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Nipple Discharge: Role of Ductoscopy in Comparison with Standard Diagnostic Tests

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Keywords

Breast cancer · Ductoscopy · Nipple discharge · Mammography · Sonography

Summary

Background: This study aims to assess the role of ductoscopy for detecting intraductal anomalies in patients with nipple discharge in comparison to conventional tests and to find an effective combination of both approaches. **Materials and Methods:** Prior to duct excision, ductoscopy was performed in 97 women. Histologic and all other diagnostic results were compared. Sensitivity, specificity, and efficiency were calculated for all methods. These parameters were also calculated for all possible test combinations in 12 patients who had completed all tests. **Results:** Breast sonography reached the highest sensitivity (64.1%) and efficiency (64%); mammography had the highest specificity (100%). The sensitivity of ductoscopy was 53.2%, its specificity 60%, and its efficiency 55.1%. Among combinations of all methods, the combination ductoscopy + galactography was the most sensitive (80%). Mammography, magnetic resonance imaging, and ductoscopy were each 100% specific. Ductoscopy was the most efficient (75%) single method. **Conclusion:** Ductoscopy is a valuable test for diagnosing intraductal lesions in patients with nipple discharge. It is more efficient than conventional tests in patients undergoing all tests.

Schlüsselwörter

Brustkrebs · Duktoskopie · Mamillensekretion · Mammografie · Sonografie

Zusammenfassung

Hintergrund: Es wurde die Wertigkeit der Duktoskopie bei sekretorischen Mammaerkrankungen hinsichtlich des Erkennens intraduktaler Auffälligkeiten im Vergleich zur Standarddiagnostik bestimmt und nach einer effektiven Kombination dieser Verfahren gesucht. **Material und Methoden:** 97 Frauen wurden vor gezielter Milchgangsexstirpation duktoskopiert. Histologische Ergebnisse wurden mit den Befunden aller diagnostischen Verfahren verglichen. Anschließend wurden Sensitivität, Spezifität und Effizienz für die Einzelverfahren berechnet. Für 12 Patientinnen, bei denen alle diagnostischen Methoden zum Einsatz kamen, wurden diese Parameter ebenfalls für alle möglichen Kombinationen der verschiedenen diagnostischen Methoden berechnet. **Ergebnisse:** Bei den Einzelverfahren erreichte die Mammasonografie die höchste Sensitivität (64,1%) und Effizienz (64%). Die höchste Spezifität wurde für die Mammografie mit 100% berechnet. Die Duktoskopie erreichte eine Sensitivität von 53,2%, eine Spezifität von 60% und eine Effizienz von 55,1%. Bei den Patientinnen, bei denen alle Untersuchungen durchgeführt wurden, erzielten mit 80% die Zweier-Kombinationen Duktoskopie + Mammasonografie und Duktoskopie + Galaktografie die höchste Sensitivität. Eine Spezifität von 100% wurde bereits mit der Mammografie, der Magnetresonanztomographie und der Duktoskopie als Einzelverfahren erreicht. Die höchste Effizienz erreichte mit 75% die Duktoskopie als Einzelverfahren. **Schlussfolgerung:** Die Duktoskopie nimmt einen hohen Stellenwert in der Diagnostik intraduktaler Läsionen und sekretorischer Mammaerkrankungen ein. Bei den Patientinnen, die mit allen Methoden untersucht wurden, war die Duktoskopie die effizienteste Methode zur Erkennung intraduktaler Läsionen.

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Introduction

Since many diseases of the breast originate in the breast ducts, it is extremely important to detect intraductal lesions. It is of note that 40–75% of breast cancers are of the invasive ductal type [1]. Pathologic nipple discharge is a frequent symptom of benign papillomatous and proliferative ductal processes and of premalignant and invasive breast diseases. An underlying carcinoma is detected in 2–15% of patients with nipple discharge [2]. Conventional diagnostics comprise indirect tests such as mammography, breast sonography, magnetic resonance imaging (MRI), and galactography. Another indirect method, cytologic analysis of material obtained by nipple smears or ductal lavage, fails to identify the involved duct [3]. Ductoscopy is the first test capable of assessing intraductal lesions directly. It can also detect periductal processes leading to obstruction. Visualization extends from directly beyond the orifice of the duct well into the periphery [3]. Endoscopic appearance can predict the histological diagnosis [4, 5]. If an invasive process is suspected in hemorrhagic discharge, the most common treatment is 'blind' retroareolar resection as described by Urban et al. [6]. This approach is associated with false-positive and false-negative results [7]. Only 5% of women undergoing this procedure have a premalignant or a malignant lesion. Ductoscopy is more than a mere diagnostic tool because it may, e.g. in the treatment of solitary papillomas, permit targeted intraductal excision instead of more radical surgery [8–11].

Materials and Methods

This retrospective analysis included 97 patients who, between June 2002 and September 2006, underwent ductoscopy followed by open biopsy. Patients were referred to us because of pathologic nipple discharge and/or abnormal diagnostic findings. Initially, non-breast causes of nipple discharge such as hyperprolactinemia and inflammatory processes were ruled out by lab tests. To rule out intraductal carcinomas, all patients with nipple discharge underwent mammography and breast sonography. The mammographic findings were classified in accordance with the Breast Imaging Reporting and Data System (BI-RADS) [12]. Sonography complemented mammography, and the results were classified by the BI-RADS-analogue DEGUM criteria [13]. MRI and/or galactography were used if indicated and feasible. The indications for ductoscopy and open biopsy were based on the presence of pathologic discharge and/or abnormal imaging results. All surgical interventions were completed under general anesthesia. We used either ductuscopes manufactured by Karl Storz®, Tuttlingen Germany, (nos. 11521, 11522, 11570) or the equivalent products made by PolyDiagnost®, Pfaffenhofen, Germany. The endoscopes were 9 cm long and had a diameter of 0.55–1.30 mm. The scope's working channel can accommodate tools such as biopsy forceps. After ductoscopy, open biopsies were performed, or the target duct was excised (fig. 1).

Recorded data were retrospectively analyzed. Since all patients underwent open biopsy or target duct excision, we could determine how the histology of the intraductal lesion correlated with the results of mammography, breast sonography, MRI, galactography, and ductoscopy. Data were analyzed with the 'SPSS 14.0' (SPSS Inc., Chicago, USA) software. A contingency table was used for calculating sensitivity, specificity, and efficiency. The latter formed the basis for an efficiency ranking. 18 distinct histopathologic entities were reported on the open biopsy specimens, including intraductal papilloma, papillomatosis, ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ, and invasive carcinoma. Extraductal lesions without intraductal histopathologic anomalies included fibroadenoma, mastopathy, and cysts (table 1). After calculating the sensitivity, specificity, and efficiency of mammography, breast sonography, galactography, MRI, and ductoscopy, the same parameters were also determined for all possible test combinations, an assessment based on data from those 12 patients in whom all 5 methods had been used. We obtained 10 combinations of 2, 10 combinations of 3, 5 of 4, and 1 combination of 5 tests. A result was considered positive if at least 1 test suggested an intraductal anomaly, and negative when all tests suggested an unremarkable duct.

Table 1. Histopathologic results

Histopathology	n (%)
Unremarkable	1 (1.0)
Ductal hyperplasia	8 (8.0)
DCIS	9 (9.0)
Sclerosing adenosis	8 (8.0)
Sclerosing adenosis + micropapillary proliferation	8 (8.0)
Ductal papilloma	26 (26.0)
Papillomatosis	10 (10.0)
ADH	3 (3.0)
Invasive carcinoma	2 (2.0)
Papilloma + ADH	7 (7.0)
Fibroadenosis	2 (2.0)
Sclerosing adenosis + ADH	2 (2.0)
Papilloma + ductal hyperplasia	1 (1.0)
Sclerosing adenosis + fiboadenoma	3 (3.0)
Papilloma + sclerosing adenosis + ADH	2 (2.0)
Papillomatosis + fibroadenoma + ADH	1 (1.0)
Sclerosing adenosis + fibroadenoma + papillomatosis	2 (2.0)
Scerosing adenosis + papilloma	5 (5.0)

DCIS = Ductal carcinoma in situ; ADH = atypical ductal hyperplasia.

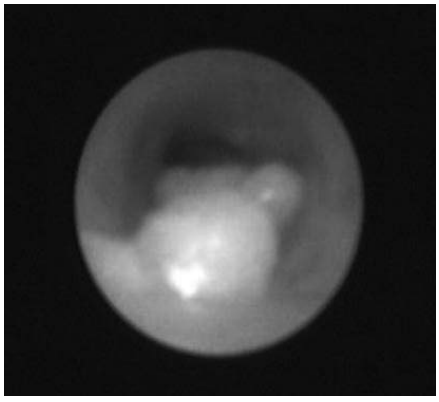

Fig. 1. Breast duct with an intraductal, polypoid, yellow, well demarcated lesion. Histology: ductal papilloma.

Results

Since 1 breast was assessed in 97 women and both breasts in 3, 100 'cases' were analyzed in total. Patients were between 21 and 78 years old (mean 53.3 years). Mammography and sonography were conducted in all cases (100%), galactography in 25 (25%). The latter had been theoretically feasible

in 61 cases. In the remaining cases, the discharge was milky, or a discharge could only be elicited by applying significant pressure. Galactography was considered in 40 cases, but not performed in 15, e.g. because there was no discharge at the time of the scheduled procedure or because no duct was found to be probe-patent. MRI was completed in 57 (57.0%) and ductoscopy in 98 cases (98%). Intraductal lesions were found in 78 cases (78%), no intraductal anomalies were seen in 22 cases (22%). Malignant processes were found in 11 cases (11%).

Mammography had a sensitivity of 9%, a specificity of 100%, and an efficiency of 29%. For detecting intraductal lesions, breast sonography was 64.1% sensitive, had a specificity of 61.9% and an efficiency of 64%. Because of insufficient ductal contrast, 4 out of 25 galactographies permitted no diagnostic conclusions, leaving 21 of 100 cases (21%). The sensitivity was 50%, specificity 66.7%, and efficiency 52.4%. Since 1 of the MRI scans did not lend itself to a definitive diagnosis, 56 cases were analyzed. The sensitivity was 60%, specificity 66.7% and efficiency 62.5%.

In 2 cases, duct dilation was insufficient for ductoscopy. Therefore, 98 cases (98%) were entered into the final analysis. Ductal length ranged from 1 to 9 cm. The ductoscope could be inserted to a mean depth of 3.6 cm. The maximal depth was 9 cm, i.e. the length of the instrument. 49 ductoscopies demonstrated suspicious findings, 41 lesions could be confirmed by histopathology. The sensitivity for detecting intraductal lesions was 53.2%, the specificity 60% and the efficiency 55.1%.

Sonography was the most sensitive test for detecting intraductal lesions, followed by MRI, ductoscopy, and galactography. Mammography had the lowest sensitivity (9%). The most specific test (100%) was mammography, followed by MRI and galactography (66.7%). Sonography and ductoscopy had the lowest specificities. Sonography was the most efficient (64%) method, followed by MRI, ductoscopy, and galactography. Mammography had the lowest efficiency (29%).

We also determined the sensitivity, specificity, and efficiency of all possible test combinations in the 12 cases who had undergone all 5 tests. Among the combinations of 2 tests, the highest sensitivities (80% each) were found for breast sonography + ductoscopy and for galactography + ductoscopy. The highest specificities (100% each) were calculated for MRI + mammography, MRI + ductoscopy and mammography + ductoscopy. The highest efficiency (75% each) was reached by ductoscopy combined with any conventional test.

Among the triple tests, the best sensitivities (80%) were found for MRI + galactography + ductoscopy, MRI + breast sonography + ductoscopy, breast sonography + galactography + ductoscopy, breast sonography + mammography + ductoscopy, and for mammography + galactography + ductoscopy. The combination of MRI + mammography + ductoscopy had the highest specificity (100%). The highest efficiencies (75% each) were found for all triple combinations that included ductoscopy.

The highest sensitivities (80% each) among quadruple combinations were found for the 4 combinations that included ductoscopy. All quadruple combinations had a specificity of 50%. Quadruple combinations that included ductoscopy also had the highest efficiency (75%).

A sensitivity of 80% was calculated for the combination of mammography + sonography + galactography + MRI + ductoscopy. Its specificity was 50%, the efficiency 75%.

The combination with the highest sensitivity (80%) were seen with the following 2 combinations of 2 tests: sonography + ductoscopy and galactography + ductoscopy. The pentuple combination had a sensitivity of 80% as well, illustrating that combining 3 or more tests did not lead to an additional sensitivity increase.

The highest specificity (100% each) was found for 2 combinations of 2 tests, i.e. for mammography + ductoscopy and for MRI + ductoscopy. In terms of its capability to detect intraductal lesions, the pentuple combination had a specificity of 50%. The specificity decreased by 50% from the double combinations to the pentuple combination.

The highest efficiency (75% each) was found for all combinations that included ductoscopy. Pentuple combinations did not increase the efficiency beyond the efficiency of double combinations.

Discussion

The data on mammography as an only test correspond to the findings by Vargas et al. [14] and by Adepoju et al. [15], who found sensitivities in the range of 7–10% and specificities of 94–100%. In their study on 71 patients, Grunwald et al. [16] reported a sensitivity of 37.9% and a specificity of 92.3%. The low sensitivity and efficiency data in our study can be explained by the large numbers of false negatives. Due to its low efficiency, mammography needs to be called into question as a method for detecting intraductal lesions.

The method with the best results is breast sonography, which found 50 out of 78 lesions. This underscores the good yield of this method for detecting intraductal lesions in patients with nipple discharge, a finding in line with previous results: Grunwald et al. [16] reported a sensitivity of 67.3% and a specificity of 61.5%. Kamali et al. [17] reported that sonography is 72% sensitive for detecting papillomatous intraductal lesions. This contrasts with sensitivities of only 36% and 26% reported by Adepoju et al. [15] and Vargas et al. [14] who found specificities of 68% and 97%.

Despite its shortcomings, galactography is considered the method of choice. The assessment of ductal obstructions is limited because the method cannot make a definitive distinction between intra- and extraductal processes [3]. Data vary widely in earlier publications. Reported sensitivities range from 69 to 94%, specificities from 41 to 62% [15, 16, 18–20]. Our results are therefore close to earlier results. Dinkel et al.

[21] reported 20–30% false negatives. These data suggest that close follow-up is advisable in patients with a negative ductogram and persisting nipple discharge.

In our patients, galactography was associated with 9 out of 11 false negatives. If technically feasible, galactography is very sensitive. Our results are poorer than previously published data.

With respect to MRI, our data are close to the results obtained by Nakahara et al. [22] and Ishikawa et al. [23], who reported a sensitivity and a specificity of 75%. Liberman et al. [24] found sensitivities of 86–100% and specificities of 39–97%. The corresponding figures published by Grunwald et al. [16] are 65.2% and 25%.

Other than mammography, MRI is unaffected by parenchymal density. Fuchsjäger et al. [3] considered the high costs and limited availability shortcomings. Diffuse parenchymal contrast agent enhancement can be misleading [25]. We found that MRI performs well as a sole diagnostic test. Because of its complexity and the associated expense, it should be reserved for highly selected cases.

Ductoscopy has the benefit of finding partially obstructive as well as multiple lesions. Due to its the high (60-fold) magnification, it can detect anomalies which remain below the threshold of other methods [26–28]. Our study confirms that ductoscopy is most often technically feasible. As an only diagnostic test, the performance of ductoscopy was average when compared to 4 conventional tests. Several studies revealed the importance of ductoscopy: Reviewing 71 patients with nipple discharge, Grunwald et al. [16] compared ductoscopy with breast sonography, galactography, and MRI. For detecting intraductal lesions, ductoscopy was as sensitive and as specific as the other tests. In 65 patients with nipple discharge, Yamamoto et al. [29] evaluated galactography and ductoscopy for detecting intraductal anomalies and found the following sensitivities: galactography 89.1%, ductoscopy 97.4%, both methods combined 97.5%. Diagnostic ductoscopy rarely leads to complications as pointed out by Beechey-Newman et al. [30]. It is limited by the complex anatomy of the breast. Scope diameter and length restrict visualization to parts of the duct [26]. Several authors, e.g. Badve et al. [31], reported that the majority of carcinomas are located peripherally. Similar data were obtained by Hou et al. [32] on 118 patients with nipple discharge. Most carcinomas were located in the periphery of the ducts, whereas benign lesions were more common in central locations. This was corroborated by Shen et al. [33], who found most intraductal papillomas at an average depth of 2.7 cm in the proximal ducts.

In our study, the mean visualized depth was 3.6 cm, the maximum depth 9 cm, findings in line with the mean depth of 5.2 cm reported by Beechey-Newman et al. [30]. Dooley et al. [34] were able to visualize ducts to an average depth of 7.5 cm. As of now, ductal assessment mostly focuses on the proximal segments, but in the future, smaller endoscopes should extend visualization and detection of lesions to the periphery.

Combining multiple tests compared favorably to using just a single method. One needs to take into account, however, that our case numbers for single tests varied between 21 and 100, while only 12 cases were available for analyzing all tests combined. The comparison of individual tests with combinations of tests is therefore limited. Due to the low case numbers, the results of all calculations involving multiple tests have to be viewed critically.

Summary

Ductoscopy plays an important role in the diagnosis of breast disease. Its advantages include direct visualization. Our data show that ductoscopy is more efficient for diagnosing intraductal lesions than mammography and galactography. High resolution sonographic examination of the ducts remains an important diagnostic tool. Sonography was the most sensitive test (64.1%). The highest sensitivity of 80% was reached by the 2 double combinations ductoscopy + breast sonography and by ductoscopy + galactography. Pentuple combinations do not increase the sensitivity. The specificity decreases from 100% for the individual tests to 50% for pentuple combinations, the result of a higher error rate with multiple tests. The best single method efficiency (mammography, 64%) can be increased to 75% by double combinations that include ductoscopy. One should reflect on the most cost effective combination of tests. The good performance of ductoscopy shows that additional studies need to clarify the role of this test in comparison to other tests, addressing several questions: When is preoperative galactography needed prior to ductoscopy? Could complete ductal excision be avoided if both ductoscopic assessment and biopsy reveal a benign finding? The low number of cases in the analysis of combinations has to be taken into account. A retrospective multicenter study launched in 2006 addresses the diagnostic value and therapeutic role of ductoscopy in comparison to conventional tests [35, 36]. We envision a future with precisely defined indications for ductoscopy and less frequent open biopsies.

Disclosure Statement

There is no conflict of interest. All authors declare that they have no financial or other interest in any of the companies mentioned in the paper or in any competing company. The presentation is independent and product neutral.

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