

# Diagnostic Value of Ductoscopy in the Diagnosis of Nipple Discharge and Intraductal Proliferations in Comparison to Standard Methods

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## Key Words

Nipple discharge · Papilloma · Galactography ·  
Mammary ductoscopy · Breast cancer

## Summary

**Background:** Ductoscopy is gaining increased importance in the diagnosis of nipple discharge of unclear origin and intraductal proliferation. For this reason we compared its diagnostic value and feasibility to standard diagnostic methods. **Material and Methods:** Ductoscopy was compared to mammography, galactography, sonography, magnetic resonance imaging (MRI), nipple smear, fine needle aspiration cytology (FNAC), and high-speed core biopsy; feasibility, sensitivity, and specificity were investigated for each method. **Results:** 71 ductoscopies were evaluated, which were followed up by open biopsies. Here, 3 invasive and 8 ductal carcinomas in situ were found, as well as 3 atypical ductal hyperplasias, 44 papillomas/papillomatoses, and 13 benign findings. Feasibility of ductoscopy was in this series 100%. Duct sonography showed the highest sensitivity (67.3%), followed by MRI (65.2%), galactography (56.3%), ductoscopy (55.2%), and FNAC (51.9%). The highest specificity was shown by FNAC, core biopsy, and galactography (each 100.0%), followed by mammography (92.3%), nipple smear (77.8%), ductoscopy, and duct sonography (each 61.5%); the lowest specificity was displayed by MRI (25.0%). **Conclusion:** The results confirm that ductoscopy can be performed within the same range of sensitivity and specificity as other techniques. In order to make conclusive statements about ductoscopy, especially in order to precisely define the indications for this method, a prospective multicenter study was initiated.

## Schlüsselwörter

Mamillensekretion · Papillom · Galaktografie · Duktoskopie ·  
Brustkrebs

## Zusammenfassung

**Hintergrund:** Die Duktoskopie erlangt zunehmende Bedeutung in der Diagnostik der unklaren Mamillensekretion und der intraduktalen Proliferationen. Deshalb wurden ihr diagnostischer Stellenwert und ihre Durchführbarkeit mit den derzeitigen Standardverfahren verglichen. **Material und Methoden:** Die Duktoskopie wurde mit der Mammografie, Galaktografie, Sonografie, Magnetresonanztomografie (MRT), dem Mamillenabstrich, der Feinnadelaspirationszytologie (FNAZ) und Hochgeschwindigkeits-Stanzbiopsie verglichen. Durchführbarkeit, Sensitivität und Spezifität jeder Methode wurden untersucht. **Ergebnisse:** 71 Duktoskopien wurden ausgewertet, bei denen nach Diagnostik eine offene Biopsie erfolgte. Dabei fanden sich 3 invasive und 8 duktales In-situ-Karzinome, 3 atypische duktales Hyperplasien, 44 Papillome/Papillomatosen und 13 benigne Befunde. Die Durchführbarkeit der Duktoskopie betrug 100%. Die Duktosonografie zeigte die höchste Sensitivität (67,3%), gefolgt von der MRT (65,2%), der Galaktografie (56,3%), Duktoskopie (55,2%) und FNAZ (51,9%). Die höchste Spezifität hatten FNAZ, Stanzbiopsie und Galaktografie (je 100,0%), gefolgt von der Mammografie (92,3%), dem Mamillenabstrich (77,8%), der Duktoskopie und Duktosonografie (je 61,5%); die MRT zeigte die geringste Spezifität (25,0%). **Schlussfolgerung:** Die Duktoskopie ist ohne Einschränkungen durchführbar und hat eine vergleichbare Sensitivität und Spezifität wie die Standarddiagnostik. Um endgültige Aussagen zur Duktoskopie treffen zu können, insbesondere um ihre Indikationsstellungen präzise festzulegen, wurde eine prospektive Multicenter-Studie initiiert.

## Introduction

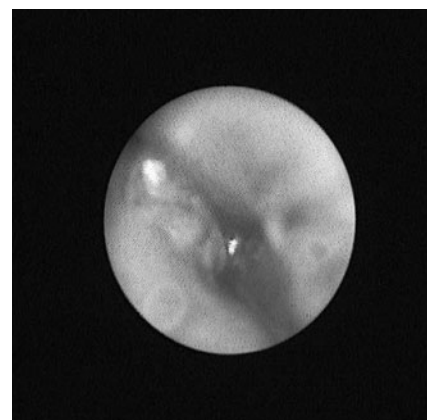
In secretory diseases of the mammary glands there are extramammary causes which can be physiological (galactorrhea) or pathological. Intramammary, morphological changes in the mammary glands are, for the most part, associated with benign diseases. However, malignant changes such as invasive and in situ carcinomas (ductal carcinoma in situ: DCIS) are also secretory in the extent of 0.5–12%. Because approx. 80% of all mammary carcinomas are ductal neoplasias, i.e. originate in the lacteal ducts, the exact diagnosis of the lacteal ducts, if possible using a minimal-invasive method, is gaining increased significance. The early detection of intraductal precanceroses and noninvasive carcinomas in particular must be intensified. There are different diagnostic imaging modalities available for the diagnosis of secretions of unclear origin. In the treatment of secretory breast diseases, after ruling out extramammary causes, the preferred therapies are retroareolar resection, sonography-supported vacuum biopsy [1] or duct excision. The use of endoscopy of the lactiferous duct, or ductoscopy, was first described in 1988 in a publication by Teboul [2], followed in 1991 by Kamio et al. [3] and Okazaki et al. [4]. But it was only with the development of smaller instruments [5] and the possibility of intraductal biopsy in recent years that the significance of ductoscopy has increased consistently [6–8]. As such, in the work of Pereira and Mobkel [9], their account of the development of ductoscopy describes the evolution of this method and in particular its prospects for the future through the combination of endoscopy with molecular diagnostic markers or high-frequency ablation.

## Materials and Methods

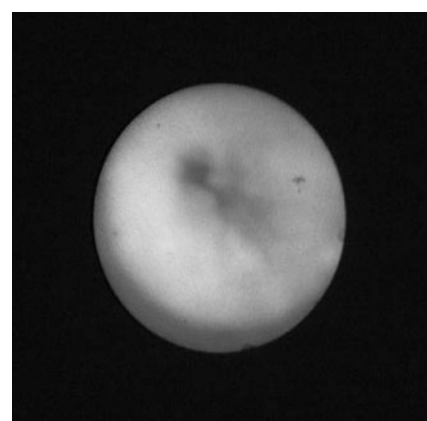
Mammary ductoscopies have been applied in our institute [6–8, 10] since 1999. Following a corresponding primary diagnosis, patients with indications for an open biopsy are given ductoscopy under general anesthesia prior to this operation. The indication results from conspicuous cytological or histological preliminary findings or from conspicuous intraductal image findings in a mammography, galactography or sonography of the breast.

For this study a ductoscope (outer diameter 1.3 mm, length 7.5 mm) was used (Karl Storz, Tuttlingen, Germany (No. 11570)) with 3,000 pixels and a work shaft upon which a manual NaCl rinse is fixed. A 1-mm straight lens system can be introduced through the ductoscope.

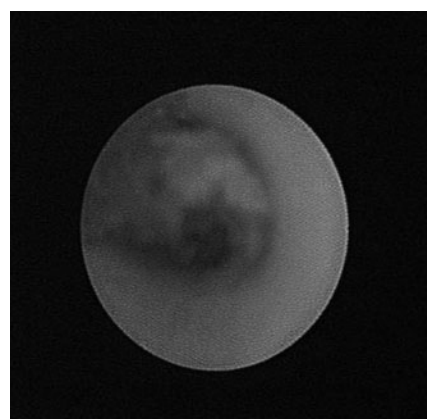
For the presented analysis, 71 ductoscopies with subsequent biopsies performed between 1999 and May 2005 were retrospectively included. All of the traditional diagnostic modalities (mammography [11]; galactography; sonography; magnetic resonance imaging; MRI; nipple smear; fine needle aspiration cytology: FNAC; high-speed core biopsy) are represented, and ductoscopy is compared with the histological diagnosis (after open biopsy with targeted duct excision). Mammography and breast sonography were obligatory before every procedure. The further noninvasive and minimal-invasive preoperative examinations were conducted according to their potentiality and feasibility. These included galactography, MRI, FNAC, high-speed core biopsy, and the cytological investigation of the nipple smears. The statistical evaluation was done to examine the performance of the individual diagnostic methods using a four-field contingency table. This was



**Fig. 1.** Intraductal proliferation (histological finding: ductal carcinoma in situ).



**Fig. 2.** Intraductal proliferation (histological finding: atypical ductal hyperplasia).



**Fig. 3.** Intraductal occlusion with polypoid proliferation (histological finding: milk duct papilloma).

used to calculate the sensitivity and specificity. For prediction of tissue dignity each diagnostic method was evaluated regarding its conformity with the histopathological results. In this respect, a histologically normal lactiferous duct epithelium was considered 'healthy'; all histopathological deviations, independent of their benignity, were classified as 'diseased'.

## Results

In total 71 ductoscopies with a subsequent targeted extirpation of the lactiferous duct were carried out on 64 patients (57

**Table 1.** Results and number of *non-invasive* examinations, with prediction of benignity and histopathological results, whereby a histologically normal lactiferous duct epithelium is designated as 'healthy', all histopathological deviations from a normal lactiferous duct epithelium, independent of their benignity, are designated as 'diseased'.

Criterion	Total conducted	Prediction of histological finding		Number of individual findings	Histopathological result	
		'diseased'	'healthy'		'diseased'	'healthy'
Mammography (BI-RADS classification)	71	23	48	1× BI-RADS 0 2× BI-RADS 1 45× BI-RADS 2 20× BI-RADS 3 3× BI-RADS 4 0× BI-RADS 5	58	13
MRI	27	18	9	7× normal 11× suspected papilloma 2× suspected malignancy 5× benign focus findings 2× could not be evaluated	23	4
Duct sonography	71	44	27	6× normal 40× suspected papilloma 4× suspected malignancy 21× benign focus findings	58	13
Cytology of the nipple smear	58	20	38	33× normal 5× eosin red 19× suspected papilloma 1× suspected malignancy	49	9

times on one side, 7 times on both sides). The average age of the patients was 52.3 years (range 21–77 years). The ductal accessibility was technical possible in depths between 0.5 and 7.5 cm, on average a depth of 3.3 cm was achieved.

*Histopathological findings* showed 3 invasive carcinomas, 8 DCIS (fig. 1), 3 atypical ductal hyperplasias (ADH) (fig. 2), 44 papillomas (fig. 3), and 13 benign (out of duct) findings.

The *clinical examination* yielded 12 palpable and 59 nonpalpable findings. In 9 cases no secretion appeared, there were 62 cases of exudation indicated, 23 of these were reddish, 20 milky, 15 serous, and 4 otherwise colored. The occurrence of the secretion was spontaneous in 49 cases and only as a result of applied local pressure in 13 cases.

A *nipple smear* was realizable 58 times in total for 62 anamnestically indicated secretions; in 4 cases no secretion could be provoked (table 1). The sensitivity was 36.7%, the specificity 77.8% (table 2).

The sensitivity of *mammography* (n = 71), evaluated according to BI-RADS classification [11], was 37.9%, the specificity 92.3%; for ductoscopy the results showed a sensitivity of 67.3% and a specificity of 61.5% (tables 1, 2).

Considered in detail, the duct-oriented *ultrasound examination of the breast* (n = 71) yielded suspicion of malignancy 4 times (2 times true positive in 3 histologically proven carcinomas; n = 2/3, 66.7%), suspicion of a papilloma 40 times (31 times true positive in 44 histologically proven papillomas; n = 31/44, 70.5%), and the suspicion of a most likely benign focus 1 time (true positive 6 times in 12 histopathologically proven benign findings; n = 6/12, 50.0%). The other 6 cases were found to be normal (true positive 2 times, n = 2/6, 33.3%;

false negative 4 times, n = 4/6, 66.7%; the histological findings yielded one papilloma here) (tables 1, 2).

*Galactography* was requested 29 times, but due to technical difficulties (no secretion could be provoked) was not feasible in 10 cases (n = 10/29, 34.5%), so that the examination was actually conducted 19 times (n = 19/29, 65.5%). In 8 normal findings with galactography, an open biopsy yielded 7 intraductal findings (n = 7/8, 87.5% false negative), the 9 galactographies with abnormal findings were all true positive (table 3). The sensitivity was 56.3%, the specificity 100% (table 2). The high specificity is the result of the presence of only one normal histological finding after an open biopsy, which was also described as normal by galactography.

The *MRI* was applied 27 times (table 1). The sensitivity was 65.2%, the specificity only 25.0% (table 2).

The sensitivity of *FNAC* (n = 34) was 51.9%, the specificity 100% (tables 2, 3).

A sonographically controlled *core biopsy* was done 11 times (table 3). The sensitivity was 42.9%, the specificity 100% (table 2).

As regards *ductoscopy* (table 3), which was feasible for all of the patients (n = 71/71, 100%), the sensitivity was 55.2% and the specificity 61.5% (table 2).

## Discussion

In this paper the diagnostic significance of ductoscopy is retrospectively compared to traditional diagnostic procedures in extension of a previous analysis [10]. A preoperative mammogra-

phy and sonography were conducted for each patient, the further diagnostic procedures such as galactography, MRI, nipple smear, FNAC, and high-speed core biopsy were used according to their feasibility and the indications. This resulted in a large, but heterogeneous series of patients and examination methods, as not every patient received all of the diagnostic examinations. According to Heywang-Köbrunner and Schreer [12] the indications for galactography are pathological secretions (spontaneous, not milky) for the most part on one side, originating from one or more ducts, bloody secretions and cytologically suspicious secretions, however, not secretions which appear only as a result of very great pressure. This meant that in our patient group 49 spontaneous secretions indicated the necessity of an X-ray contrast medium examination of the breast. Because often no secretion could be provoked when the patients were in the radiology department (34.5%) or because the examination was aborted due to pain, this examination was waived. This knowledge is probably one reason why galactography has only been requested 29 times in our institute. The restricted feasibility of galactography is seen as a significant disadvantage. The high specificity (100.0%) of galactography in our survey can be explained by the fact that in 8 galactographies, intraductal masses were determined (compared to 58 histopathological findings) which were all histopathologically true positive, whereby the small number of cases should be taken into consideration. The references provide specificity statistics ranging between 55 and 62.4%, the sensitivity is indicated as 68.8–83% [13, 14]. In our study the sensitivity is remarkably lower with 56.3%.

In a study conducted by Yamamoto et al. [15], galactography was compared to ductoscopy in respect to the detection rate of intraductal abnormalities in 65 patients with nipple discharge. The results for galactography were 89.1% and for ductoscopy 97.4%; a combination of both procedures resulted in 97.5%. In a study by Dietz et al. [16] with a group of 119 patients with pathological secretions, galactography determined abnormalities in 76%, ductoscopy yielded positive results in 90%. The pathological examination showed abnormalities in 88% of the cases (5× carcinoma, 84× papilloma, 16× hyperplasia). It follows from the above that, given the availability of ductoscopy, there is no longer a need for preoperative galactography.

With respect to the MRI examination, which was conducted 27 times in our study, poor specificity is shown, whereby this disadvantage of MRI is known. In contrast, however, the work of Nakahara et al. [17] evaluated three-dimensional contrast medium MRI as the most precise method of determining and classifying malignant diseases (especially DCIS) with nipple discharge as a symptom.

For the duct-oriented, high-frequency ultrasound examination of the breast we were able to determine altogether a good sensitivity (67.3%) and specificity (61.5%). Of the 44 papillomas which were proven histopathologically, 31 (70.5%) were detected by sonography.

**Table 2.** Number, sensitivity, and specificity of the individual examination methods

Examination	Number	Sensitivity, %	Specificity, %
Nipple smear	58	36.7	77.8
Mammography	71	37.9	92.3
Galactography	19	56.3	100
Duct sonography	71	67.3	61.5
MRI	27	65.2	25.0
FNAC	34	51.9	100
Core biopsy	11	42.9	100
Ductoscopy	71	55.2	61.5

FNAC = Fine needle aspiration cytology.

Minimal-invasive preoperative diagnostics with ultrasound view such as FNAC (n = 34) and core biopsy (n = 11) were conducted by us. The high specificity of these examinations (100%) can be traced to no false-positive findings; these results must be seen with some reservation due to the small number of patients examined. In addition, the sensitivity of 51.9% (FNAC) and 42.9% (core biopsy) is not satisfactory. The size of the lesions must be taken into consideration here; the reduction of accuracy due to the nature of minimal-invasive diagnostics can be an explanation for the false-negative results.

Nipple smears were spontaneously indicated 62 times, the examination was conducted a total of 58 times, whereby the specificity of 77.8% is satisfactory, but the sensitivity of 36.7% rather poor. These results, however, correspond with the findings of Dinkel et al. [14], who indicate a specificity of 97.4% and sensitivity of 31.2% in cytology of nipple smears, whereby 173 smears with subsequent open biopsy were compared. In a study by Schulz-Wendtland et al. [18] including 22 patients with bloody secretions, the cytological examination of nipple smears, mammasonography and galactography were compared; the authors found that the best diagnostic results were yielded by endoscopic lactiferous duct imaging. Whereas 20 benign and 2 malignant lesions were histologically proven, both galactography and the cytological examination of the nipple smears determined only benign findings; endoscopy was able to determine one malignant finding. According to these results, the tissue dignity prediction is equally good using galactography or cytological examination of nipple smears.

In the evaluation of the cytological findings, ductal lavage cytology has established itself; in this context Yamamoto et al. [15] indicated a specificity of 94.3%, a sensitivity of 50%, and an efficiency of 89.7% for ductal lavage during ductoscopy. Lavage cytology was not considered in our evaluation.

In our examinations we were able to depict the lactiferous ducts on the average to 3.3 cm, whereby the greatest peripheral depth was 7.5 cm (limited by the length of the ductoscope). This corresponds with other studies. In this respect, the ductoscopic visualization done by Dooley [19] reached a depth of

**Table 3.** Results and number of *minimal-invasive* examinations and ductoscopy, with prediction of benignity and histopathological results, whereby a histologically normal lactiferous duct epithelium is designated as 'healthy', all histopathological deviations from a normal lactiferous duct epithelium, independent of their benignity, are designated as 'diseased'.

Criterion	Total conducted	Prediction of histological finding		Number of individual findings	Histopathological result	
		'diseased'	'healthy'		'diseased'	'healthy'
Galactography	19	9	8	2× could not be evaluated 8× normal 9× suspected intraductal masses	16	1
Fine needle aspiration cytology	34	16	18	16× normal 14× suspected papilloma 2× suspected malignancy 2× cystic contents	27	7
Core biopsy	11	4	7	7× mastopathy 2× papilloma 1× sclerogenic adenosis and/or fibroadenoma 1× ductal carcinoma in situ	7	4
Ductoscopy	71	37	34	32× normal 2× inflammation 36× papilloma 1× suspected malignancy	58	13

7.5 cm, Kothari et al. [20] state a maximum depth of 8.9 cm; in 66% of the cases the visualization reached to a depth of over 2 cm into the mammary duct system. In contrast, in other publications the use of ductoscopy is only considered for the central ducts [21, 22].

As regards the endoscopic intraductal findings, we determined a sensitivity of 55.2% and a specificity of 61.5% for ductoscopy. Comparisons with published results cannot be made, as the evaluation schemes are too different. The sensitivity and specificity are still restricted, but the advantage over galactography is obvious, as only 8 abnormal findings were detected using this examination. On the other hand, with ductoscopy 23 of the 44 histologically proven papillomas were correctly detected and the lactiferous ducts were described as normal 23 times.

The intraoperative application of ductoscopy minimizes the extent of surgical resections. This was shown in a study by Dooley [19], whereby he postulates that in cases of bloody nipple discharge as a result of a high incidence of multiple lesions, the classical 'blind' retroareolar resection with limited depth should no longer be conducted without supplemental ductoscopy. An open biopsy and ductoscopy were conducted on 27 patients with bloody nipple discharge. In 26 of 27 cases it was possible to conduct the examination, in all of these cases the cause of the bloody secretions was seen, whereby in 70% of the cases multiple lesions were prominent. Two cancers were detected, whereby in both cases a papilloma of the same lactiferous duct was to be found further proximal. Leris and Mobkel [23] also consider ductoscopy as an excellent diagnostic and therapeutic opportunity because of the reduction of the number and size of open biopsies for patients with pathological nipple discharge.

An open biopsy is of course necessary in the case of malignan-

cy; in a study done by Ito et al. [24] on nipple discharge and negative nipple smears, followed by open segment resection for nonpalpable mammary carcinoma (n = 26), this is the method described as the therapy of choice.

In a total of 71 open biopsies in our study, the postoperative histological findings indicated that the operation was necessary in 58 cases (81.7%; 44 papillomas, 3 times an ADH, 8 DCIS, and 3 invasive carcinomas); accordingly, an unnecessary open biopsy was done on the 13 benign findings (18.3%). This results in the ratio of necessary open operations/unnecessary open operations of 4.5:1. In order to further reduce the rate of unnecessary open biopsies, a further improvement of intraductal diagnostics is needed. This can be achieved by the use of more modern instruments, as was displayed by Jacobs et al. [5]. The safe execution and the reliability of the method is shown here to be due to the availability of newer instruments with smaller outer diameters and the creation of grasping instruments. Ductoscopy with a 0.55–0.95 mm diameter endoscope was conducted on 11 women with pathological nipple discharge without any intraoperative or postoperative complications, thereby showing a trend towards a further minimal-invasive diagnostic method. The use of additional technologies such as autofluorescence endoscope [25] or high-frequency ablation [9] extends the spectrum of minimal-invasive methods.

The results presented here were evaluated retrospectively; in addition, not all diagnostic procedures were available for all of the patients. Today, in cases of nipple discharge of unclear origin, the abundance of diagnostic procedures – a 'diagnostic dilemma' – becomes apparent, because unequivocal indications and a current, standardized examination sequence are presently not available [26]. In order to make a definitive statement with regard to the diagnostic efficiency of the indi-

vidual diagnostic methods, a prospective study comparing all of the procedures is necessary. This is ensured in the international multicenter study (Germany and Switzerland) which began in September 2006 and includes approx. 300 patients. The evaluation is planned in about 2 years, so that a statement is then expected on the exact indication status for ductoscopy and therewith possibly also a reduction of the number of examinations for the individual patient. In addition, we hope that this will also lead to a reduction of the rate of unnecessary biopsies.

## Conclusions

In all cases of nipple discharge of unclear origin, ductoscopy was feasible without any limitations and showed to have comparable sensitivity and specificity to standard diagnostic techniques like mammography, galactography, sonography, MRI, nipple smear, FNAC, and high-speed core biopsy. In order to make conclusive statements about ductoscopy, especially in order to precisely define the indications for this method, a prospective multicenter study was initiated.

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