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Correlation of Ductoscopic and Histopathological Findings and Their Relevance as Predictors for Malignancy: A German Multicenter Study

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Abstract. *Background/Aim: The study aimed at investigating the correlation between ductoscopic and histopathological findings and clarify whether the former allow for accurate prediction of malignancy. Patients and Methods: The prospective national multi-center study covered a sample of 224 patients with pathologic nipple discharge. A total of 214 patients underwent ductoscopy with subsequent extirpation of the mammary duct. The ductoscopic findings were categorized according to shape, number, color and surface structure of lesions and vascularity and compared to the histological results and analyses. Results: Ductoscopy revealed lesions in 134 of 214 patients (62.2%). The criteria "multiple versus solitary lesion" differed significantly between malignant and benign lesions. All other criteria were not statistically significant. Malignant tumors were more frequently presented as multiple lesions, benign lesions or masses as solitary lesions (80% vs. 24.8%; p=0.018). Conclusion: The ductoscopic criterion "solitary vs. multiple lesion" appears to have a low diagnostic prediction of malignancy or benignity.*

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Nipple discharge is a common symptom of breast disease. It represents the second leading common symptom after mastodynia for which most women appear in specialized breast departments/clinics (1). A total of 5-7% of all women going to a special breast clinic suffer of nipple discharge (2-4), which may be caused by a benign or malignant lesion. The incidence of pathologic nipple discharge and papilloma has been most frequently described (43-66% of cases), followed by ductal ectasia (15-20%) and carcinomas (10-28%) (1, 2, 4-7). In addition to anamnesis talk and physical examination, further diagnostic methods in cases of pathologic nipple discharge are necessary. These are ultrasound of the breast, mammography, galactography, smear of the nipple, ductal lavage and in some reasonable cases an MRI examination (5, 8, 9). The whole excision of the secretory duct by using a blue dye technique remains the gold standard for patients with conspicuous nipple discharge. Since the end of the eighties (1980), ductal endoscopy including ductoscopy and galactography is available for a direct visualisation of the small milk ducts (1). Ductoscopy is a minimally invasive endoscopic technique that enables direct intraductal visualization (10). The most promising investigation technique of nipple discharge with unclear causes is actually ductoscopy (1, 2) and has already been

described in numerous studies (1, 3, 5-8). Today ductoscopy is already viewed and shown as an effective method to identify intraductal proliferations. Ductoscopy is a useful procedure for guiding subsequent breast surgery in the treatment of nipple discharge, and the appearance may be essential in treating breast cancer patients with nipple discharge (11). Most pathologic nipple discharge (PND) is benign, but duct excision has been advised to exclude malignancy (12). The purpose of this study was to evaluate the ductoscopic criteria towards predicting benignity or malignancy.

Patients and Methods

Study design. This prospective national multi-center study was performed from September 2006 up to May 2009 and seven Clinics were involved. The study protocol was approved by the local Ethics Commission.

Patients. The study included 224 female patients with pathological nipple discharge of intramammary origin for whom ductectomy was indicated. Before undergoing the ductoscopy and extirpation of the milk duct, all patients signed an informed consent. Inclusion criteria were the presence of pathologic nipple discharge which indicated a biopsy, suspicious cytological results from nipple smear and a suspicious intraductal lesion on imaging. Exclusion criteria were discharge during hormonal imbalances including prolactinoma, cases of drug-induced galactorrhea, patients with no sanguinary discharges, clear, milky discharges and inconspicuous imaging.
Ductoscopy and ductal extirpations. Ductoscopy was performed using two semi-flexible ductoscopes (Karl Storz GmbH & Co., Tuttlingen, Germany), with outer diameters of 0.85 and 1.25 mm and a length of 9 cm. Ductoscopy and subsequent extirpations of the milk duct were performed under general anesthesia. In order to identify the correct mammillary duct, nipple discharge was provoked. The pars infundibularis was then expanded using salivary gland dilatator. The ductoscope was inserted using a trocar under direct visualization of the glandular duct.

A marking wire (Somatex® Medical Technologies GmbH, Teltow, Germany) was inserted to the lesion using the working channel of the ductoscope. The affected milk duct was then intraductally marked and subsequently excised through a periareolar incision. The entire ductoscopic procedure was digitally recorded and documented.

Histopathological examination. All excised milk ducts were suture marked and pathological workup was performed according to standard protocol for diagnostic excisional specimens.

Documentation and statistics. All data were recorded in a standardized protocol using the database ODS®mimi (Aschheim, Germany), a software application from the working-group for minimally invasive mamma intervention ("Arbeitsgemeinschaft Minimalinvasive Mammaintervention") of the German Senology Society ("Deutsche Gesellschaft für Senologie"). The exact endoscopic findings were documented using a classification model developed in 2010 at the Department of Obstetrics and Gynecology, Ernst-Moritz-Arndt-University, Greifswald, Germany, by Ohlinger *et al*. (13) (Table I). Every lesion detected *via* ductoscopy was described as follows: form (flat or polypoid), number (solitary or multiple), color (white, yellow or red), surface of the lesion (smooth or fissured), as well as the presence of hemorrhaging and/or atypical vessels.

Statistical analysis. Statistical analysis of the compiled data was performed using the SPSS 15.0 Software Package (Statistical Package for Social Sciences; SPSS, Inc., Chicago, IL, US). The results from histopathological testing on the excised milk ducts were used as reference criteria. Findings were categorized as either "malignant" or "benign". The benign group included ductal breast papilloma (DBP), other benignities (fibroid adenoma, ductal ectasia, sclerosing adenosis, typical ductal hyperplasia and others) and atypical ductal hyperplasia (ADH). The malignant category included findings of invasive ductal carcinoma and ductal carcinoma in situ (DCIS). By statistically examining the frequencies of the five classification criteria of the intraductal appearance for each lesion, we tried to identify a possible correlation/association between the said criteria and the malignancy or benignity of the lesion. These correlations were tested for statistical significance using the two-tailed Fisher's exact test, with $p<0.05$ being regarded as statistically significant (14).

Results

Between September 2006 and May 2009, 224 female patients were included in the study, while 214 (95.5%) patients underwent successful ductoscopy. In 6 cases the procedure had to be aborted due to viae falsae. In 1 patient no mammillary duct could be located, while 1 other patient could not undergo ductoscopy because no discharge could be provoked. In 2 cases the ductoscope could not be inserted far enough into the duct, allowing only insufficient depth of visualization. In total, ductoscopy could not be performed in 10 of 224 cases (4.5%).

No post-operative complications appeared during the trial. The average age of patients was 52.2 years (minimum: 19 years; maximum: 86 years). In 134 of the 214 patients ductoscopy showed intraductal lesions/suspicious abnormalities which results in a detection rate of 62.6% (Table II). Histological examination of the 134 removed milk ducts revealed 83 (61.9%) DBP, 45 (33,6%) other benignities (fibroid adenoma, ductal ectasia, sclerosing adenosis, typical ductal hyperplasia among others), one case (0.7%) of ADH and 5 (3.8%) of DCIS.

A total of 5 malignancies were diagnosed, all of them DCIS. No invasive ductal carcinoma was diagnosed by histological examination. All other suspicious lesions (n=129) were classified as benign. Ductoscopy revealed no suspicious lesions in 80 of 214 cases (37.4%). In these cases, histopathological analysis of the excised milk ducts revealed 27 (33.7%) DBP, 44 (55%) other benignities, 5 (6.2%) DCIS, 3 (3.8%) ADH and one (1.3%) invasive carcinoma.

Ductoscopic findings. A total of 57 of 129 (44.2%) benign lesions were classified as flat, compared to 0 among the malignant findings. In fact, all malignant lesions had a polypoid appearance, while this appeared for only 72 of the 129 (55.8%) benign lesions ($p>0.05$). One out of 5 (20%) malignant

Table I. *Overview of descriptors for intraductal lesions from previous reports and summary as seen in (13).*

Report	Reference	Lesion/Form	Number	Color	Surface	Vessels
Okazaki *et al*. (1991)	(33)	Solid nodule, bridging, spreading, fragile, flat to slightly protruding lesion	Solitary, multiple	Pallid pink, yellow, ash gray, white	Shiny, smooth, Jaggy	No, yes
Matsunaga *et al*. (2001)	(20)	Papillary, hemispherical, flat protrusion	Solitary, multiple	Yellow, white		Rare to seldom, frequent
Shen *et al*. (2001)	(18)	Polypoid, mushrooming			Smooth borders, irregular borders	Yes
Yamamoto *et al*. (2001)	(23)				Smooth surface, smooth borders, jagged surface, irregular borders	No, yes
Japanese Association of Mammary Ductoscopy and Makita *et al*. (2001/2002)	(21, 26)	Polypoid lesion, superficial lesion Combined type	Solitary, multiple	Redness	Erosive surface	
Makita *et al*. (2006)	(19)		Solitary, multiple, uncountable	Yellow, red, white, colorless	Spherical, lobular, mulberry, amorphous	
Summary and classification for this trial		None, flat, polypoid	Solitary, multiple	Red, yellow, white	Fissured, smooth	Blood and/or atypical vessels: yes, no

specimens was classified as a solitary lesion, compared to 97 out of 129 (75.2%) of the benign findings. Four out of 5 malignant findings (80%) were classified as multiple lesions, compared to only 32 out of 129 (24.8%) of the benign group, which was significant according to Fisher's exact test ($p<0.05$). None of the lesions found to be malignant through histopathological analysis appeared white (0 of 5). Two out of 5 malignant lesions were yellow (40%), 3 out of 5 were red (60%). The benign findings showed a clear tendency towards a particular color: 45 of 129 (34.9%) were white, 35 of 129 (27.1%) were yellow and 49 of 129 (38%) were red ($p>0.05$). Four out of 5 (80%) malignant lesions and 84 out of 129 (65.1%) benign lesions were smooth-surfaced. The surface of 45 out of the 129 (34.9%) benign findings had a fissured appearance, as did only 1 out of 5 (20%) of the malignant cases ($p>0.05$). Hemorrhaging and/or atypical vessels were observed in 1 out of 5 (20%) malignancies, and in 30 out of 129 (23.3%) of the benign findings ($p>0.05$). The frequency distribution of the 5 classification criteria in the malignant and the benign group are presented in Table II. The only criterion which presented a significant difference was "solitary *vs*. multiple lesion".

Discussion

In this study patients presenting with pathologic nipple discharge were ductoscopically examined. The aim was to evaluate the criteria (visual characteristics) appearing in ductoscopy and correlate them to histopathological results and findings.

Previous studies have often described carcinomas as superficial lesions or flat protrusions (15, 16). In this study, the shape of the lesion was classified as either "flat" or "polypoid". Five out of 5 DCIS were classified as polypoid lesions. In a study by Rose *et al*. (13) all invasive carcinomas (4 out of 4) and 8 out of 9 DCIS (88.9%) were polypoid lesions. Yamamoto *et al*. (17) used the classification system of the "Japanese Association of Mammary Ductoscopy" and described invasive carcinomas as "polypoid-solitary" lesions. Simpson *et al*. (16) who also used the Japanese classification system, described 23 of 23 ductal breast papillomas as "polypoid-solitary" lesions. Not only all malignant findings were categorized as polypoid – 72 of the 129 (55.8%) benign cases in our study had a polypoid appearance. Shen *et al*. likewise reported that ductal breast papillomas were more frequently described as polypoid lesions (18). Our data revealed no significant difference (p=0.072) whether they had a polypoid or a flat appearance, rendering the latter appearance criterion (polypoid *vs*. flat) unsuitable and insufficient for predicting malignancy.

In our study, malignant findings were more associated with multiple lesions (4 of 5, 80%), while benign findings were more frequently described as solitary lesions (97 of 129, 75.2%). Thus, the number of lesions (solitary *vs*. multiple) observed in ductoscopy was a significant predictor (p=0.018) for malignancy. These findings reflect the results by Makita *et al*. that malignant lesions appear significantly more often as multiple lesions, while intraductal papillomas

Table II. *Patients for whom ductoscopy revealed suspicious abnormalities (n=134). Histology and ductoscopic appearance.*

	Malignant (%)* n=5	Benign (%)** n=129	*p*-Value***
Lesion			
Flat	0 (0)	57 (44.2)	0.072
Polypoid	5 (100)	72 (55.8)	
Number			
Solitary	1 (20)	97 (75.2)	0.018
Multiple	4 (80)	32 (24.8)	
Color			
White	0 (0)	45 (34.9)	0.268
Yellow	2 (40)	35 (27.1)	
Red	3 (60)	49 (38)	
Surface			
Smooth	4 (80)	84 (65.1)	0.66
Fissured	1 (20)	45 (34.9)	
Blood – and/or atypical vessels			
Yes	1 (20)	30 (23.3)	1.0
No	4 (80)	99 (76.7)	

*DCIS (n=5). **DBP (n=83), other benign findings (n=45) and ADH (n=1). ***By the Fisher's exact test.

are more frequently categorized as solitary lesions (19). In our multi-center study, no malignant lesion was described with a white appearance.

Out of 5 DCIS, 3 were classified as red (60%) and 2 were classified as yellow (40%). Nor did the benign findings show a clear tendency towards a particular color: 49 of 129 (38%) were red, 45 of 129 (34.9%) were white and 35 of 129 (27.1%) were yellow. Thus, there was no statistically significant association with the color of a lesion (p=0.268), rendering the color unsuitable predictor for malignancy. Makita *et al.* and Matsunaga *et al.* received similar results in their studies (19, 20). Rose *et al.*, by contrast, concluded that the color yellow was a predictor for benignity (13).

The surface of 4 out of our 5 (80%) malignant findings appeared smooth. In contrary to Rose *et al.*, who described 4 out of 4 invasive carcinoma and 7 out of 9 (77.8%) DCIS with fissured surface (13), and to Makita *et al.*, who also observed a fissured, rough surface more frequently in their malignant findings (21). Liu *et al.* described the only invasive ductal carcinoma of the study with surface abnormalities which were not described in detail (22). A smooth surface could also be observed for the majority of benign lesions in our study (84 out of 129, 65.1%), with a *p*-value of 0.66. A dignity prediction based on the surface appearance and structure did not seem sensible.

In our study hemorrhage and/or atypical vessels were observed in 1 out of 5 (20%) malignant cases, and in 30 out of 129 (23.3%) benign cases. Thus, this criterion, appears to be unsuitable as a basis for predicting the malignancy/benignity of a lesion, as is strongly expressed by the *p*-value of 1.0. Matsunaga *et al.* observed hemorrhage from the lesion in 16 out of 38 (42.1%) carcinomas and in 16 out of 115 (13.9%) intraductal papillomas (20). By contrast, Rose *et al.* reported a presence of blood and/or atypical vessels for 4 out of 4 carcinomas and 6 out of 9 (66.7%) DCIS (13). Also, Yamamoto *et al.* observed 2 out of 2 intracystic papillary carcinomas as tending to bleed and 3 out of 3 intracystic papillomas without bleeding (23). Another consideration suggested to perform an HPV test if there were any papillomas, as Balci *et al.* noted that the risk was higher to develop a papilloma or breast cancer with proven HPV (24). All in all, utilization of localization needles under fiberoptic ductoscopy guidance for non-palpable breast lesions is a safe and effective procedure according to the latest knowledge, and is helpful in the diagnosis of breast cancer. With the help of this procedure, more malignant lesions can be localized and surgically removed (25).

Limitations of the study. The correlation between ductoscopic appearance and the results from histological testing has been the subject of only a few studies. Comparability between these studies is, however, strongly compromised, since the different studies employed different classification systems and criteria for describing ductoscopic appearance. The classification of the "Japanese Association of Mammary Ductoscopy" (21, 26) exists since 2001. This classification divides ductoscopic findings into 4 categories: 1. polypoid-solitary, 2. polypoid-multiple, 3. superficial, 4. combined type (polypoid and superficial). Some authors use this classification, others have adapted it. Al Sarakbi *et al.* developed a score system for diagnosing whether a suspicious finding is malignant or not based on ductoscopic appearance (27). However, no reference is made in the study to the criteria along the lines of which this distinction is to be made.

Ling *et al.* classified intraductal appearance into the categories G0 to G5. Exact ductoscopic criteria and the respective therapeutic consequences were allocated to each category. Those intraductal criteria and attributes include: irregular thickening of the lumen, ulcerating proliferation, cross-bridging structures and extrinsic compression of the ducts (15). Other authors used the terms "papilloma-like", "inflammatory changes", "red patches", "ductal obstructions", "solitary papillomatous or multiple papillomatous lesion" and "surface abnormalities" to describe the intraoperative appearance of lesions during ductoscopy (22, 28, 29, 30). Rose *et al.* took previous studies into consideration and published a classification system that was consistently and uniformly applied in our study (13) (Table I). Due to the low number of malignant findings, both in our sample but also in previous studies, the results should be critically interpreted.

Conclusion

The only criterion that could be statistically significantly associated with histopathological results, and that could serve as a predictor for malignancy is the appearance of solitary compared to multiple lesions using ductoscopy. Due to the low number of malignant cases in our sample, further prospective multi-center studies should be conducted involving larger sample with more malignant cases so as to substantiate and statistically verify this suspicion. In doing so, devising a uniform, international classification of the ductoscopic appearance of lesions should be the overriding goal. Another consideration would be to include a new or additional investigation method by means of galactomosynthesis to create digital 3-dimensional images of suspicious findings. Schulz-Wendtland *et al*. (31) presented the opinion that breast tomosynthesis used in galactography could be a useful complementary procedure for the diagnosis of breast anomalies and could herald a renaissance of this method. Another possibility would be fluorescence imaging (32). Ductoscopy can be safely used as an alternative for surgery in the work-up for PND (10).

Conflicts of Interest

The Authors have no conflict of interest to declare.

Authors' Contributions

All contributions were made in collaboration. All Authors participated in the multicenter study, collected and entered data and proofread the publication. This work was written by Prof. Dr. med. Ralf Ohlinger in close cooperation with Dr. med. Carolin Flieger. He was also a study participant. The statistics were compiled by Prof. Dr. med. Thomas Kohlmann and evaluated by Dipl.-Psych. Ines Buchholz. The pathological assessment and evaluation was carried out by Dr. med. Kirsten Utpatel. The data acquisition was carried out by Dr. med. Wenke Hahndorf, Dr. med. Ulrike Rechenberg, Dr. med. Andrea Stomps, Dr. med. Oumar Camara, Prof. Ulrich Deichert and Dr. med. Uwe Peisker. Further work on all parts, such as acquisition, correction and data entry was carried out by Prof. Dr. med. Markus Hahn, Dr. med. Stefan Paepke, Prof. Dr. med. Jens-Uwe Blohmer, Dr. med. Susanne Grunwald, Dr. med. Katrin Hegenscheid and Prof. Marek Zygmunt. Literature research was also carried out by Dr. med. Robert Flieger and Dr.med. Zaher Alwafai.

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