Title:

**The potential of diagnostic and interventional ductoscopy in women with nipple-discharge**

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**Zusammenfassung:**

Die Duktoskopie (Milchgangsendoskopie) stellt eine endoluminale Technik zur Darstellung von Milchgangsveränderungen dar. Der Einsatz ergibt sich aus dem Indikationsbereich der intraduktalen papillomatösen und proliferativen Milchgangserkrankungen sowie präkanzerösen oder invasiven Veränderungen, deren erstes Symptom eine spontane oder provozierbare zum Teil blutige Sekretion sein kann. Eine neue Gerätegeneration von Duktoskopen hat einen Aussendurchmesser von nur 0,55 bis 1,1 mm (LaDuScope®, Polydiagnost GmbH, Pfaffenhofen). Bisherige Analysen des klinischen Einsatzes der Duktuskopie fussen auf der Bewertung als bildgebende Zusatzdiagnostik zu den Standardverfahren wie Galaktographie und Duktallavage und determinieren die Empfehlung, die Duktoscopie als diagnostische Methode in die Abklärung der auffälligen Milchgangsekretion aufzunehmen.
Durch die in die neue Gerätegeneration integrierbaren Zusatzinstrumente eröffnen sich Möglichkeiten der interventionellen diagnostisch-therapeutischen Duktoskopie Über einen Arbeitskanal können optisch kontrollierte, gezielte intraduktale zytologische und mikro-bioptische Probeentnahmen erfolgen. Zukünftig könnten über diesen minimal-invasiven diagnostisch-therapeutischen Zugriff offen-chirurgische Biopsien, wie die selektive Milchgangsexstirpation zum Ausschluss maligner Veränderungen vermieden werden.

Stichworte: Milchgangsendoskopie – Mikrozytologiebürste – Mikrobiopsie – intraduktale Drahtmarkierung - Autofluoreszenzduktoskopie

**Summary:**

Ductoscopy (breast duct endoscopy) constitutes an endoluminal technique for the visualization of changes in the ductal system. The application arises from the indication areas of intraductal papillary and proliferative duct disease as well as precancerous or invasive changes, whose first symptom can be a spontaneous or provoked, and sometimes bloody, secretion. A new generation of ductoscopes has an external diameter of only 0.55 to 1.1 mm (LaDuScope®, Polydiagnost GmbH, Pfaffenhofen, Germany). Prior analyses of the clinical application of ductoscopy are based on the assessment of its potential as a supplemental diagnostic imaging technique to the standard techniques of galactography and ductal lavage and the evaluation of the recommendation that ductoscopy should be considered as a standard part of the evaluation process for patients with suspicious nipple discharge. New horizons open in interventional diagnostic-therapeutic ductoscopy with the introduction of the newest generation of instruments which allow the integration of additional instruments. Visually monitored, targeted intraductal cytological and microbiopsy sampling can be performed via a working channel. In the future, open surgical biopsies such as selective duct extirpation for the ruling out of malignant changes can be avoided through the use of this minimally invasive diagnostic-therapeutic intervention.

Key words: nipple discharge – breast ductoscopy – microcytobrush - microbiopsy – intraductal marking wire - autofluoreszenzductoscopy -

## Introduction

*Nipple discharge*

Nipple discharge that is bilateral and nonspontaneous and emenates from multiple ducts after breast manipulation or stimulation is considered benign, whereas spontaneous, persistent, bloody or clear nipple discharge that originates unilaterally from a single duct is considered pathologic. In published series, the proportion of breast carcinoma cases associated with nipple discharge is very low and ranges from 1.6 – 13 %. Patients with breast carcinoma accompanied by nipple discharge presented primarily with early-stage breast cancer associated with DCIS. Occult NAC involvement was not an uncommon finding [1]. The Incidence of occult nipple-areola complex involvement was 16% (3of 19) in Stage 0-I disease. The rate of nipple involvement in patients with breast carcinoma as determined by pathologic evaluation of mastectomy specimens has been reported to be between 5.6 – 21% [2, 3].

## Breast ductoscopy

Nipple discharge can present a diagnostic problem, suggesting the need for histologic confirmation before the initiation of surgical therapy [4]. Patients in the clinically benign group were managed conservatively, without surgical intervention, whereas all patients with clinically pathologic discharge underwent surgery. Only approximately 5% of women with these symptoms exhibit a precancerous or malignant change; that means that 95% undergo a selective or often complete duct extirpation only because no reliable diagnostic methods are available. The histology of duct resection often exhibits no pathological finding but merely chronic inflammatory changes or papilloma [5,6]. Because of this, the need arises for an accurate diagnostic tool for confirmation that the underlying process is benign to prevent a more extensive invasive surgical diagnostic technique. Imaging techniques play a major role in the diagnostic and therapeutic management of patients with nipple discharge. On ductography (galactography), filling defects, filling defects with dilation, cutoff signs, irregularities, and duct ectasia with dilatation were considered abnormal findings [7]. There are variant approaches to intraductal breast diagnostic:

ductography (Galactography), cytology from nipple smear or nipple aspiration, ductal lavage and ductoscopy. But, in breasts with cancer ductal lavage appears to have low sensitivity (17%), high specifity (100%) and a accuracy of 19%, possibly because cancer-containing ducts fail to yield fluid or have benign or mildly atypical cytology [8]. Because discharge originates from the ductal system, intraductal approaches such as ductography and, recently, ductoscopy have become the diagnostic procedure of choice, especially for patients with normal findings on other imaging studies [9]. The potential that ductoscopy has shown thus far is an improved diagnostic method using intraluminal visualization of lesions that could only be indirectly visualized in galactography by interrupting the flow of the contrast medium. Thus Dietz et al found 76% of anomalies by galactography but up to 90% by ductoscopy, with confirmation of changes in 88% (carcinoma, papilloma, hyperplasias) [10,11]. The work of Yamamoto et al showed a detection rate of 89.1% with galactography, 97.4% with ductoscopy, and 97.5% with a combination of both methods. Ductoscopic guided ductal lavage shows a distinct improvement in sensitivity of 50%, with a specificity of 94.3% and an efficiency of 89.7% [12 ].

*New minimally invasive diagnostic-therapeutic interventional breast ductoscopy*

Ductoscopy as endoluminal duct endoscopy has been available for some time and is currently experiencing a renaissance with increasing technical sophistication and the noticeable reduction in the diameter of the endoscope. Among others, the micro-ductoscopy system (PolyDiagnost LaDuScope®) is available with an external diameter of 0.55mm and another LaDuScope with an external diameter of 0.95 - 1.1 mm, whereby the latter is provided with a working channel [13] that facilitates the introduction of a cytology brush for targeted intraductal swabs, or micro-biopsy forceps with a 0.8 mm branch width. The working length of the ductoscope is 75 mm with which the visualization of the central duct system is made possible, beginning directly posterior to the junction point of the milk ducts at the mamilla surface to deep into the periphery where they branch into the terminal ductolobular units, the preferential site of origin for malignant changes. Optics with 0 degrees direct view and 3000-6000 pixels afforded a satisfactory resolution up to now; current ones experience considerable improvement through use of a resolution of 30,000 pixels. The feasibility of a micro-biopsy system that can make use of ductoscopic guidance

for obtaining intraductal biopsies revolutionizes the technique. The microbiopsy forceps (Polydiagnost GmbH, Pfaffenhofen, Germany) consist of a 15 cm long flexible shaft with the actual forceps part having 0.8mm branches. The secretory duct is visualized ductoscopically, the lesion responsible is visualized, and a multiple micro-biopsy is performed. [14]. The application up to now indicates a correlation of over 80% with the final histological result after selective duct removal, for samples, 0.1 – 0.3 mm in size, that were taken with the microbiopsy forceps. The microcytology-brush and the microbiopsy-system in combination with the LaDuScope® lead to a sensitive and specific confirmation of visible changings in the intraductal system [14]. After confirmation of these results with a larger numbers of cases in prospective studies, complete removal of the duct or the duct system in cases of benign histology could be avoided in the future. After detection of a pathological change, targeted duct excision or a segmental excision can subsequently be performed after marking the region of interest by means of a marking wire that is also introducible via the working channel. A visionary application is the use of auto-fluorescence ductoscopy using a combination of a fluorescent light source (DAFE®System, Richard Wolf Endoskope, Knittlingen, Germany) and a fluorescent ductoscope (PolyDiagnost GmbH, Pfaffenhofen, Germany), which allows switching to autofluorescence mode in addition to white light microscopy, making direct visualization of ductal changes at the cellular level possible and, if necessary, enables the representation of any gradual histological tissue changes on a proportional color scale. Prototypes are already in experimental use [15].

## Perspectives

### *Role in breast cancer risk assessment*

With growing acknowledgement that breast carcinoma occurs in one ductal system [16] it has to consider the breast as a collection of ductal systems. About 75% or more of breast cancers arise in the epithelial lining of mammary ducts from morphologically identifiable precursor lesions. It is possible, that each ductal system represents a different microenvironment [17]. Ductoscopy potentially can detect precancerous lesions or breast cancer before detection by mammography. Ductoscopy, lavage, cytology, and pathologic correlation studies currently are

evolving to address this question [18,19, 20,21]. In particular, the value of ductoscopy as an early detection method for women with an elevated risk of breast cancer and as a supplement to breast cancer screening should be investigated [22].

*Role in breast conservation surgery*

Patients who underwent ductography-guided surgery or any surgical procedure involving a localization study were significantly more likely than patients who underwent central duct excision alone to have a specific underlying lesion identified. Although use of intraductal approaches i.e. cytology from nipple exprimates, ductal lavage and nipple aspirate fluid in diagnosis of intraductal precancerouses or malignant disease has been a subject of great interest, there is no clear evidence that these techniques improve the detection rate. The low sensitivity of all cytology-procedures has been reported [8]. The proportion of diagnostic DCIS is continuously increasing with the implementation of mammography as a screening method. Microcalcification serves as marker lesion although this hardly represents the total extent of the finding. It is problematic to assess the correct extent of the DCIS intraoperatively with it, and to completely resect the tumor. This is similar within the context of breast-preserving operations in cases of invasive carcinoma that are associated with DCIS. Ductoscopy is ascribed a place of value here. Early results have been able to show that ductoscopy could be successfully performed in 74.6% of the cases, leading to a reduction of the excisional margin affected by the tumor from 23.5% to 5.0%. [23]. Kim et al put this into perspective based on their investigation with patients who underwent a partial mastectomy, where the majority of the lesions found ductoscopically were either benign or were already located within the field of resection [24]. As a result, the method requires clarification in further studies.

**Outlook**

Prior analyses of the clinical application of ductoscopy are based on the assessment of its potential as an auxillary diagnostic imaging technique to the standard techniques of galactography and ductal lavage [18, 21, 25,26,27,28,29]. New horizons open in interventional ductoscopy with the introduction of the newest generation of instruments which allow integration of additional instruments. Visually

monitored, targeted intraductal cytological and microbiopsy sampling can be performed via a working channel [14,18]. Open surgical biopsies such as selective duct extirpation for ruling out malignant changes can be avoided through the use of this minimally invasive diagnostic-therapeutic intervention.

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