Original Article

Performance of Breast MRI with MR Ductography in Evaluation of Pathologic Nipple Discharge

Chayakulkheeree J, MD[1], Likitkumchorn N, MD[1]

[1] Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Objective: To determine diagnostic value of contrast-enhanced breast magnetic resonance imaging (CE-breast MRI) with magnetic resonance (MR) ductography in evaluation of patients with pathologic nipple discharge focusing on sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV) for malignant detection.

Materials and Methods: The present study retrospectively reviewed 66 Asian patients with pathologic nipple discharge who underwent CE-breast MRI with MR ductography between 2011 and 2017. Comparison between imaging findings and gold standards, pathological diagnosis, and clinically or radiographic 2-year follow-up data were performed. Sensitivities, specificities, PPV, and NPV were evaluated. The AUC was achieved to assess the performance of each modality.

Results: Over seven years, 66 patients underwent CE-breast MRI with MR ductography for evaluation of pathologic nipple discharge. All 13 malignancies were detected by MRI. Two patients (15%) showing occult malignant lesions on mammogram and ultrasound were diagnosed by MRI. MRI showed 100% sensitivity and 100% NPV, suggesting the ability to rule out malignant lesion. The specificity and PPV were 38% and 28%, respectively.

Conclusion: CE-breast MRI with MR ductography is a useful and less-invasive tool for the evaluation of patients with pathologic nipple discharge because of its high performance in detection of malignancy by means of high sensitivity (100%), high NPV (100%), and fair specificity (38%). It is especially useful in cases of pathologic nipple discharge with negative conventional imaging. However, overestimation was found in papillomas or inflammation, benign lesions that mimic malignancy due to vivid enhancement.

Keywords: Breast MRI, MR ductography, Nipple discharge, Ductography

Received 25 Jun 2019 | Revised 4 Oct 2019 | Accepted 17 Oct 2019

J Med Assoc Thai 2020;103(1):76-82
Website: http://www.jmatonline.com

Nipple discharge is a common symptom with unclear definite work up and management[1]. It is the third most common breast-related chief complaint after lump and breast pain and has a prevalence of 5% to 10%[1-3]. Furthermore, approximately 80% of women will develop at least one episode of nipple discharge during their lifetime[1].

There are two types of nipple discharge. The first is physiologic nipple discharge, which can occur due to pregnancy or breastfeeding, following breast stimulation or in those who are taking certain medications, including estrogens and some antidepressant medications. Second is pathologic nipple discharge, which should be a concern for underlying breast disease. There are some characteristics of pathologic nipple discharge such as secreted spontaneously from the unilateral breast and single duct or persistent or intermittent with various appearances (clear, serous, or bloody discharge). These pathologic nipple discharges can be caused by various conditions that include benign lesions (intraductal papilloma or papillomatosis, nipple adenoma, and duct ectasia) or malignant lesions (ductal carcinoma in situ [DCIS], invasive ductal carcinoma [IDC], and Paget's disease). The most common cause of pathologic nipple discharge is intraductal papilloma or papillomatosis, which were

Correspondence to:

Chayakulkheeree J.

Department of Radiology, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.

Phone: +66-2-2564417

Email: Jatuporn.C@chula.ac.th

How to cite this article: Chayakulkheeree J, Likitkumchorn N. Performance of Breast MRI with MR Ductography in Evaluation of Pathologic Nipple Discharge. J Med Assoc Thai 2020;103:76-82.

found in 35% to 48%[4] of the patients. Most nipple discharge is usually caused by benign lesions but 5% to 21% turned out to be malignant with commonly missed diagnoses.

Currently, the investigation of choice for pathologic nipple discharge consists of mammography and ultrasound (US) as primary modalities follow by ductography, contrast-enhanced breast magnetic resonance imaging (CE-breast MRI), and magnetic resonance (MR) ductography, which depends on availability[1,5]. In the past, conventional ductography was the diagnostic procedure of choice in patients with nipple discharge. However, it was invasive, time-consuming, and was potentially related to complications.

At present, CE-breast MRI has been increasingly used in the evaluation of breast problems including pathologic nipple discharge. It potentially gives more benefits than those conventional imaging modalities. Some previous studies published the advantages of CE-breast MRI over conventional ductography, including non-invasiveness and the ability to detect enhancing intra or extraductal lesions. Moreover, adding sequence MR ductography tends to improve diagnostic values in demonstrating ductal visualization, distribution of intraductal lesion, and can differentiate benign and malignant lesions[2].

Thus, the objectives of the present study were to determine the diagnostic value of CE-breast MRI with MR ductography in the evaluation of patients with pathologic nipple discharge focusing on the sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV) for malignant detection.

Materials and Methods

Patients

From the present study radiological and clinical databases, the authors retrospectively identified all patients with pathologic nipple discharge who underwent CE-breast MRI with MR ductography in the present institution, which is an academic medical center in Thailand, between January 1, 2011 and January 31, 2017. The present study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (COA No.579/2016 and IRB No.287/59).

Imaging technique and interpretation

The MRI technique was used for breast imaging over the seven-year period of this study. All exams were performed with 1.5 Tesla (Magnetom Espree, Global Siemens Healthcare, Erlengen, Germany). Each study included axial turbo spinecho (TSE) T2 weighted image (T2WI), axial short T1 inversion recovery (IR), axial 3D T1 weighted image (T1WI) with fat suppression (FS), coronal T1WI, coronal T2WI and six-phase dynamic (every one minute) post contrast 3D T1WI with FS with and without subtraction after intravenous administration of a gadolinium-based agent using a weight-based dosing protocol, axial post contrast 3D T1WI high resolution, axial diffusion weighted image (DWI) and apparent diffusion coefficient (ADC), and sagittal post contrast T2WI with FS. Adding heavily T2WI (TE 180 to 200 msec) in axial and sagittal planes and 3D heavily T2WI with maximal intensity projection (MIP) reconstruction for indirect ductography sequences were noted.

Data collection

The hospital electronic medical records and synapses were searched for all patients with pathologic nipple discharge who underwent CE-breast MRI with MR ductography. The authors also reviewed patient demographic data such as age, gender, characteristic of nipple discharge, imaging findings, pathological results from microdochectomy and surgical excisions, and clinical and radiographic follow-up data for two years. Patients who did not fulfill criteria, comprising patients with incomplete data of nipple discharge characteristics, no histopathologic results by biopsy or surgery, and who were lost follow-up were excluded from the present study.

CE-breast MRI with MR ductography were retrospectively reviewed by two radiologists with 10 years' experience, blinded to the final diagnosis. The consensus of all imaging findings were retrospectively compared with the gold standards. All the findings were assessed according to the American College of Radiology Breast Imaging Reporting and Data System (ACR-BIRADS) 2013 (fifth edition)[7].

Statistical methods

Diagnostic agreement between CE-breast MRI with MR ductography with the gold standards were assessed by 2×2 contingency table analyses. Measures agreement included sensitivity, specificity, PPV, and NPV with 95% confidence interval (CI). The AUC, area under the receiver operating characteristic (ROC) curve was performed to assess the performance of each modality. Results were considered statistically significant if the p-value was less than 0.050 (StataCorp. 2017. Stata Statistical Software: Release

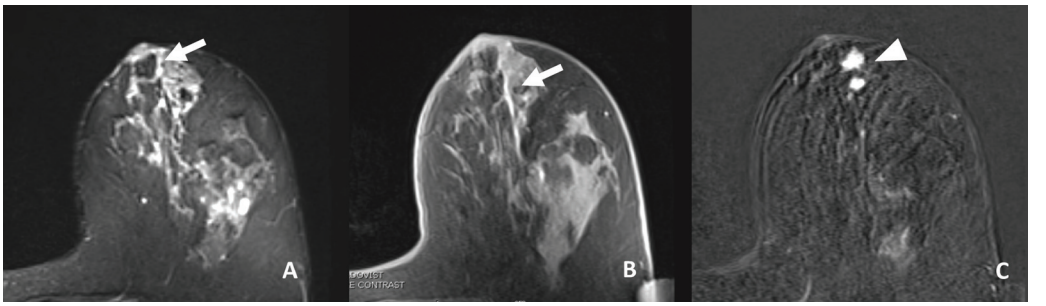

Figure 1. A 33-year old female patient presented with spontaneous bloody nipple discharge from left breast. Left breast MRI showed dilatation of subareolar duct (arrow) in axial T2WI (A) with hyper intense in T1WI (B) which represented blood product within duct. After gadolinium was given, there were two irregular enhancing masses (arrowhead) in post contrast axial T1WI with subtraction (C). Pathology was grade II IDC and intraductal papillomas on histopathology.

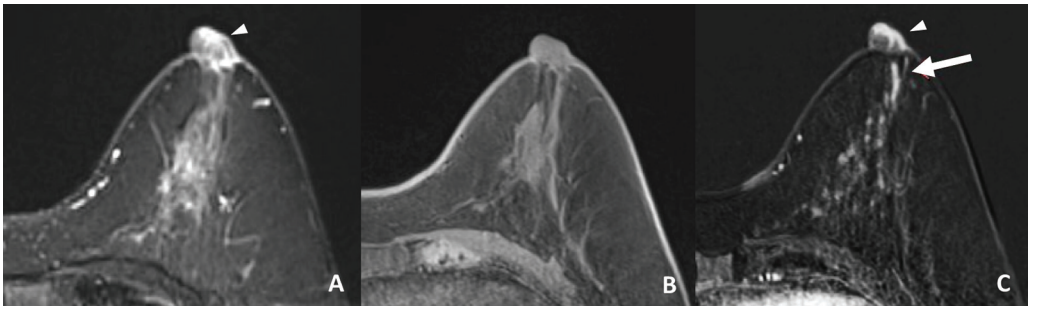

Figure 2. A 63-year old female patient presented with nipple discharge and chronic eczema at left nipple. There was enlarge left nipple with hyperintense in axial T2WI (arrowhead) (A) and isointense on axial T1WI (B). After given gadolinium injection, there was heterogeneous enhancement of left nipple (arrowhead) with ductal enhancement extending from left (arrow) nipple in post contrast axial T1WI with subtraction (C). Pathology revealed high grade DCIS and Paget's disease.

Table 1. Demographic characteristics

Characteristics	n (%)
Number of patients	66
Age (years); mean (range)	47 (22 to 83)
Sex (female/male)	65/1 (98/2)
History of Surgery	7 (11)
Sides (left)	36 (55)
Characteristics of nipple discharge	
Spontaneous vs. provoked	23 (35) vs. 2 (3)
Persistent vs. intermittent	1 (2) vs. 5 (8)
Clear/serous/bloody vs. mild/cream/dark green	42 (64) vs. 3 (5)
Nipple ulcer/lesion	3 (5)

15. College Station, TX: StataCorp LLC).

Breast MRI findings classified by ACR-BIRADS 2013 categories 4 to 5 were considered low-high suspicious for malignancy, while those with ACR-BIRADS categories 0 to 3 were considered negative or benign lesions.

Results

Sixty-six Asian patients underwent CE-breast MRI with MR ductography for the evaluation of pathologic nipple discharge (mean age 47, range 22 to 83 years), and included sixty-five female patients (98%) and one male patient (2%). Forty-six patients (70%) underwent mammogram and US and twelve patients (18%) underwent only the US. Forty-seven patients (71%) underwent microdochectomy or surgical excision and all sixty-six patients (100%) had clinical or radiographic follow-up about two years after presentation. All sixty-six patients had at least one feature of pathologic nipple discharge and three patients (5%) experienced nipple ulcer, Paget's disease (Table 1).

The data were compared with final diagnoses in all cases, including histopathologic results (47 cases) and clinical or radiographic follow-up about two years after presentation (19 cases). In the present study, malignant lesions were found in thirteen patients including six cases (46%) of DCIS, ten cases (77%) of IDC (Figure 1), and two cases (15%) of Paget's

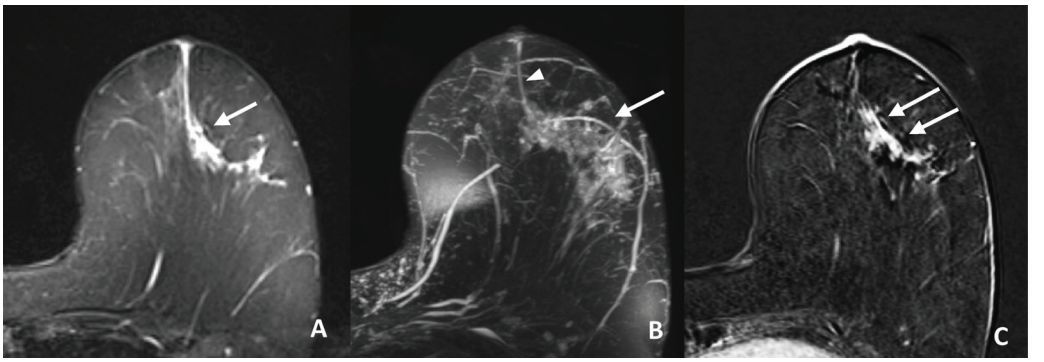

Figure 3. A 67-year old female patient presented with bloody nipple discharge from left breast. T2WI (A) showed segmental duct dilatation (arrow) at left outer middle part. MR ductography (MIP with heavy T2WI) (B) showed more emphasized extension and distribution of dilated duct from central (arrowhead) to peripheral region (dash arrow). In post contrast axial T1WI with subtraction (C) showed clumped enhancement of the dilated duct. Pathology revealed IDC and grade II DCIS.

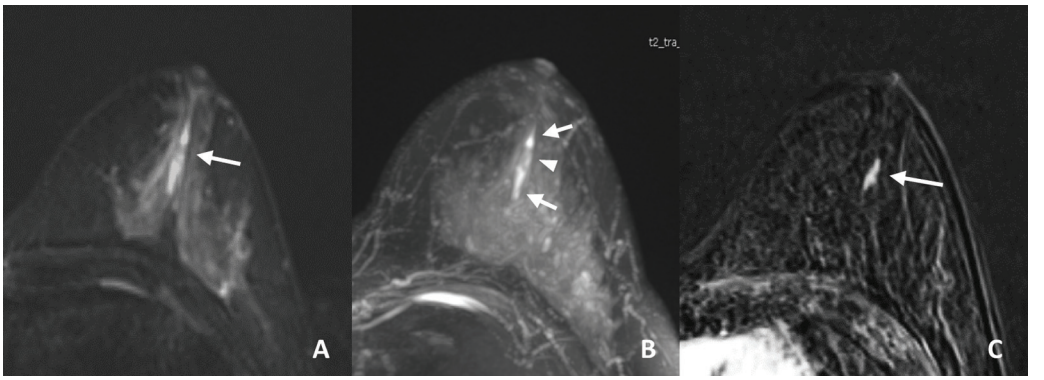

Figure 4. A 23-year old female patient presented with spontaneous bloody nipple discharge from left breast. There was focal dilatation of central duct with hypointense intraductal lesion (arrow) in axial T2WI (A). MR ductography (MIP with heavy T2WI) (B) demonstrated intraductal lesion (arrowhead) with dilate proximal and distal dilatation (arrow). After gadolinium injection in axial T1WI with subtraction (C), there was circumscribed homogeneous enhancing mass (dash arrow). Pathology reviewed intraductal papilloma.

Table 2. Histopathologic data

Pathology	n (%)
Benign	34 (72)
Intraductal papilloma/papillomatosis	23 (68)
Nipple adenoma	2 (6)
Duct hyperplasia	7 (21)
Fibrocystic change	10 (29)
Inflammation/abscess/mastitis	4 (12)
Not mention cell type	1 (3)
Malignant	13 (28)
Pure DCIS	6 (46)
IDC (± DCIS)	10 (77)
Paget's disease	2 (15)

DCIS=ductal carcinoma in situ; IDC=invasive ductal carcinoma

disease (Figure 2). Five cases were diagnosed with both DCIS and IDC, pathologically (Figure 3). Thirty-four lesions were pathologically proven benign and included twenty-three cases (68%) of intraductal papilloma or papillomatosis (Figure 4), two cases (6%) of nipple adenoma, seven cases (21%) of duct hyperplasia, ten cases (29%) of fibrocystic change, and four cases (12%) of inflammation of the breasts (Table 2). Nineteen patients showed stable lesion or improvement of clinical or radiographic follow-up at least two years after presentation, classified as benign.

The MRI findings of thirteen patients diagnosed with malignant lesions, which accounted for DCIS, IDC, and Paget's disease were 69% enhancing masses (nine cases), 46% segmental ductal dilatation (six cases), 85% enhancing duct (eleven cases), and 31% intraductal lesions (four cases). The present study

Table 3. Associated ductal involvement data

	Intraductal papilloma/papillomatosis (n=23)	DCIS (n=10)	IDC (n=6)	Paget's (n=2)
Mass enhancement	16	8	4	1
Segmental duct dilatation	3	6	4	0
Duct enhancement	15	9	5	2
Introductal lesions	14	4	2	0

DCIS=ductal carcinoma in situ; IDC=invasive ductal carcinoma

Table 4. MRI findings

MRI findings	Benign (n=34) n (%)	Malignant (n=13) n (%)
Mass	23 (68)	10 (77)
Shape		
• Oval, lobulated, round	20 (87)	5 (50)
• Irregular	3 (13)	5 (50)
Margin		
• Circumscribed, smooth	20 (87)	4 (40)
• Non-circumscribed, irregular, speculated	3 (13)	6 (60)
Internal enhancement		
• Homogeneous	7 (30)	0 (0)
• Heterogeneous	15 (65)	7 (70)
• Rim enhancement	0 (0)	2 (20)
NME	5 (15)	3 (23)
Distribution		
• Focal	4 (80)	0 (0)
• Segmental	1 (20)	2 (67)
• Diffuse	0 (0)	1 (33)
Enhancement		
• Heterogeneous	2 (67)	2 (67)
• Clumped	2 (40)	1 (33)
Associated ductal involvement	29 (85)	13 (100)
Dilatation		
• Focal	23 (79)	7 (54)
• Regional	0 (0)	0 (0)
• Diffused	1 (3)	0 (0)
• Segmental	5 (17)	6 (46)
Enhancement	20 (69)	11 (85)
HyperTI content	4 (14)	4 (31)
Intraductal lesion(s)	17 (59)	4 (31)
Associated nipple involvement	7 (21)	2 (15)
Asymmetry	2 (29)	2 (100)
Inverted	2 (29)	0 (0)
Enhancement	5 (71)	2 (100)

MRI=magnetic resonance imaging; NME=non-mass enhancement

MRI findings of twenty-three intraductal papilloma or papillomatosis lesions, the most common cause of pathologic nipple discharge, showed as 70% enhancing circumscribed masses (16 cases), 13% segmental ductal dilatation (three cases), 65% enhancing duct (15 cases), and 61% intraductal lesions (14 cases) (Table 3, 4).

The sensitivity of CE-breast MRI with MR ductography for diagnostic malignancy was 100% (13 out of 13 cancers). The specificity of MRI ductography was 38% (33 false positive cases and 20 true negative cases). The PPV and NPV were 28% and 100%, respectively. Twenty-one (57%) of the thirty-seven patients with MR ductography coded as BIRADS 4 were pathologically diagnosed as benign conditions with twenty-one intraductal papillomas or papillomatosis, two nipple adenomas, one duct hyperplasias, two fibrocystic changes, and four inflammatory processes such as breast abscesses or mastitis. On the other hand, all thirteen malignant lesions were detected by CE-breast MRI with MR ductography.

The present study of CE-breast MRI with MR ductography showed 100% sensitivity and 100% specificity in detected intraductal papillomas and papillomatosis. The PPV and NPV were 100% and 39%, respectively.

Furthermore, the subgroup of the nine cases coded as BIRADS 5 by CE-breast MRI with MR ductography were diagnosed correctly to be malignant lesions, showing 100% specificity and 100% PPV. The sensitivity and NPV in detecting BIRADS 5 were 69% and 93%, respectively.

The CE-breast MRI with MR ductography was the expedient diagnostic study in two patients with negative mammogram and US. MRI could identify suspicious lesions and upgraded ACR-BIRADS to 4 and 5, whereas mammogram and US were coded as BIRADS 1 and 2. These two lesions were pathologically proven as DCIS and Paget's disease, respectively.

Diagnostic performances of CE-breast MRI

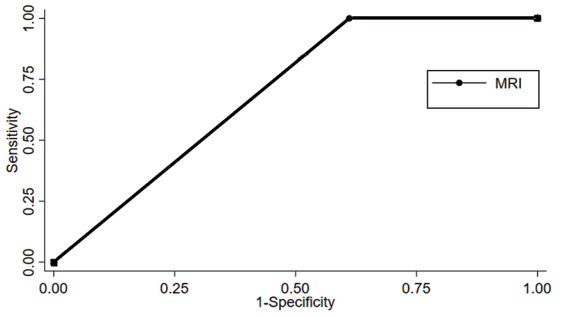

Figure 5. AUCs of breast MRI with MR ductography.

with MR ductography were presented with the AUCs which was 69% (Figure 5).

Discussion

Pathologic nipple discharge has become a challenging concern in breast health issues worldwide. The choice of imaging modalities and management of this condition remains a controversy. There were some literatures that proposed using CE-breast MRI adding sequences of ductal examination called MR ductography allowed for improvement in treatment planning compared to the conventional imaging modalities, mammography, US and ductography[1,2,5]. The present study is one of the largest studies to determine the ability of CE-breast MRI with MR ductography in evaluating pathologic nipple discharge.

The authors found CE-breast MRI with MR ductography showed high sensitivity (100%) in the detection of malignancy and high NPV (100%), suggesting the ability of this diagnostic modality to rule out malignant lesions. Thus, negative MR ductography in patients with symptomatic pathologic nipple discharge may obviate the need for unnecessary surgical intervention.

Moreover, subgroup analysis of selected coded BIRADS 5 cases by CE-breast MRI with MR ductography revealed excellent performance of MRI to confirm malignant lesions with 100% specificity and 100% PPV. Although, there was limitation due to small data of BIRADS 5 cases, the results are still promising.

Additionally, the present study showed great ability of MRI in detecting intraductal lesions as intraductal papillomas/papillomatosis by 100% sensitivity and specificity, agreeing with other studies that reported the usefulness of MRI for its high sensitivity for papillary lesions[8,9]. However, papillomas usually mimic malignancy because they always present as intraductal lesions with vivid enhancement[8,9]. Similar to the present study, twenty-one (57%) of the thirty-seven suspicious for malignant lesions (BIRADS 4) on MRI were mostly pathologically confirmed as intraductal papillomas or papillomatosis. The authors also found that inflammatory breast lesions such as abscesses and mastitis caused false positives in mammogram, US, and MRI.

In addition, breast MRI with adding MR ductography, shows high value in evaluating intraductal lesions, their extension of the diseases and extraductal portion of the lesions in both benign and malignancy, and can be useful in guiding the surgical approach.

For male patients, the incidence of cancer was higher than female in the setting of pathologic nipple discharge (23% to 57%)[10,11]. The study had one male patient with negative mammogram and US. His CE-breast MRI with MR ductography showed ductal enhancement at subareolar region. The final pathology turned out with low grade DCIS with intraductal papilloma.

Conclusion

CE-breast MRI with MR ductography is a useful and less-invasive tool for the evaluation of intraductal lesion in patients with pathologic nipple discharge for its high performance in detection of malignancy, showing high sensitivity (100%) and high NPV (100%). However, there is overestimation in the diagnosis of papilloma or inflammation, which are benign lesions that often mimic malignancy due to vivid enhancement. Decisively, CE-breast MRI with MR ductography could help in cases of pathologic nipple discharge with negative mammogram and US.

What is already known on this topic?

Few studies have shown that CE-Breast MRI have benefit on evaluating patients with pathologic nipple discharge. As compared to conventional ductography, which is the prior method, CE-Breast MRI is less invasive and be able to visualize enhancing lesion. However, only few studies of adding MR ductography were established, especially in Asian women. However, due to expensiveness, time consuming, and less availability of breast MRI, the cost effectiveness or patient selection method for doing breast MRI is questionable.

What this study adds?

As the authors add MR ductography as an

additional sequence in patient with pathologic nipple discharge to visualize inside the duct has some problem. The procedure has benefit in patient with negative mammogram and US but strong clinical symptom. Moreover, the procedure shows fair specificity due to overestimation of papilloma and inflammation, which is the limitation of CR-Breast MRI.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Lippa N, Hurtevent-Labrot G, Ferron S, Boisserie-Lacroix M. Nipple discharge: The role of imaging. Diagn Interv Imaging 2015;96:1017-32.
2. Tokuda Y, Kodama Y. Suspicious nipple discharge diagnostic evaluation. In: Tabar L, editor. Imaging of the breast-technical aspects and clinical implication; London: InTechOpen; 2012. p. 199-216.
3. Choudhury S, Isomoto I, Hyashi K. Magnetic resonance imaging features of breasts in patients with nipple discharge. Bangladesh Med Res Counc Bull 2008;34:44-7.
4. Di Pastena F, Ballesio L, Gigli S, Pasinati G, Tardioli S, Giuliani IA, D'Ambrosio I. Breast MRI in patients with unilateral hematic nipple discharge: comparison with galactography. European Congress of Radiology 2013. doi: 10.1594/ecr2013/C-2200.
5. Bahl M, Baker JA, Greenup RA, Ghate SV. Evaluation of pathologic nipple discharge: What is the added diagnostic value of MRI? Ann Surg Oncol 2015;22 Suppl 3:S435-41.
6. Hirose M, Nobusawa H, Gokan T. MR ductography: comparison with conventional ductography as a diagnostic method in patients with nipple discharge. Radiographics 2007;27 Suppl 1:S183-96.
7. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA. ACR BI-RADS ATLAS: Breast imaging reporting and data system (BI RADS). 5th ed. Reston, VA: American College of Radiology; 2013.
8. Nicholson BT, Harvey JA, Patrie JT, Mugler JP 3rd. 3D-MR ductography and contrast-enhanced MR mammography in patients with suspicious nipple discharge; a feasibility study. Breast J 2015;21:352-62.
9. Lorenzon M, Zuiani C, Linda A, Londero V, Girometti R, Bazzocchi M. Magnetic resonance imaging in patients with nipple discharge: should we recommend it? Eur Radiol 2011;21:899-907.
10. Morrogh M, King TA. The significance of nipple discharge of the male breast. Breast J 2009;15:632-8.
11. Muñoz Carrasco R, Álvarez Benito M, Rivin del Campo E. Value of mammography and breast ultrasound in male patients with nipple discharge. Eur J Radiol 2013;82:478-84.