

# A Clinical Analysis of 640 Inpatients With Pathologic Nipple Discharge

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## Research Article

**Keywords:** Clinical Analysis, Pathologic Nipple Discharge, 640 Inpatients, breast diseases, fiberoptic ductoscopy (FDS)

**Posted Date:** October 12th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-900917/v1>

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# Abstract

**Objective** To discuss the value of early confirmation of breast cancer in patients with pathologic nipple discharge based on double surgical indications under fiberoptic ductoscopy (FDS) followed by staining with methylene blue.

**Methods** From October 2012 to October 2019, a total of 640 inpatients with pathologic nipple discharge from Wuhan University Zhongnan Hospital underwent fiberoptic ductoscopy, followed by injection of methylene blue into the lesional duct through the discharged hole that would be resected as a segment according to the range of the staining duct on the next day. Based on double surgical indications, different findings by fiberoptic ductoscopy were defined as surgical indications, both with space-occupying intraductal lesions scanned by FDS and without space-occupying intraductal lesions but with dark red bloody fluid or yellow serous fluid spillage at the opening of the terminal mammary duct or extensive erosive duct lesions. We retrospectively analyzed the relations between results from fiberoptic ductoscopy and pathologic diagnosis.

**Results** Inpatients with pathological neoplasm accounted for 87.3%(452/518) of the 518 inpatients with space-occupying intraductal lesions scanned by FDS, but the 122 inpatients without space-occupying intraductal lesions only accounted for 28.7%(35/122) of the patients ( $P=0.00$ ). However, patients pathologically diagnosed with breast cancer accounted for 11.8% (61/518) of the 518 inpatients with space-occupying lesions and 10.7%(13/122) of the 122 inpatients without space-occupying lesions ( $P=0.728$ ).

**Conclusions** According to the double standards of surgical indication with or without space-occupying intraductal lesions scanned by fiberoptic ductoscopy, the method of fiberoptic ductoscopy followed by staining of the mammary duct by methylene blue could not only avoid missed diagnosis of breast cancer caused by ductoscopy itself, but also reduce the rate of missed diagnosis on account of inoperative inaccurate resection range, which greatly improved the early diagnosis rate of breast cancer with nipple discharge as the only initial clinical manifestation.

## Background

Pathologic nipple discharge accounts for 10% of breast diseases, and space-occupying intraductal lesions, such as invasive breast cancer, ductal carcinoma in situ, intraductal papilloma, and intraductal papillomatosis, as well as ductal ectasia and acute and chronic inflammation of the lactiferous duct, are common causes of nipple discharge. Pathologic nipple discharge can be divided into watery, serous, and bloody according to the nature of discharge, and serous and bloody nipple discharge indicates the risk of breast cancer.

The initial clinical manifestations of breast cancer are as follows: breast mass, breast calcifications, occult breast cancer, and nipple spillage. The first three manifestations can be diagnosed by color Doppler ultrasound, mammography, magnetic resonance imaging, and core needle biopsy; however,

breast cancer with nipple discharge as the only first clinical manifestation can often not be diagnosed by the location and biopsy through color Doppler ultrasound, mammography, or magnetic resonance imaging due to very small tumor foci. Mammary ductography can assist in the diagnosis of the presence or absence of space-occupying intraductal lesions located in lactiferous ducts, but it cannot accurately guide the target lesion or identify benign and malignant tumors. Cytopathological examination of spillage of the liquid cannot be used as the evidence for the diagnosis of benign and malignant breast tumors, and it also cannot be useful for accurate localization. Fiberoptic ductoscopy (FDS) is a routine examination and diagnostic method for nipple discharge[1]. It is not easy to differentiate intraductal papilloma from breast cancer morphologically through FDS, nor can it distinguish benign lesions from dysplasia. The diagnosis of breast cancer based on the morphology of the lesion often depends on the experience of the operator through FDS. Local biopsy indicates a high false negative rate due to small size of the lesion. FDS provides the basis for surgery in patients with specific space-occupying lesions, which is important for further definitive pathological diagnosis. Since FDS has been applied to clinical practice, the diagnostic rate of early breast cancer with nipple discharge as the only initial symptom has greatly improved, which is also in line with the principle of early detection and early diagnosis of malignant tumor. However, owing to the limitations of FDS itself, the complexity of intraductal lesions, and differences in the operator's experience, it is difficult for clinicians who did not see a clear neoplasm with pathologic nipple discharge to make a surgery decision[2, 3]. This study retrospectively analyzed the results of FDS and postoperative pathological diagnosis in 640 inpatients with pathologic nipple discharge admitted to Wuhan University Zhongnan Hospital from October 2012 to October 2019.

## **Patients And Methods**

### **1.1 Study design**

This study was a pragmatic, single center, prospective clinical trial, and it was approved by the Ethics Committee for Clinical Trials in Wuhan University Zhongnan Hospital. Written consent from inpatients was obtained before enrolment, and inpatients had the right to withdraw from the trial at any time.

### **1.2 Study participants**

Between October 2012 and October 2019, a total of 640 inpatients with pathologic nipple discharge admitted to Wuhan University Zhongnan Hospital were screened in this study.

### **1.3 Study intervention**

A total of 640 inpatients with pathologic nipple discharge were scanned by fiberoptic ductoscopy. According to the traditional surgical indication, 518 inpatients with space-occupying intraductal lesions under FDS underwent resection of the diseased duct and its segment. The other 122 inpatients without space-occupying intraductal lesions under FDS also underwent the same surgical procedure based on another supplementary surgical indication without space-occupying intraductal lesions but with dark red

bloody fluid, or yellow serous fluid at the opening of the terminal duct and Papanicolaou staining grading of nipple spillage of 2 or higher, or extensive erosive foci seen by FDS.

## 1.4 Location approach

The breast was routinely scanned by color Doppler ultrasonography before being examined by FDS, and there were no masses in the breast with spillage. During examination by FDS, the skin was marked according to the direction of FDS and the position of the light source at the bottom of FDS. Double criteria for surgical indications were as follows: 1) space-occupying intraductal lesions seen by FDS; 2) no space-occupying intraductal lesions but with dark red bloody fluid, or yellow serous fluid at the opening of the terminal duct and Papanicolaou staining grading of nipple spillage of 2 or higher, or extensive erosive foci seen by FDS. After FDS examination, the overflow emulsion was inserted through a 4-gauge flat head needle. Further, 0.3–0.5 ml of methylene blue was slowly injected into the lesional mammary ducts for positioning and they were covered with sterile gauze. Mammary duct lesions and segmentectomy were performed on the next day.

## 1.5 Surgical procedure

The patient was operated under local anesthesia 12 to 24 hours after FDS, and the surgical approach was performed using a radial incision without splitting the nipple. During the operation, the diseased duct and its segment were removed along the blue-stained lactiferous duct from the major mammary duct to terminal duct, and the resection depth was the corresponding breast segment into the retromammary space. After locating the lesion in the lactiferous duct with silk markers during the operation, the specimen was sent to the pathology department (Fig. 1, Fig. 2).

## 1.6 Statistical analysis

Continuous datasets were described as mean  $\pm$  SD, and Student *t* test was used for analysis. Categorical datasets were reported as proportions and analyzed by Chi-square test. Statistical analysis was performed with the software SPSS 18.0 (Illinois, USA).  $P < 0.05$  was considered statistically significant.

## Results

### 1.1 Basic characteristics

Patients aged over 40 years accounted for 73.0%(467/640) of the study population. The spillage showed bloody, serous, and watery fluid, and 82.5% (528/640) of patients had bloody and serous fluid. The percentage of unilateral single-hole spillage was about 79.2% (507/640) (Table 1).

**Table 1** Basic characteristics of 640 inpatients examined by FDS

Age (y)	Case (%)	Spillage appearance	Case (%)
≥ 18, < 30	51 (8.0)	bloody	223 (34.8)
≥ 30, < 40	122 (19.0)	serous	305 (47.7)
≥ 40, < 50	288 (45.0)	watery fluid	112 (17.5)
≥ 50, < 76	179 (28.0)	unilateral single-hole spillage	507 (79.2%)

The results of pathological diagnosis were divided into the following three categories: 1) benign breast diseases: mammary duct ectasia with mastitis and intraductal papilloma; 2) precancerous breast diseases: atypical ductal epithelial hyperplasia, radiation scars, and multiple intraductal papillomas (intraductal papillomatosis); 3) breast cancer: ductal carcinoma in situ, invasive ductal carcinoma, and invasive papillary carcinoma.

The following table presents the diagnosis by FDS and the corresponding postoperative pathological diagnosis in the 640 inpatients (Table 2).

**Table 2** Various discoveries by FDS and postoperative pathological diagnosis in 640 inpatients

FDS	Cases (%)	Pathological diagnosis	
		Neoplasm* (%)	Breast cancer# (%)
<b>With space-occupying lesions</b>	518 (80.9)	452 (87.3)	61 (11.8)
<b>Without space-occupying lesions</b>	122 (19.1)	35 (28.7)	13 (10.7)
Dark red bloody fluid at the terminal duct	22 (18.0)	11 (31.4)	5 (38.5)
Yellow serous fluid at the terminal duct	11 (9.0)	8 (22.9)	2 (15.4)
Extensive erosive foci	23 (18.9)	11 (31.4)	6 (46.2)
Extensive floccule and fiber mesh	35 (28.7)	4 (11.4)	0 (0)
Dilating mammary duct and pus	31 (25.4)	1 (2.9)	0 (0)

Space-occupying lesions\*: including intraductal papilloma, intraductal papillomatosis, intraductal carcinoma, invasive papillary carcinoma, and invasive ductal carcinoma

Breast cancer#: including intraductal carcinoma, invasive papillary carcinoma, and invasive ductal carcinoma

The patients with pathological neoplasm accounted for 87.3% (452/518) of the 518 inpatients with space-occupying lesions in the mammary duct scanned by FDS, but 122 inpatients without space-occupying lesions only accounted for 28.7% (35/122) of patients ( $P=0.00$ ). However, the patients

pathologically diagnosed with breast cancer accounted for 11.8% (61/518) of 518 inpatients with space-occupying lesions and 10.7% (13/122) of 122 inpatients without space-occupying lesions ( $P=0.728$ ). In 122 patients without space-occupying lesions, breast cancer was pathologically detected mainly from fluid spillage at the opening of the terminal duct, which had the characteristic of dark red bloody fluid (5/13, 38.5%), yellow serous fluid (2/13, 15.4%), and extensive erosive foci (6/13, 46.2%).

According to the postoperative pathological results, 71 cases were confirmed as multiple intraductal papillomas. In addition, 56 cases with atypical mammary ductal epithelial hyperplasia and 2 cases with multiple intraductal papillomas combined with radiation scars were detected. Nipple spillage occurred again in these two cases after an 8-month follow-up, including 1 case with yellow serous spillage and 1 case with dark red bloody spillage. Space-occupying lesions in the mammary duct were scanned by FDS, and the diagnosis of invasive ductal carcinoma was confirmed by postoperative pathology.

## Discussion

FDS has made it relatively easy to confirm the diagnosis of pathologic nipple discharge, but there are some clinical problems: which patients require surgery? How to accurately locate and resect the lesion in patients requiring surgery, and how to accurately sample and diagnose the lesion after resection? In view of the above problems, most experts preferred to decide upon the operation after FDS examination has revealed obvious intraductal space-occupying lesions; some experts decided upon the operation by classifying intraductal elevated lesions[4, 5]. The majority of these lesions were concentrated in the main duct as well as in grade 1 to 3 ducts, and these space-occupying lesions were easily detected by FDS. However, most malignant breast tumor originated from small- and medium-sized ducts and terminal ductal lobular units, which were beyond the scope of FDS[6]. Therefore, the diagnosis was easily missed by FDS alone. At the same time, even if FDS detected space-occupying lesions without accurate localization, the extent of intraoperative resection and sampling in the pathology department were difficult; this could cause missed diagnosis.

After localization by methylene blue staining after FDS examination, not only could the lesion be accurately located, but also the pathologists could accurately perform sampling according to the staining of mammary ducts at all levels, so that some patients who were not detected by FDS but actually had space-occupying lesions in the small- and medium-sized mammary ducts underwent surgery; thus, expanding the surgical indications. In this study, among the 122 patients with nipple discharge without any obvious space-occupying lesions in the lactiferous duct, such as extensive intraductal erosions, dark red bloody fluid or yellow serous fluid spillage at the opening of the terminal duct, extensive floccules, and fibrous network, 10.7% were diagnosed as having breast cancer by postoperative pathology, and there was no statistically significant difference in the detection rate of breast cancer compared to those with obvious space-occupying lesions in the lactiferous duct by FDS. This indicated that 10.7% of the patients who did not have space-occupying lesions in the mammary duct but had dark red bloody fluid or yellow serous fluid overflow or extensive erosion at the opening of the terminal duct would not be diagnosed as having breast cancer due to the absence of space-occupying lesions in the mammary duct by FDS.

Therefore, on the basis of our double standards of surgical indication by FDS, the missed diagnosis rate of traditional surgical indication according to FDS could be further reduced.

Multiple intraductal papillomas, also known as papillomatosis, often occurred simultaneously in small ducts and terminal ductal lobular units, were prone to recurrence after surgery, and were prone to dysplasia and carcinogenesis. Mastectomy was feasible after the first operation in patients with dysplasia or radiation scars, and in patients with recurrence, it was necessary to guard against malignant transformation into breast cancer[7]. In this group, two patients with multiple intraductal papillomas and radiation scars had malignant transformation into breast cancer eight months after the first operation.

Patients with no neoplasm seen by FDS often do not undergo surgery; thus, the false negative rate cannot be judged. In this study, 13 of the 122 patients with no obvious neoplasm seen by FDS were diagnosed as having breast cancer by postoperative pathology. These 13 patients had no neoplasm detected by FDS and could be regarded as patients with missed diagnosis by FDS. For those who had no neoplasm and had less spillage at the opening of the terminal catheter under FDS, it was likely that only clinical observation without surgery would be performed. Obviously, such breast cancer patients would be missed; thus, the actual diagnostic sensitivity for breast cancer would be less than 67.6%. The possible reasons for missed diagnosis were as follows: 1) complexity of the anatomy of the lactiferous duct system; 2) influence of the predilection site of breast cancer; 3) the limitation of fiberoptic ductoscopy itself; and 4) inconsistency in the operator's experience and endoscopic diagnostic criteria. For objective reasons, such as the complexity of lactiferous duct branches, the predilection site of breast cancer, and the limitation of fiberoptic ductoscopy itself, the localization and surgical methods in this study could be used to minimize the missed diagnosis rate of breast cancer, while for subjective reasons, such as the operator's experience, it can be repeatedly learned and summarized, especially to summarize the significance of the surgical indication criteria for patients without obvious space-occupying lesions under FDS. For example, in patients with extensive ductal erosion but no obvious space-occupying lesions, an experienced operator could diagnose this entity as highly suspected breast cancer.

Although mastoidectomy offered a minimally invasive modality, it was limited to when intraductal tumor foci were visible by FDS[8, 9, 10]. According to our experience, in patients without obvious space-occupying lesions by FDS, surgical treatment should be considered in the following situations: 1) intraductal papillomatosis of the breast was often associated with intraductal carcinoma, and terminal ductal hemorrhage or yellowish serous fluid could be seen in both breast cancer and intraductal papillomatosis; thus, surgical treatment should be performed in patients with unexplained hemorrhage or yellowish serous fluid in the distal duct; 2) in patients with severe intraductal inflammation and no clear space-occupying lesions, the lesion might be hidden under inflammatory floccules, and surgery was recommended; 3) active surgery should be performed in patients with extensive erosion of the ductal wall without clear neoplasm. In patients with pathologic nipple discharge, especially in those with no mass seen on physical examination and color Doppler ultrasound and negative mammography examination, FDS combined with methylene blue staining localization provided a method for early screening of breast cancer[11, 12].

# Conclusion

FDS combined with the methylene blue staining localization method was simple and feasible. According to the double criteria of determining surgical indications with or without neoplasm by FDS, the missed diagnosis of breast cancer by FDS could be avoided. At the same time, this localization method could reduce the missed diagnosis of breast cancer due to the inaccurate resection range during surgery. Therefore, it was an early diagnosis mode of breast cancer with nipple spillage and with no mass and negative mammography examination as the clinical manifestations.

# Declarations

## Conflict of interest

The authors declare no conflict of interest.

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## Figures



Figure 1

Stained lactiferous ducts with lesion



Figure 2

Neoplasm inside the stained lactiferous ducts