# Endoscopic Appearance and Clinicopathological Character of Breast Cancer

DAIGO YAMAMOTO[1], YU TSUBOTA[1], HIDEYUKI YOSHIDA[2], SAYAKA KANEMATSU[2], NORIKO SUEOKA[1], YOSHIKO UEMURA[3], KANJI TANAKA[4] and A-HON KWON[1]

[1]*Department of Surgery, Kansai Medical University, Hirakata, Osaka, Japan;*
[2]*Department of Surgery, Kansai Medical University, Kohri, Osaka, Japan;*
[3]*Clinical Pathology, Kansai Medical University, Hirakata, Osaka, Japan;*
[4]*Breast Unit, Ribbon-rose Clinic, Osaka, Japan*

**Abstract.** *Background: The Japanese Association of Mammary Ductoscopy proposed a classification system based on the objective endoscopic appearance of intraductal lesions. This system includes four categories: solitary polypoid, multiple polypoid, superficial, and combined type. However, previous studies did not adequately compare endoscopic findings with histological findings and the prognosis. Patients and Methods: One hundred and ten patients with nipple discharge who had intraductal tumors were identified by mammary ductoscopy, and 25 breast cancer patients were identified from our database of records between 2001 and 2008. The clinicopathological data and outcomes of these patients were then reviewed. Results: Lesions in 25 breast cancer patients comprised 12 polypoid solitary type, 3 polypoid multiple type, 5 superficial type, and 5 combined type. Polypoid type showed a low sensitivity on cytological analysis (5 malignant and 10 benign). On the contrary, superficial or combined type showed a high sensitivity (4 malignant and 1 benign). Furthermore, invasive ductal carcinoma was frequently found in the solitary polypoid type. Actuarial disease-free survival for all patients at 10 years was 78%. The estrogen/progesterone receptor status and endoscopic appearance did not significantly affect disease-free survival (DFS), while there was a significant difference in DFS between ductal carcinoma in situ and invasive ductal carcinoma. Conclusion: 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.*

*Correspondence to:* Daigo Yamamoto, MD, Department of Surgery, Kansai Medical University, Hirakata, Osaka 570-8507, Japan. Tel: +81 728040101, Fax: +81 728040170, e-mail: yamamotd@hirakata.kmu.ac.jp

*Key Words:* Fiberoptic ductoscopy, breast cancer, nipple discharge.

Nipple discharge is a common complaint among women. In studies to date (1-4), the etiology is usually benign: papilloma is the most common cause (40-70%), followed by adenomatous or papillary epithelial proliferation (14%). However, 1-23% of women with pathologic nipple discharge are diagnosed with breast cancer or ductal carcinoma *in situ*; therefore, further investigations including surgical duct excision are generally recommended.

Fiberoptic ductoscopy is an emerging technique facilitating direct visual access to the ductal system of the breast through nipple orifice cannulation and exploration (5-7). Ductoscopy allows the direct observation of lesions and is not simply indirect shadowing. We reported that ductoscopy is a useful procedure for guiding subsequent breast surgery in the treatment of nipple discharge (8-11).

In 2001, the Japanese Association of Mammary Ductoscopy proposed a classification system based on the objective endoscopic appearance of intraductal lesions (6, 12). This includes four categories: solitary polypoid, multiple polypoid, superficial, and combined type. There are some studies based on this classification. However, these studies do not adequately compare endoscopic with histological findings or the prognosis. Our goal was to identify which characteristics of the endoscopic appearance might be considered risk factors for the prognosis of breast cancer patients with nipple discharge not associated with lumps in the breast or a mammographic suspicion of malignancy.

## Patients and Methods

*Patients.* From 2001 to 2008, 110 patients with nipple discharge underwent microdochectomy at three centers. Among them, the present study was based on data from 25 breast cancer patients who underwent fiberoptic ductoscopy (FDS) followed by microdochectomy. In addition, cases with not only abnormal lesions undetected by ultrasound or mammography, but also no endoscopic appearance were excluded.

Table I. *Clinicopathological factors of breast cancer: Comparison with regard to the endoscopic appearance.*

| Variables | Polypoid type | | | |
|---|---|---|---|---|
| | Superficial type (5) | Solitary (12) | Multiple (3) | Combined type (5) |
| Tumor location | | | | |
| Orifice-1st branch | 1 | 3 | 1 | 1 |
| 1st-2nd branch | 3 | 3 | 1 | 2 |
| 3rd-4th branch | 1 | 4 | 1 | 1 |
| 4th branch- | 0 | 2 | 0 | 1 |
| Bloody nipple discharge | 4 (80) | 7 (58.3) | 3 (100) | 4 (80) |
| ER and/or PgR | | | | |
| Positive | | 3 | 10 | 34 |
| Negative | | 2 | 2 | 01 |
| Cytology | | | | |
| Malignant | 4 | 4 | 1 | 4 |
| Benign (including suspicious) | 1 | 8 | 2 | 1 |
| Rate of positive tumor margin with surgery | 0 | 0 | 2 | 2 |
| Histology | | | | |
| Invasive ductal carcinoma | 2 | 8 | 2 | 2 |
| Noninvasive ductal carcinoma | 3 | 4 | 1 | 3 |

ER: Estrogen receptor; PgR: progesterone receptor.

*Mammary ductoscopy and ductal lavage*. The procedure using FDS and cytology employing ductal lavage has been described previously (8). In brief, the nipple and areola of the breast were cleaned with saline, Bowman's lacrimal dilators with their outer diameters were lubricated with xylocaine jelly, and then they were inserted into the discharging nipple orifice to dilate the ostium of the lactiferous duct. Air was sent into the duct through the air channel in the fiberscope to ensure the patency of the duct during the procedure. The lactiferous duct, lactiferous sinus, and segmental (main) duct and its branches were observed. The presence and appearance of any papillary lesions were noted. We classified the endoscopic appearances into four types: superficial type, polypoid solitary type, polypoid multiple type, and combined type according to the Japanese Association of Mammary Ductoscopy classification (Table I) and then analyzed them using video and photographic material.

*Treatment and pathological analysis*. Patients underwent breast surgery (microdochectomy). Detailed histological analysis of the extirpated tissues was carried out to evaluate abnormalities present using FDS. As surgically resected specimens were totally observed with serial sections (less than 3 mm), the feature of ducts and abnormal lesions were identified. Hormonal treatment with tamoxifen was given to all patients with estrogen receptor (ER)+ tumors, and any additional chemotherapy was administered at the discretion of the investigator. Follow-up was performed every 4 months for the first 2 years, thereafter every 6 months, and once a year after 5 years.

Table II. *Summary of variables entered into univariate analysis.*

| Variable | n | P (log-rank test) |
|---|---|---|
| Histological type | | |
| Ductal carcinoma *in situ* | 11 | |
| Invasive ductal carcinoma | 14 | 0.001 |
| Endoscopic finding | | |
| Superficial type | 5 | |
| Solitary polypoid type | 12 | 0.3 |
| Multiple polypoid type | 3 | |
| Combined type | 5 | |
| ER/PgR | | |
| Positive | 20 | 0.06 |
| Negative | 5 | |

ER: Estrogen receptor; PgR: progesterone receptor.

*Statistical analysis*. Clinicopathological data were stored. Disease-free survival (DFS) was analyzed using Kaplan–Meier estimates, and the Log-rank test was used to compare the curves. Differences with a probability value of less than 0.05 were considered significant.

## Results

*Clinicopathological characteristics*. A total of 40 out of the 110 patients, who underwent microdochectomy, were breast cancer patients. Fifteen cases were excluded because of abnormal lesions undetected by ultrasound or mammography, or they had no endoscopic appearance. Therefore, among the breast cancer patients, the clinicopathological characteristics in relation to the endoscopic appearance in 25 breast cancer patients were summarized (Table I).

According to the endoscopic appearance using fiberoptic ductoscopy, 25 patients had 12 polypoid solitary type, 3 polypoid multiple type, 5 superficial type, and 5 combined type. Intraductal lesions were seen in most segmental ducts. In addition, the preoperative diagnosis by cytology of ductal lavage was compared with the endoscopic appearance. Cytological analysis of polypoid type of cancer had a low sensitivity (5 malignant and 10 benign). On the contrary, such analysis for uperficial or combined type of cancer exhibited a high sensitivity (4 malignant and 1 benign). Furthermore, invasive ductal carcinoma was frequently found in solitary polypoid type.

*Disease-free survival*. Actuarial DFS for all patients at 10 years was 78% (Figure 1). Furthermore, we report a summary of variables considered in the univariate analysis (Table II). The ER/progesterone receptor (PgR) status and endoscopic appearance did not significantly affect DFS, while there was a significant difference in survival between patients with different histological types (Figure 2).

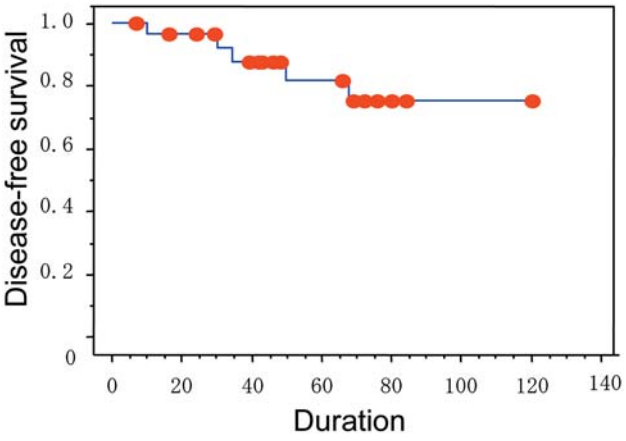


Figure 1. *Disease-free survival for all patients.*

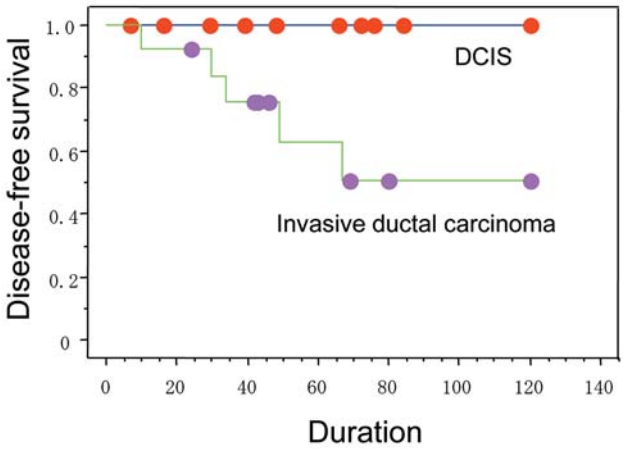


Figure 2. *Disease-free survival according to the histological type (p=0.001, log-rank test). DCIS, Ductal carcinoma in situ.*

## Discussion

Nipple discharge is an infrequent, but important symptom of breast disease, because early breast cancer cases can be diagnosed among patients whose only symptom is nipple discharge. The management of a spontaneous single duct nipple discharge without an associated mass and normal mammography remains controversial. Burton *et al.* (13) recommended that microdochectomy is a safe and effective treatment in women with nipple discharge, while papilloma was most frequently identified in pathology, and malignant or premalignant lesions were identified in some cases.

Previous studies also showed the relationship between the histology, including benign disease, and the endoscopic appearance (12-14). The results reveal that macroscopic features of intraductal lesions form the basis of an important additional diagnostic tool for the early diagnosis of malignant disease in patients with nipple discharge showing an unclear etiology (12-14). Makita *et al.* (12) showed that 88.5% of solitary polypoid tumors were benign papillary lesions and carcinoma was found in only 11.5%. The polypoid multiple types of lesions were found to be benign in some patients (35%) and malignant in others (65%). In the present study, among the breast cancer patients, most cases involved the solitary polypoid type (12 patients: 48%). Two factors may have influenced this result. First, the number of lesions is a very important consideration for endoscopic classification and histological diagnosis (7, 8). The number of lesions cannot be determined if a lesion obstructs the ductal lumen, that is to say that the polypoid type of tumor can not be distinguished from solitary and multiple types. Secondly, this was not a large study. Many pioneers stated that mammary ductoscopy was useful for the diagnosis of pathological nipple discharge (4-8). Above all, the classification of the Japanese Association of Mammary Ductoscopy is simple and correlates with histological diagnoses. Further validation studies by other researchers are needed.

However, in fact, the histological type did significantly affect DFS in the present study. To our knowledge, this is the first study to investigate the correlation between the endoscopic appearance of patients with nipple discharge and the prognosis. Patients with nipple discharge showing no abnormality on mammography or ultrasound are usually deemed to have a favorable prognosis. Indeed, there was no correlation between the macroscopic classification and DFS, but invasive ductal carcinoma was frequently identified in the solitary polypoid type, and this subsequently affected the DFS. Thus, the knowledge of endoscopic appearance is essential to treat breast cancer patients with nipple discharge, and histopathological examination may be considered the most reliable method for the final diagnosis in polypoid type cases.

Although this is a small study and the results need to be confirmed in larger definitive studies in which there are markedly more cancer cases, the advantages of FDS screening is in its ability to direct and limit subsequent surgery to remove the lesion and spare as much involved breast tissue as possible.

## References

1 Lang JE and Kuerer HM: Breast ductal secretions: clinical features, potential uses, and possible applications. Cancer Control *14*: 350-359, 2007.

2 Escobar PF, Crowe JP, Matsunaga T and Mokbel K: The clinical applications of mammary ductoscopy. Am J Surg *191*: 211-215, 2006.

3 Gulay H, Bora S, Kilicturgay S, Hamaloglu E and Goksel HA: Management of nipple discharge. J Am Coll Surg *178*: 471-474, 1994.
4 Montroni I, Santini D, Zucchini G, Fiacchi M, Zanotti S, Ugolini G, Manaresi A and Taffurelli M: Nipple discharge: Is its significance as a risk factor for breast cancer fully understood? Observational study including 915 consecutive patients who underwent selective duct excision. Breast Cancer Res Treat *123*: 895-900, 2010.
5 Kamali S, Bender O, Aydin MT, Yuney E and Kamali G: Ductoscopy in the evaluation and management of nipple discharge. Ann Surg Oncol *17*: 778-783, 2010.
6 Uchida K, Fukushima H, Toriumi Y, Kawase K, Tabei I, Akinori A, Yamashita A and Nogi H: Mammary ductoscopy: current issues and perspectives. Breast Cancer *16*: 93-96, 2009.
7 Sauter ER, Klein-Szanto A, Macgibbon B and Ehya H: Nipple aspirate fluid and ductoscopy to detect breast cancer. Diagn Cytopathol *38*: 244-251, 2010.
8 Yamamoto D, Shoji T, Kawanishi H, Nakagawa H, Haijima H, Gondo H and Tanaka K: A utility of ductography and fiberoptic ductoscopy for patients with nipple discharge. Breast Cancer Res Treat *70*: 103-108, 2001.
9 Yamamoto D, Ueda S, Senzaki H, Shoji T, Haijima H, Gondo H and Tanaka K: New diagnostic approach to intracystic lesions of the breast by fiberoptic ductoscopy. Anticancer Res *21*: 4113-4116, 2001.
10 Yamamoto D, Senzaki H, Nakagawa H, Okugawa H, Gondo H and Tanaka K: Detection of chromosomal aneusomy by fluorescence *in situ* hybridization for patients with nipple discharge. Cancer *97*: 690-694, 2003.
11 Yamamoto D and Tanaka K: A review of mammary ductoscopy in breast cancer. Breast J *10*: 295-297, 2004.
12 Makita M, Akiyama F, Gomi N, Ikenaga M, Yoshimoto M, Kasumi F and Sakamoto G: Endoscopic classification of intraductal lesions and histological diagnosis. Breast Cancer *9*: 220-225, 2002.
13 Burton S, Li WY, Himpson R, Sulieman S and Ball A: Microdochectomy in women aged over 50 years. Ann R Coll Surg Engl *85*: 47-49, 2003.
14 Makita M, Akiyama F, Gomi N, Iwase T, Kasumi F and Sakamoto G: Endoscopic and histologic findings of intraductal lesions presenting with nipple discharge. Breast J *12*: S210-S217, 2006.

*Received July 15, 2011*
*Revised August 31, 2011*
*Accepted September 2, 2011*