

# Intraductal Breast Cytology and Biopsy to the Detection and Treatment of Intraductal Lesions of the Breast

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## 1. Introduction

Detection of breast cancer at an early stage is the most effective approach to decrease mortality, and bloody nipple discharge is an important clue to detect ductal cancer. In case of bloody nipple discharge the intraductal approach is a minimally invasive method to detect intraductal lesions. The intraductal approach does not destroy the ductal structure and does not cause needle tract dissemination. Though bloody nipple discharge is a significant clue in the detection of ductal carcinoma of the breast that do not display any tumor images and calcifications, the sensitivity of discharge cytology is not sufficiently high. Mammary duct endoscopy (MS) has been employed to detect intraductal lesions and MS yields both an optical image and biopsy. Intraductal breast biopsy (IDBB) and direct ductal lavage cytology were used to obtain pathological and cytological diagnoses in intraductal lesions with nipple discharge. The usefulness of MS, IDBB and direct ductal lavage cytology for intraductal lesions, with particular regard to differential diagnosis of ductal carcinoma and intraductal papilloma.

## 2. Materials and methods

Four hundred and sixty two MS procedures were performed in 348 patients who had nipple discharge but no overt mass between October 1993 and September 2009 at Tokyo Metropolitan Cancer Detection Center (October 1993 to December 2002), Minamiaoyama Breastopia Clinic (April 2003 to June 2006), and Tokyo Medical University Hachioji Medical Center (November 2006 to Sep 2009). In these 348 cases, nipple discharge was the primary diagnostic finding and there were no specific findings on mammography or sonography. Of these 348 patients, 81 patients with breast cancer and 163 patients of intraductal papilloma (IDP) were diagnosed pathologically. The other 104 patients were diagnosed as benign with cytology and followed clinically for more than 5 years.

In these 348 patients, mammography, ultrasound and cytology of nipple discharge were performed routinely. Nipple discharge was examined with a glass slide touching the nipple directly and immediately immersed into 90% alcohol as a routine cytology method (touch method). The presence of a cluster of ductal cells was taken to indicate the presence of an intraductal papillary lesion. Nipple discharge was collected in a narrow vessel containing

cell fixation liquid three times a day for three days at home in 70 breast cancer patients (collection method). This collection method was performed to obtain much cytologic specimen. Galactography was done if a papillary lesion was suggested by cytology or if there was an obvious bloody background. MS was indicated based on the galactographic findings and the cytological findings

### 2.1 Intraductal approach to the detection of intraductal lesions

At the time of the MS procedure, 4 % procaine was sprayed on the nipple. After injecting 1% procaine into the duct, the nipple orifice and ductal sphincter were dilated with a tear duct bougie. MS measuring 0.72 mm in outer diameter (Fiber Tech Company, Tokyo, Japan) were used. Intraductal breast biopsy (IDBB) under mammoscopic observation was performed in 226 intraductal papillomas (in a total of 128 patients) and in 38 ductal carcinomas (in a total of 35 patients). In most cases, IDBB was performed using a metallic tube with a side aperture near the tip (JN Biopsy Needle, Hakko Company, Tokyo, Japan). In directed ductal lavage cytology, an epidural tube was used. After MS, the tube was inserted and advanced into the ductal branch where the papillary lesion was observed. When the lesion could not be observed by MS, emanation of bloody discharge from periphery suggested the direction of the lesion. We usually insufflated air to observe the ductal lumen by MS. Since after MS the lumen of the duct was enlarged, making it easy to selectively advance an epidural tube into an abnormal branch. When the lesion could not be observed by MS, emanation of bloody discharge from periphery suggested the direction of the lesion. An epidural tube, a 1 ml syringe of saline, and a 20 ml syringe were connected with a three-way valve. First the valve was turned to a 1-ml saline syringe and negative pressure was applied using a 20-ml syringe. Then the valve was turned to a 20 ml syringe and saline was sucked into the duct using the negative intraductal pressure. Then the valve was turned to a 1-ml syringe and intraductal fluid was collected into a 20-ml syringe. These procedures were repeated several times while changing the saline solution. Directed ductal lavage cytology was performed in this way in 38 patients. The cytologic findings were assessed by both cytology technician and a pathologist. These MS, IDBB and lavage procedures were performed in outpatient clinics..



Fig. 1. Mammary duct endoscopy (MS) and biopsy needle

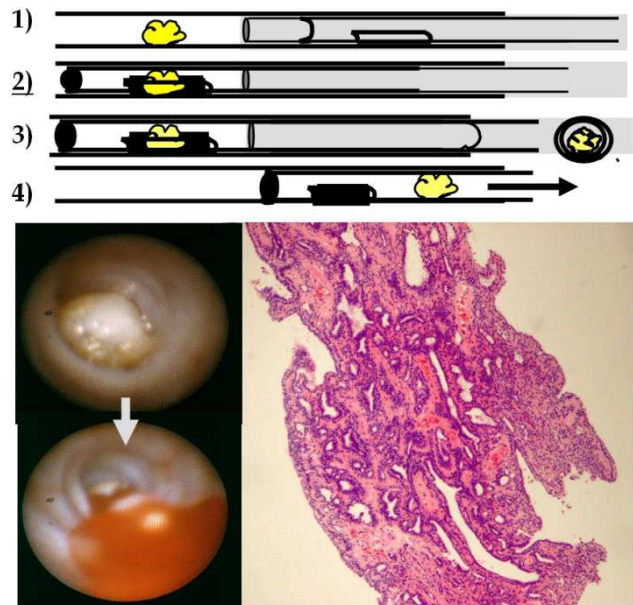


Fig. 2. Method of intraductal breast biopsy (IDBB) 1)The MS is covered with a metallic tube with a side aperture near the tip and the MS with a metallic tube is inserted into the mammary duct. 2) The metallic tube is advanced along the outside of the mammoscope to the intraductal mass and the mass is entrapped in the tube through a side aperture under observation by the MS. 3)Then the metallic tube was turned to cut off the intraductal mass. 4) Afterwards, the MS is removed and then the tissue piece within a metallic tube is collected by manually applied negative pressure. The specimen was diagnosed as IDP.

## 2.2 Assessment of ductal cytology and IDBB

The cytologic findings were classified into 4 categories; cancer, suspected cancer, suspected benign papillary lesion with the presence of a ductal cells cluster without atypia, and considered normal without any cluster. Cancer and suspected cancer categories were defined as positive findings. The diagnostic accuracy of these three methods , i.e. touch, collection, and directed ductal lavage were compared to IDBB in detecting malignancy. The therapeutic effect of IDBB for intraductal papillomas was also studied in 73 patients followed for more than 5 years (consisting of a total of 78 ducts).

## 3. Result

### 3.1.1 Visualization of intraductal lesions with MS

The normal mammary duct wall is white or light pink in color. The wall is smooth and lustrous with discharge and capillary veins might be observed. Of 81 breast cancer lesions, intraductal lesions were observed in 50 (61.7%) by MS. Then feature of MS were classified into three types; hemispheric, papillary and flat, irregular ductal wall. The hemispheric and papillary shape were most common in intraductal papilloma and the flat irregular pattern was most common in ductal carcinoma. In the other 26 lesions, bloody secretion emanating

from the periphery suggested the presence of ductal carcinoma were observed. So the lesional ductal branches were recognized in 76/81 cases (93.8%). Five carcinoma lesions could not be recognized by MS because the MS could not be advanced into the peripheral duct.



Fig. 3. Shape of intraductal lesions observed with MS. 1) Left; carcinoma, Right; IDP 2) Left; IDP, Right; cancer 3) Both cancer

Shape	total	solitary	multiple
hemispheric	6	4	2
papillary	6	4	2
flat irregular and mixed	38	16	22

Table 1. Recognition of intraductal lesions of cancer with MS

### 3.1.2 Ability of IDBB in obtaining specimen

IDBB was performed 38 times in 35 of 47 cancer cases in which intraductal lesions were observed. Of the 35 cases, IDBB yielded diagnostic specimens in 29 cases (82.9%) but in the remaining 6 there was insufficient material for diagnosis. With IDBB it was difficult to collect diagnostic specimens in some carcinoma cases because the lesion located periphery and low tissue cohesiveness compared with intraductal papilloma. IDBB provided a definite diagnosis of carcinoma in 15 of the 35 (42.9%), while 9 lesions were in the carcinoma suspected category (atypical papillary lesion; 25.7%) and 5 were diagnosed as intraductal papilloma (14.3%). In 4 of 5 cases which were misdiagnosed as intraductal papilloma, coexistence of intraductal papilloma and carcinoma were confirmed on the resected specimen. In these 35 cases, the sensitivity of IDBB was 68.6% (24/35), directed ductal lavage cytology was 82.8% (29/35), and conventional touch cytology was 37.1% (13/35). The sensitivity of IDBB was 82.8% limited in successful IDBB cases (24/29) and it was equal to directed ductal lavage cytology. IDBB was performed in 226 IDP lesions from 128 patients. The diagnostic specimen was obtained in 197 of 226 IDBB (87.1%) and the successful IDBB yielded IDP in all 197 cases.

### 3.1.3 Comparison in detecting cells cluster between each method of cytology with regard to diagnostic cell cluster

Touch cytology yielded no false positive result among the 348 patients. Twenty eight of 81 cancer cases were diagnosed as cancer or cancer suspected category. The sensitivity of touch cytology was 34.6% (28/81) and specificity was 100%. The presence of a cluster of ductal cells was the clue to take diagnostic procedure to detect intraductal papillary lesions and the

method to obtain a lot of cells must be considered. Collection method and direct ductal lavage method were performed to obtain much cytologic specimen.

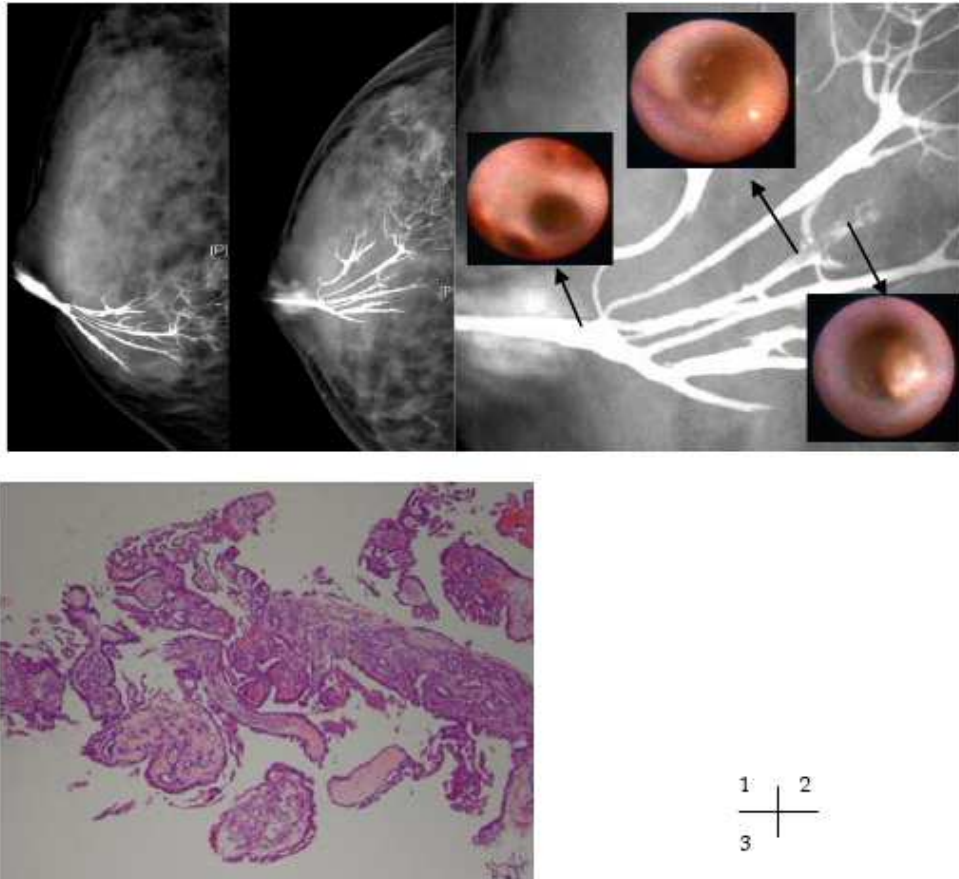


Fig. 4. A 27 years old woman with right bloody nipple discharge. 1) Galactography showed multiple filling defects in proximal branches. 2) MS views corresponding to galactography were shown. There was intraductal papillary masses at the third bifurcation. 3) IDBB was performed to the papillary lesion at the third bifurcation and presence of large stalks and biphasic structure with mioepithelial cells were revealed. These character indicated IDP.

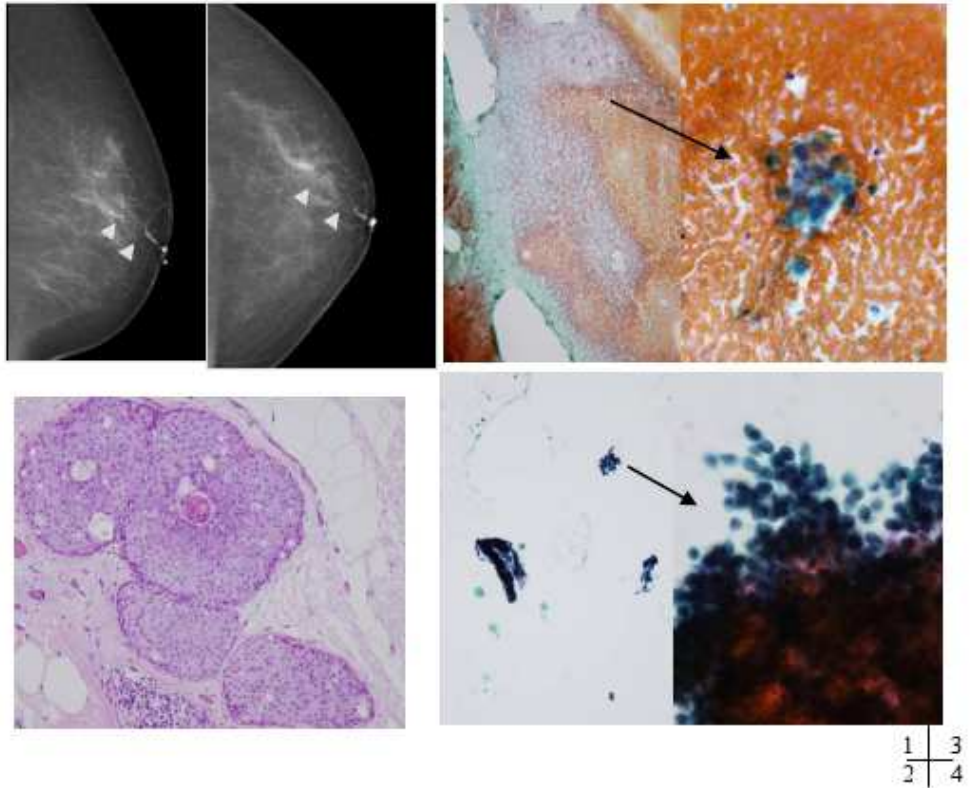


Fig. 5. A 78 years old woman with left bloody nipple discharge. 1) Galactography showed irregularity and defect of duct (arrow heads). 2) Excisional biopsy revealed DCIS, extended 8 mm in maximum diameter with comedo~solid intraductal component. 3) Only a few cells clusters without atypia were recognized in touch cytology and diagnosed as benign. 4) MS could not be advanced into the lesion because of the narrow ductal caliber and directed ductal lavage cytology was performed. A diagnostic large papillary cells clusters were obtained by directed ductal lavage cytology and could be diagnosed as cancer.

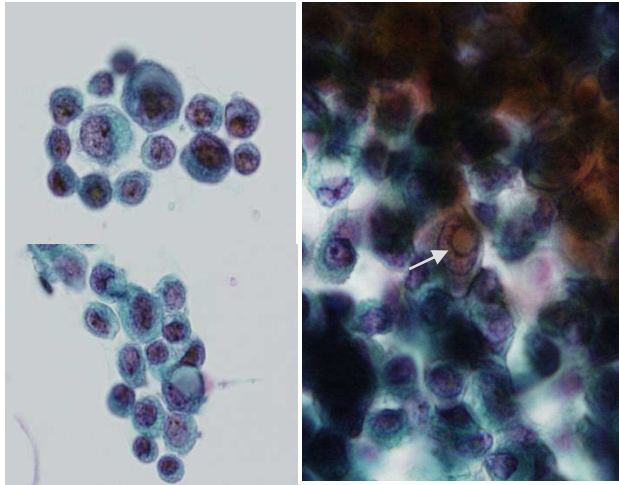


Fig. 6. Magnified view of directed lavage cytology. High NC ratio atypical cells, uneven distribution of nucleus, intranuclear enclosed body (arrow), and lack of cohesiveness were recognized.

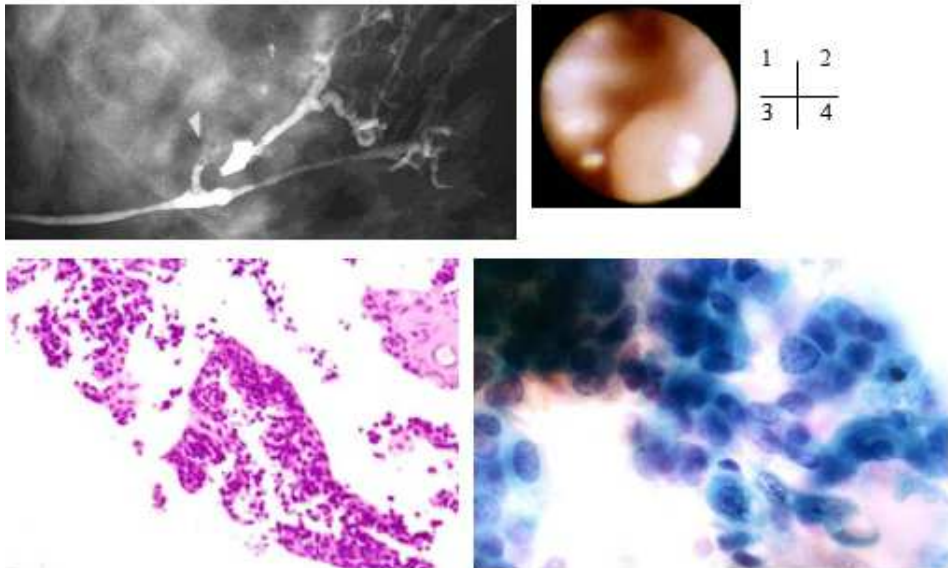


Fig. 7. A 35 years old woman with right bloody nipple discharge. 1) Galactography showed irregularity and defect at second branch (arrowhead). 2) Hemispheric intraductal mass and flat irregularity were observed with MS. 3) IDBB suggested atypical papillary lesion. 4) Ductal lavage cytology suggested atypical papillary lesion. Excisional biopsy was recommended for definite diagnosis but was denied. After 3 years, breast lump occurred at this area and it was proven to be cancer.

### 3.2.1 Comparison of the accuracy in detecting malignancy

The sensitivities of the cytologic methods differed somewhat. The collection method was applied in 243 benign cases and only one case was converted from the benign category on touch cytology to the cancer suspected category by the collection method. The rate of atypia (involving the suspicious category) increased from 35.0% in touch cytology to 37.1% in collection cytology and 84.2% in directed ductal lavage cytology. Collection and directed ductal lavage cytology were not performed when cancer was already diagnosed by a prior modality. The presence of a cluster of ductal cells indicated the presence of papillary lesion. Of 38 cases of cancer lesions, papillary clusters were detected in 37 by directed ductal lavage, (sensitivity in 97.4%). The remaining case had a mucinous intraductal component and the lesion was located beyond second bifurcation and about 4 cm length from nipple (Table 2). In 35 cases who underwent IDBB, the rate of atypia was 68.6% (24/35) in IDBB, 82.8% (29/35) in directed ductal lavage cytology, and 37.1% (13/35) in conventional touch cytology.

Method	n	carcinoma	Suspicious		benign normal
			atypical papillary	benign papillary	
Touch	81	16 19.8%	12 14.8%	37 45.7%	16 12.3%
Collecting	70	16 22.8%	10 14.2%	24 34.3%	20 28.6%
Lavage	38	21 55.3%	11 28.9%	5 13.2%	1 2.6%
IDBB	35	15 42.9%	9 31.4%	5 14.3%	insufficient; 6

Table 2. Sensitivity of cytology and IDBB in detecting cancer

### 3.2.2 Sensitivity of cytology and localization of the lesions

The locations of the lesions were described as in the thoraco-bronchial tree, as the number of divergences of ductal branches approached from the nipple orifice. When cancer was recognized in a major duct (nondivergent), sensitivity of touch cytology was 73.3% (11/15). The sensitivity was 35.0% (7/20) in the first divergent branch, 35.3% in the second branch and 35.8% in the third branch and beyond. The sensitivity was extremely high only when cancer was present in a major duct (Table 3). The sensitivity of directed ductal lavage cytology was also studied in relation to the location of intraductal cancer. The sensitivity rates were 85.7% for lesions in a major duct, 75.0% for those in the first bifurcation, 72.7% beyond the second bifurcation, and 100% for those beyond the third bifurcation. The sensitivity of directed ductal lavage cytology did not depend on the location at the number of divergences of ductal branches (Table 4).

There were 15 cases in which coexistence of benign and malignant papillary lesions in the same duct-lobular unit was confirmed pathologically by sequential section slices at 3 mm of the surgically resected specimen. In these 15 cases, papillary lesions in which severe atypia was not recognized and myoepithelial cells remained in the side of proximal to the nipple orifice and ductal cancer was present in a more internal location. Coexistence of intraductal papilloma in a major duct and ductal cancers separately in a peripheral duct were recognized in 4 cases. In these 4 cases, IDBB revealed IDP in a major duct. Multiple foci of



benign and malignant papillary lesions beyond the first bifurcation were recognized in 11 cases. In these 15 cases, 3 cases were positive by touch cytology (20.0%). Collection cytology was performed in 14 cases and 5 cases were positive (35.7%). Directed ductal lavage cytology was performed in 11 cases and 5 cases were positive (45.5%). IDBB was performed in 14 of these 15 cases. The coexistence of papilloma and carcinoma was confirmed by the first IDBB in a case (Fig. 9). Of these cases, the diagnosis obtained by IDBB was definitely cancer in 2, atypical papillary lesions in 4, intraductal papilloma in 5, and insufficient material in 3. In a case of a 31-year-old woman, IDBB was performed 4 times during 8 months and finally atypia was diagnosed (Fig. 10,11).

Bifurcation	diagnosis of cytology			
	cancer	atypia	benign	
			cluster+	cluster-
0	5	6	3	1
1	4	3	9	4
2	3	3	9	2
3~	4	0	16	9
<b>Total</b>	<b>16</b>	<b>12</b>	<b>37</b>	<b>16</b>

Table 3. Localization of intraductal lesions and sensitivity of touch cytology

Bifurcation	diagnosis of cytology			
	cancer	atypia	benign	
			cluster+	cluster-
0	3	3	1	0
1	4	2	2	0
2	4	4	2	1
3~	10	2	0	0
<b>Total number</b>	<b>21</b>	<b>11</b>	<b>5</b>	<b>1</b>

Table 4. Localization of intraductal lesions and sensitivity of ductal lavage cytology

### 3.2.3 Therapeutic effect of IDBB

Of 218 IDBB for 128 IDP patients, 197 specimens were diagnostic materials. There were 73 patients with IDP (composing a combined total of 78 lesions) who were followed for more than 5 years. Of these 73 patients, 39 experienced cessation of nipple discharge after the first IDBB and another 13 experienced cessation of nipple discharge after a subsequent IDBB. Thus the nipple discharge was halted in a total of 52 patients (71.2%). In another 5 patients, the bloody background and papillary clusters of ductal cells were not recognized after IDBB and intraductal masses could not be detected on either ductography or MS. Thus the therapeutic effectiveness of IDBB was recognized in 57 of 73 intraductal papilloma patients (78.1%). There was a tendency for lesions in the effective IDBB to be located in a major duct and hemispheric or papillary shape. There was less therapeutic efficacy of IDBB in flat lesions and in multiple nipple discharge orifices and intraductal lesions.

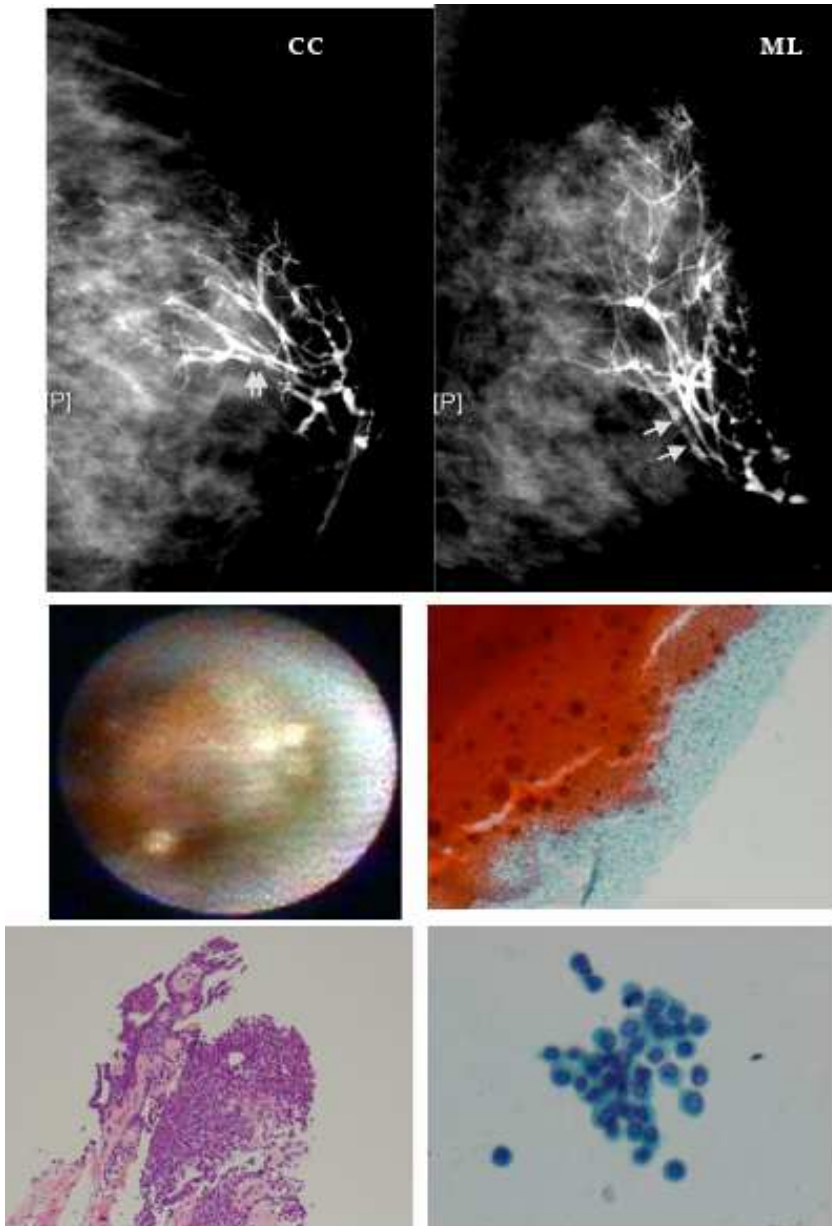


Fig. 8. A case of ductal cancer; Ductography showed defect beyond third bifurcation of the duct (upper, arrows). The hemispheric intraductal mass was detected by MS (middle, left). There was no atypical cell obtained by touch cytology (middle, right) but carcinoma was indicated by direct ductal lavage cytology and IDBB (lower left; IDBB and right; lavage cytology).

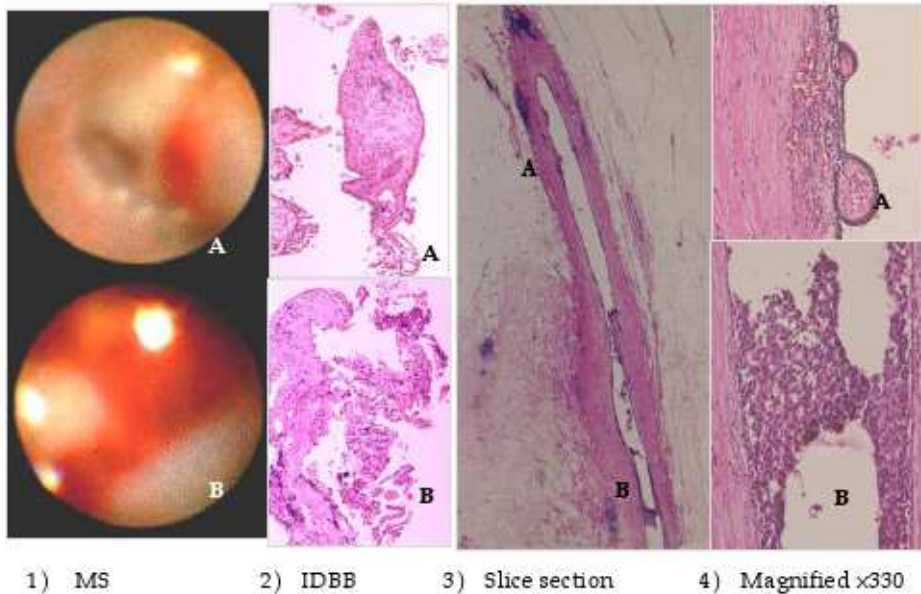


Fig. 9. 1&2) Yellow hemispherical and red papillary intraductal masses (A) were recognized in a proximal duct and were diagnosed as IDP by IDBB. A whitish-yellow flat mass coated with bloody discharge (B) was recognized distal to the site shown in A. This was diagnosed as ductal carcinoma by IDBB. 3) The slice section just on the line of the major duct in the direction of the nipple showed intraductal papilloma in the proximal duct (A; side central to the nipple) and ductal carcinoma in the distal duct (B). 4) The epithelium of the intraductal papilloma was abraded and was mechanically exfoliated by IDBB (A; HE stain, X330). Ductal cancer was recognized in the distal duct (B; HE stain, X330). In this case, the IDP was located at the proximal portion and the breast cancer was located at the distal portion to the IDP. Cancer was overlooked by discharge cytology alone. The value of MS lay in observation of the peripheral lesion by inserting the MS to the periphery beyond the proximal lesion after removing the proximal mass and biopsying the distal lesion and sampling with directed ductal lavage cytology.

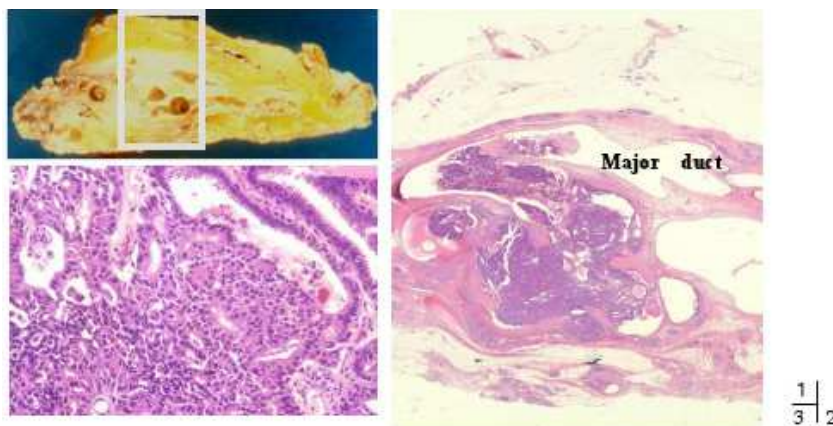


Fig. 10. 1) Section slice of intraductal lesion. The square surrounded part was the lesion concerned. 2) The slice section of major duct to the periphery where the intraductal papillary lesion existed. 3) Magnification of the area of intraductal lesions in which coexisted biphasic (upper area) and lack of biphasic structure (lower area).

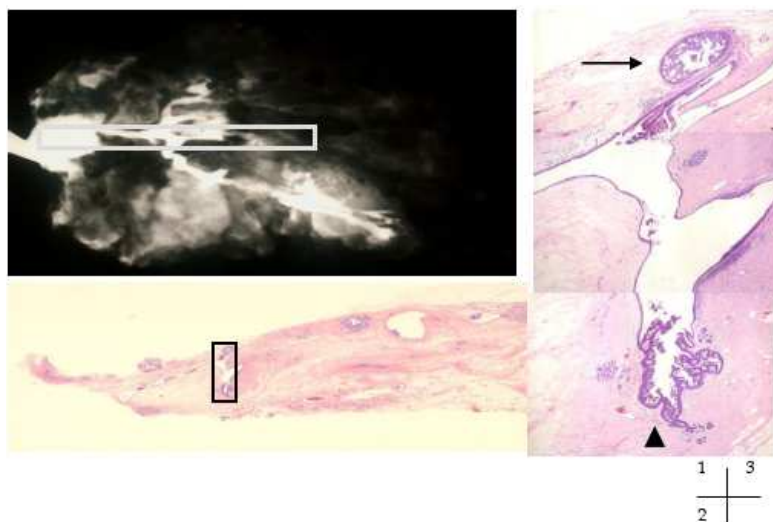


Fig. 11. 1) Specimen galactography. A 24 gage cannula was inserted into nipple orifice and the dye (methylene blue) was injected during excisional biopsy (microdochectomy). After excision, specimen galactography was performed. 2) The slice section just on the line of the major duct in the direction from specimen galactography (the square surrounded part of the specimen 1). There were multiple intraductal lesions in periphery (the square surrounded part). 3) Magnification of the area of intraductal papillary lesions. The myoepithelial cells were seen in the lesion shown with arrow head but were few in the lesion shown with arrow. The structural and cellular atypia were observed in the latter lesion. There was coexisted biphasic (arrow head) and lack of biphasic structure (arrow) and diagnosed as ductal cancer.

#### 4. Discussion

Surgical excision previously was the only method available for pathological diagnosis and treatment for nipple discharge. MS contributes not only to the diagnosis of cases of nipple discharge, but also is of benefit in the treatment of IDP. The development of the MS has opened a new era in the diagnosis and treatment of secreting IDP by IDBB under direct observation. The MS helps to eliminate unnecessary surgical excision for benign lesions. Surgical excision has now been superseded by IDBB under endoscopic observation for the treatment of solitary IDP. In the previous report, neither the amount of specimen collected nor the amount of residual lesion after IDBB had a significant influence on the effect of treatment for nipple discharge. Some morphological changes after MS were also reported. It was speculated that the necrosis of IDP could be caused by the biopsy procedure. One factor related to the poor therapeutic effects of IDBB for IDP is lesion multiplicity. It was suggested that there was a tendency towards multifocal generation of intraductal papillary lesions in cases with multiple nipple orifices. Duct-lobular unit distribution patterns are infinite and all mammary ductal branches could not always be visualized by galactography. When IDP was located in a branch diverging at a sharp angle, only the proximal margin in a major duct could be detected by MS.

MS was also effective in cases of coexisting intraductal papilloma and carcinoma in the same duct-lobular unit. In these cases, the IDP is usually located at the proximal portion of the duct-lobular unit, and the breast cancer could be overlooked by discharge cytology and galactography. The value of MS in such cases lay in observation of the peripheral lesion by inserting the MS to the periphery beyond the proximal lesion or removing the proximal mass and biopsying the peripheral lesion. Thus MS finally contributed to the pathological diagnosis of intraductal masses with limited invasiveness compared with excisional biopsy. Although IDBB is a definitive method for cancer diagnosis but the drawback of IDBB is the difficulty of obtaining diagnostic specimen. In addition, pathological diagnosis of intraductal papillary lesions was difficult in IDBB even with sufficient materials. Because of these technical defects of IDBB, the most reliable method in detecting ductal cancer was turned out to be directed ductal lavage cytology. The usefulness of cytologic specimens of nipple aspirate fluid has been reported in the evaluation of prognostic and predictive factors of breast cancer. Fluorescence in situ hybridization of ductal lavage samples was reported to be more effective in identifying malignancy. Ductal lavage was reported to detect intraductal breast cells 3.2 times more frequently than nipple aspiration but the actual cytological materials are very similar to those obtained by nipple aspiration devices. Directed ductal lavage cytology was complementary and helps to obtain most sensitive results, detecting intraductal papillary lesions in 97.4%. In only one case of mucinous intraductal component, was mucous fluid thought to be a negative factor for collecting peripheral ductal cells by lavage.

At present, the terminal duct-lobular unit from which carcinoma originates cannot be observed with MS. But MS contributes to the diagnosis of intraductal lesions through observation of the proximal portion of intraductal carcinoma and to in obtaining specimens. MS contribute the high sensitivity in cancer detection by directed ductal lavage cytology by selecting the abnormal branch to which the tube is advanced. The MS can be an important adjunct in breast-conservation management. Multiple intraductal lesions in peripheral ducts suggest cancer development. Surgical excision should be performed in patients with atypical papillary lesions revealed by IDBB or directed ductal lavage cytology. There were 2

patients in whom carcinoma was detected 3 years after IDBB showed no malignancy. Follow-up at a 6-month interval with ultrasound, checking for nipple discharge by palpation and annual mammography is considered appropriate instead of excision in patients with multiple lesions in peripheral ducts, when ductal lavage cytology showed benign result. The patients without surgical resection after IDBB showed no malignancy should be followed up as long as possible in principle (mean follow-up interval was 74.2 months; 36 to 204 months in our survey).

Cancer arises more frequently in the duct-lobular unit with bloody nipple discharge and bloody nipple discharge is thought to be an independent risk factor. Even in cases of nipple discharge with no atypia the associated relative risks for breast cancer increased compared with women who have no nipple discharge. Clinical follow-up was thought to be important to the patients with bloody nipple discharge. In previous study, carcinoma was detected in 3 patients during follow-up among 89 patients with negative MS and cytology. In these 3 patients, nipple discharge ceased after MS and carcinomas were detected at the different areas from previous galactography.

## 5. Conclusion

Directed ductal lavage cytology was the most sensitive method in detecting malignancy. MS and IDBB were benefit in the treatment of intraductal papilloma.

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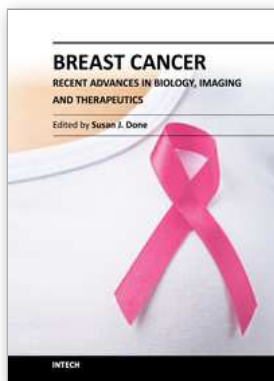
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## **Breast Cancer - Recent Advances in Biology, Imaging and Therapeutics**

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In recent years it has become clear that breast cancer is not a single disease but rather that the term encompasses a number of molecularly distinct tumors arising from the epithelial cells of the breast. There is an urgent need to better understand these distinct subtypes and develop tailored diagnostic approaches and treatments appropriate to each. This book considers breast cancer from many novel and exciting perspectives. New insights into the basic biology of breast cancer are discussed together with high throughput approaches to molecular profiling. Innovative strategies for diagnosis and imaging are presented as well as emerging perspectives on breast cancer treatment. Each of the topics in this volume is addressed by respected experts in their fields and it is hoped that readers will be stimulated and challenged by the contents.

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