of the 215 patients developed a (mild) mastitis after (attempted) ductoscopy requiring antibiotics. There were no significant differences in infection between successful and unsuccessful ductoscopy procedures.

In 1 case, a granulomatous mastitis was diagnosed post ductoscopy, finally requiring surgical incision and drainage of abscesses. This was the only serious complication found after ductoscopy. Because her follow-up time was less than 3 months, this case was left out of the final analysis regarding long-term follow-up after ductoscopy.

Discussion

Ductoscopy is an established minimally invasive endoscopic technique that makes it possible to visualize the ductal tree in patients with PND. In recent years, it is also possible to endoscopically remove intraductal lesions during ductoscopy procedures with the use of an endobasket. The current retrospective study describes 215 patients with PND undergoing ductoscopy for further clinical validation. We found that interventional ductoscopy is able to detect (pre)malignant lesions and can prevent unnecessary diagnostic surgical procedures in 2 of 3 patients suffering from PND.

In this study, ductoscopy was considered successful when it was possible to visualize the ductal tree. However, previous studies define cannulation as a successful ductoscopy.[20-22,27-30] This might explain why we experienced a slightly lower success rate compared with these previous studies. On the other hand, the proportion of successful visualization of the ducts (70.2%) is higher in our study than previously described.[28] As one might expect, we found that non-reducible nipple retraction and previous surgery of the mammilla are strong negative predictors for successful ductoscopy. Therefore, in the future, these patients should perhaps not be offered ductoscopy as a primary diagnostic tool for PND. Omitting these patients in our current series would have led to a successful ductoscopy rate of 77.7%.

Currently, most women suffering from PND as their only complaint are offered surgery to rule out malignancy, even in the absence of radiologic suspicion of malignancy. Our study, however, shows that ductoscopy is a very useful tool in the diagnostic workup in these cases, preventing unnecessary surgery in a significant percentage of women with PND. Ninety-five of the 151 successful ductoscopy procedures revealed intraductal lesions causing PND (68 polypoid lesions, 19 non suspicious flat epithelial lesions including ductitis, 8 suspicious lesions, and 4 not otherwise specified). Forty-nine (51.6%) of these lesions could be (partially) extracted using the endobasket, leaving room for improvement. Thirty-four (69.4%) removed lesions were finally suitable for histologic analysis, which showed 33 (97.1%) papillomas and 1 (2.9%) case of normal tissue. Owing to its technical limitations, the endobasket is only useful as a tool in obtaining a histologic diagnosis in polypoid lesions. Because there are still no other suitable biopsy tools available yet for ductoscopic use, this remains a drawback in the success rate of ductoscopy. Effort should therefore be made to develop new small grasping biopsy tools suitable for use during ductoscopy procedures, making histologic diagnosis of all lesions found possible, including flat lesions. With such tools, the number

Table 2 Findings At and After Ductoscopy of 215 Patients With PND

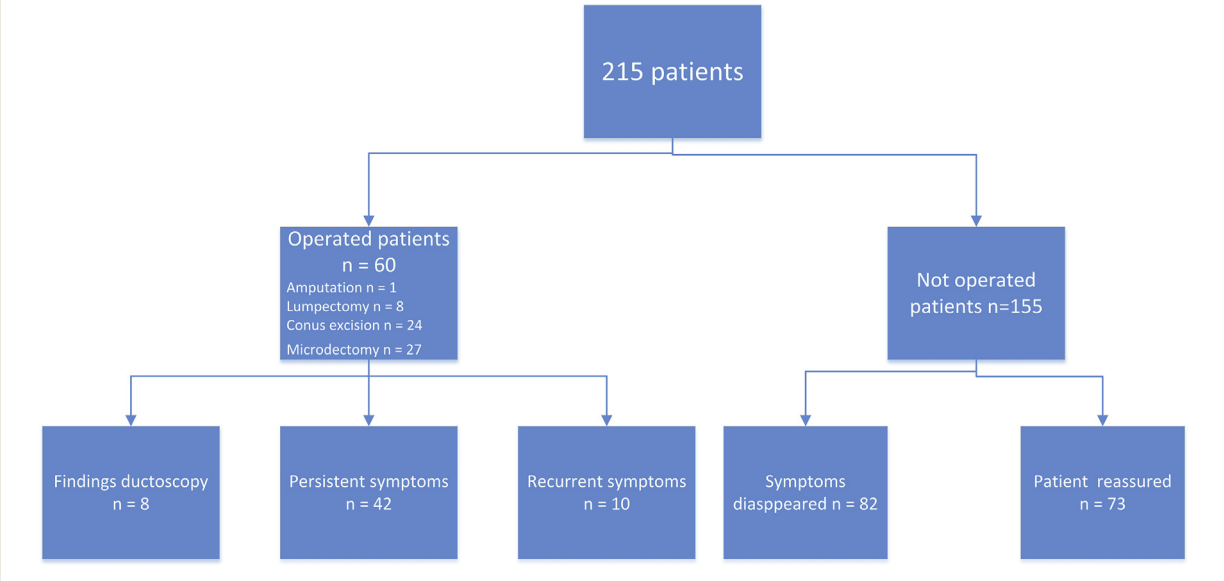
	Successful Ductoscopy, N = 151 (%)	Unsuccessful Ductoscopy, N = 64 (%)	*P* Value
Ductoscopic diagnosis			
Polypoid lesion	68 (45.6)	NA	
Epithelial lesion	19 (12.7)	NA	
Dilated ducts	1 (0.7)	NA	
Normal	49 (32.9)	NA	
Suspicious	8 (5.4)	NA	
Other	4 (2.7)	NA	
Lesion (partially) removed			
No	84 (63.2)	NA	
Yes	49 (36.8)	NA	
Pathologic analysis of (partially) removed lesion			
Papilloma	33 (97.1)	NA	
Normal tissue	1 (2.9)	NA	
Pain after ductoscopy			
No	131 (86.8)	52 (81.3)	.182[a]
Little	15 (9.9)	6 (9.4)	
High	5 (3.3)	6 (9.4)	
Infection after ductoscopy			
No	148 (98)	62 (96.9)	.635[b]
Yes	3 (2)	2 (3.1)	
PND stopped after ductoscopy			
No	60 (39.7)	45 (70.3)	<.001[b]
Yes, spontaneous before ductoscopy	7 (4.6)	1 (1.6)	
Yes, after ductoscopy	84 (55.6)	18 (28.1)	
Operated after ductoscopy			
Not operated	115 (76.2)	40 (62.5)	.047[b]
operated	36 (23.8)	24 (37.5)	
Pathologic diagnosis after operation			
Benign	7 (21.2)	7 (31.8)	.598[b]
(Pre)malignancy	7 (21.2)	2 (9.1)	
Papilloma	17 (51.5)	11 (50)	
Widened ducts	2 (6.1)	2 (9.1)	
Decision whether to operate after ductoscopy			
Persistent symptoms	21 (13.9)	21 (32.8)	<.001[b]
Recurrent symptoms	7 (4.7)	3 (4.7)	
Findings ductoscopy	8 (5.3)	0 (0)	
No operation, patient is reassured	46 (30.4)	27 (42.2)	
No operations, no complaints	69 (45.7)	13 (20.3)	

Abbreviations: N = number; NA = not applicable; PND = pathologic nipple discharge
[a] *P* values determined using the χ^2 test.
[b] *P* values determined using the Fisher exact test.

of unnecessary surgical procedures in women suffering PND can probably be reduced even more.

There was a mean follow-up of 14.5 months, ranging from 3 months to 44.6 months. PND stopped without the need for surgery in 93 (43.2%) patients, which is less than previously reported in the literature by Makita et al, who reported disappearance of PND in 85.1%.[29] However, they only reported on the cases in which an intraductal lesion was excised during ductoscopy, and they had a median follow-up of 5.5 years. In 18 cases in our series, PND stopped even after an unsuccessful ductoscopy, supporting the notion of the self-limiting nature of PND and the possible effect of ductal lavage in some patients, especially in ductectasia and/or

Figure 3 Flowchart Showing Rationale whether or Not to Operate in the 215 Patients Undergoing Ductoscopy for Pathologic Nipple Discharge Suitable for Analysis



ductitis or in the absence of a true intraductal lesion. This finding shows that careful selection of patients for surgery is adamant and that ductoscopy can be used as a useful selection tool.

Our main objective in introducing ductoscopy as a diagnostic tool in women with PND was reduction of the percentage of "unnecessary" surgery in these patients. In the present series, only 60 (27.9%) patients underwent surgery after (attempted) ductoscopy (Figure 3), much less than previously described.[22,28,30,31] The most prominent reason to perform surgery was suspicious findings during ductoscopy. The most common indications for post-ductoscopy surgery were persistence and recurrence of PND. On the other hand, reassurance of the patient (ie, absence of a serious lesion) turned out to be important, in some cases even after unsuccessful ductoscopy.

The current study shows that ductoscopy is safe. The reported complications were post procedural pain (14.8%) and infection (2.3%). This is in line with previously published literature.[32]

Eight (3.7%) patients with PND and no suspicious radiologic or pathologic findings prior to ductoscopy were eventually diagnosed with DCIS after surgery. This is slightly less than the 5% to 10% we expected based on the literature.[6,7] During ductoscopy, 8 patients with suspicious lesions were seen, of which 5 finally turned out to be (pre)malignant and 3 turned out to be benign after pathologic analysis. Two patients who turned out to have (pre)malignancy did not have suspicious findings during ductoscopy. However, in one of these patients, the DCIS was discovered by mere chance after breast reduction therapy almost 4 years after the ductoscopy. It is therefore difficult to assess whether the (pre)malignancy was missed during ductoscopy. The second patient with malignancy (invasive carcinoma) without suspicious ductoscopic findings underwent duct excision in which the histopathologic report was negative for (pre) malignancy. Only after subsequent surgery owing to persistent symptoms was (pre)malignancy diagnosed.

Sensitivity and specificity for the detection of malignancy was 71.4% (with a broad confidence interval) and 97.9%, respectively. The broad CI of the sensitivity is explained by the low prevalence of (pre)malignancy. Additionally, the negative predictive value was 98.6%. Sensitivity, specificity, and negative predictive values were similar to previously conducted research in patients with an increased risk for the development of breast cancer.[33] All other results are in line with previous studies conducted.[20-22,28,29,31]

In recent years, MRI is sometimes used to find the cause of PND. However, small lesions are often missed, and it is difficult to differentiate benign from malignant lesions. Furthermore, outcome of an MRI has little effect on therapeutic choice for PND because a (surgical) biopsy is usually needed when a possible causing lesion is found.[12,14,34] Sensitivity of MRI varies, when ultrasound and mammography are negative, from 40% to 86%. The specificity of MRI to rule out breast cancer in patients with PND also ranges from 76% to 99%.[12,35,36] Figure 4 shows a proposed flowchart for the indication of the usage of MRI and ductoscopy in the diagnostic process. Additionally, cytologic examination of PND has a low sensitivity for ruling out malignancy and may even lead to many false-positive results.[37,38] Our study not only shows that (interventional) ductoscopy has a high specificity and negative predictive value when it comes to the detection of malignancy, but it also has a therapeutic potential to stop the PND itself.

In our experience, ductoscopy is an easy to learn procedure for breast surgeons. Zagouri et al already described a learning curve of ductoscopy in ex vivo mastectomy specimens and suggest that an average surgeon requires 13 procedures to master this technique.[39] We expect that the addition of the intervention (basket extraction)

Table 3 Patients With (Pre)malignancy and Increased Risk for Breast Cancer

Patient ID	Ductoscopic Failure	Ductoscopic Diagnosis	Palpable Abnormalities	US Abnormalities	Mammography Abnormalities	MRI Abnormalities	PND Stopped	Operation After Ductoscopy	Reason for Operation	Diagnosis After Surgery
1	Narrow ducts	NA		BI-RADS I	BI-RADS I		Yes, after ductoscopy	Amputation	Recurrent symptoms	DCIS
2	No	Suspicious		BI-RADS I	BI-RADS I		No	Yes, microdochectomy	Findings ductoscopy	DCIS
3	No	Papilloma		BI-RADS I	BI-RADS I	BI-RADS I	Yes, after ductoscopy	Yes, microdochectomy	Recurrent symptoms	DCIS
4	No	Ductitis		BI-RADS I	BI-RADS I		No	Yes, microdochectomy	Biopsy of nipple	DCIS
5	No	Suspicious	No	BI-RADS II	BI-RADS I		No	Yes, lumpectomy	Biopsy of nipple	Morbus Paget
6	No	Benign	No	BI-RADS I	BI-RADS I		No	Microdochectomy	Persistent symptoms	DCIS
7	No	Suspicious	No	BI-RADS I	BI-RADS I		No	Microdochectomy	Findings ductoscopy	DCIS
8	No	Suspicious		BI-RADS I	BI-RADS I		No	Yes, conus excision	Findings ductoscopy	LCIS
9	Wrong indication	NA	No	BI-RADS I	BI-RADS I		No	Yes, lumpectomy	Persistent symptoms	DCIS

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; NA = not applicable; PND = pathologic nipple discharge; US = ultrasound

Table 4 Detection of Malignancy With Ductoscopy in Patients With PND Undergoing Ductoscopy

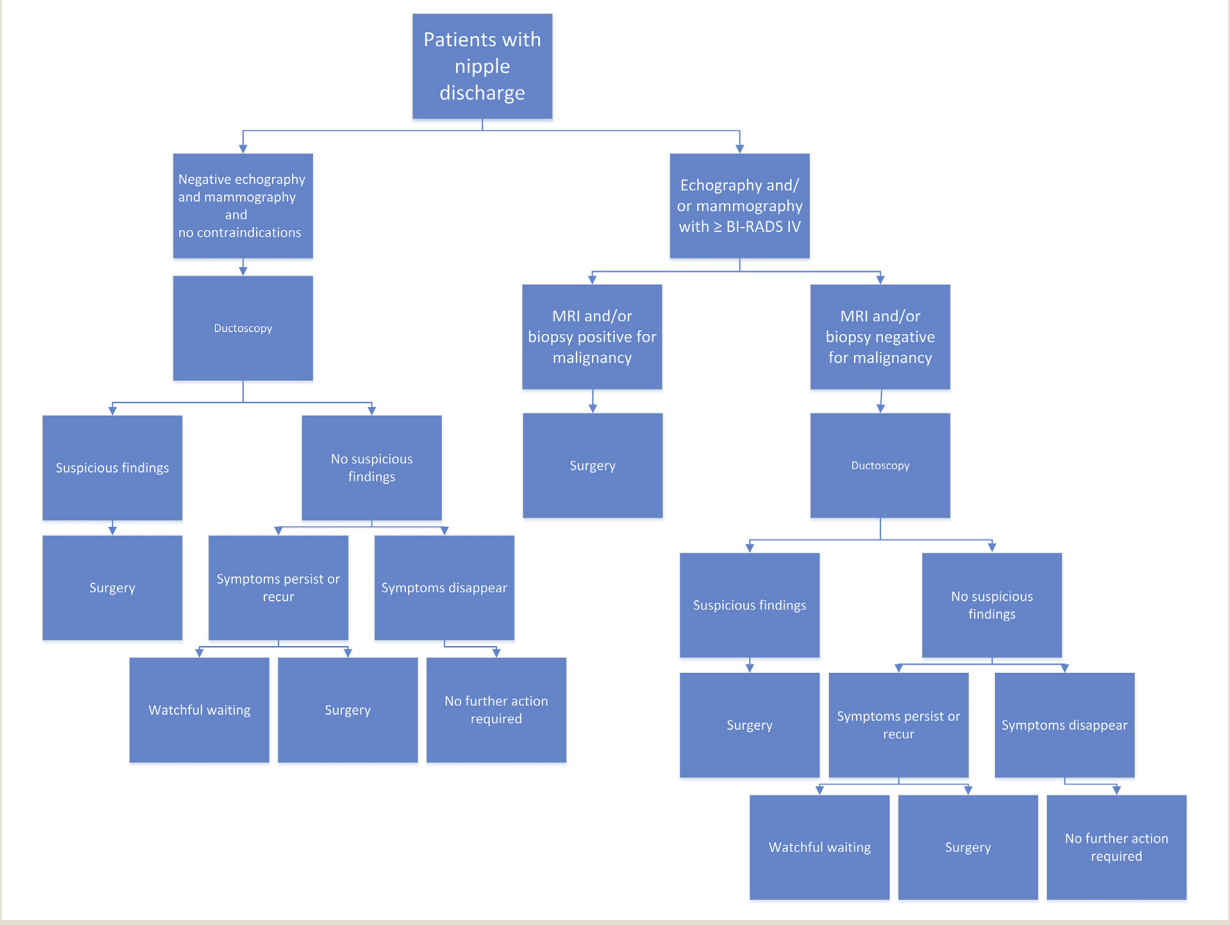
	Patient Had (Pre)malignancy	Patient Did Not Have (Pre) malignancy	Total
Ductoscopy showed suspicious lesions	5	3	8
Ductoscopy did not show suspicious lesions	2	141	143
Total	7	144	151

Abbreviation: PND = pathologic nipple discharge

has no influence on the learning curve. Although we did not perform a formal cost analysis study comparing ductoscopy with duct excision surgery, we think it is safe to emphasize that using ductoscopy as a selection tool for surgery saves health care costs. Ductoscopy can be performed under local anesthesia in the outpatient clinic. It is a simple and relatively quick procedure, usually taking 15 to 30 minutes, which can be performed by a breast surgeon and only 1 trained nurse. Patients usually experience few or no side effects and can go back to work the same day or the next day. In our institution, the reimbursement for ductoscopy is one-half of the reimbursement for major duct excision, whereas in our hands, ductoscopy was able to select two-thirds of patients with PND in which surgery can safely be omitted. This being said, we can assume that even if a number of patients require surgery after ductoscopy, the total costs (ductoscopy and surgery) would probably be lower than if all patients with PND undergo surgery. However, a cost analysis study would be interesting to confirm these assumptions.

In conclusion, our study shows that ductoscopy is safe, with a high specificity and negative predictive value to detect (pre)

Figure 4 Flowchart Showing in Which Phase During Pathologic Nipple Discharge Diagnosis Ductoscopy is Useful and What Are the Consequence of Ductoscopic Findings



Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; MRI = magnetic resonance imaging.

malignancy and to treat PND. This makes ductoscopy a useful tool in deselecting women for major duct excision or microdochectomy, preventing the use of unnecessary surgery in many women with PND.

Clinical Practice Points

- PND is, after palpable lumps and pain, the most common breast-related reason for referral to the breast surgeon and is associated with breast cancer. However, with negative mammography and ultrasound, the chance of PND being caused by malignancy is between 5% and 8%. Nevertheless, most patients with PND still undergo surgery in order to rule out malignancy.
- Ductoscopy is a minimally invasive endoscopic technique that enables direct intraductal visualization. Ductoscopy is currently used to detect, and sometimes remove, lesions that cause PND. Ductoscopy is intended for use to detect the cause of PND when ultrasound and/or mammography show no signs of malignancy.
- This study analyzed 215 consecutive patients undergoing ductoscopy between 2010 and 2017. In 151 (70.2%) patients, ductoscopy was successful. Sixty of the 215 patients were eventually operated, 8 owing to suspicious findings during ductoscopy, 42 owing to persistent PND, and 10 because of recurrent PND. In 5 patients, a malignancy was found (5 of them classified as suspicious during dusctoscopy). This means that ductoscopy not only avoids surgery in around 2 out 3 patients with PND for malignancy, but also detects malignancy when conventional imagery is negative.
- Ductoscopy might therefore be a useful tool for the diagnosis of high-risk (BRCA1/2) women. Adding new imaging techniques (such as auto fluorescence) to ductoscopy in addition to an improved biopsy tool might further increase the sensitivity of ductoscopy.

Disclosure

The authors have stated that they have no conflicts of interest.

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