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Ductoscopic Detection of Intraductal Lesions in Cases of Pathologic Nipple Discharge in Comparison with Standard Diagnostics: The German Multicenter Study

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Keywords
Nipple discharge · Endoscopic breast ductoscopy · Breast cancer · Intraductal lesion

Summary
Background: According to the literature, ductoscopy is gaining increasing importance in the diagnosis of intraductal anomalies in cases of pathologic nipple discharge. In a multicenter study, the impact of this method was assessed in comparison with that of standard diagnostics. **Patients and Methods:** Between 09/2006 and 05/2009, a total of 214 patients from 7 German breast centers were included. All patients underwent elective ductoscopy and subsequent ductal excision because of pathologic nipple discharge. Ductoscopy was compared with the following standard diagnostics: breast sonography, mammography, magnetic resonance imaging (MRI), galactography, cytologic nipple swab, and ductal lavage cytology. The histological and imaging results were compared and contrasted to the results obtained from the nipple swab and cytologic assessment. **Results:** Sonography had the highest (82.9%) sensitivity, followed by MRI (82.5%), galactography (81.3%), ductoscopy (71.2%), lavage cytology (57.8%), mammography (57.1%), and nipple swab (22.8%). Nipple swabs had the highest (85.5%) specificity, followed by lavage cytology (85.2%), ductoscopy (49.4%), galactography (44.4%), mammography (33.3%), sonography (17.9%), and MRI (11.8%). **Conclusion:** Currently, ductoscopy provides a direct intraoperative visualization of intraductal lesions. Sensitivity and specificity are similar to those of standard diagnostics. The technique supports selective duct excision, in contrast to the unselective technique according to Urban. Therefore, ductoscopy extends the interventional/diagnostic armamentarium.

Introduction

Female breast disorders are frequently associated with nipple discharge (ND) [1]. Pathologic ND needs to be distinguished from physiologic discharge, such as discharge during pregnancy and breast-feeding. Medications can also cause ND [1, 2]. Spontaneous unilateral discharge from one or several ducts signifies pathological discharge [2, 3]. Both benign and malignant breast disorders can be associated with ND. Among benign lesions associated with ND, papilloma is especially important: Approximately 50% of patients with a papilloma

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have ND, and 5–17% of papillomas will eventually turn malignant [4–6]. ND is also observed in 0.5–12% of malignant breast lesions, especially in ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) [1, 2]. It is thought that 85% of malignant and premalignant breast disorders originate in the ductal epithelium [7–10]. Conventional imaging and cytologic diagnostics provide only indirect information on the ducts. Which duct is affected cannot be specified [11]. Ductoscopy can directly depict intraductal lesions and shows other pathologies indirectly, i.e. in cases of ductal obstruction. To a certain extent, the endoscopic findings provide information about the probable histologic diagnosis [12, 13].

Recent technical advances have provided endoscopes with a working channel permitting tissue biopsies [14–17]. Thereby, ductoscopy plays an important role in the efforts to minimize unnecessary open biopsies [18].

This multicenter trial aimed to assess to what extent ductoscopy is capable of detecting intraductal anomalies in conditions associated with ND, in comparison with conventional diagnostic methods. We compared the sensitivities, specificities, and efficiencies of the diverse methods.

Patients and Methods

From September 2006 to May 2009, a total of 214 patients with pathologic ND underwent ductoscopy and subsequent ductal excision under general anesthesia. 7 German centers participated in this multicenter study, which was not randomized. Patients with spontaneous or elicited uni- or bilateral ND were included. All patients gave their consent to participate in the study. Any extramammary etiology of ND was a criterion for exclusion. The ethics commission of the Ernst-Moritz-Arndt University Greifswald approved the study.

Preoperative diagnostics included breast sonography, mammography, breast magnetic resonance imaging (MRI), galactography, nipple swab, and ductal lavage cytology. All patients received a ductal excision after ductoscopy was completed, to compare the results of preoperative diagnostics and ductoscopy with the histological findings.Figure 1 gives an overview of the study design.

The mammographic results were classified in accordance with the Breast Imaging Reporting and Data System (BI-RADS) [19]. All ultrasonographic findings were reported in accordance with the BI-RADS-analogous criteria of the DEGUM (Deutsche Gesellschaft für Ultraschall in der Medizin, German Society for Ultrasound in Medicine [20].

Ductoscopy was performed with endoscopes equipped with 0.9-mm optics (Karl Storz GmbH and Co. KG, Tuttlingen, Germany) under general anesthesia. ND was elicited by application of steady areolar pressure and the affected duct was then dilated with Hegar dilators. The mammary ducts were visualized under hydrodilatation with saline solution injected through the working channel of the ductoscope. The ductoscope was either left in place at completion of ductoscopy or a marking wire was placed for the subsequent open excision of the affected duct. The specimen was marked with sutures to permit spatial orientation for the histologic analysis. The histopathologic result served as a reference in calculating the sensitivity, specificity, and efficiency figures associated with the various diagnostics, regardless of the benign or malignant character of the ductal epithelium. Data were analyzed with the IBM SPSS Statistics software version 19.0.

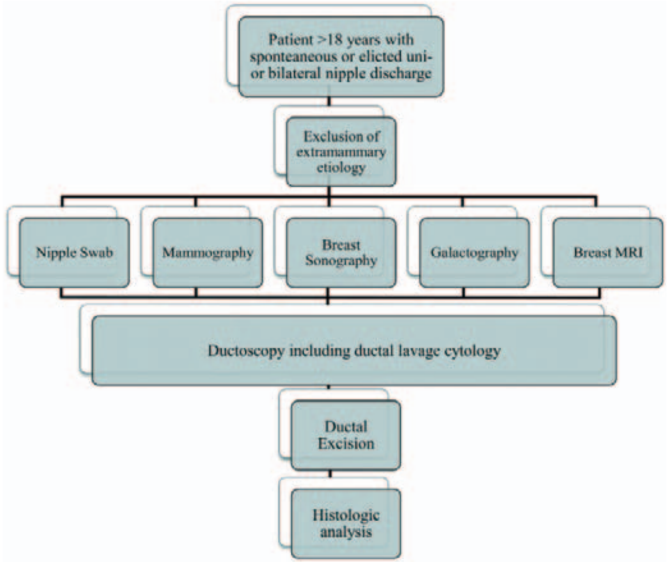

Fig. 1. Overview of the study design.

Results

The study included 261 women. 47 women were excluded: In 23 cases, ductoscopy was not followed by duct excision, a false passage was created in 7 cases, no mammary duct could be identified in 1 case, and in 2 cases, the ductoscope could not be advanced far enough and the procedure was prematurely aborted. These cases were counted as 'not completed'. Intraoperatively, no discharge could be elicited in 1 woman. 10 women underwent duct excision without prior ductoscopy. Data entry had been duplicated in 3 women. The mammary duct was successfully visualized in a total of 214 patients. All patients included in this study received a ductoscopy. Among these, no postoperative complications occurred, such as wound infections, duct perforation, pain or postoperative hemorrhage.

The average patient age was 52.2 years (age range: 19–86 years). The mean number of visualized ducts was 2.3 (range: 1–12 ducts) and the average depth was 42.3 mm (range: 1–90 mm).

Table 1 demonstrates the general results.

Due to different reasons (e.g. refusal of the diagnostic method by the patient, contraindication, lack of funds, missing data), it was not possible to give each woman all diagnostics as planned in the study design. Therefore, each diagnostic method shows variable case numbers.

Sonography was performed in 212, mammography in 191, MRI in 88, galactography in 120, nipple swabs in 134, and ductal lavage in 72 patients. These respective results were correlated with the ductoscopic findings.

The histology was benign in 89 cases (41.6%) (cell detritus, galactophoritis, fibroadenomas), mammary duct papillomas were found in 110 cases (51.4%), atypical ductal hyperplasia (ADH) in 4 cases (1.9%), DCIS was observed in 10 cases

Table 2. Summary of the performance of the various diagnostics for detecting intraductal anomalies

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Efficiency, %
Galactography	81.3	44.4	70.9	58.8	67.5
Ductal lavage cytology	57.8	85.2	86.7	54.8	68.1
Ductoscopy	71.2	49.4	66.4	55.0	62.1
Breast MRI	82.5	11.8	61.0	36.4	57.9
Breast ultrasonography	82.9	17.9	58.3	43.2	55.7
Nipple swab	22.8	85.5	69.2	43.5	48.5
Mammography	57.1	33.3	58.6	32.0	48.2

PPV = Positive predictive value, NPV = negative predictive value.

(4.7%) and invasive cancer in 1 case (0.5%). The following histologic results were considered conspicuous: papilloma, ADH, DCIS, invasive carcinoma. Cell detritus, galactophoritis, and fibroma were treated as unremarkable findings.

Breast sonography was performed in 212 patients (99.1%). Ultrasonographic findings according to BI-RADS classification were recorded in 175 cases. There were 123 conspicuous and 89 unremarkable final histologic findings. The calculated sensitivity was 82.9% and the specificity 17.9%.

Mammography was completed in 191 patients (89.3%). Mammographic correlates evaluated according to BI-RADS classification were found in 116 cases. Unremarkable histologic findings were recorded in 72 and conspicuous findings in 119 cases. Mammography had a sensitivity of 57.1% and a specificity of 33.3%.

MRI was performed in 88 women (41.1%), revealing 77 suspicious findings. There were 34 unremarkable and 54 conspicuous histologic results. MRI had a calculated sensitivity of 82.5% and a specificity of 11.8%.

Galactography was completed in 120 cases (56.1%). The ductal system was unremarkable in 34 cases. Possible intraductal lesions were reported in 86 cases. Final histologic analysis revealed 45 unremarkable and 75 suspicious findings. Galactography had a sensitivity of 81.3% and a specificity of 44.4%.

Nipple swabs were performed in 134 patients (62.6%). Unremarkable mammary ductal epithelium was seen in 108 of these; evidence for a papilloma or carcinoma was found in 26 cases. Final histology revealed 55 unremarkable findings and 79 conspicuous lesions. The sensitivity was 22.8% and the specificity 85.5%.

Ductal lavage cytology was completed in 72 patients (33.6%). In 42 cases, mammary duct epithelial cells were described as unremarkable, and suspicious findings were reported in 30 cases. Final histologic workup revealed unremarkable findings in 27 and suspicious findings in 45 cases. Ductal lavage cytology had a calculated sensitivity of 57.8% and a specificity of 85.2%.

Ductoscopy revealed lesions in 134 of 214 cases (62.6%) and no lesions in 80 cases (37.4%). The final histology analyses of the ductal excision were unremarkable in 89 and suspicious in 125 cases. Ductoscopy had a sensitivity of 71.2% and a specificity of 49.4%. Table 2 summarizes the results of all techniques.

Discussion

This multicenter center study compared the sensitivity, specificity; and efficiency of ductoscopy in cases of pathologic ND to the respective results of standard diagnostics.

The suitability of mammography for diagnosing the cause of ND is limited. Detecting intraductal processes in mammograms is difficult (sensitivity 57.1%, specificity 33.3%). The figures in the literature range from 7 to 10% for sensitivity and from 94 to 100% for specificity [21, 22]. In their study on 71 patients, Grunwald et al. [10] reported a sensitivity of 37.9% and a specificity of 92.3%. In their retrospective study, Albrecht et al. [23] calculated a sensitivity of 9% and a specificity of 100%, explaining the low sensitivity with a large number of false-negative results.

Breast high-resolution ultrasound is optimally suited for imaging intraductal lesions, with a sensitivity of 82.9% and a specificity of 17.9% in this study. Other researches show sensitivities between 26 and 67.3% and specificities of 61.5 and 97% [10, 21–23]. Due to fluid surrounding intraductal processes, ultrasonography of the ducts is very sensitive in uncovering such lesions. If pathological discharge correlates with a sonographically detected lesion, such lesions can be reliably diagnosed by vacuum biopsy [24].

Only a small number of studies have addressed MRI as a diagnostic in cases of pathologic ND, with a sensitivity of 82.5% and a specificity of 11.8%. The literature reports sensitivities ranging from 60 to 77% corresponding with specificities between 25 and 66.7% [10, 23, 25]. Differences between our results and those reported in previous studies can be explained by variations in image interpretation. Nakahara et al. [26] compared breast sonography, galactography and 3-dimensional MRI, finding the latter the most suitable method for localizing and for sizing lesions. Hirose et al. [27] also compared contrast MRI with 2-dimensional galactography. Again, contrast MRI was superior.

Galactography is currently considered the 'state of the art' for diagnosing intraductal lesions [2]. The technique has the shortcoming that it cannot clarify if any observed duct narrowing is in- or extrinsic [2, 11]. It achieved a sensitivity of 81.3% and a specificity of 44.4% in our study. The respective figures in the literature vary: Reported sensitivities are in the range of 50–94%, specificities in the range of 41–66.7% [10, 22, 23, 28, 29].

Cytologic ductal lavage performed during ductoscopy had a sensitivity of 57.8% and a specificity of 85.2% in this study. Yamamoto et al. [30] reported a specificity of 94.3%, a sensitivity of 50%, and an efficiency of 89.7%. Matsunaga et al. [31] compared nipple swab, biopsy, and cytologic ductal lavage. In their study, cytologic lavage had a sensitivity of 82.8%.

In our study, nipple swab achieved a low sensitivity (22.8%). Grunwald et al. [10] reported a sensitivity of 36.7% while Dinkel et al. [29] revealed a sensitivity of 31.2%. Some authors continue to recommend nipple swabs despite their poor sensitivity.

Ductoscopy is an innovative method for visualizing intraductal breast lesions. It is especially advantageous for detecting partially obstructive lesions. The method can also identify multiple lesions affecting a duct. This diagnostic technique had a sensitivity of 71.2% and a specificity of 49.4% in our multicenter study. These data are significant and consistent with several preliminary studies. In their retrospective study, Grunwald et al. [10] computed a sensitivity of 55.2% and a specificity of 61.5%. Albrecht et al. [23] reported a sensitivity of 53.2% and a specificity of 60%. Yamamoto et al. [30] compared ductoscopy and galactography in 65 patients. In these authors' study, intraductal anomalies were detected by galactography in 89.1%, by ductoscopy in 97.4%, and in 97.5% of the cases with both methods combined. Dietz et al. [32] published a study on 119 patients with pathologic ND, reporting that galactography detected 76% and ductoscopy 90% of the underlying anomalies. Schultz-Wendtland et al. [33] evaluated 22 patients with hemorrhagic ND, finding 20 benign and 2 malignant lesions. With 95.5%, ductoscopy achieved the highest accuracy while galactography and nipple swabs detected only benign lesions. Only 12 lesions were found by breast sonography; no diagnostic information was obtained in the remaining 10 cases.

Ductoscopy has a low complication rate [2, 34, 35]. In this study, a false passage was created in 7 cases, and in just 1 case, no duct was any longer identifiable. No further complications were reported.

In addition to evaluating the particular diagnostic methods individually, we attempted to maximize the diagnostic yield by combining methods. Because of the variable case number for each technique, combinations of three and more methods did not include a sufficient number of patients to calculate meaningful sensitivities and specificities. Feasibility and cost effectiveness are additional issues. Clear conclusions on the significance of combinations would require matching numbers of tests. A follow-up for this study is planned and will be part of a different publication.

Conclusion

Ductoscopy provides direct intraoperative visualization of intraductal anomalies in patients with pathologic ND. The endoscope's working channel and wire marking provide options for selective excision of intraductal lesions. Ductoscopy is an easily performed technique with a high sensitivity and a low rate of complications.

Disclosure Statement

There is no conflict of interest. All authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Online Supplemental Table

Table 1. General results

To access the online supplemental table please refer to *www.karger.com/?DOI=000368338.*

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