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Suspicious Nipple Discharge Diagnostic Evaluation

Yukiko Tokuda[1] and Yoshinori Kodama[2]
National Hospital Organization Osaka National Hospital
Department of Radiology[1] and Pathology[2]
Japan

1. Introduction

Nipple discharge (ND) is the third most common breast-related complaint after breast pain and breast mass, and accounts for nearly 7% of all breast symptoms (Hussain et al., 2006; Simmons et al., 2003 citing Leis et al., 1998).

The diagnosis of ND begins with its characterization as either a physiological or pathological condition (Simmons et al., 2003). Physiological discharge, often a manifestation of breast manipulation, is usually bilateral, is white or green, and emanates from many ducts (Simmons et al., 2003). Possible causes of persistent physiological discharge include oral contraceptives, antihypertensives, tranquilizers, hypothyroidism, and pituitary adenoma (Simmons et al., 2003). Most NDs are physiological and are not associated with an underlying benign or malignant breast neoplasm (Sickles, 2000). A pathological discharge is generally unilateral, spontaneous, persistent, clear, watery, serous or bloody in appearance, and emanates from a single duct (Morrogh et al., 2007). Most of the common pathological causes of ND are benign (Hou et al., 2001; Hussain et al., 2006), and the most frequently encountered benign causes are intraductal papilloma, followed by ductal ectasia and fibrocystic disease (Hou et al., 2001; Morrogh et al., 2010; Sickles, 2000). The most important cause of pathological discharge is breast cancer. For single duct nipple discharges, the incidence of malignant or high-risk pathology is reported to be as high as 15% (Orel et al., 2000 citing Carty et al., 1994; Fung et al., 1990; Leis et al., 1989; Piccoli et al., 1998; Tabar et al., 1983; Winchester et al., 1996). In some cases, ND is the only sign of carcinoma (Hou et al., 2001). NDs that are bloody or serous in appearance, associated with a mass, and present in an elderly patient are more likely to be caused by malignant tumors (Das et al., 2001; El-Daly & Gudi, 2010; Pritt et al., 2004; Tabar, 1983; Tjalma, 2004 citing Seltzer et al., 1970).

We defined suspicious ND as pathological ND, which is spontaneous, unilateral, and localized to a single duct, combined with at least one of the following characteristic findings associated a high risk of malignant disease: bloody or serous appearance, associated with a mass, and occurrence in elderly patients.

If ND is multi-duct or bilateral, breast imaging is not required. However, single-duct ND is considered an indication for further investigation by mammography (MMG) and/or ultrasonography (US) (EUSOMA, 2010).

[1] Current Affiliation: NTT West Osaka Hospital, Japan

In this chapter, we review several methods of diagnostic evaluation including MMG, US, conventional ductography (DG), ND cytology, fine needle aspiration (FNA) and histopathology. We also demonstrate how to use the findings of contrast-enhanced magnetic resonance imaging (CEMRI) studies, including direct and indirect MR ductography (MRDG), to localize the causative lesion and to differentiate malignant lesions from benign ones in cases of suspicious ND.

2. Mammography (MMG)

While MMG is considered the standard initial imaging examination and may reveal microcalcifications and other signs of malignancy, it rarely provides information about the etiology of ND (Rissanen et al., 2007 citing Cabioglu et al., 2003; Dillon et al., 2006; Funovics et al., 2003; Sardanelli et al., 1997; Tabar et al., 1983). In the study by Tabar et al. (1983), only half of the patients who presented with ND and were diagnosed with breast cancer had an abnormal mammogram. In the study by Morrogh et al. (2010), the sensitivity of MMG among all patients with pathological ND was 18%. Conversely, MMG had a high negative predictive value (NPV) and specificity (94%), suggesting that MMG can be used to select patients with physiological ND for whom clinical observation alone may be a reasonable management approach.

3. Ultrasonography (US)

Breast US is a non-invasive diagnostic method that has proven to be useful in the evaluation of patients with ND (Sakorafas, 2001). However, US has limitations with respect to depicting causative lesions of small masses and ductal carcinomas in situ (DCIS), especially those in peripheral regions without ductal dilatation or those in high adipose-containing breasts (Berg & Gilbreath., 2000; Nakahara et al., 2003 citing Chung et al., 1995).

The most common sonographic features are duct dilatation, particularly in cases associated with solid internal echoes and duct wall thickening in generally central and/or subareolar areas (Ballesio et al., 2008). Berg & Gilbreath (2000) reported that US identified 45 of 48 (94%) invasive tumor foci and 7 of 16 (44%) foci of DCIS while only 9 of 64 (14%) malignant foci were detected by US. Rissanen et al. (2007) reported that in 52 patients with unilateral nipple discharge, 80% of papillomatous lesions, 58% of other benign lesions, and 20% of malignant lesions were sonographically positive, and among the 6 cases in which duct dilatation was the only sonographic finding, 3 (50%) were malignant lesions and the other 3 (50%) were papillomas and other benign lesions. In a study of 55 patients with bloody ND, Nakahara et al. (2003) reported that of all findings, only the hypoechoic masses with smooth margins (NPV = 90.9%) and hypoechoic masses with irregular margins (positive predictive value (PPV) = 85.7%) were statistically significant.

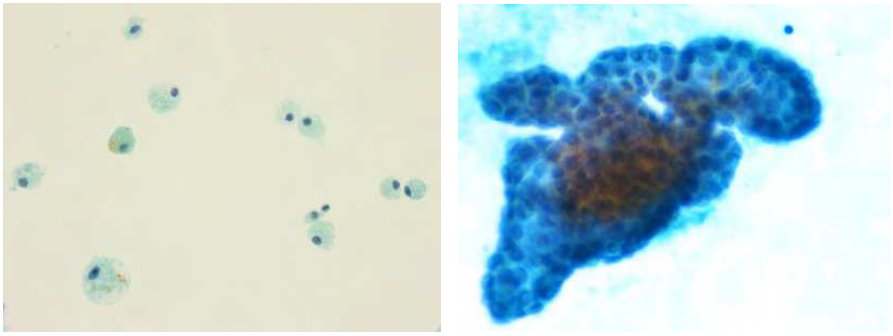
In addition to the patient's clinical history and cytological evaluation of the ND, performing a US-guided FNA is fundamental for differentiating between malignant and benign lesions (Ballesio et al, 2008 citing Sardanelli et al., 1997).

4. Nipple discharge (ND) cytology

ND cytology is a simple and noninvasive method that includes simply touching the nipple, obtaining a smear of the fluid, or gently scraping the surface of a lesion. Breast

pumping, breast massage, or nipple aspiration may be attempted if the discharge does not occur spontaneously during collection of the samples (Gupta et al., 2004; Krishnamurthy, et al., 2003). Gupta et al. (2004) have suggested that the use of routine ND cytology is limited by the small samples obtained and that ND cytology cannot always distinguish between physiological processes, fibrocystic disease, and papillomas. However, studies based on a large number of cases suggest that ND cytology is a reasonable method for diagnosing malignant and suspicious cases (Das et al., 2001; El-Daly & Gudi, 2010; Gupta et al., 2004; Pritt et al., 2004). Cytological examination of ND is valuable mainly for detecting such cancers. The efficiency of ND cytology remains controversial, as an older study has demonstrated low sensitivity, for detection of malignancy, ranging from 11% to 31.2% (Dinkel et al., 2001). However, studies that are more recent have reported higher sensitivity of ND cytology. For example, Pritt et al. (2004) determined a sensitivity and specificity of 85% and 97%, respectively. Likewise, a sensitivity of 58.3% and 63% and a specificity of 100% and 100% were reported by Lee (2003) and El-Daly & Gudi (2010), respectively. Therefore, ND cytology can be useful in the diagnosis of malignant and suspicious cases.

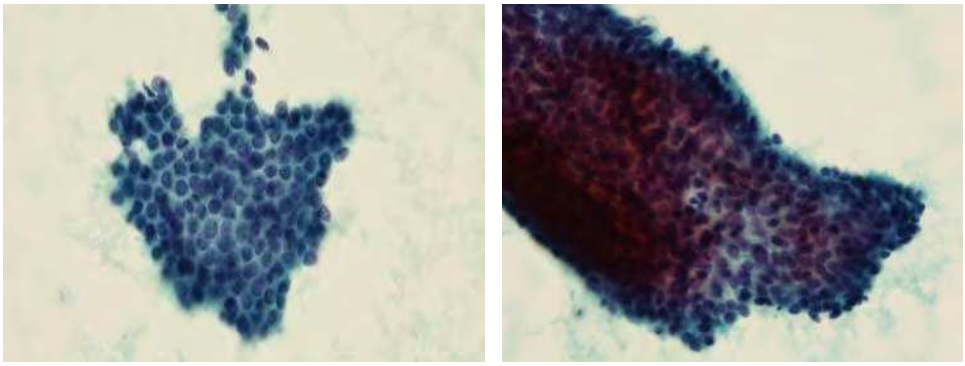
Foam cells are the predominant cytological feature in tissues being subjected to in inflammatory processes, mastopathy, or fibrocystic disease (Fig. 1a). Its secretion occasionally contains duct epithelial cells (Fig. 1b). Apocrine metaplasia of duct epithelial cells is sometimes seen. In intraductal papillomas, large, cohesive clusters of normal duct cells may be observed (Fig. 2).



(a) (b)

Fig. 1. Nipple discharge cytology of benign lesions. (a) Several foam cells are observed but no epithelial cells are present. (b) A number of clusters composed of duct cells forming a papillary structure can be seen. (Histological diagnosis, duct papillomatosis)

Clusters of apocrine cells may also be seen. In some cases, papillary structures composed of spherical clusters of large duct cells with atypical features such as cytoplasmic vacuoles, enlarged nuclei, and visible nucleoli may be present. In ductal carcinoma, the clusters composed of atypical cells may be loosely structured and are sometimes thick or spherical. They may also form papillary structures. Necrosis is commonly seen in high-grade lesions (Fig. 3).



(a) (b)

Fig. 2. ND cytology of intraductal papilloma. (a, b) Cohesive clusters composed of benign duct cells. The histological diagnosis was intraductal papilloma (see Fig. 8)

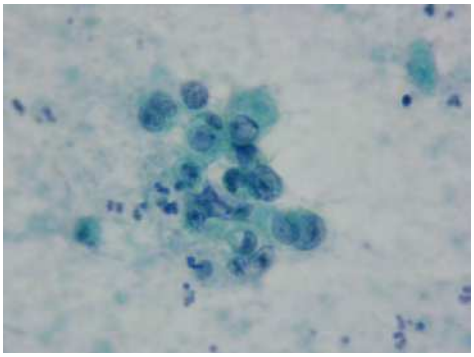


Fig. 3. ND cytology of a malignant lesion. The smear shows clusters of atypical cells with enlarged, irregular-shaped nuclei, and high nuclear cytoplasmic ratios. There are necrotic cells in the background.

5. Fine needle aspiration (FNA)

FNA cytology is now a popular widely used tool for assessing breast tumors. It has been reported that ND cytology is as specific as concomitant FNA cytology but slightly less sensitive for detecting papillomas or malignant lesions (Lee, 2003). However, ND samples are often inadequate. Gupta et al. (2004) showed that 492 of 1948 ND smears (25%) were inadequate for diagnosis. Lee (2003) reported that ND cytology was non-diagnostic in 43 of 82 cases (52%), whereas FNA cytology was non-diagnostic in only 1 of 34 cases (2.9%). Therefore, ND cytology has little complementary diagnostic value. FNA cytology is a sensitive and effective method of diagnosing breast cancer.

6. Ductography (DG, also called Galactography)

DG is a diagnostic modality used for identification of the secreting duct, which is cannulated and injected with a sterile water-soluble contrast material. This is followed by

MMG (Sakorafas, 2001). DG is more sensitive than ND cytology and MMG in detecting intraductal lesions (Rongione et al., 1996; Chung et al., 1995; Orel et al., 2000). It was found that when a standard evaluation was negative for a lesion, the addition of DG localized 19 of 25 (76%) otherwise occult malignant/high-risk lesions and 80 of 88 (91%) benign lesions (Morrogh et al., 2010). The incidence of malignancy, despite negative clinical breast examination and conventional imaging, was found to be as high as 10% (Morrogh et al., 2008). Ductographic findings suggestive of carcinoma include irregular filling defects, ductal irregularities (distortion, displacement, complete obstruction of contrast flow, and non-iatrogenic contrast extravasation), and a deeper position of the lesion (Cardenosa et al., 1994; Ciatto et al., 1998; Tabar et al., 1983). Smooth intraductal filling defects, complete ductal obstruction, ductal expansion with apparent distortion, and irregularity of the ductal wall are more common ductographic features obsreved for solitary papillomas (Cardenosa et al., 1994; Nakahara et al., 2003). Unfortunately, evidence for a predictive role for DG is less convincing because a positive study does not differentiate between malignant and benign causes of discharge and a negative study does not exclude the presence of an underlying carcinoma. The PPV and NPVs of DG have been reported to be 19% and 63%, respectively (sensitivity, 76%; specificity, 11%); these values are consistent with those of other studies and confirm that DG is not effective in distinguishing between malignant and benign causes of nipple discharge (Morrogh et al., 2007). The routine use of DG in cases of suspicious ND remains controversial (Rongione et al., 1996; Chung et al., 1995; Orel et al., 2000).

DG is invasive and time-consuming with potential complications including intense pain, mastitis, lymphatic opacification, and duct perforation (Cardenosa et al., 1994; Lorenzon et al., 2011; Tabar et al., 1983). The rate of incomplete and/or technically inadequate conventional DG has been reported to be as high as 10–15% (Morrogh et al., 2008; Sickles, 2000). All of these technical difficulties may result in the failure to detect and surgically treat the lesion, as most cases of pathological ND have no detectable lump and negative or undefined ultrasonographic findings (Schwab et al., 2008).

7. Contrast-Enhanced Magnetic Resonance Imaging (CEMRI)

Negative or benign findings identified by physical examination, MMG, US, cytological analysis of discharge, and DG are not sufficient to rule out the presence of underlying malignant lesion (Rongione et al., 1996; Tabar et al., 1983), but the physician must still decide whether to manage expectantly or proceed to major duct excision (Morrogh et al., 2010). CEMRI is increasingly being used as a diagnostic modality for breast cancer, with diagnostic sensitivities of 86–100% and 40–100% for invasive and intraductal cancers, respectively (Orel et al., 2001; Tjalma & Verslebers, 2004 citing Esserman et al., 1999; Vichweg et al., 2000).

Preliminary research on the application of CEMRI for evaluation of patients with ND suggests that it is useful for the localization of otherwise occult diseases, identification of both benign and malignant causes of ND, and noninvasiveness relative to DG. However, the available data are limited (Nakahara et al., 2003; Orel et al., 2000; Tjalma & Verslebers, 2004). Therefore, the gold standard diagnostic and therapeutic approach for patients with pathological ND is surgical duct excision (Morrogh et al., 2010 citing Nelson & Hoehn, 2006). However, a frequent criticism of this blind approach is that the pathologists may not always identify a discrete lesion responsible for the discharge. In addition, major duct

excision is expected to be undesirable for a woman of childbearing age. Therefore, there is a need to develop more effective tools for localizing the lesions responsible for ND and for distinguishing between malignant and benign causes of ND, the 2 most important roles of imaging (Morrogh et al., 2007; Yau et al., 2011).

7.1 Localization of the disease causing the ND

There is evidence in the literatures that CEMRI offers high diagnostic performance for detecting lesions in patients with suspicious ND, even when no lesions are identified by conventional imaging and when DG is not feasible or inconclusive (Sardanelli et al., 2008 citing Daniel et al., 2003; Hirose et al., 2006; Nakahara et al., 2003; Orel et al., 2000). Lorenzon et al. (2011) found that CEMRI could identify 5/5 cancers (sensitivity = 100%) and 13/14 high-risk lesions (sensitivity = 92.9%) (overall sensitivity, 94.7%; overall specificity, 78.9%). In addition, it was found that 3 of 5 cancers (1 invasive, 1 in situ, 1 contralateral invasive) and 2 of 14 high-risk lesions could be detected only by CEMRI. CEMRI was significantly more sensitive than either MMG or US ($p < 0.0001$ and $p = 0.042$, respectively). Morrogh et al. (2007) reported that the PPV and NPV of CEMRI for detection of the disease causing the ND were 56% and 87%, respectively (sensitivity, 83%; specificity, 62%), and CEMRI performed after negative standard evaluation detected 75% of otherwise occult malignant/high risk lesions. Nakahara et al. (2003) reported that CEMRI identified all malignant lesions (100%) including DCIS. Kramer et al. (Van Goethem et al., 2009 citing Kramer et al., 2000) used CEMRI alone and in combination with MMG and DG to assess 48 women with pathological ND. The sensitivity and specificity values of DG for detection of papillomas were 94% and 79%, respectively, whereas only 1 carcinoma was detected by MMG/DG. CEMRI had a sensitivity of 89% (8/9) for malignant lesions. These authors have concluded that while MMG in combination with DG remains the primary diagnostic tool, the addition of CEMRI can demonstrate the location and distribution of lesions, especially in malignant cases, and therefore recommend performing a CEMRI to detect underlying lesions that may have been misdiagnosed by conventional imaging (Lorenzon et al., 2011; Van Goethem et al., 2009).

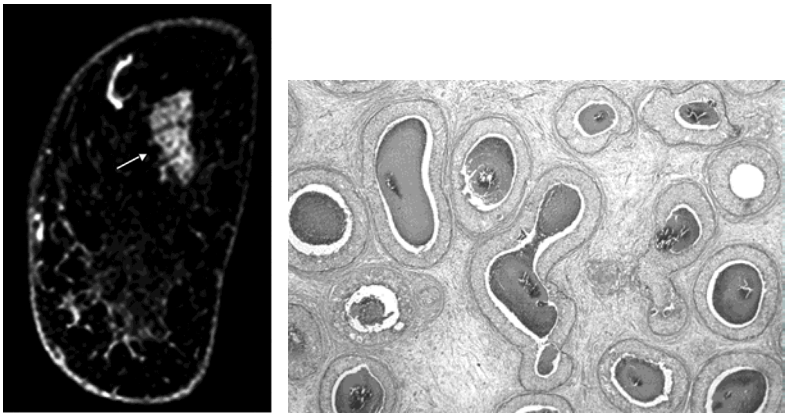
7.2 Differentiation of malignant and benign lesions

Predicting whether the causative lesion is malignant or benign is important because it affects the physician's choice of clinical follow-up or surgical treatment.

Nakahara et al. (2003) reported that segmental clumped enhancement (PPV = 100%), a focal mass with a smooth border (NPV = 91.7%), and diffuse or regional stippled enhancement (NPV = 94.1%) were statistically significant features that can be used for differentiating between malignant and benign lesions. Ballesio et al. (2008) reported that 5 papillomatosis lesions appeared as patchy, homogeneously enhanced areas, that among 15 intraductal papillomas, some had an oval appearance with well-defined margins, while other had areas of homogeneous enhancement with a linear shape at the periareolar or subareolar sites, moreover, they reported 2 cases of atypical ductal hyperplasias with diffuse nodular enhancement. One micropapillary DCIS, 1 papillary carcinoma, and 1 invasive ductal carcinoma were visualized as 2 segmental areas of enhancement and 1 mass-like enhancement with poorly defined margins. Morrogh et al. (2007) reported that MRI was use as the first-line test in 32/52 (63%) patients in whom it was performed and yielded a breast imaging reporting and data system (BI-RADS) MRI (American College of Radiology, 2003) ≥

4 diagnosis in 11/32 (34%) patients. Seven of 11 (64%) patients proceeded directly to major duct excision and demonstrated 1 invasive cancer, 2 DCIS, 2 high-risk lesions, and 2 benign lesions. MRI was negative in 21 patients (BI-RADS MRI score, ≤3). Among this group, 4 patients proceeded to major duct excision, yielding 1 invasive cancer and 3 benign lesions. Therefore, an evaluation based using only BI-RADS MRI descriptors has a limited ability to distinguish between malignant and benign lesions.

We analyzed MRI findings in patients with suspicious ND using BI-RADS MRI descriptors and clustered ring enhancement criteria (Tokuda et al., 2009), and compared them with histopathological diagnoses to assess the accuracy of differentiating between malignant and benign lesions. Clustered ring enhancement is characterized by clusters of minute ring enhancements. The clusters include enhanced foci constituting enhanced ring-like patterns, and heterogeneous enhancement of minute internal ring patterns (Tozaki et al., 2006) (Fig. 4). Breast CEMRI was performed on 47 patients to identify lesions causing suspicious ND. The 39 lesions for which histopathological diagnoses were obtained consisted of 17 carcinomas and 22 benign lesions. The types of carcinoma identified included DCIS (n = 10), invasive ductal carcinoma (IDC) with intraductal components (n = 2), and IDC (n = 5). The benign lesions included fibrocystic disease (n = 11), intraductal papillomas (n = 5), duct papillomatosis (n = 2), fibrosis (n = 3), and a fibrous nodule (n = 1). Table 1 shows the frequencies of the BI-RADS MRI descriptors and the presence of clustered ring enhancement for benign and malignant lesions. Among the non-mass-like enhancement patterns, no distribution modifiers such as "linear," "regional," or "multiple regions" were observed, and no internal enhancements such as "reticular" enhancement were detected. Only 2 lesions showing mass enhancement were not diagnosed by histopathology.



(a) (b)

Fig. 4. Images of the breast of a 54-year-old woman with suspicious microcalcifications observed by mammography. (a) Coronal first contrast-enhanced T1-weighted MR image of the left breast shows regional enhancement in the upper outer quadrant (arrow). The lesion demonstrates heterogeneous enhancement with interior clustered minute ring enhancements (clustered ring enhancement). (b) A photomicrograph of the histopathological specimen shows a ductal carcinoma in situ with intraluminal necrosis and microcalcifications. Clustered ring enhancement corresponds to periductal stroma. However, intraductal cancer cell involvement in the enhancement cannot be ruled out. Reprinted from Tozaki et al. (2006)

Descriptor	**Benign (n=22)**	**Malignant (n=17)**	**P***
Non-mass-like enhancement			
Distribution modifiers			
Ductal	10 (45)	3 (18)	NS
Focal	1 (5)	1 (6)	NS
Regional	0 (0)	0	NS
Segmental	8 (36)	10 (59)	NS
Diffuse	3 (14)	1 (6)	NS
No enhancement	0	2 (11)	NS
Internal enhancement			
Homogeneous	2 (9)	1 (7)	NS
Heterogeneous	9 (41)	9 (57)	NS
Stippled,punctuate	11 (50)	3 (22)	NS
Clumped	0	2 (14)	NS
Reticular	0	0	NS
Clustered ring enhancement	2	9	0.002

Numbers shown in parentheses indicate percentages.
Masses were not diagnosed by histopathology were excluded from this table.
*Fisher's exact test was used.
NS indicates not significant.

Table 1. Frequency of MRI parameters in cases of suspicious nipple discharge. Reprinted from Tokuda et al. (Tokuda et al., 2009)

The 22 benign and the 17 malignant lesions comprised 15 non-mass-like enhancements and 2 non-enhanced lesions, which had DCIS foci measuring 2 and 2.5 mm in diameter without stromal changes.

The most common findings of the benign lesions were stippled (50%), ductal (45%), and heterogeneous (41%), whereas those of the malignant lesions were segmental (59%) and heterogeneous (57%). Both lesions (2/2) showing clumped internal enhancement were IDCs with an intraductal component. Clustered ring enhancement was observed in 60% (9/15) of the malignant enhancing lesions but in only 9% (2/22) of the benign lesions ($p = 0.002$). Of the 11 lesions showing clustered ring enhancement, 9 were malignant and 2 were benign. The highest PPVs for carcinoma were associated with the clumped (100% or 2/2), clustered ring enhancement (82% or 9/11), and segmental (56% or 10/18) descriptors.

The specificity of clustered ring enhancement was 90% (20/22). Among the lesions showing clustered ring enhancement, 8 exhibited segmental distribution and 3 ductal enhancement. Both the malignant lesions with clumped enhancement (100% or 2/2) also showed clustered ring enhancement. Although the distribution pattern alone was not useful for differentiating between malignant and benign lesions, the combination of segmental distribution and clustered ring enhancement showed a significant association with breast cancer ($p = 0.004$). Twelve patients did not undergo a surgical procedure, and no histopathological diagnoses were obtained. We show cases with (Fig. 5) and without (Fig. 6) clustered ring enhancement. Images in Figures 5 and 6 are similar to images in Tokuda et al., (2009) but were obtained using a MRI device with a standard breast-dedicated coil. The most common kinetic pattern observed in the malignant lesions was the plateau pattern (40% or 6/15), and the most common kinetic pattern in the benign lesions was the persistent pattern (55% or 12/22). The

washout pattern had the highest PPV for carcinoma, 100% ($p = 0.02$). The highest PPVs for carcinoma were associated with a clumped internal enhancement (100%), clustered ring enhancement (82%), and a washout pattern (100%).

Tozaki et al. (Tozaki et al, 2006) reported that clustered ring enhancement combined with the BI-RADS MRI descriptors appear to be useful in differentiating between benign and malignant lesions. Most of the lesions causing suspicious ND were observed to have non-mass-like enhancement. Many DCISs have been reported to have non-mass-like enhancement and a segmental or ductal distribution and clumped internal enhancement (Liberman et al., 2002; Morakkabati-Spitz et al., 2005). Tozaki et al. (2006) reported that all lesions showing segmental distribution were malignant. In this study, of the lesions showing segmental distribution, 8 were benign and 10 were malignant. In addition, among the lesions showing ductal distribution, 10 and 3 were benign and malignant, respectively, and the difference was insignificant. The PPV of segmental distribution alone was 44%. Morakkabati-Spitz et al. reported that segmental distribution and linear enhancement were the most common features of DCIS on dynamic MRI. In that study, 13 fibrocystic disease lesions showed segmental distribution. The PPV of segmental distribution in our study was similar to that reported by Morakkabati-Spitz et al. (2005), but was markedly lower than that of Tozaki et al. (2006). This may be due to different biases in patient selection for MRI. We analyzed lesions causing suspicious ND, Morakkabati-Spitz et al. (2005) examined lesions showing a segmental distribution and linear enhancement, and Tozaki et al. (2006) evaluated lesions showing non-mass- like enhancement. Similar to the results reported by Tozaki et al. (2006), the most common internal enhancement patterns was a heterogeneous pattern for the malignant lesions (59%) and a stippled/punctuate pattern for the benign lesions (45%); this difference was not significant. In this study, both the clumped internal enhanced lesions (2/2) were found to be malignant. Although the number of cases studied was small, Liberman et al. (2002) reported similar results (Liberman et al., 2002).

All lesions (4/4) showing a washout kinetic pattern were malignant. Ten benign and 6 malignant lesions showed a plateau pattern. Kuhl et al. (Kuhl et al., 1999) pointed out that segmental and ductal enhancements are the imaging hallmarks of DCIS in breast MRI and concluded that the sensitivity of breast MRI for the detection of DCIS can be increased by performing additional morphological analysis of the enhancement pattern. However, in this study, the combination of distribution modifiers and a washout pattern was not significant. The presence of clustered ring enhancement was useful for differentiating between malignant and benign lesions ($p = 0.002$) and had a high PPV (82%) for breast cancer. Although the distribution pattern alone was not useful for differentiating between malignant and benign lesions, the combination of segmental distribution and clustered ring enhancement showed a significant association with breast cancer ($p = 0.004$) and a high PPV (88%). This indicates that clustered ring enhancement is a useful parameter in CEMRI analysis.

We conclude that the most common CEMRI finding in patients with suspicious ND is non-mass-like enhancement. The combination of segmental distribution and clustered ring enhancement showed the highest PPV for malignancy, and MRI can provide clinically useful information for distinguishing between benign and malignant causes of suspicious ND.

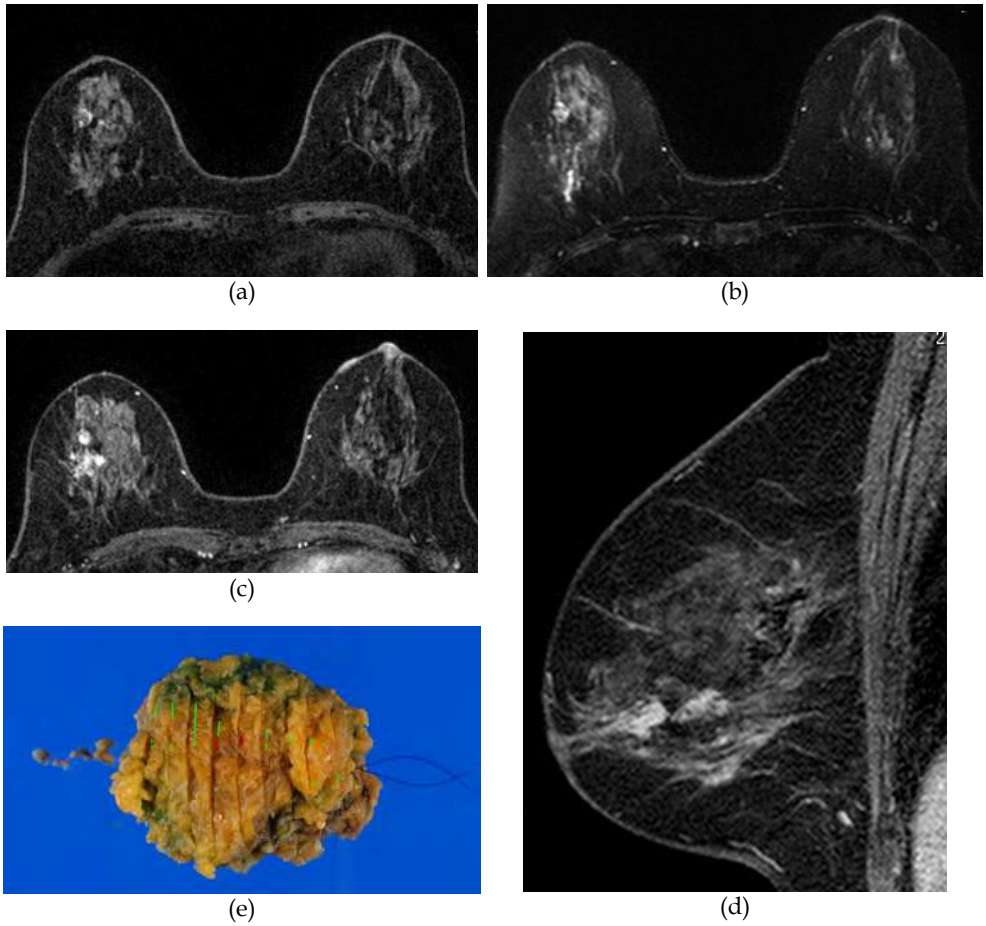


Fig. 5. Images of the breasts of a 70-year-old woman who presented with bloody discharge from the right nipple. (a) Pre-contrast enhanced fat-suppressed T1-weighted image showing intraductal high intensity corresponding to bloody discharge. (b) A fast short-tau inversion-recovery (STIR) image showing peripheral duct ectasia and intraductal fluid accumulation. (c) Dynamic contrast-enhanced early phase image showing clumped enhancement with segmental distribution. (d) Post-contrast-enhanced sagittal image showing heterogeneous tramline-like and clustered ring enhancement. The histopathological diagnosis was invasive ductal carcinoma with predominant intraductal components. (e) Mapping of the lesion (green line area, ductal carcinoma in situ; red line area, invasive ductal carcinoma).

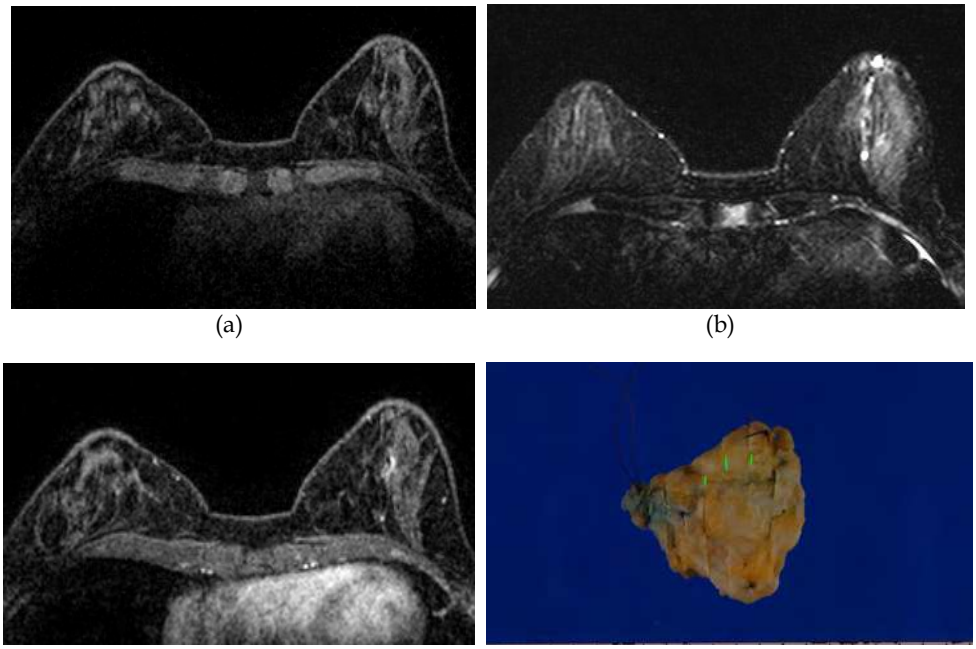


Fig. 6. Images of the breasts of a 49-year-old woman who presented with bloody discharge from the left nipple. (a) Pre-contrast fat-suppressed T1-weighted MR image showing no intraductal abnormal intensity. (b) STIR MR image showing duct ectasia and intraductal fluid accumulation. (c) A contrast-enhanced T1-weighted MR image showing homogeneous ductal enhancement. (d) Mapping of the lesion (green line area, intraductal papilloma.).

MRI findings may improve patient selection and treatment planning. However, MRI should not be used as an alternative for a breast biopsy to determine whether a given lesion is malignant, and it should not replace major duct excision as the gold standard for ruling out malignancy in patients with ND and a negative evaluation (Morrogh et al., 2007; Bluemke et al., 2004).

7.3 MR ductography (MRDG, also called MR galactography)

Several approaches to MRI of the secreting breast have been suggested, including direct (Schwab, 2008; Wenkel, 2011) and indirect MRDG and fusion MR imaging of contrast-enhanced and indirect ductography (Hirose et al., 2007).

7.3.1 Direct MRDG (direct MR galactography)

Direct MRDG is performed by filling the discharging duct with gadolinium-diethylene-triamine-pentaacetic acid (Gd-DTPA) diluted in saline, using a DG needle as for the conventional DG procedure, and obtaining 3D MRI sequences (Schwab et al., 2008). Schwab et al. (2008) reported findings in 23 patients with pathological discharge. Direct MRDG showed pathological findings in 82% of all findings, while indirect MRDG produced

pathological findings in 33% of all findings with significant ($p < 0.01$) differences in the detection of ductal disease between indirect MRDG and all direct MRDG sequences. Wenkel et al. (2011) reported observations of 30 women who underwent conventional DG and direct MRDG. There was no significant difference in sector localization between conventional DG and direct MRDG. It was concluded that because direct MRDG is more effective in identifying the disease than indirect MRDG, conventional DG, direct MRDG may have the potential to become an alternative to conventional DG.

7.3.2 Indirect MRDG (indirect MR galactography)

Intraductal fluid accumulation and duct ectasia can be detected in 40–73% with patients with pathological ND (Daniel et al., 2003; Orel et al., 2000; Schwab et al., 2008), just as MR hydrography can noninvasively depict fluid-fluid tubular structures such as the bile and pancreatic ducts, the ureters, and the semicircular canals (Jara et al., 1998). This method, known as indirect MRDG, can demonstrate the peripheral part of the duct of the point obstructed by an intraductal lesion (Hirose et al., 2006). Advantages to this technique are that it is noninvasive; uses no radiation or contrast material; and causes none of the potential complications associated with cannulation of the duct and injection of contrast medium, including duct perforation, extravasation, and mastitis (Hirose et al., 2007).

The EUSOMA working group suggests that in countries where DG is considered a routine test for suspicious ND, non-contrast T2-weighted and CEMRI can be considered if DG fails for technical reasons or if the patient refuses the procedure.

Indirect MRDG does not identify ducts that are not dilated, although conventional DG may show an undilated duct after cannulation. In some cases, the fluid within the duct has a high signal intensity on T1-weighted images and a low signal intensity on heavily T2-weighted images. This suggests either hemorrhage or the presence of proteins (Hirose et al., 2007).

The single 3D fused image obtained by combining data from indirect MRDG and CEMRI not only demonstrates the existence of an intraductal abnormality but also reveals the shape, size, and extent of the lesion, and can clarify the relationship between the duct and the intraductal lesion (Hirose et al., 2006) (Fig.7).

8. Histopathological diagnosis

Most NDs are caused by benign lesions such as papillomas and duct ectasia. Microdochectomy or major duct excision is often performed on patients with ND to exclude the possibility of underlying ductal carcinoma. Morrogh et al. (2010) analyzed the histopathological findings in biopsies or surgical specimens obtained from patients with pathological ND and identified cancer in 65 of 287 (22%) cases. Among the 287 cases, 121 (42%) were papillomas (Morrogh et al., 2010). Another report identified cancer in 9 of 211 cases (4.3%). Among the 211 cases, 81 (38%) were papillomas (Dillon et al., 2006). A papilloma (Fig. 8a, b) consists of a proliferation of ductal epithelium supported by a fibrovascular stroma. The epithelium of the stromal supporting layer is composed of epithelial and myoepithelial cells. Many papillomas have a complex structure as a result of stromal overgrowth (Fig. 8c), epithelial hyperplasia, or a combination of both of these processes. Foci of apocrine metaplasia are often observed in papillomas (Fig. 8d). Ductal carcinoma (Fig. 9) shows various histopathological patterns.

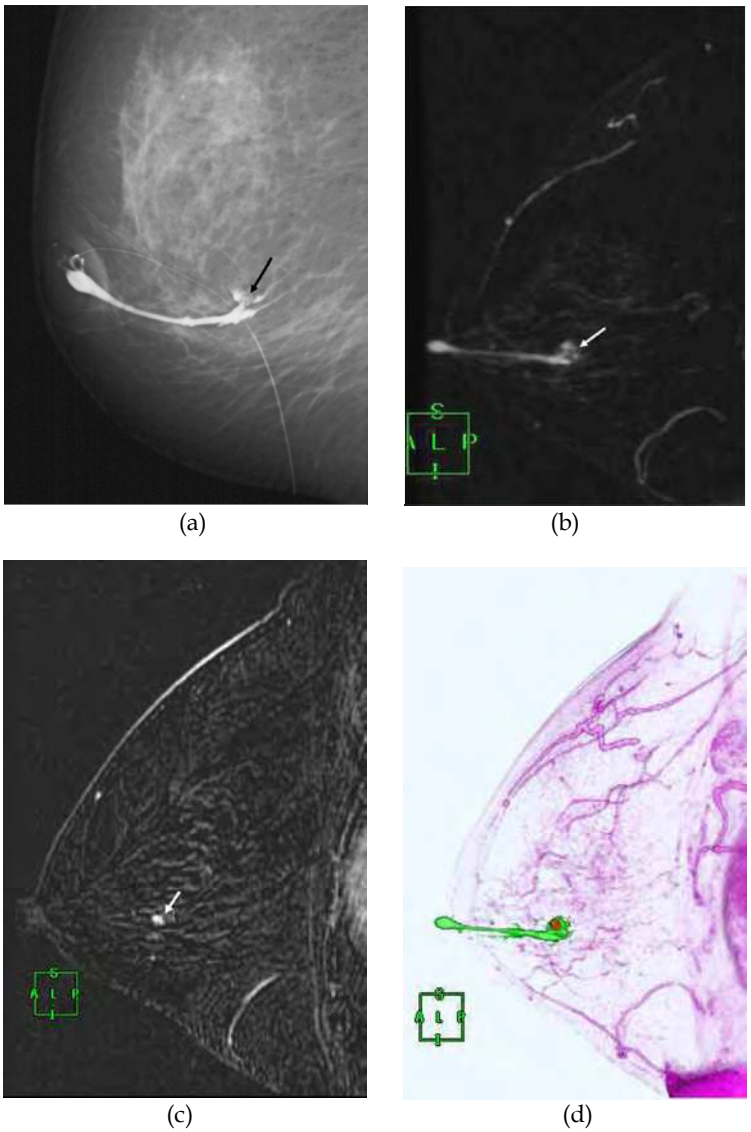
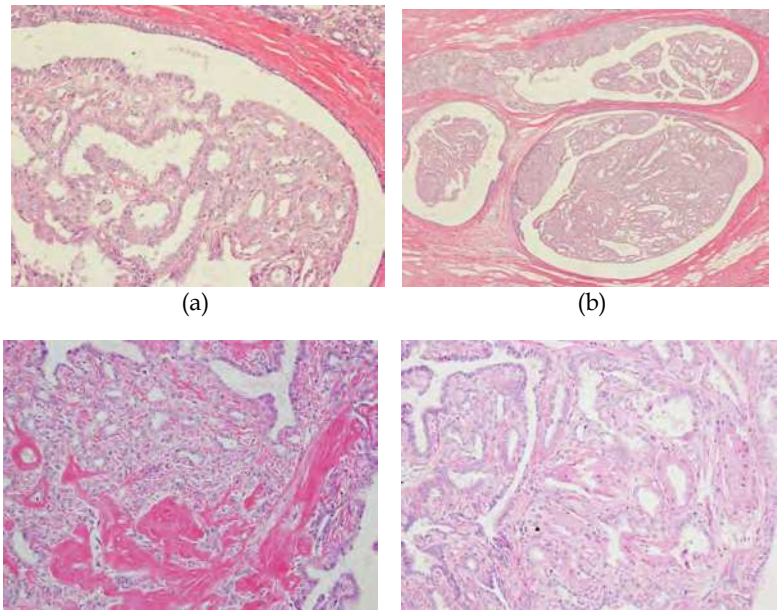


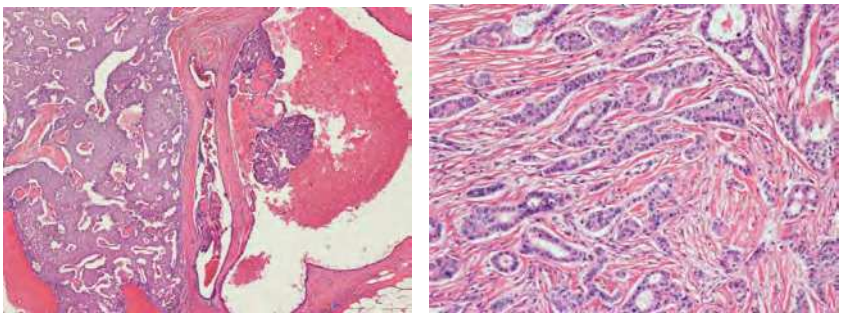
Fig. 7. Images of an intraductal papilloma in a 75-year-old woman. (a) The conventional ductogram and (b) indirect MR ductogram (MIP image) both show a dilated duct with a filling or signal defect (arrow), which represents an intraductal papilloma. (c) The MR mammogram (MIP image) shows a well-circumscribed enhanced lesion (arrow) that indicates the presence of a tiny papilloma. (d) The 3D fusion image shows the dilated duct (green) and the intraductal lesion (red). Reprinted from Hirose et al. (2006).



(a) (b)

(c) (d)

Fig. 8. Intraductal papilloma. (a) Low magnification. (b) Part of the papilloma in a cystically dilated duct. (c) Well-developed stromal sclerosis is present. (d) Apocrine metaplasia is observed.



(a) (b)

Fig. 9. Ductal carcinoma. (a) Ductal carcinoma in situ. Cystically dilated ducts contain hemorrhage. (b) Invasive ductal carcinoma.

9. Conclusion

MRI provides clinically useful information in patients with suspicious ND and negative standard evaluation. A larger prospective study to determine the use of MRI in the detection and differentiation of benign and malignant lesions causing ND is warranted.

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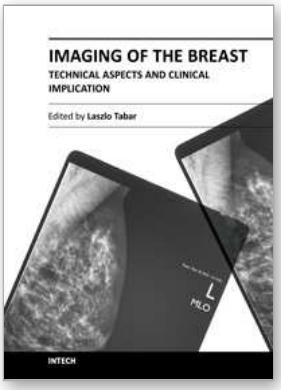

Imaging of the Breast - Technical Aspects and Clinical Implication

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Early detection of breast cancer combined with targeted therapy offers the best outcome for breast cancer patients. This volume deal with a wide range of new technical innovations for improving breast cancer detection, diagnosis and therapy. There is a special focus on improvements in mammographic image quality, image analysis, magnetic resonance imaging of the breast and molecular imaging. A chapter on targeted therapy explores the option of less radical postoperative therapy for women with early, screen-detected breast cancers.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821