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Original Article

Evaluation of ipsilateral increased vascularity in differentiating benign and malignant breast lesions

Haili Wang[1], Yaping Xu[3], Zhigang Yao[2], Haiyu Zhan[1], Qingwei Liu[1]

Departments of [1]Radiology, [2]Pathology, Shandong Provincial Hospital, Affiliated to Shandong University, Shandong Province, China; [3]Department of Obstetrics and Gynecology, Shandong Provincial Third Hospital, Shandong Province, China

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Abstract: The present study aimed to evaluate one-sided increased vascularity in contrast-enhanced breast MRIs in differential diagnosis of benign and malignant breast lesions. A total of 36 patients with breast lesions were included. They were examined by MRIs and tissue samples were subjected to pathological diagnosis. Maximum intensity projections (MIPs) were scored, according to a previously published method. Differences in vascularity between benign and malignant breast lesions were analyzed and compared. According to MRIs for these 36 patients, there were 36 lesions (14 benign and 22 malignant lesions based on histological detection). The mean vessel number in breasts with malignant lesions was 4.0 ± 1.5, significantly higher than in breasts with benign lesions (2.2 ± 1.6 vessels). Mean MIP scores for breasts with malignant and benign lesions were 2.4 ± 0.5 and 1.6 ± 0.8, respectively. Moreover, overall sensitivity and specificity percentages of one-sided increased vascularity associated with ipsilateral malignancy were 100% and 36%, respectively. Based on morphologic and kinetic data analysis, sensitivity and specificity of breast MRIs were 100% and 64%, respectively. However, according to morphologic, kinetic, and vascular map analyses, sensitivity and specificity of breast MRIs were 100% and 57%, respectively, without increased specificity. Vessel numbers and mean MIP scores differed between breasts with benign and malignant lesions. Therefore, ipsilateral increased vascularity might be a reliable sign for differentiating benign and malignant breast lesions.

Keywords: Ipsilateral increased vascularity, breast cancer, benign and malignant lesion, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), differential diagnosis

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has gradually become a more important method in the diagnosis and management of breast lesions. DCE-MRI has been increasingly used in detecting malignant lesions (which are difficult to detect in the mammographically dense breast tissue), differentiating benign lesions from malignancies, preoperative local tumor staging, predicting and monitoring the response of breast cancer patients to neoadjuvant chemotherapy, differentiating residual or recurrent tumors from surgery/radiotherapy-induced scars, and screening of patients with a high risk for breast cancer [1].

In clinic, MRIs present a high-resolution and non-invasive 3D detection method. For DCE-MRIs, the detection sensitivity for breast carcinoma would be up to 94%-100%, especially for invasive breast cancers (almost 100%) [2]. However, values of detection specificity are relatively more variable, ranging from 20% to 100% [3-8]. Therefore, more and more novel MRI techniques have been developed for diagnosis and management of breast lesions, especially with improved overall specificity. Previous studies have shown that breast cancers might be associated with higher ipsilateral vascularity [9, 10].

Breast cancer is a vascular-dependent disease. Its angiogenic properties could be reflected by DCE-MRIs. In fact, increased blood vessels in breast tumors have been indicated by color Doppler ultrasonography and positron emission tomography [11, 12]. However, this association has not yet been well established as a criterion and further investigation is certainly required. In this prospective study, the diagnostic utility of vascular map analysis in dynamic breast MRI was investigated. Its specific contribution to differential diagnosis of enhancing lesions in DCE-MRIs was discussed.

Materials and methods

Study design and study subjects

For this prospective study, a standard protocol was tailored to determine the diagnostic utility of vascular map analysis in dynamic breast MRIs, as well as its contribution to differential diagnosis of enhancing lesions in DCE-MRIs. To ensure data objectiveness, vascular maps of patients were analyzed and scored by two experienced analysts, with no information about clinical outcomes nor mammographic or ultrasonographic imaging data. Histopathology was used as a reference standard. Overall sensitivity, specificity, accuracy, PPV (positive predictive value), and NPV (negative predictive value) values of one-sided increased vascularity, associated with ipsilateral malignancy, were calculated. Comparison of breast vessels between malignant and benign lesions was also performed.

A total of 36 consecutive patients, aged 23-68 years (with an average age of 45.0 ± 13.4 years), with 36 enhancing lesions, were included in this study. They were admitted from August 2016 to December 2017. The only inclusion criterion was the detection of breast lesions mammographically, ultrasonographically, or clinically. For each of these patients, mastectomy or lumpectomy was performed 2 to 14 days after DCE-MRIs. They were then diagnosed and confirmed by pathological detection. Prior written and informed consent was obtained from each patient and the study was approved by the local Ethics Review Board.

Breast MRI protocol

All patients were subjected to breast MRIs, in the prone position, with the breast fixed in the double breast coil. MRIs were performed with the 3.0 T system (Siemens Symphony, Erlangen, Germany). Using the double breast coil, comparisons could be conducted between the two breasts within one image. Imaging protocol included a localizer followed by the transverse turbo-spin echo T2-weighted sequence. It also included Short Time Inversion Recovery (STIR), three-dimensional (3D) fast low angle shot imaging (FLASH) T1-weighted sequence without fat suppression, and the sagittal T2-weighted STIR sequence. Dynamic examinations with serial imaging were performed using the 3D transverse FLASH T1-weighted sequence, with fat suppression. One pre- and five post-contrast sequences for DCE-MRIs were acquired.

After the first pre-contrast sequence, an intravenous bolus injection of gadopentetate dimeglumine was given (0.1 mmol/kg body weight) using an automatic injector. It was given at a rate of 2 mL/s, followed by a flush of 20 mL saline. The total acquisition time of the dynamic study was 6.7 minutes. Post-processing was performed by creating the subtraction images of each post-contrast sequence and maximum intensity projection (MIP) images. The breast blood vessels were clearly imaged in the transverse and coronal MIP images.

MRI data analysis

MRI data were analyzed on the post-processing workstation (Siemens Medical Solutions). The first post-injection phase images were analyzed. These are the best for showing the angiographic vascular map [13]. Transverse and coronal MIP images were analyzed by two analysts, with over 5 years of experience in breast radiology. They were not given patient clinical and imaging data (such as mammographic and ultrasonographic information). Breast MIP reconstruction was scored using the one-on-one format, free windowing, electronic magnification, and distance measurement.

According to an approach previously proposed by Sardanelli et al., the vessel number, size, length, and conspicuity were scored from 0 (absent or low breast vascularity) to 3 (high breast vascularity). Scores of 2-3 were regarded as increased breast vascularity, which were associated with ipsilateral cancer. In each breast, vessels with a length ≥ 3 cm and maximal transverse diameter ≥ 2 mm were counted, scored as follows: 0, complete absence of vessels or presence of vessels with length < 3 cm and maximal transverse diameter < 2 mm; 1, low vascularity (only one vessel with a length ≥ 3 cm and maximal transverse diameter ≥ 2 mm; 2, moderate vascularity (two to four vessels with length ≥ 3 cm and maximal transverse diameter ≥ 2 mm); and 3, high vascularity (five or more vessels with length ≥ 3 cm and maxi-

Table 1. MIP scores for breasts with benign and malignant lesions

MIP score	0	1	2	3	Total
Benign	0	7	5	2	14
Malignant	0	0	11	11	22
Total	0	7	16	13	36

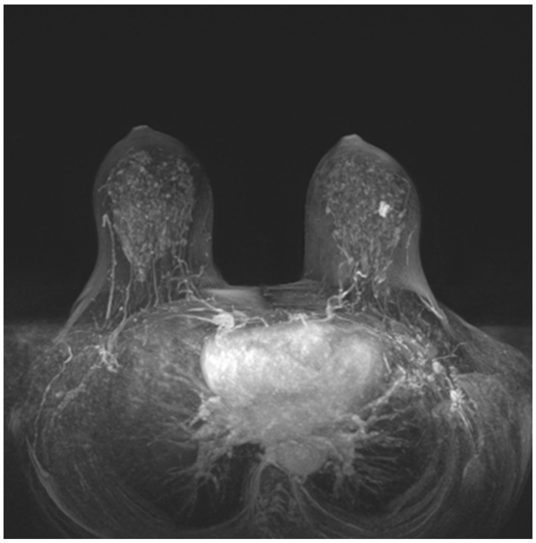

Figure 1. A patient with a palpable lump in the left breast detected by palpation. Transverse MIP image shows low vascularity. Histopathologic report revealed fibroadenoma.

mal transverse diameter ≥ 2 mm) [14]. Differences in vascularity were compared between benign and malignant breast lesions, with histopathology as a reference standard.

Histopathological diagnosis

After DCE-MRIs, the patients were subjected to surgical excisions. Histopathological examinations were performed on their breast lesions. Histopathological diagnosis was determined by two pathologists with over 10 years of experience in breast histology. The breast lesions were histopathologically classified as malignant and benign, respectively. Vascular asymmetry was a true-positive finding when malignant lesions with increased ipsilateral vascularity were histopathologically diagnosed.

Statistical analysis

SPSS 19.0 software was utilized for statistical analysis. Differences in mean vessel numbers and MIP scores between benign and malignant breast lesions were analyzed using the Mann Whitney U-test. Differences in sensitivity, specificity, accuracy, PPV, and NPV, evaluated by different methods, were assessed by the χ^2 test. $P < 0.05$ indicates statistical significance.

Results

Pathological findings and vascularity of all lesions

According to MRI detection, for the 36 enrolled patients, there were 36 breast lesions, including 14 benign and 22 malignant lesions (based on the histological detection). In the 14 benign breast lesions, there were 4 cases of cyclomastopathy, 1 case of chronic inflammation with abscess formation, 1 case of lacteal cyst, 1 case of intraductal papilloma, 2 cases of mammary duct dilation, and 5 cases of fibroadenoma. In the 22 malignant breast lesions, there was 1 case of phyllodes tumor, 2 cases of intraductal carcinoma with partial infiltration, 3 cases of intraductal carcinoma *in situ*, and 16 cases of invasive breast ductal carcinoma.

To observe the vascularity of all lesions, vessel number and MIP scores were calculated. Results showed that the average vessel number in breasts with malignant lesions was 4.0 ± 1.5, significantly higher than in breasts with benign lesions (2.2 ± 1.6) ($P < 0.01$). Moreover, the average MIP score for breasts with malignant lesions was 2.4 ± 0.5, with an average MIP score of 1.6 ± 0.8 for breasts with benign lesions ($P < 0.01$) (**Table 1**) (**Figure 1**). Moreover, cancer was found with moderate and high vascularity (scores 2 and 3) (**Figure 2A-D**). Present results suggest that one-sided increased breast vascularity might be closely related to ipsilateral breast cancer, especially in breasts with high vascularity.

Diagnostic performance based on vascular mapping and morphologic and kinetic data analysis

To observe the diagnostic performance of vascular maps, the related values were analyzed. Results showed that overall sensitivity, specificity, accuracy, PPV, and NPV values for one-sided increased vascularity, associated with ipsilateral malignancy, were 100% (22/22), 36% (5/14), 75% (27/36), 71% (22/31), and 100% (5/5), respectively (**Table 2**). Based on morphologic and kinetic data analysis, sensitivity, specificity, accuracy, PPV, and NPV values were

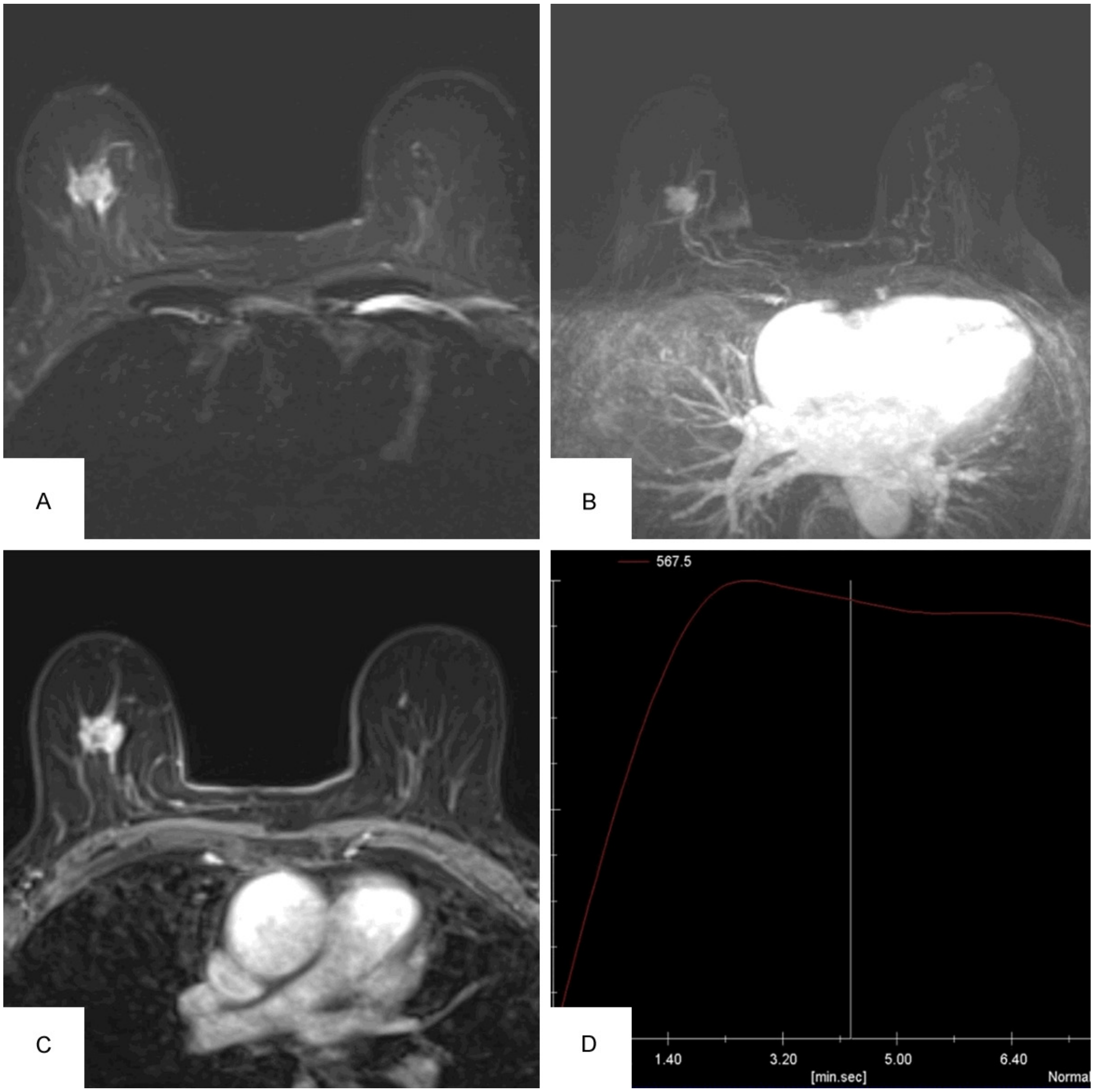

Figure 2. A-D. A 63 year-old patient with a palpable lump in the right breast detected by palpation. A. Fat-suppressed T2-weighted axial breast MR image revealed an 18 mm × 15 mm irregular lobulated nodule in the right breast with peritumor edema. B. The lesion showed moderate vascularity on the MIP. C. Fat-suppressed T1-weighted axial contrast-enhanced breast MR image shows the lesion with heterogenous enhancement. D. The lesion shows type III enhancement kinetics. Histopathologic report revealed invasive ductal carcinoma.

Table 2. One-sided increased breast vascularity as an indicator of ipsilateral breast cancer

Ipsilateral increased vascularity	Histopathologic reference-standard result		
	Positive	Negative	Total
Positive (scores 2+3)	22	9	31
Negative (scores 0+1)	0	5	5
Total	22	14	36

100% (22/22), 64% (9/14), 86% (31/36), 81% (22/27), and 100% (9/9), respectively. Based on morphologic, kinetic, and vascular map analysis, sensitivity, specificity, accuracy, PPV, and NPV values were 100% (22/22), 57% (8/14), 83% (30/36), 79% (22/28), and 100% (8/8), without increased specificity ($P > 0.05$). Present results suggest that the diagnostic performance of vascular mapping was limited.

According to Sardanelli scoring, all 22 malignant lesions were correctly diagnosed. A total of 7 malignant lesions showed peritumor edema. For the 14 benign lesions, however, 9 were found in breasts with moderate and/or high vascularity (scores 2 and 3, which would be a malignancy according to Sardanelli scoring) and 5 were diagnosed as malignancies based on morphologic and kinetic data analysis. In one case with fibroadenoma misdiagnosed as a malignancy, according to Sardanelli scoring, the diagnosis based on DCE-MRI was consistent with pathological findings. Present findings suggest that application of Sardanelli scoring did not contribute to increased specificity.

Discussion

Breast MRIs have always been considered adjunct tools to conventional mammography. Clinical indications for breast MRIs mainly include: (1) Detecting primary breast lesions for patients with axillary lymph node adenocarcinoma confirmed by biopsy (while with normal physical examination and negative breast mammography); (2) Assessing the disease extent in dense breast tissues that other methods cannot reveal for patients with breast cancer (identified by biopsy); (3) Determining the spatial extent of breast cancer; (4) Identifying multifocal and multicentric lesions in dense breasts; and (5) Defining the disease extent in patients with locally advanced breast cancer. With the improvement of specificity, breast MRIs should become more widely applied.

Breast cancer is a vascular-dependent disease. Angiogenesis not only plays an extremely important role in tumor growth and development, but is also closely related to tumor invasion and metastasis. Characteristics of breast tumor blood vessels mainly include structural abnormalities of blood capillary walls, increased permeability of intra-tumoral vascular endothelial cells, and arteriovenous communication of tumor blood vessels (resulting in short circuit). In contrast, malignant tumors will secrete angiogenesis factors (such as vascular endothelial growth factor, VEGF) which promote differentiation and generation of tumor capillaries, with increased tumor blood vessels. In turn, increased tumor blood vessels will accelerate tumor growth. Thus, tumor angiogenesis, increased microvessel density (MVD), and capillary permeability provide the physiological basis for diagnosis of breast cancers [15, 16]. DCE-MRIs can reflect angiogenic properties of breast cancers. Transverse and coronal MIP images of breasts could directly and clearly indicate lesions and vessels. Increased breast vascularity has been correlated with abundant blood supply from arterioles and angiogenic activity. This includes variable VEGF expression from tumor cells, which is a complex result from tumor angiogenesis and the microcirculatory environment [17-19].

Present study results showed that one-sided increased breast vascularity was closely associated with ipsilateral breast cancer, especially in breasts with high vascularity. All of the cancers were found in breasts with moderate and/or high vascularity (scores 2 and 3), whereas no cancer was found in breasts with absent and/or low vascularity (scores 0 and 1). Differences in average vessel numbers between breasts with benign and malignant lesions were observed. However, results showed that one-sided increased breast vascularity could be seen not only in malignant breast lesions but also in benign ones. Two breasts with benign lesions were scored as 3. However, there were no statistically significant differences in mean MIP scores between breasts with benign and malignant lesions, according to pathological examinations. It was implied that the vessel scoring system could be further improved. In specific, breasts having two vessels with a length ≥ 3 cm and maximal transverse diameter ≥ 2 mm could be scored as 2, indicating moderate vascularity. Present results showed that 5 breasts with benign lesions and 11 breasts with malignant lesions were scored as 2, all of which would be regarded as malignant lesions according to Sardanelli scoring.

In these 36 lesions, 6 patients with benign lesions were overestimated as malignancies by both DCE-MRIs and Sardanelli scoring. The histopathological report indicated 1 case of chronic inflammation with abscess formation, 1 case of lacteal cyst, 1 case of intraductal papilloma, 1 case of cyclomastopathy, and 2 cases of mammary duct dilation. In the case with fibroadenoma, misdiagnosed as a malignancy according to Sardanelli scoring, diagnosis based on DCE-MRIs was consistent with pathological findings. In situations where DCE-MRIs and Sardanelli scoring are not in agreement, it would be difficult to figure out which one would be more reliable. Morphologic and kinetic data analysis should be performed first, supplemented by vascular map analysis. In addition, focal edema is commonly associated with malignancy, except for previous procedures, including biopsy and surgery. Present results suggest that specificity, based on morphologic, kinetic, and vascular map analysis, did not increase, compared with that based on morphologic, kinetic, and vascular map analysis alone.

Association between one-side increased vascularity on vascular maps and ipsilateral cancer has been previously reported [10]. Sardanelli et al. [14] retrospectively scored the breast vascularity on MIPs. They obtained an overall sensitivity, specificity, accuracy, PPV, and NPV of 88% (44/50), 82% (14/17), 87% (58/67), 94% (44/47), and 70% (14/20), respectively, for one-sided increased vascularity as an indicator for ipsilateral malignancy. Moreover, they retrospectively compared three different doses of gadobenate dimeglumine (i.e., 0.05, 0.10, and 0.20 mmol/kg) for MRI evaluation of breast vessels. They concluded that effective doses for MRI evaluations of breast vessels could be as low as 0.05 mmol/kg.

Recently, Schmitz et al. [20] studied 54 patients (25 cases of malignancies and 31 cases of benign lesions) that underwent contrast-enhanced 3.0 T breast MRIs after administration of 0.1 mmol/kg gadobutrol. Results showed sensitivity, specificity, accuracy, PPV, and NPV values of 100% (25/25), 74% (23/31), 86% (48/56), 76% (25/33), and 100% (23/23), respectively. After adjusting for breast vascularity, the specificity was significantly increased to 87% (27/31), with sensitivity not affected. PPV increased to 86% (25/29), NPV increased to 100% (27/27), and accuracy increased to 93%. Compared with the above specificity, lower values were obtained in present findings. This discrepancy might be partially explained by atypical imaging features of some benign lesions and the overlap of enhancement patterns between benign and malignant lesions.

In this study, patients were administrated with a bolus injection of 0.1 mmol/kg gadopentetate dimeglumine. Sardanelli et al. [21] concluded that gadobenate dimeglumine is effective for MRI evaluations of breast vessels at doses as low as 0.05 mmol/kg. Some comparative studies have indicated that gadobenate dimeglumine shows higher contrast efficacy for MR angiography [22-24]. Gadobenate dimeglumine differs from the conventional gadolinium-based contrast agents in that it possesses a two-fold higher T1 relaxivity *in vivo* because of weak and transient interactions between the gadolinium chelate and serum albumin. Increased T1 relaxivity could be transformed into greater contrast enhancement, which greatly contributes to improvements in detection, visualization, and delineation of lesions in clinic [25, 26]. Goyen et al. [27] showed that MRA image quality for total-body MRA provided by the administration of gadobutrol is superior to that obtained by gadopentetate dimeglumine. However, other studies have shown that gadopentetate dimeglumine might be appropriate for depicting ipsilateral higher vascularity [10]. Indeed, the blood vessels of breasts were clearly shown in present cases administrated by an injection of gadopentetate dimeglumine. Of course, further in-depth studies are required to determine the superiorities of these contrast agents [28-30].

There were several limitations to the present study. First, the patient size was relatively small. Patients included were all from candidates with breast lesions detected with mammography, ultrasonography, or clinical impression. Whether these results could be suitable for lesions diagnosed by DCE-MRI requires further investigation. Second, evaluation of breast vascular maps was performed without masking the enhancing lesions. This might have introduced bias in the assessment of side-based prevalence of vascularity. Third, the histopathologic types of breast tumors were relatively limited.

Conclusion

Present results suggest that one-sided increased vascularity was closely correlated with ipsilateral breast cancer. Breasts with malignant lesions had more blood vessels than benign cases. Statistically significant differences in vessel numbers and MIP scores were observed between breasts with benign and malignant lesions. Analysis of vascular maps, combined with morphologic and kinetic data analysis, could not help to increase specificity. When diagnosis results based on the DCE-MRIs and Sardanelli scoring are inconsistent, morphologic and kinetic data analysis should be performed first, along with vascular map analysis, peritumor edema and analysis of medical history, physical examinations, and other imaging data. In conclusion, present study findings may contribute to the differential diagnosis of benign and malignant breast lesions.

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Disclosure of conflict of interest

None.

Address correspondence to: Qingwei Liu, Department of Radiology, Provincial Hospital, Affiliated to Shandong University, Jingwu Road 324#, Jinan 250021, Shandong Province, China. Tel: +86-053168773662; E-mail: doctorlqw@163.com

References

[1] Mann RM, Balleyguier C, Baltzer PA, Bick U, Colin C, Cornford E, Evans A, Fallenberg E, Forrai G, Fuchsjager MH, Gilbert FJ, Helbich TH, Heywang-Kobrunner SH, Camps-Herrero J, Kuhl CK, Martincich L, Pediconi F, Panizza P, Pina LJ, Pijnappel RM, Pinker-Domenig K, Skaane P and Sardanelli F. Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 2015; 25: 3669-3678.

[2] Pinker-Domenig K, Bogner W, Gruber S, Bickel H, Duffy S, Schernthaner M, Dubsky P, Pluschnig U, Rudas M, Trattnig S and Helbich TH. High resolution MRI of the breast at 3 T: which BI-RADS(R) descriptors are most strongly associated with the diagnosis of breast cancer? Eur Radiol 2012; 22: 322-330.

[3] Macura KJ, Ouwerkerk R, Jacobs MA and Bluemke DA. Patterns of enhancement on breast MR images: interpretation and imaging pitfalls. Radiographics 2006; 26: 1719-1734; quiz 1719.

[4] Morrow M, Waters J and Morris E. MRI for breast cancer screening, diagnosis, and treatment. Lancet 2011; 378: 1804-1811.

[5] Uematsu T, Kasami M and Watanabe J. Can T2-weighted 3-T breast MRI predict clinically occult inflammatory breast cancer before pathological examination? A single-center experience. Breast Cancer 2014; 21: 115-121.

[6] Froeling V, Diekmann F, Renz DM, Fallenberg EM, Steffen IG, Diekmann S, Lawaczeck R and Schmitzberger FF. Correlation of contrast agent kinetics between iodinated contrast-enhanced spectral tomosynthesis and gadolinium-enhanced MRI of breast lesions. Eur Radiol 2013; 23: 1528-1536.

[7] Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG and Peeters PH. Meta-analysis of MR imaging in the diagnosis of breast lesions. Radiology 2008; 246: 116-124.

[8] Song SE, Park EK, Cho KR, Seo BK, Woo OH, Jung SP and Cho SB. Additional value of diffusion-weighted imaging to evaluate multifocal and multicentric breast cancer detected using pre-operative breast MRI. Eur Radiol 2017; 27: 4819-4827.

[9] Petrillo A, Fusco R, Filice S, Granata V, Catalano O, Vallone P, Di Bonito M, D'Aiuto M, Rinaldo M, Capasso I and Sansone M. Breast contrast enhanced MR imaging: semi-automatic detection of vascular map and predominant feeding vessel. PLoS One 2016; 11: e0161691.

[10] Monticciolo DL. Magnetic resonance imaging of the breast for cancer diagnosis and staging. Semin Ultrasound CT MR 2011; 32: 319-330.

[11] Wilson CB, Lammertsma AA, McKenzie CG, Sikora K and Jones T. Measurements of blood flow and exchanging water space in breast tumors using positron emission tomography: a rapid and noninvasive dynamic method. Cancer Res 1992; 52: 1592-1597.

[12] Seifalian AM, Chaloupka K and Parbhoo SP. Laser Doppler perfusion imaging--a new technique for measuring breast skin blood flow. Int J Microcirc Clin Exp 1995; 15: 125-130.

[13] Del Maschio A, De Gaspari A and Panizza P. Magnetic resonance in breast imaging. Radiol Med 2002; 104: 253-261.

[14] Sardanelli F, Iozzelli A, Fausto A, Carriero A and Kirchin MA. Gadobenate dimeglumine-enhanced MR imaging breast vascular maps: association between invasive cancer and ipsilateral increased vascularity. Radiology 2005; 235: 791-797.

[15] Su MY, Cheung YC, Fruehauf JP, Yu H, Nalcioglu O, Mechetner E, Kyshtoobayeva A, Chen SC, Hsueh S, McLaren CE and Wan YL. Correlation of dynamic contrast enhancement MRI parameters with microvessel density and VEGF for assessment of angiogenesis in breast cancer. J Magn Reson Imaging 2003; 18: 467-477.

[16] Mori N, Mugikura S, Takahashi S, Ito K, Takasawa C, Li L, Miyashita M, Kasajima A, Mori Y, Ishida T, Kodama T and Takase K. Quantitative analysis of contrast-enhanced ultrasound imaging in invasive breast cancer: a novel technique to obtain histopathologic information of microvessel density. Ultrasound Med Biol 2017; 43: 607-614.

[17] Matsubayashi R, Matsuo Y, Edakuni G, Satoh T, Tokunaga O and Kudo S. Breast masses with peripheral rim enhancement on dynamic contrast-enhanced MR images: correlation of MR findings with histologic features and expression of growth factors. Radiology 2000; 217: 841-848.

[18] Zhu D, Shen Z, Liu J, Chen J, Liu Y, Hu C, Li Z and Li Y. The ROS-mediated activation of STAT-

3/VEGF signaling is involved in the 27-hydroxycholesterol-induced angiogenesis in human breast cancer cells. Toxicol Lett 2016; 264: 79-86.

[19] Raghunathachar Sahana K, Akila P, Prashant V, Sharath Chandra B and Nataraj Suma M. Quantitation of vascular endothelial growth factor and interleukin-6 in different stages of breast cancer. Rep Biochem Mol Biol 2017; 6: 33-39.

[20] Schmitz AC, Peters NH, Veldhuis WB, Gallardo AM, van Diest PJ, Stapper G, van Hillegersberg R, Mali WP and van den Bosch MA. Contrast-enhanced 3.0-T breast MRI for characterization of breast lesions: increased specificity by using vascular maps. Eur Radiol 2008; 18: 355-364.

[21] Khouri Chalouhi K, Papini GDE, Bandirali M, Sconfienza LM, Di Leo G and Sardanelli F. Less is better? Intraindividual and interindividual comparison between 0.075 mmol/kg of gadobenate dimeglumine and 0.1 mmol/kg of gadoterate meglumine for cranial MRI. Eur J Radiol 2014; 83: 1245-1249.

[22] Bueltmann E, Erb G, Kirchin MA, Klose U and Naegele T. Intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for contrast-enhanced magnetic resonance angiography of the supra-aortic vessels at 3 Tesla. Invest Radiol 2008; 43: 695-702.

[23] Prokop M, Schneider G, Vanzulli A, Goyen M, Ruehm SG, Douek P, Dapra M, Pirovano G, Kirchin MA and Spinazzi A. Contrast-enhanced MR Angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. Radiology 2005; 234: 399-408.

[24] Pediconi F, Catalano C, Occhiato R, Venditti F, Fraioli F, Napoli A, Kirchin MA and Passariello R. Breast lesion detection and characterization at contrast-enhanced MR mammography: gadobenate dimeglumine versus gadopentetate dimeglumine. Radiology 2005; 237: 45-56.

[25] Pediconi F, Catalano C, Roselli A, Padula S, Altomari F, Moriconi E, Pronio AM, Kirchin MA and Passariello R. Contrast-enhanced MR mammography for evaluation of the contralateral breast in patients with diagnosed unilateral breast cancer or high-risk lesions. Radiology 2007; 243: 670-680.

[26] Gilbert FJ, van den Bosch HC, Petrillo A, Siegmann K, Heverhagen JT, Panizza P, Gehl HB, Pediconi F, Diekmann F, Peng WJ, Ma L, Sardanelli F, Belli P, Corcione S, Zechmann CM, Faivre-Pierret M and Martincich L. Comparison of gadobenate dimeglumine-enhanced breast MRI and gadopentetate dimeglumine-enhanced breast MRI with mammography and ultrasound for the detection of breast cancer. J Magn Reson Imaging 2014; 39: 1272-1286.

[27] Goyen M, Herborn CU, Vogt FM, Kroger K, Verhagen R, Yang F, Bosk S, Debatin JF and Ruehm SG. Using a 1 M Gd-chelate (gadobutrol) for total-body three-dimensional MR angiography: preliminary experience. J Magn Reson Imaging 2003; 17: 565-571.

[28] Philpotts LE. Will improved vascular mapping achieved with gadobenate dimeglumine aid in interpretation of breast MR images? Radiology 2005; 235: 717-718.

[29] Yang X, Liu G, Yu X, Zhang Q, Zhang W and Guo Y. [Controlled study of gadobenate dimeglumine versus gadopentetate in breast tumor MR dynamic enhancement scanning]. Zhonghua Yi Xue Za Zhi 2015; 95: 2003-2005.

[30] Escribano F, Sentis M, Oliva JC, Tortajada L, Villajos M, Martin A and Ganau S. Dynamic magnetic resonance imaging of the breast: comparison of gadobutrol vs. Gd-DTPA. Radiologia 2018; 60: 49-56.