J Surg Med. 2019;3(10):749-753.
DOI: 10.28982/josam.632294

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Role of contrast-enhanced breast magnetic resonance angiography in characterizing suspicious breast lesions and evaluating the relationship between prognostic factors

Şüpheli meme lezyonlarını karakterize etmede ve prognostik faktörler arasındaki ilişkiyi değerlendirmede kontrastlı meme manyetik rezonans anjiyografisinin rolü

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Ethics Committee Approval: Ethics committee approval was received from Erzincan Binali Yıldırım University Ethics Committee (number 2019.38.19).
Etik Kurul Onayı: Etik kurul onayı Erzincan Binali Yıldırım Üniversitesi Etik Kurulu'ndan alınmıştır (no: 2019.38.19).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 10/25/2019
Yayın Tarihi: 25.10.2019

Abstract

Aim: Breast cancer is the most commonly diagnosed cancer in women, and mammography and ultrasonography are the most frequently used diagnostic radiological methods. Although they are highly sensitive, their specificity is low. Angiography can be added as a standard breast magnetic resonance imaging (MRI) protocol to increase specificity. In this study, we aimed to investigate the effectiveness of breast vascularity by evaluating the presence of an adjacent vessel sign (AVS) and increased ipsilateral breast vascularity (IIBV) in characterizing breast masses.

Methods: 135 patients with a mean age of 47 years with radiologically or clinically suspicious breast masses underwent breast MRI before biopsy. The contrast-enhanced three-dimensional MR angiograms of the breasts were investigated for the presence of AVS and IIBV to characterize suspicious breast masses, and their correlation with histopathological prognostic factors were evaluated.

Results: Patients' age, tumor size, and the presence of AVS and IIBV were significantly higher in malignant masses than in benign masses (P<0.001). The sensitivity, specificity, and accuracy of AVS and IIBV in predicting malignant masses from benign ones were 75%, 79.3%, 77% and 56.9%, 90.4% and 72.5%, respectively. In malignant masses, AVS and IIBV were both significantly associated with ER (P=0.005, P<0.001) and PR expression (P=0.003, P<0.001). We found no relationship between AVS, IIBV and C-ERBB2 expression (P=0.245 and P=0.085, respectively).

Conclusion: The presence of AVS and IIBV as determined from contrast-enhanced 3D MR angiograms may be reliable parameters for further characterizing suspicious breast masses, both of which seem to be related with ER and PR expression.

Keywords: Angiography, Breast, Magnetic resonance imaging

Öz

Amaç: Meme kanseri, kadınlarda en sık tanı alan kanser olup, mamografi ve ultrasonografi en sık kullanılan radyolojik yöntemlerdir. Bu yöntemlerin duyarlılığı yüksek olmasına rağmen, özgüllükleri düşüktür. Anjiyografi, özgüllüğü artırmak için standart bir meme manyetik rezonans görüntüleme (MRG) protokolü olarak eklenebilir. Bu çalışmada amacımız, komşu damar işareti (KDİ) ve artmış ipsilateral meme vaskülaritesi (AİMV) içeren meme damarlanmasının, meme kitlelerini karakterize etmedeki etkinliğini araştırmak ve histopatolojik prognostik faktörlerle korelasyonunu ortaya koymaktır.

Yöntemler: Mart 2017 - Ocak 2019 tarihleri arasında radyolojik veya klinik olarak şüpheli meme kitleleri olan 135 hastaya (yaş aralığı: 19-79 yıl, ort. Yaş: 47 yıl) biyopsi öncesi meme MRG yapıldı. Kontrastlı 3D meme MR anjiyografileri, KDİ ve AİMV varlığı açısından şüpheli meme kitlelerini karakterize etmek için incelendi. Bu bulgular histopatolojik prognostik faktörler ile korele edildi.

Bulgular: Hastaların yaşı, tümör boyutu, KDİ ve AİMV bulunsı malign kitlelerde benign kitlelere göre anlamlı derecede yüksekti (P<0,001). KDİ %75 duyarlılık, %79,3 özgüllük ve %77 doğrulukla, AİMV varlığı ise %56,9 duyarlılık, %90,4 özgüllük ve %72,5 doğrulukla benign kitleleri malign olanlardan ayırt etmiştir. Malign kitlelerde KDİ ve AİMV, ER (sırasıyla P=0,005, P<0,001) ve PR ekspresyonuyla (sırasıyla P<0,001, P=0,003) ilişkiliydi. Ancak çalışmamızda, KDİ, AİMV ile C-ERBB2 ekspresyonu arasında ilişki saptanmadı (P=0,245 ve P=0,085, sırasıyla).

Sonuç: Kontrastlı 3D MR anjiyogramlarından elde edilen KDİ ve AİMV varlığı, şüpheli meme kitlelerinin karakterize edilmesi için güvenilir bir yöntemdir ve ER ve PR ekspresyonu ile ilişkili görünmektedir.

Anahtar kelimeler: Anjiyografi, Meme, Manyetik rezonans görüntüleme

How to cite / Atıf için: Küpeli A, Koçak M, Danışan G, Ufuk F, Kaya F, Taşkent İ. Role of the contrast-enhanced breast MR angiography in characterizing suspicious breast lesions and evaluating the relationship between prognostic factors. J Surg Med. 2019;3(10):749-753.

Introduction

Breast cancer is the most commonly diagnosed cancer in women, and mammography and ultrasonography are the most commonly used radiological methods [1,2]. Although these methods have high sensitivity, their specificity is low [3,4]. For this reason, magnetic resonance imaging (MRI) is an increasingly applied diagnostic method for the evaluation of breast masses.

Angiogenesis plays a significant role in the uncontrolled growth, invasion and metastasis of malignant tumors, similar to the other major prognostic factors of breast cancer, such as size, histologic grade, tumor type, and lymph node and distinct metastasis [5-7]. The contrast enhancement features, including the kinetic curve and enhancement ratio from the breast MR images, are related to microvessel density and hypervascularity [8-10]. Because of the relationship between hypervascularity and these enhancement features, angiogenesis can be assessed through breast MRI.

MR angiography can be added as a standard breast MRI protocol to increase specificity. No additional time is required to perform dynamic contrast enhanced (DCE) imaging. The maximum intensity projection (MIP) images are acquired from post processing the obtained images, and MIP images can provide useful information for tumor characterization by visualizing the feeding vascular structures and enhancing the lesions on the vascular map [11]. The adjacent vessel sign (AVS) is identified by the existence of one or more vessels in contact with the breast lesion and can be employed as a marker of tumor angiogenesis [12-14]. Increased ipsilateral breast vascularity (IIBV) is described as an increased number of vascular structures compared with the vascularity of the contralateral normal breast [15-17].

There are several studies concerning the use of MR angiography for evaluating breast masses, but few studies include histopathologic predictors. In this study, we aimed to determine the diagnostic efficacy of contrast-enhanced MR angiography for evaluating the presence of an AVS and IIBV to characterize suspicious breast masses and to investigate the relationship between the presence of an AVS and IIBV and histopathologic factors in malignant breast masses.

Materials and methods

Study group

Patients who underwent breast MRI between March 2017 and January 2019 due to suspicious mammographic, ultrasonographic or clinical findings were retrospectively determined with a keyword search in our patient database. Among the 389 patients identified, those with unilateral and histopathologically diagnosed breast masses were included in our study. Patients who underwent unilateral mastectomy, had bilateral breast cancer or a history of radiation therapy were excluded from the study. Ultimately, 135 patients were included. This study was approved by the institutional ethics committee (Approval number 2019.38.19).

Magnetic resonance imaging protocol

All patient examinations were performed with a 1.5 T device (Aera, Siemens, Erlangen, Germany) with an eight-channel breast receiver coil. The patients were placed in the prone position with their arms beside their bodies during the examination. A standard breast DCE-MRI protocol was applied with fat suppression and three-dimensional (3D) T1-weighted spoiled gradient-echo sequences for all patients. The parameters were as follows: repetition time (TR)/echo time (TE): 2/4.5, flip angle: 18°, matrix size: 290 × 320, field of view: 380 × 420 mm, and slice thickness. 1.5 mm. First, one unenhanced pre-contrast image was obtained. Then, a single dose of 0.1 mmol/kg body weight gadobutrol (Gadovist, Bayer Schering Pharma) was administered intravenously at a rate of 2 mL/s, followed by a 20-mL saline flush, and six postcontrast axial 3D data sets were obtained within 56 seconds each. The MR angiogram images were obtained by subtracting the contrast-enhanced images from the unenhanced images, on which MIP reconstruction was performed.

Analysis of the magnetic resonance imaging

The MR images of the patients were evaluated together by two radiologists (A.K. with 8 years of experience and M.K. with 7 years of experience) at a workstation (Syngo, Siemens Healthcare) to reach a consensus. The radiologists were blinded to histopathologic outcomes. After identifying the suspicious index lesion on the sonograph or the mammograph, the longest diameter of the identified lesion was measured on the DCE-MR images. The largest tumor was evaluated for multifocality or multicentricity. The vascularity of the lesion and breast were evaluated with free windowing rotation.

Based on the description of Sardanelli et al. [11], we identified the following four vascularity grades for both breasts: Absent (no 3-cm-long and 2-mm-wide vessels), low (one 3-cm-long and 2-mm-wide vessel), moderate (two to four 3-cm-long and 2-mm-wide vessels), and marked (more than four 3-cm-long and 2-mm-wide vessels). IIBV was defined as the breast lesion showing at least two more vessels than the contralateral normal breast. The AVS was defined as the presence of a vessel entering or contacting the enhanced lesion on MIP images.

Regarding the histopathologic features, estrogen receptor (ER) and progesterone receptor (PR) expression were categorized as negative when the immunoreactive cells were equal to or less than 10% positive. C-ERBB2 expression was scored between 0 and 3. Accordingly, a score less than 3 was classified as negative, and a score of 3 was classified as positive.

Statistical analysis

All data analyses were performed with MedCalc statistical software version 16.8 (MedCalc Software bvba, Ostend, Belgium) and SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including the means and ranges, were calculated for age, tumor size, and mean number of vessels of both breasts for benign and malignant breast tumors. Normal distributions were verified using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze the mean number of vessels, and student's t-tests was used to analyze age and tumor size. Chi-square test was used to examine the differences in AVS and IIBV positivity for benign and malignant breast tumors. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AVS and IIBV were calculated. To determine the effect of tumor size on the diagnostic performance of AVS and IIBV, the lesions were classified into two groups: Those equal to or smaller than 2 cm and those larger than 2 cm. Chi-square test was used for the evaluation of the relationships between AVS, IIBV positivity and ER, PR and C-ERBB2 expression. *P*-value of less than 0.05 indicated statistical significance.

Results

Among 135 suspicious breast masses, 72 (53.3%) were malignant and 63 (46.7%) were benign. Malign histopathological diagnoses included 58 invasive ductal carcinomas (IDCs), 7 invasive lobular carcinomas (ILCs), 4 papillary carcinomas, 2 mucinous carcinomas and 1 ductal carcinoma in situ. Benign masses included 32 fibroadenomas, 11 fibrocystic changes, 9 sclerosing adenoses, 4 papillomas, 3 mastitises, 2 phyllodes tumors, and 2 lesions with other benign histopathologies. Among all masses, 10 (7.4%) were classified as Breast Imaging Reporting and Data System (BI-RADS) 3, 63 (46.6%) as BI-RADS 4 and 52 (45.9%) as BI-RADS 5. Biopsies were performed for BI-RADS 3 masses either because of clinically suspicious findings or patient preferences.

Patient age, tumor size, the mean number of vessels in the ipsilateral and contralateral breast, presence of AVS and IIBV, and ER, PR and C-ERBB2 expression in the benign and malignant tumors are presented in Table 1. The mean patient age was 42 years (range 19–65) and 51 years (range 25–79) for the benign and malignant groups, respectively (P<0.001). The malignant masses had more vessels that were longer than 3 cm and wider than 2 mm than the benign masses in the ipsilateral breast (P<0.001). However, there were no significant differences in the mean number of vessels between benign and malignant masses in the contralateral breast (P=0.199). The prevalence of AVS and IIBV positivity were significantly higher in malignant masses (P<0.001) (Figure 1, 2). The diagnostic performances of the AVS and IIBV are presented in Table 2. AVS and IIBV distinguished benign masses from malignant ones with 75.0% sensitivity, 79.3% specificity, and 77.0% accuracy and 56.9% sensitivity, 90.4% specificity, and 72.5% accuracy, respectively. When the masses were stratified into two groups according to size, it was found that sensitivity of AVS and IIBV was lower and specificity was higher in the small lesion group.

Among 72 malignant masses, 48 (66.6%), 52 (72.2%) and 31 (43.0%) masses were positive for ER, PR and C-ERBB2 expression, respectively (Table 3). AVS and IIBV were significantly associated with ER (P=0.005, P<0.001) and PR expression (P=0.003, P<0.001), and not associated with C-ERBB2 expression (P=0.245 and P=0.085, respectively).

Table 1: The comparison of age, mass size, number of vessels in ipsilateral and contralateral breasts and presence of adjacent vessel sign and increased ipsilateral breast vascularity between benign and malignant breast masses

	Benign	Malignant	*P*-value
Number	63	72	
Age (years)	42.3 (9.8)	51.9 (11.2)	<0.001
MS (mm)	21.7 (10.8)	24.1 (9.8)	<0.001
NVIB	1.12 (1.33)	2.88 (1.35)	<0.001
NVCB	1.01 (0.87)	1.05 (0.82)	0.459
Presence of AVS			<0.001
Present	13	54	
Absent	50	18	
Presence of IIBV			<0.001
Present	6	41	
Absent	57	31	

Results are presented as number, mean (standard deviation), MS: Mass Size, NVIB: Number of vessels in ipsilateral breast, NVCB: Number of vessels in contralateral breast, AVS: adjacent vessel sign, IIBV: increased ipsilateral breast vascularity, Values are mean values ± SD, *P*-value: significance level for all pairs

Table 2: Diagnostic performances of the adjacent vessel sign, increased ipsilateral breast vascularity

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
AVS (n=135)	75.0	79.3	80.5	73.5	77.0
IIBV (n=135)	56.9	90.4	87.2	64.7	72.5
Mass size ≤2cm (n=64)					
AVS	42.8	94.4	85.7	68.0	71.8
IIBV	42.8	100.0	100.0	69.2	75.0
Mass size >2cm (n=71)					
AVS	95.4	59.2	79.2	88.8	81.6
IIBV	65.9	77.7	82.8	58.3	70.4

AVS: adjacent vessel sign, IIBV: increased ipsilateral breast vascularity, PPV: positive predictive value, NPV: negative predictive value

Table 3: Relationship between adjacent vessel sign, increased ipsilateral breast vascularity and histopathological predictors

	ER		PR		C-ERBB2	
	Negative (n=24)	Positive (n=48)	Negative (n=20)	Positive (n=52)	Negative (n=41)	Positive (n=31)
AVS						
Present	13	41	10	44	29	25
Absent	11	7	10	8	12	6
P-value	0.005		0.003		0.248	
IIBV						
Present	4	37	4	37	20	21
Absent	20	11	16	15	21	10
P-value	<0.001		<0.001		0.085	

ER: estrogen receptor, PR: progesterone receptor, AVS: adjacent vessel sign, IIBV: increased ipsilateral breast vascularity, *P*-value: significance level for all pairs

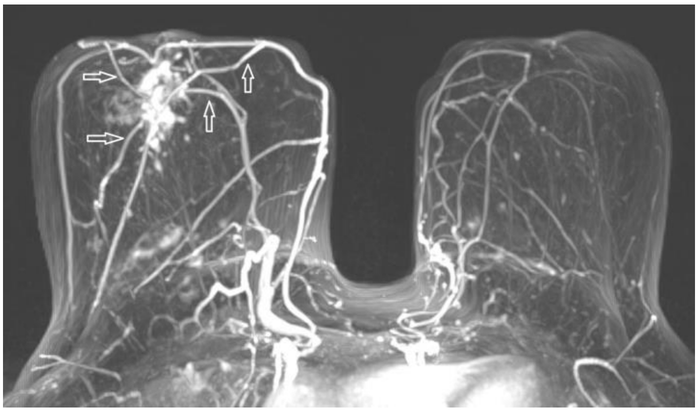

Figure 1: 43-year-old woman with invasive ductal carcinoma of right breast. Maximum-intensity-projection image shows presence of adjacent vessel sign (arrows) and increased ipsilateral breast vascularity.

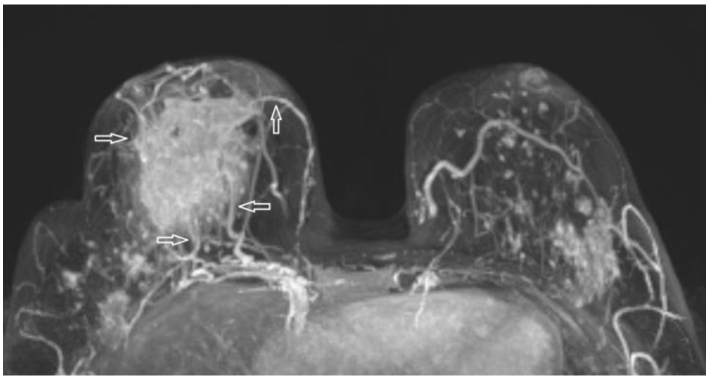

Figure 2: 27-year old woman with mastitis of right breast. Maximum-intensity-projection image represents false-positive findings for adjacent vessel sign (arrows) and increased ipsilateral breast vascularity.

Discussion

To grow and metastasize, tumor tissue requires nutrients and oxygen supplied by blood vessels with angiogenesis. Although physiological angiogenesis plays a significant role in embryo development, wound healing, and collateral vessel formation and abnormal angiogenesis in growing cancer tissue is related to active endothelial cells that release many angiogenic proteins [18]. The increased vascularity in breast cancer can be evaluated with Doppler ultrasound, positron emission tomography (PET) and MR angiograms [12,19,20].

MR angiography of the breast has been added to standard breast MRI to increase specificity when DCE images are obtained. The obtained MIP images can provide a vascular map of the breast and the location of the enhanced masses. Additionally, arteries and veins of the breast and internal mammary vessels can be assessed for symmetry and the overall number of vessels.

Gadobutrol, gadobenate dimeglumine and gadopentetate dimeglumine are the main contrast agents for angiographic imaging. Herborn et al. [21] reported that gadobutrol and gadobenate dimeglumine showed better signal-to-noise and contrast-to-noise than gadopentetate dimeglumine. We used gadobutrol for vascular mapping of the breast from the DCE images in our study.

Several studies have investigated the relationship between asymmetrically increased vascularization and ipsilateral breast cancer and to reveal a strong association [11-16,22-25]. In these studies, the sensitivity and specificity of the AVS and IIBV for detecting breast cancer were quite different [11-16,22-25]. The sensitivity and specificity of AVS and IIBV were reported in the range of 68–92% and 57–100%, respectively. Consistent with these results, in our study, we obtained sensitivities of 75% and 56.9%, specificities of 79.9% and 90.4% and accuracies of 77% and 72.5% for AVS and IIBV, respectively. We also found that the AVS had a significantly higher degree of accuracy than IIBV in characterizing breast lesions. However, vascular evaluation alone was not sufficient for performing the isolation technique to characterize suspicious breast masses. The diagnostic performance of standard breast MRI can be enhanced with the addition of the AVS and IIBV to facilitate morphologic and dynamic analyses.

Mussurakis et al. [26] showed that the periphery of masses had greater diagnostic value than the central portion, and carcinomas revealed higher peripheral enhancement than benign masses. AVS may be related to neoangiogenesis and the higher microvessel density of the periphery of the lesion. We also investigated the relationship between the AVS and prognostic factors, including hormone expression, and found that AVS was significantly associated with ER and PR expression, but not with C-ERBB2 expression. Dietzel et al. [14] and Han et al. [27] reported that AVS was significantly associated with all histopathologic predictors of ER, PR and C-ERBB2 expression. However, AVS is a highly subjective parameter in terms of interpretation, and no criterion exists for the evaluation of the number and size of vessels in contact with the suspicious lesions. The vascularity of both breasts can be evaluated with MR angiograms, and IIBV is reportedly related to ipsilateral invasive breast cancer, multifocality and axillary lymph node metastasis [16].

In our study, the malignant masses had a significantly larger mean mass than the benign masses. When the masses were grouped according to size, the small masses showed decreased sensitivity and increased specificity compared to the large masses. These changes suggest that there may be a positive correlation between tumor size, AVS and IIBV. Additionally, Kul et al. [12] revealed sensitivity increased and specificity decreased with increasing lesion size, which may be due to angiogenic stimulation, increased metabolic demand and decreased flow resistance. Malignant breast masses are believed to induce angiogenesis for invasion, uncontrolled growth, and metastasis [5,6].

None of the fibroadenomas, except for five, were AVS-positive in our study. Similar to malignant masses, fibroadenomas can show higher degrees of vascularity with increased size. Although fibroadenomas are usually detected by ultrasound, a vascularity evaluation might be useful for differentiating a fibroadenoma from a well-marginated breast cancer.

There were three patients with mastitis in whom malignancy was suspected in our study. We found that all lesions with mastitis were positive for an AVS and IIBV. Breast inflammation is related to the angiogenic process, and mastitis can stimulate vascular structures to increase in both number and size [28]. For this reason, vascular evaluations with MR angiography may lead to false positive findings for inflammatory lesions.

None of the 11 fibrocystic changes had AVS or IIBV in our study. The ultrasound images of the cystic changes may vary with morphological changes. AVS and IIBV may be helpful in discriminating lesions with fibrocystic changes from malignant masses.

We detected eight papillary lesions, including four papillary carcinomas and four papillomas. We revealed that all papillary carcinomas, except for one, and three papillomas had an AVS. In total, two papillary carcinomas and papillomas had IIBV. Both benign and malignant papillary lesions can show high vascularity, so the AVS and IIBV have limited efficacy in characterizing papillary lesions.

Limitations

This study has several limitations. First, we evaluated the MRI images based on a consensus and did not take into consideration the inter- and intraobserver variability. Second, the sample sizes were also relatively small for subtypes of benign and malignant masses. Further prospective studies with large sample sizes are required to clarify the effectiveness of these methods and the relationship between various prognostic factors. Third, we only evaluated contrast-enhanced lesions, so our results cannot be applied to all lesions. Fourth, we did not evaluate other prognostic factors such as lymph node involvement, distant metastasis, or follow-up results.

Conclusion

Breast vascularity can be evaluated with MR angiograms obtained from DCE images without the need for additional acquisition time. MR angiography might increase the specificity of breast MRI and become a reliable method of further characterizing suspicious breast masses. In addition, AVS and IIBV both seem to be related with ER and PR expression.

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Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine