Original Investigation

Differential Diagnosis of Benign and Malignant Breast Papillary Neoplasms on MRI With Non-mass Enhancement

Juan Zhou, MD[1], Mei Li, MS, Dongqing Liu, MS, Fugeng Sheng, MD, Jianming Cai, MD[1]

Rationale and Objectives: To explore the differential diagnosis of benign and malignant papillary neoplasms on MRI with non-mass enhancement.

Materials and Methods: A total of 48 patients with surgically confirmed papillary neoplasms showing non-mass enhancement were included. Clinical findings, mammography and MRI features were retrospectively analyzed, and lesions were described according to the breast imaging report and data system (BI-RADS). Multivariate analysis of variance was used to compare the clinical and imaging features of benign and malignant lesions.

Results: Fifty-three papillary neoplasms were shown on MR images with non-mass enhancement, including 33 intraductal papilloma and 20 papillary carcinomas (9 intraductal papillary carcinoma, 6 solid papillary carcinomas, and 5 invasive papillary carcinoma). Mammography showed amorphous calcification in 20% (6/30), of which 4 were in papilloma and 2 were in papillary carcinoma. On MRI, papilloma mostly showed linear distribution in 54.55% (18/33), clumped enhancement in 36.36% (12/33). Papillary carcinoma showed segmental distribution in 50% (10/20), clustered ring enhancement in 75% (15/20). ANOVA showed age ($p = 0.025$), clinical symptoms ($p < 0.001$), apparent diffusion coefficient (ADC) value ($p = 0.026$), distribution pattern ($p = 0.029$) and internal enhancement pattern ($p < 0.001$) were statistically significant between benign and malignant of papillary neoplasms. Multivariate analysis of variance suggested that the internal enhancement pattern was the only statistically significant factor ($p = 0.010$).

Conclusions: Papillary carcinoma on MRI with non-mass enhancement mostly showed internal clustered ring enhancement, while papilloma mostly showed internal clumped enhancement; additional mammography is of limited diagnostic value, and suspected calcification occurs mostly in papilloma.

Keywords: Breast; Papillary Neoplasm; Mammography; Magnetic Resonance Imaging; Non- Mass Enhancement.

INTRODUCTION

Breast papillary neoplasms include a heterogeneous group of diseases ranging from benign and atypical lesions to malignant tumors with or without invasion. They are defined by the presence of fibrovascular cores surrounded by epithelial proliferation. In the 5th edition of 2019 WHO classification of breast Tumors (1−3), papillary neoplasms comprise intraductal papilloma, papillary ductal carcinoma in situ, encapsulated papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma. In pathology, papillary neoplasms are classified into several types based on the following: location in large ducts or small ducts (terminal duct lobular units, TDLU); nature of the proliferating epithelial cells; presence and location of myoepithelial cells; morphology of papillary carcinoma (4). Management of breast papillary neoplasms diagnosed as benign with core needle biopsy is controversial because of the wide range of reported upgrade rates (0−33%) to intraductal papillary carcinoma in situ or invasive carcinoma at subsequent surgical excision (5,6). The diversity of papillary neoplasms in pathology leads to a variety of imaging findings, which makes diagnosis difficult.

Breast magnetic resonance imaging (MRI) is the most sensitive imaging method for the diagnose of breast diseases (7). MRI was reported to have a higher sensitivity in detecting

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From the Department of Radiology, 5th Medical Center of Chinese PLA General Hospital, 8 Dongda St, Fengtai District, Beijing, 100071 China (J.Z., D.L., F.S., J.C.); Department of Radiology, PLA Middle Military Command General Hospital, Wuhan, China (M.L.). Received January 13, 2023; revised February 8, 2023; accepted February 9, 2023. **Address correspondence to:** J.Z. e-mail: zjuan122@163.com

[1] Juan Zhou and Jianming Cai contributed equally to the article.

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the number and extent of the papillary neoplasms than mammography and ultrasound (8–14). The papillary neoplasms with multiple duct involvement or multiple papillary neoplasms within a single duct are usually manifest nonmass enhancement (NME) on MR imaging. Understanding the imaging characteristics of these lesions is helpful for the diagnosis and differential diagnosis of breast lesions. In this study, clinical manifestation, mammography and MRI features of papillary neoplasms on MRI with nonmass enhancement were analyzed, to explore the differential diagnosis of benign and malignant papillary neoplasms.

MATERIAL AND METHODS

This was a retrospective study from February 2013 until December 2019, and was approved by the institutional review board of our institution. Written informed consent was waived.

Inclusion criteria: (1) Papillary neoplasms proved by surgical pathology; (2) MRI examination obtained before surgery; (3) MR imaging showed nonmass enhancement. Exclusion criteria: (1) Previous history of surgery, radiotherapy or chemotherapy for breast tumor; (2) Incomplete imaging data or poor image quality; (3) only biopsy or vacuum-assisted removal were performed.

Mammography

All mammography were obtained from the digital breast machine (Hologic Selenia Dimensions, United States). Automatic exposure was adopted, and all imaging parameters were automatically selected according to the thickness and density of the breast. Cephalocaudal (CC) and medial-lateral-oblique (MLO) images were taken routinely, and additional projection positions were taken when necessary.

Magnetic Resonance Imaging Protocol

Magnetic resonance imaging was done using a 1.5-T system (Magnetom Espree Pink; Siemens, Munich, Germany) equipped with an 8-channel breast coil. Patients were examined in the prone position, with both breasts positioned naturally in the coil cavity. Conventional plain scans were carried out using the following parameters: axial T2-weighted image trim (repetition time/echo time [TR/TE], 2900/60 ms; matrix, 640× 640; slice thickness, 4 mm); axial T1WI 3-dimensional (3D) non−fat-suppressed (TR/TE, 8.7/4.7 ms; matrix, 896×896; slice thickness, 1 mm); bilateral sagittalT2-weighted image pair (TR/TE, 3800/85 ms; matrix, 512 × 512); axial diffusion-weighted imaging (DWI) (b=0, 1000 s/mm^2) was performed(TR/TE, 5800/104 ms; slice thickness, 4 mm). Dynamic MRI was undertaken using a 3D fat-suppressed volumetric interpolated breath-hold examination sequence before and 7 times after bolus injection of gadopentetate dimeglumine (0.1 mmol/kg; Magnevist; Bayer, Berlin, Germany) at 2 ml/s followed by flushing with 20-mL physiological (0.9%) saline using an automatic injector. Both breasts were examined for 7 minutes in the axial plane. Parameters of dynamic MRI were as follows: TR/TE, 4.53/1.66 ms; matrix, 384 × 384; slice thickness, 1.0 mm. Images of each phase were subtracted automatically, and maximum intensity projection reconstruction was carried out automatically on the first phase of postcontrast subtraction images.

Clinical and Imaging Features Analysis

The radiologists had knowledge of the clinical indication for examination when available. According to the lexicon of Breast Imaging Reporting and Data System (BI-RADS) (15), two radiologists engaged in breast imaging diagnosis independently analyzed the clinical and imaging features, and reached a consensus through negotiation when opinions were not unanimous.

According to the pathology results, the cases were classified into the papilloma and papillary carcinomas. Masses and calcifications on mammography were recorded. The amount of fibroglandular tissue (FGT), background parenchymal enhancement (BPE), apparent diffusion coefficient (ADC) value, maximum amplitude of enhancement; ductal precontrast high signal on T1 weighted imaging and kinetic curve were also recorded.

Golden Standard

According to the pathological results, it can be classified into benign papilloma and papillary carcinoma. Intraductal papilloma, intraductal papilloma with ordinary epithelial hyperplasia and intraductal papilloma with atypical epithelial hyperplasia are classified as benign lesions. Intraductal papillary carcinoma, encapsulated papillary carcinoma, and solid papillary carcinoma with or without invasion were classified as malignant lesions.

Statistical Analysis

Analyses were performed by using the Python language and the StatsModels tool (https://www.statsmodels.org/stable/index.html, and a p value less than 0.05 was regarded as statistically significant. Univariate and multivariate analysis of variance were employed to identify clinical manifestation and MRI diagnostic risk indicators between papilloma and papillary carcinomas. The variables which showed p values less than 0.05 in the univariate analysis were selected for the multiple linear regression analysis.

RESULTS

There were 53 papillary neoplasms were shown on MR images with non-mass enhancement in 48 patients enrolled in Figure 1. Demographics, clinical manifestation and mammography characteristics of papillary neoplasms were shown in

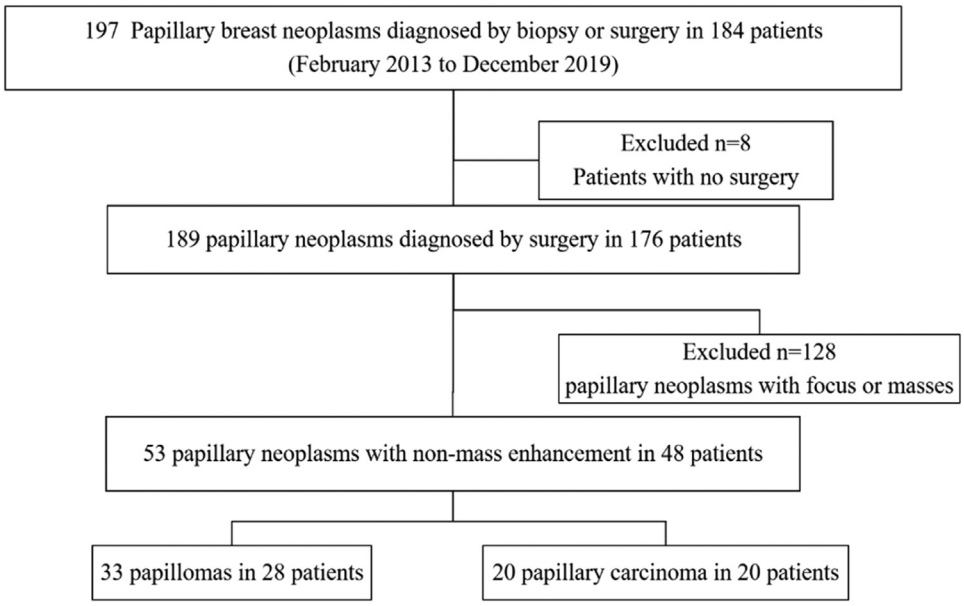

Figure 1. Flowchart shows the enrolled cases of papillary neoplasms with nonmass enhancement.

Table 1. There were 33 intraductal papilloma and 20 papillary carcinomas (9 intraductal papillary carcinoma, 6 solid papillary carcinomas and 5 invasive papillary carcinoma). All patients were female, the mean patient age (±standard deviation) was 53.08±10.50 years old. The clinical symptoms were nipple discharge (50.94%, 27/53), palpable mass (43.40%, 23/53), both mass and nipple discharge (1.89%, 1/53) and asymptomatic (3.77%, 2/53). The corhort contained 27 cases of nipple discharge in 24 cases of intraductal papilloma, 23 cases of mass in 15 cases of papillary carcinoma, both mass and nipple discharge in 1 case of papillary carcinoma.

Thirty cases of mammography were reviewed (Table 1). The X-ray showed amorphous calcifications (20%, 6/30), mass (50%, 15/30) and negative (30%, 9/30). Grouped (66.67%, 4/6), linear (16.67%, 1/6) and regional (16.67%, 1/6) distribution were observed in suspicious calcifications. Six cases of suspicious calcifications were found in 4 cases of intraductal papilloma and 2 cases of papillary ductal carcinoma in situ.

MRI features of papillary neoplasms with non-mass enhancement were shown in Table 2. In papilloma, the mean age was 50.88 ± 9.19 years, the mean ADC value was (1.405 ± 0.320) mm^2/s and the maximum amplitude of enhancement was (166.12 ± 64.78) %; Heterogeneous fibroglandular tissue accounted for 66.67% (22/33), mild BPE accounted for 42.42% (14/33) and ductal high signal on T2W imaging accounted for 90.91% (30/33). MRI features involved ductal precontrast high signal on T1 weighted imaging (51.52%,17/33), linear distribution (54.55%,18/33), clumped pattern (36.36%,12/33) and persistent curve (48.48%,16/33) in papilloma. In papillary carcinomas, the mean age was 57.5 ± 11.45 years, the mean ADC value was (1.178 ± 0.393) mm^2/s and the maximum amplitude of enhancement was (176.67 ± 53.35) %. Scattered fibroglandular tissue accounted for 40% (8/20), mild BPE accounted for 45% (9/20) and ductal high signal on T2W imaging accounted for 75% (15/20). MRI features involved ductal precontrast high signal on T1 weighted imaging (50%,10/20), segmental distribution (50%,10/20), clustered ring (75%,15/20) and washout curve (60%,12/20) in papillary carcinomas.

TABLE 1. Demographics, Clinical and Mammography features of Papillary Neoplasms with NME*

Variate	Number
Patients	48
Cases	53
Age(y)#	53.38±10.50
Sex	48
Female	48
Male	0
Clinical Manifestation	53
Nipple Discharge	27
Palpable Mass	23
Mass and Nipple Discharge	1
No Symptom	2
Pathology Classification	53
Intraductal papilloma	33
Papillary ductal carcinoma in situ	9
Solid papillary carcinoma in situ	6
invasive papillary carcinoma	5
Mammography	30 (15 papillomas, 15 papillary carcinomas)
Amorphous Calcification	6
Grouped	4 (2 papillomas,2 papillary carcinomas)
Linear	1(papilloma)
Regional	1(papilloma)
Mass	15 (5 papillomas,10 papillary carcinomas)
Negative	9

TABLE 2. Univariate and Multivariate Analysis of MRI Features of Papillary Neoplasms with Non-mass Enhancement

Variate		Papillomas	Papillary Carcinomas*	Total Number	F (univariate)	*p** value (univariate)	F (multivariate)	*p** value (multivariate)
Age(y)		50.88±9.19	57.5±11.45	53.38±10.50	5.36	**0.02**	1.19	0.28
ADC# value(mm^2/s)		1.41±0.32	1.18±0.39	1.32±0.36	5.29	**0.03**	0.00	0.97
Maximum amplitude of enhancement (%)		166.12±64.78	176.67±53.35	170.1±60.40	0.377	0.54	/	/
Ductal high signal on T2W imaging		30	15	45	2.48	0.12	/	/
Ductal precontrast high signal on T1W imaging		17	10	27	0.01	0.92	/	/
Amount of fibroglandular tissue (FGT)	Entirely fat	3	3	6	3.35	**0.03**	0.29	0.84
	Scattered	6	8	14				
	Heterogeneous	22	5	27				
	Extreme	2	4	6				
Background parenchymal Enhancement (BPE)	Minimal	3	5	8	1.03	0.39	/	/
	Mild	14	9	23				
	Moderate	5	2	7				
	Marked	11	4	15				
NME#-Distribution	Focal	1	0	1	2.77	**0.03**	1.65	0.17
	Linear	18	7	25				
	Segmental	3	10	13				
	Reginal	2	1	3				
	Multiple regions	6	1	7				
	Diffuse	3	1	4				
NME#-Internal enhancement patterns	Homogeneous	10	0	10	15.07	**0.00**	4.40	**0.01**
	Heterogeneous	6	5	11				
	Clumped	12	0	12				
	Clustered ring	6	15	21				
Kinetic Curve	Persistent	16	3	19	3.57	**0.04**	0.70	0.50
	Plateau	7	5	12				
	Washout	10	12	22				
Total Number		33	20	53				

Note: *Include papillary ductal carcinoma in situ, solid papillary carcinoma in situ and invasive papillary carcinoma.

#NME = non-mass enhancement; ADC = apparent diffusion coefficient; FGT = fibroglandular tissue; BPE = background parenchymal.

**P* value less than 0.05 was regarded as statistically significant.

According to univariate analysis of variance, there were significant differences in age (p = 0.02), clinical manifestation (p = 0.00), FGT (p = 0.03), kinetic curve (p = 0.04), ADC value (p = 0.03), NME distribution (p = 0.03) and internal enhancement patterns (p = 0.00) between the two groups. However, ductal high signal on T2W imaging (p = 0.12), BPE (p = 0.39), ductal precontrast high signal on T1W imaging (p = 0.92), maximum amplitude of enhancement (p = 0.54) and mammography had no significant differences. The variables which showed p values less than 0.05 in the univariate analysis were selected for the multiple linear regression analysis. Multivariate analysis of variance showed internal enhancement patterns were the only statistically significant factor (p = 0.01) (Table 2).

DISCUSSION

Papillary neoplasms are papillary proliferative lesions originating from epithelium. Nipple discharge is the most common clinical manifestation, followed by clinically palpable masses. Nipple discharge is more common in intraductal papilloma (13), however, the mass is more common in papillary carcinoma (16), which had statistically significant difference as our study demonstrated. The mean age of intraductal papilloma were lower than that of papillary carcinomas, and there was a significant statistical difference between the two groups, which is consistent with the age distribution of different pathological types of papillary tumors as reported in the literature (17).

Of the 53 cases of papillary neoplasms on MR images with non-mass enhancement in this study, 45 showed definite ductal dilatation on T2-weighted images (84.91%), but there was no statistically significant difference between papilloma and papillary carcinomas. Twenty-seven cases of papillary neoplasms could show ductal precontrast high signal on T1W imaging (50.94%), it may indicate intraductal bleeding, but there was no statistically significant difference between papilloma and papillary carcinomas. Moreover, there was no statistically significant difference in the maximum enhancement between the two groups in our study.

Studies (18,19) reported that 55.0−72.7% cases of benign papilloma showed washout curves. However, in our cases, 48.48% cases of papilloma on MR images with non-mass enhancement had persistent curves, which was similarly another research (66.7%) (20). Typical papilloma is mainly located in the large catheter behind the papilloma, which is basically manifest as mass wash-out curve on MR image. Wash-out curves are rarely seen in branched ducts. The larger sample size may be one reason for the difference in kinetic curve types, only nonmass enhancement cases were enrolled may be another reason. Our sample is larger, and literature reports generally enroll masses or include a part of non-mass enhancement, and the number of non-mass enhancement is relatively small. Our study showed that kinetic curve types had a great value for differential diagnosis.

Yildiz et al (21) reported that the malignant papillary lesions (0.744×10) mm^2/s exhibited significantly lower mean ADC values than the benign lesions (1.339×10) mm^2/s. Our cases also demonstrated that the mean ADC value of papillary carcinomas (1.18 ± 0.393) mm^2/s was lower than papilloma (1.41 ± 0.320) mm^2/s, the statistics showed ADC value was helpful in distinguishing papilloma from papillary carcinomas. In our study, the enrolled cases were all non-mass enhancement lesions, which may be the reason why ADC values were higher than those reported in literature.

Wang et al (20) reported 37 cases of the segmental or regional distribution indicated a nonbenign papilloma. Moritani et al (22) considered that a lesion with a segmental abnormality in at least one breast imaging modalities indicated malignancy and should be surgically resected, implying that DCIS and papilloma existed in the same duct system. In our study, there is no papillary neoplasms mixed with ductal carcinoma in situ or invasive ductal carcinoma, only contain papillary carcinoma in situ or with invasion. We consider that the segmental distribution is more commonly observed in papillary carcinoma than papilloma, itself really reflects the characteristics of papillary carcinoma. Sarica et al (16,23) found that the segmental enhancement was more

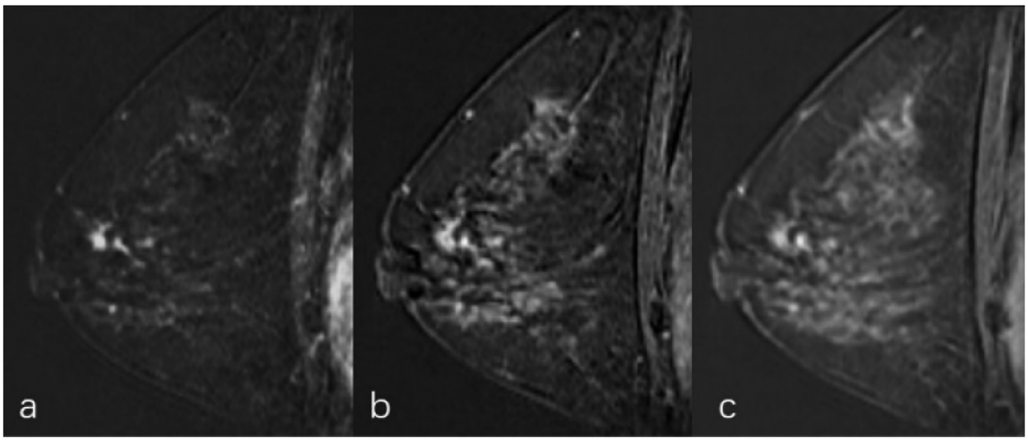

Figure 2. A 46-year-old woman with intraductal papilloma, the clinical manifestation is nipple discharge of left breast. Mammography is negative, MR shows linear distribution and clumped enhancement on postcontrast first (a), second (b) and the last phase (c) of dynamic scan.

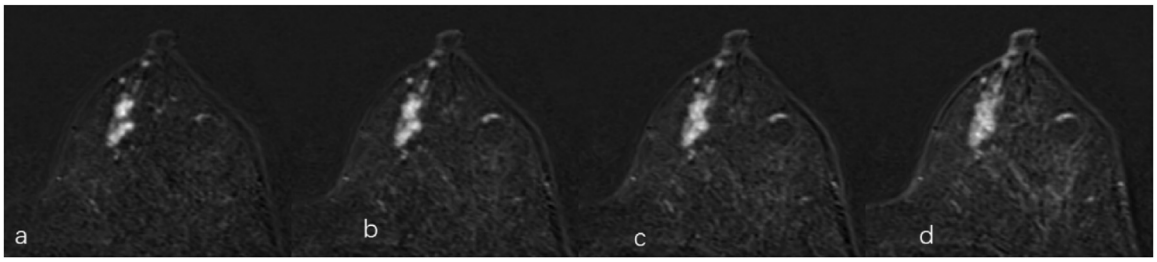

Figure 3. A 59-year-old woman with solid papillary carcinoma with invasion, the clinical manifestation is palpable mass of left breast. Mammography is negative, MR shows segmental distribution and clustered ring enhancement on postcontrast first (a), second (b), third (c) and the last phase (d) of dynamic scan.

frequently seen in papillomatosis and malignant papillary lesions than benign papilloma. Our study also demonstrated that the segmental distribution indicated papillary carcinoma (Figs 2 and 3).

To our knowledge, our study is the first to demonstrate the diagnostic value of internal enhancement patterns in papillary neoplasms on MR images with non-mass enhancement by the largest number of cases. Clumped enhancement (36.36%) and homogeneous enhancement (30.30%) were more commonly observed in papilloma, while clustered ring (75%) was more commonly in papillary carcinomas (Figs 2 and 3). There were statistically significant differences between papilloma and papillary carcinomas by univariate analyses. Multivariate analysis strongly suggested that only internal enhancement patterns had a statistically significant difference among all variates (Table 2).

There are some limitations in our study, it is a single-center study, and the MRI field is 1.5T instead of 3.0T; in addition, the enrolled cases in this paper are not so large, so it is hoped that more cases can be included for multicenter study in the next research.

In conclusions, papillary carcinoma on MR images with non-mass enhancement mostly showed internal clustered ring enhancement, while papilloma mostly showed internal clumped enhancement; additional mammography is of limited diagnostic value, and suspected calcification occurs mostly in papilloma.

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REFERENCES

1. Tan PH, Ellis I, Allison K, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020; 77(2):181–185.
2. Wei S. Papillary lesions of the breast: an update. Arch Pathol Lab Med 2016; 140(7):628–643.
3. Tay T, Tan PH. Papillary neoplasms of the breast-reviewing the spectrum. Mod Pathol 2021; 34(6):1044–1061.
4. Rakha EA, Ellis IO. Diagnostic challenges in papillary lesions of the breast. Pathology 2018; 50(1):100–110.
5. Choi HY, Kim SM, Jang M, et al. Benign breast papilloma without atypia: outcomes of surgical excision versus US-guided directional vacuum-assisted removal or US follow-up. Radiology 2019; 293(1):72–80.
6. Fuentes J, Martinez C, Casadiego A, et al. Papillary breast lesions diagnosed by percutaneous needle biopsy: management approach. Ecancermedicalscience 2019; 13:902.
7. Riedl CC, Luft N, Bernhart C, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 2015; 33(10):1128–1135.
8. Bahl M, Gadd MA, Lehman CD. JOURNAL CLUB: diagnostic utility of MRI after negative or inconclusive mammography for the evaluation of pathologic nipple discharge. AJR Am J Roentgenol 2017; 209(6):1404–1410.
9. Lorenzon M, Zuiani C, Linda A, et al. Magnetic resonance imaging in patients with nipple discharge: should we recommend it? Eur Radiol 2011; 21(5):899–907.
10. Patel BK, Falcon S, Drukteinis J. Management of nipple discharge and the associated imaging findings. Am J Med 2015; 128(4):353–360.
11. Berger N, Luparia A, Di Leo G, et al. Diagnostic performance of MRI versus galactography in women with pathologic nipple discharge: a systematic review and meta-analysis. AJR Am J Roentgenol 2017; 209(2):465–471.
12. Expert Panel on Breast Imaging Lee SJ, Trikha S, et al. ACR appropriateness criteria((R)) evaluation of nipple discharge. J Am Coll Radiol 2017; 14(5S):S138–S153.
13. Zacharioudakis K, Kontoulis T, Vella JX, et al. Can we see what is invisible? The role of MRI in the evaluation and management of patients with pathological nipple discharge. Breast Cancer Res Treat 2019; 178 (1):115–120.
14. Sarica O, Uluc F, Tasmali D. Magnetic resonance imaging features of papillary breast lesions. Eur J Radiol 2014; 83(3):524–530.
15. Rao AA, Feneis J, Lalonde C, et al. A pictorial review of changes in the BI-RADS Fifth Edition. Radiographics 2016; 36(3):623–639.
16. Sarica O, Dokdok M. Imaging findings in papillary breast lesions: an analysis of ductal findings on magnetic resonance imaging and ultrasound. J Comput Assist Tomogr 2018; 42(4):542–551.
17. Hashmi AA, Faraz M, Rafique S, et al. Spectrum of papillary breast lesions according to world health organization classification of papillary neoplasms of breast. Cureus 2020; 12(10):e11026.
18. Kurz KD, Roy S, Saleh A, et al. MRI features of intraductal papilloma of the breast: sheep in wolf's clothing? Acta Radiol 2011; 52(3):264–272.
19. Zhu Y, Zhang S, Liu P, et al. Solitary intraductal papillomas of the breast: MRI features and differentiation from small invasive ductal carcinomas. AJR Am J Roentgenol 2012; 199(4):936–942.
20. Wang LJ, Wu P, Li XX, et al. Magnetic resonance imaging features for differentiating breast papilloma with high-risk or malignant lesions from benign papilloma: a retrospective study on 158 patients. World J Surg Oncol 2018; 16(1):234.
21. Yildiz S, Toprak H, Ersoy YE, et al. Contribution of diffusion-weighted imaging to dynamic contrast-enhanced MRI in the characterization of papillary breast lesions. Breast J 2018; 24(2):176–179.
22. Moritani S, Ichihara S, Hasegawa M, et al. Uniqueness of ductal carcinoma in situ of the breast concurrent with papilloma: implications from a detailed topographical and histopathological study of 50 cases treated by mastectomy and wide local excision. Histopathology 2013; 63 (3):407–417.
23. Sarica O, Uluc F, Tasmali D. Magnetic resonance imaging features of papillary breast lesions. Eur J Radiol 2014; 83(3):524–530.