

Diagnostic and therapeutic value of ductoscopy in nipple discharge and intraductal proliferations compared with standard methods

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Abstract

Background Fiberoptic ductoscopy is a practical and direct approach that allows the visualization of intraductal breast disease. The aim of this study was to assess the efficacy of ductoscopy in the diagnosis and management of intraductal lesions.

Methods Data on 357 ductoscopic investigations from patients with nipple discharge were collected prospectively. Seventy-five patients were diagnosed as having intraductal papillary lesions and these cases were evaluated by final histopathology (55 solitary, 14 multiple papillomatosis, 6 premalignant or malignant lesions). Results of classical diagnostic studies using ultrasonography, mammography, and galactography were compared with those of ductoscopy and pathology.

Results The sensitivities of investigation methods for papillomas in this study were 72 % in ultrasonography, 62.9 % in mammography, 81.4 % in galactography, and 86.6 % in ductoscopy. With ductoscopic papillomectomy

(DP), almost 30 % of patient with solitary papilloma did not require further extensive surgery.

Conclusion Since there is an increased risk of malignancy, surgical excision is recommended for multiple, larger papillomas and for papillomas with atypia and in addition for papillomas where diagnostic tools produce suspicious findings. On the other hand DP is a minimally invasive intervention and can aid in the follow-up of lesions proven to have no atypia.

Keywords Intraductal papillary lesions · Intraductal papilloma · Ductoscopy · Ductoscopic papillomectomy · Nipple discharge

Introduction

Spontaneous nipple discharge (SND) is defined as a non-physiologic unilateral nipple discharge from a single duct unit. It is usually benign, caused primarily by intraductal disorders among which papillary lesions (PL) are frequent [1–3]. Intraductal PL account for 1–2 % of all breast neoplasms and have a wide morphologic spectrum, varying from a single papilloma to a ductal carcinoma in situ (DCIS) and invasive cancer of the breast [2, 4, 5].

When a PL is encountered within the breast ducts, the most important question is whether it is benign or malignant and to decide which treatment modality to use [2]. The general practice in radiologically diagnosed cases is to surgically excise and remove the dilated duct. In general, the risk of cancer development in a solitary papilloma (SP) is approximately 4–11 %, but in cases of atypical papillomas or peripherally located lesions, the risk is higher (33 %). Thus, surgical excision is recommended by most surgeons for all papillomas, even those without atypia [2, 6, 7].

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Fiberoptic ductoscopy is a practical and direct approach that allows the visualization of intraductal disease. It also provides a targeted lavage and aspirate for the cytological analysis of intraductal sampling. Additionally, fiberoptic ductoscopy limits the extent of surgical resection more than a blind retro-areolar resection. Mammary ductoscopy may also play a therapeutic role in the direct removal of the PL with papillomectomy and may provide a basis for office follow-up in selected cases [8, 9]. This study was designed to examine the efficacy of ductoscopy in the diagnosis of intraductal lesions as well as the concomitant advantages in determining the management of such lesions.

Materials and methods

Patients

Following approval by the ethics committee, 335 female patients suffering from SND were assessed using fiberoptic ductoscopy from November 2005 to March 2010. Informed consent was obtained from each patient.

The data were collected prospectively from 357 examinations. Fifty-five ductoscopic examinations could not be completed owing to narrow ducts, duct perforation, or discharge from ectopic nipples. The total success rate for ductoscopy was 302/357 (84.5 %). All ductoscopic procedures were performed by the same surgical team.

Overall, 105 ductoscopic investigations did not reveal any intraductal lesions, and the ductal lavage examinations were reported as a benign cytology. These patients were reassured and monitored in routine follow-up.

Patients with a final pathology of an SP (55 patients) or papillomatosis (14 patients) and patients who had malignant or potentially malignant lesions (6 patients) were recruited into the study. The work-up included a complete history and physical examination, any mammography results within the last 3 months (54 patients), and ultrasonography (US) examinations (present for all 75 patients in the study), as well as ductal lavage cytology. Twenty-eight patients also agreed to undergo galactography.

Procedure

The nipple–areola complex was cleaned with a povidone–iodine solution and alcohol, and the ductoscopic investigation was then performed under local anesthesia using prilocaine HCl. The procedure is not completely comfortable for the patient without analgesia. Application of a local anesthetic allows the easier introduction and manipulation of the endoscope. Although patients with SND may already have a somewhat dilated nipple orifice, an expander system (SoLeX[®]—soft lumen expander) was introduced into the

nipple orifice to reach the lactiferous ducts. A fiberoptic scope was then introduced into the orifice.

Ductoscopic papillomectomy (DP)

The patients who were assessed did not have any questionable lesions, either under the mammographic or US investigations, that required surgery. After completing a successful fiberoptic ductoscopy that did not reveal any additional pathology other than a papilloma or papillomatosis, we endoscopically removed the lesions that had a smooth appearance and fitted into the grasping basket (Fig. 1) [9, 10].

Data and statistical analysis

The prospectively collected data were evaluated retrospectively. To assess the sensitivity of the modalities, the following results were accepted as positive findings: papilloma(s), cystic lesion(s), and ductal ectasia on US; mass, structural distortion, or papilloma on mammography; malignant appearance, papilloma, intraluminal free particles, and ductal wall calcifications upon galactography. An accepted positive result for pathology was the presence of either a papilloma, or multiple papillomas (MP), in the specimen or malignancy. Any intraductal papillomatous lesion or surface abnormalities were considered as positive findings during ductoscopy.

Ductoscopic attempts that were incomplete or ductoscopic findings that did not necessitate further follow-up, but had continuing symptoms that eventually required surgery that resulted in the discovery of papillomatous lesions or malignant–pre-malignant conditions, were considered as false-negative results from the fiberoptic ductoscopy.

Results

Histopathologic investigations of surgically excised or ductoscopically removed lesions after mammary ductoscopic evaluations revealed that 55 patients had an SP and that 14 patients had MP.

Three patients with an SP and 3 patients with MP upon ductoscopy underwent operation, and 1 patient was diagnosed as having invasive breast cancer (IBC), 3 patients had DCIS, and 2 patients had atypical ductal hyperplasia (ADH).

The duration of nipple discharge ranged from 2 to 60 months, with a mean duration of 13.5 months. Thirty-six patients had right-sided and 39 patients had left-sided breast discharge. According to the patients' descriptions, the color of the discharge was dark brown and bloody in 44 patients (58.5 %), yellowish-light brown in 28 patients (37.3 %), or whitish-milky in 3 patients (4 %).

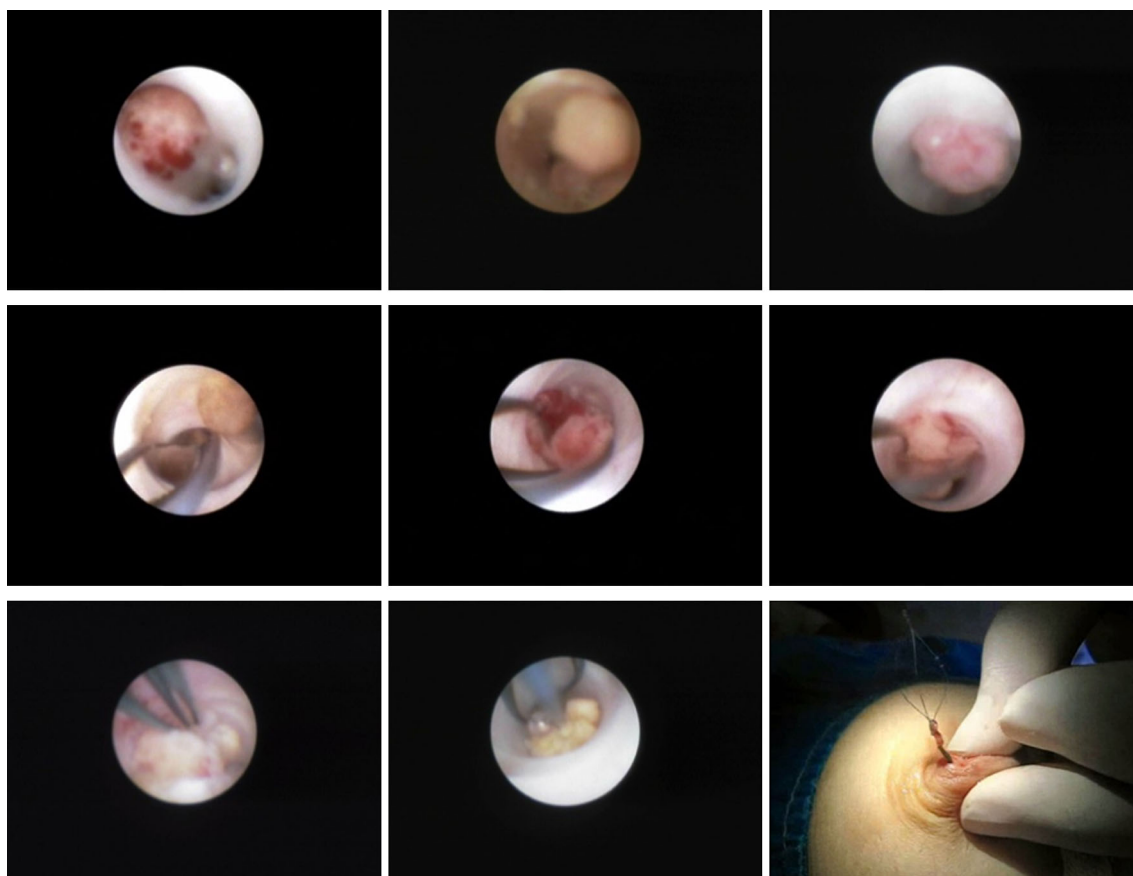


Fig. 1 Papillomas and basket resection

All the data obtained during ductoscopy were recorded. The mean duration for cannulation was 10.7 min (range 2–20 min) and was 29.2 min (range 5–110 min) for the ductoscopic procedure. The intraductal lesions were found within 1–8 cm from the nipple orifice and the mean distance from the nipple to the lesion was 3.1 cm. The patients were followed up between 2 and 53 months (mean 22 months).

Assessment of investigations in patients ($n = 55$) who had SP on final histopathology (Tables 1, 2)

Mammary ductoscopy revealed that 47 of the lesions were SP. Preceding US investigations of these lesions indicated an SP for 12 lesions and MP for one lesion. In addition, 7 patients had normal US results and 11 had ductal ectasia on US. Of 47 lesions, 14 had no intraductal pathology with US, mammography, or galactography, but ductoscopy revealed an SP, and the lesions that were removed by surgery or DP also exhibited an SP on histopathology. For 22 lesions, DP was successful. DP failed in 19 lesions because the basket failed to grasp the large papillomas, and the lesions were removed by surgery. One lesion with a suspicious cytological result, 2 lesions appearing as either

MP or a malignant lesion upon galactography and one lesion reported as MP on US were also removed by surgery. Including 2 lesions that were operated during the initial phases of ductoscopic experience, a total of 25 surgical excisions were applied for the 47 lesions.

Three patients were diagnosed as having MP upon ductoscopy and were operated on. Two patients were diagnosed as having ductal wall irregularities after ductoscopy: one had MP on a preceding US, and another had an SP on mammography. Surgical excision of the lesions revealed that they were SPs with periductal mastitis upon the histopathologic examination. In 2 patients with SP upon US and 1 patient with ductal dilatation upon galactography, mammary ductoscopy did not reveal any pathology, but subsequent histopathologic examination of surgically excised material revealed SPs in the affected ducts.

Assessment of investigations in patients ($n = 14$) who had MP on final histopathology (Table 3)

Mammary ductoscopy showed MP in 8 patients. Two patients had previous US reports showing MP, and both patients had lesions on mammography that were suggestive

Table 1 Solitary papillomas ($n = 55$)

Ductoscopy (55)	US (55)	Mammography (39)	Galactography (19)
SP (47)	SP (12)	Microcalcification (1) Soft tissue mass (5) Distortion (1) Other (1) Normal (2)	SP (1) SP (1) Filling defect (1)
	MP (1) Ductal ectasia (11)	Distortion (1) Normal (1) Soft tissue mass (3) Distortion (2) Dens (3)	SP (1) Int. dens fluid (1)
	Int. dens fluid (1) Normal (7)	Other (1) Distortion (3) Normal (1)	SP (1) Normal (1)
	Other (15)	Normal (2) Soft tissue mass (5) Microcalcification (1) Other (1)	SP (1) SP (3) MP (1)
MP (3)	SP (3)		Malignant (1) SP (1)
Intraluminal irregular mass (1)	SP (1)	Dens (1)	
Wall irregularity (1)	MP (1)	SP (1)	
Failure (3)	SP (2)	Soft tissue mass (1) Distortion (1)	SP (1) SP (1)
	Cystic lesion (1)		Ductal dilatation (1)

SP solitary papilloma, MP multiple papillomas, Int. dens fluid intraductal dens fluid

of an intraductal pathology, such as a soft tissue mass or microcalcifications. Also, one of them had a filling defect upon galactography, whereas the other examination was normal. Two other patients showed an SP upon US, and although their mammography results were normal, the histopathological examinations revealed MP. One of the two patients with ductal ectasia upon US had a filling defect on galactography. One patient with both a normal US and galactography, who underwent a DP because of an SP that had been found during mammary ductoscopy, complained of unresolved nipple discharge after 15 days and had another mammary ductoscopy that showed MP.

Ductoscopy showed an SP in 3 patients, including one who underwent DP again because of an SP and had recurrent nipple discharge 7 months after the initial

procedure. The lesions were removed by surgery, and histopathology revealed MP.

Another patient whose ductoscopy revealed thick, dark intraluminal fluid was still complaining about the recurrent nipple discharge 18 months after the examination. A repeat ductoscopy was performed but did not show any other pathology than the intraluminal fluid, and the patient was operated on to remove the affected duct. The pathology examination revealed MP.

Assessment of investigations in patients ($n = 6$) who had malignant/premalignant lesions (Table 4)

Mammary ductoscopy diagnosed SPs in 3 patients, including a patient who 14 months previously had a

Table 2 Management of solitary papillomas ($n = 55$)

Ductoscopy (55)	Procedure	Reason
SP (47)	DP (22)	
	Surgery (25)	Large papilloma (19)
		Suspect ductal cytology (1)
		Galactography (2)
		Early experience (2)
US (1)		
MP (3)	Surgery (3)	MP
Intraluminal irregular mass (1)	Surgery (1)	Irregularity
Wall irregularity (1)	Surgery (1)	Irregularity
Failure (3)	Surgery (3)	Failure

SP solitary papilloma, MP multiple papillomas, large papilloma failed to fit within the excision basket, early experience surgery performed because experience in ductoscopic papillomectomy was not well developed during the initial phases of ductoscopy

Table 3 Multiple papillomas ($n = 14$)

Ductoscopy (14)	US (4)	Mammography (11)	Galactography (7)
MP (8)	MP (2)	Soft tissue mass	Normal
		Microcalcification	Filling defect
	SP (2)	Normal (2)	
		Fibroadenoma	Distortion
		Duct ectasia (2)	
SP (3)	Normal (1)	Normal	Normal
		SP (1)	Distortion
	Intraductal dens fluid (1)	Soft tissue mass	
Wall irregularity (1)	Duct ectasia (1)	Soft tissue mass	Intraductal papilloma
		Filling defect	
Intraluminal secretion/debris (1)	Duct ectasia (1)	Normal	
Ductal calibration changes (1)	SP (1)		Intraductal papilloma

SP solitary papilloma, MP multiple papillomas

ductoscopic removal of an SP but had microcalcifications on mammography during her routine follow-up. She had her lesion removed by guidewire-assisted excision, whereas the other patients had surgical excisions of their lesions because of the lesions' sizes. Histopathology

revealed DCIS in 2 patients, including the guidewire excised one and an ADH in the other one.

Three patients with MP on ductoscopy were diagnosed histopathologically as having ADH, DCIS and IBC in nearby tissues, respectively.

All patients in the study period with pathologically proven malignancy had their treatment appropriately managed.

Comparisons of all investigation methods with the pathology results are demonstrated in Table 3. The sensitivity of the investigation methods for papillomas was 72 % in US, 62.9 % in mammography, 81.4 % in galactography, and 86.6 % in ductoscopy.

Discussion

PL of the breast account for 1–2 % of breast neoplasia and 10 % of benign breast tumors [5]. PL comprise a wide spectrum of lesions, ranging from benign papillomas to papillary adenocarcinomas. Most papillary breast lesions (PBLs) (75 %) are located within the central part of the breast. Nipple discharge, either with or without blood, is the primary symptom. Discharge is more common (86 %) in centrally located rather than peripherally located diseases (29 %). SP is usually located within the central breast tissue and in patients of middle age (40–50 years of age), whereas multiple papillomatosis are found frequently in the peripheral tissue and in younger patients [6].

Physical examinations, US, and ductography aid in the diagnosis. A papilloma must reach a certain size and be located close to the nipple to be palpable during a physical examination.

Upon radiographic investigation, PBLs show an architectural distortion, abnormal density or mass with or without associated microcalcifications. However, neither mammography nor US can reliably distinguish between malignant and benign lesions [7].

Grunwald et al. [3] found that US sensitivity was higher (sensitivity 67.3 %, specificity 61.5 %) than other investigative methods, including ductoscopy. Although we found that US had a high sensitivity, too, we suspect that this high rate was in part due to broad positive findings criteria (e.g., ductal ectasia and cystic lesions) used by breast non-specific radiologists.

Although it has a poor positive predictive value (16.7 %), mammography is recommended for any patient with an abnormal nipple discharge [11]. Although some reports claim that it has a sensitivity between 37.9 and 59 % [3, 11], these results are debatable. We found a sensitivity of 62.9 %. Generally, studies use BIRADS assessments; we used the image characteristics on mammography so that if there was a possibility of intraductal

Table 4 Malignant/premalignant lesions

Pathology	Ductoscopy (6)	US (6)	Mammography (4)	Galactography (1)	Procedure	Reason
ADH	SP	Normal	Normal	Normal	Surgery	Large papilloma
DCIS	SP	SP	–	–	Surgery	Large papilloma
DCIS	SP	Other	Normal	–	DP + surgery	Routine examinations
DCIS	MP	Normal	Microcalcification	–	Surgery	MP
Inv. Ca.	MP	SP	–	–	Surgery	MP
ADH	MP	Intraductal dens fluid	Soft tissue mass	–	Surgery	MP

ADH atypical ductal hyperplasia, DCIS ductal carcinoma in situ, Inv. Ca. invasive ductal carcinoma, SP solitary papilloma, MP multiple papillomas

proliferations it would result in higher sensitivity results. Reports in the literature indicate that galactography has a sensitivity of 56–73 % [3, 12]. We found it to be higher, at 81.4 %. Because the galactographic investigations were performed in breast-specific departments and all patients were administered both US and Doppler US preceding galactography, these procedures might have increased the sensitivity for PL.

Yamamoto et al. [1] reported that ductoscopy had a 97.5 % sensitivity and a 97.5 % positive predictive value. Grunwald reported a 55.2 % sensitivity, whereas Denewer found a value of 85 % [3, 12]. Vughan et al. discovered that ductoscopy had a 73 % sensitivity for papilloma and 89 % for general assessment [13]. One patient on whom we performed a DP for intraductal papilloma had microcalcifications upon mammography 14 months later. A guide-wire-directed excision of the lesion demonstrated a DCIS. In two more patients, because we could not pass the ductoscope beyond a large SP, the lesions were diagnosed as DCIS for one and ADH for the other, after excision. The treatment protocol for the patients was not changed. We operated on 2 patients because they had an increased ductal diameter and intraluminal debris combined with suspicious finding on both US and mammography. The lesions were determined to be MP. When we added one other patient with ductal wall irregularities and three others for whom we failed to complete ductoscopy, we ended up with 9 patients for whom ductoscopy alone was insufficient for a diagnosis, and the sensitivity was calculated to be 88 %.

In a study concerning how many procedures should be experienced to acquire the skills to perform a successful mammary ductoscopy, Zagouri et al. reported that a mean of 13 procedures should be completed [14]. In our experience, performing a ductoscopic examination is not very difficult but requires a bit of a learning curve such that the number of administrations should be no less than 10 to successfully manage the ductoscope within the mammary ductal system. However, to assess the images obtained during the ductoscopy requires considerably more experience. Multicentric studies should plan to prepare a common

reporting system [15]. Evaluating the images during ductoscopy requires more knowledge and skill than performing the procedure. All patients from the beginning of the ductoscopy were included in this study. We believe that combining other investigation methods will increase the ductoscopic sensitivity. Papillomas that were observed during ductoscopy but that fell into lumen during DP and could not be removed, although pathology did not demonstrate the presence of papilloma, were excluded from the study ($n = 2$).

The conventional treatment of intraductal papillomas is surgical excision of the lesions with surrounding tissue, which provides the diagnosis of possible premalignant and malignant tissues. The majority of SPs are benign, but they can be associated with cytological atypia and may be related to in situ or invasive cancer [5]. Atypical papillomas coexist with carcinomas in 22–67 % of cases. In particular, malignancy is a higher risk factor with MP [16].

Makita et al. reported that solitary polypoid papillomas are correlated with benign PL. Most combined or superficial lesions were breast cancers, and multiple polypoid lesions might be either benign or malignant [17]. Matsunaga et al. reported that the hemispheric and papillary shapes were most common in cases of intraductal papilloma and that the flat protrusion type was most common in cases of carcinoma [18]. Okazaki et al. reported that irregular alterations along the duct wall represent malignancy [19]. Ahmadiyah stated that malignancy was present in 9 of 40 patients (22.5 %) that had papillomatous lesions with a core biopsy demonstrating atypia but in only 1 of 29 patients (1 %) without atypia [7].

Of the 6 patients who had either MP (3 patients) or SP (3 patients), we demonstrated that 4 patients had malignant and 2 patients had premalignant lesions, which resulted in 8 % of the papillomatous lesions carrying a malignancy risk.

It is of primary importance to confirm whether there is atypia in the lesions or not. To do this, it may be appropriate to perform US-guided core biopsies or surgery. With ductoscopy, as Shen et al. reported, 83 % of lesions can be

correctly diagnosed and biopsied [16]. Direct ductoscopic excision of the lesion may be effective for a single papilloma. Matsunaga et al. demonstrated that ductoscopic treatment and intraductal biopsy was possible in 38 of 46 intraductal papillomas [18]. Ductal papillomectomy is a minimally invasive, one-stage further, continuation of this treatment option. It is important to remember that ductoscopic evaluation of the lesions and correct diagnosis are mandatory and that diagnostic accuracy is directly correlated with the experience of the performer and the center.

We removed 24 lesions from 55 patients with ductal SP by DP. One of the patients was diagnosed as having DCIS during follow-up, and another patient who complained of a continued discharge was determined after surgery to have MP. The remainder of the patients did not have further complaints, and no additional treatment was necessary during follow-up. Thus, ductoscopy provided a treatment without surgery in 22 of 75 patients (29.3 %). In particular, the ductoscopic excision of centrally located papillomas and the pathologic confirmation allow the patients to be followed up without undergoing unnecessary surgery.

Okazaki et al. treated intraductal papillomas by laser vaporization through a fiberoptic endoscope [19], which took many hours. In addition, no specimen was available for pathologic examination, so this method cannot replace the basic approach. Ductal marking by ductoscopy, in cases in which surgery is appropriate, and ductoscopy-guided microdocheotomy are more accurate and minimally invasive approaches to treating intraductal lesions [20].

To perform ductoscopy in the appropriate settings, nipple discharge should have presented. It is difficult to find the affected canal and introduce the apparatus into a non-dilated duct in cases of radiologically suspicious papillomas but no nipple discharge. In this case, to include a sufficient volume of tissue so that a correct pathological examination can be performed to exclude malignancy, a US-guided, vacuum-assisted biopsy may be appropriate. It can also provide treatment in addition to diagnosis [5]. An alternative diagnostic tool is the 14G core biopsy [21].

Failure of the ductoscopic visualization of centrally located papillomas is infrequent, but this may be problematic in cases of peripherally located papillomas or multiple papillomatosis. The use of the additional diagnostic tools mentioned above and the addition of a cytological study of the intraductal lavage fluid may resolve this visualization issue. Even with centrally located papillomas, after the removal of the lesion by DP, the duct should be further evaluated for the presence of any other papillomas. It should be kept in mind that the presence of MP is correlated with the presence of premalignant or malignant lesions.

Another important point is that the size and appearance of the papilloma are of primary consideration. Chang et al.

reported that papillomas with a diameter greater than 15 mm radiologically had a higher malignant potential [21]. The ductal wall structure, patient age, previous breast disease, or history of breast malignancy should be interpreted simultaneously to determine the appropriate treatment [8].

In conclusion, mammary ductoscopy is useful in diagnosing intraductal lesions, and its value is augmented when it is combined with other investigative methods. Moreover, it can lessen the requirement of surgery by DP and can lessen the severity of the required surgery by ductoscopy-assisted surgery in the affected duct.

The authors acknowledge that ductoscopy is still considered an investigative method in controlled study groups and is not recommended as a routine diagnostic tool by The National Comprehensive Cancer Network (NCCN). With the expanding use of ductoscopy, however, the authors believe that it can be utilized as an additional tool for the breast surgeon.

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