



The value of adjacent vessel sign in malignant breast tumors

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PURPOSE

The aim of this study was to evaluate the prognostic quality of adjacent vessel sign (AVS) in malignant breast tumors by comparing it with classical prognostic pathological biomarkers and magnetic resonance imaging (MRI) findings.

METHODS

A total of 124 patients with 133 malignant lesions were included. All the imaging was performed on a 1.5T Avanto scanner and the images were interpreted according to BI-RADS-MR® (fifth ed.) atlas. Maximum intensity projection (MIP) images were constructed from subtracted post-contrast images and were used to investigate AVS. Histopathological results and MRI findings were compared with AVS.

RESULTS

Interobserver agreement about AVS status was substantial ($\kappa=0.64$). AVS positive lesions were significantly bigger in size ($P < .001$, AVS negative: median 12 mm, AVS positive: median 31 mm). AVS was significantly associated with increased Ki-67 index and axillary lymph node metastasis ($P=.009$ and $P=.019$, respectively). Between AVS and lymphovascular invasion (LVI), there was a trend toward positive relationship ($P=.076$). MRI findings of T2 hypointensity, peritumoral edema, irregular shape, non-homogeneous contrast enhancement, rapid early contrast enhancement, and skin infiltration showed significant positive relation with AVS ($P < .001$, $P < .001$, $P < .001$, $P=.02$, $P=.021$, and $P=.021$, respectively). AVS is found to be associated with increased Ki-67 index, axillary lymph node metastasis, and some MRI findings that point to malignancy or poor prognosis.

CONCLUSION

AVS indicates poor prognosis since it is related to axillary lymph node metastasis, increased Ki-67 index, LVI, peritumoral edema, rapid early contrast enhancement, increased background enhancement, skin extension, T2 hypointensity, non-homogeneous contrast enhancement, irregular lesion shape, and larger tumor size. AVS is an easy to use sign that shows substantial interobserver agreement.

Breast cancer is the number one cause of cancer-related deaths in women.¹ Tumor cells need neovascularization to stay alive, grow, invade, or spread. Studies show that contrast enhancement pattern in magnetic resonance imaging (MRI) is related to microvessel density, neovascularization, and prognostic parameters.²⁻⁵ Also, tumor-bearing breast shows increased vascularity compared to the contralateral breast, and this is found to be related to prognostic indicators.⁶⁻⁸ Asymmetrical increased vessels, first mentioned by Sievert in 1997, were later described by Sardaneli in 2005 as increased number of vessels 2 mm or thicker and 3 cm or longer, compared with the contralateral breast.^{6,7,9,10} As one can easily appreciate, this method is laborious, time-consuming, and impractical. On the other hand, an adjacent vessel sign (AVS) is more easily and rapidly applicable. AVS was first defined by Carriero et al.¹¹ as a vessel (either artery or vein) in contact with a lesion or entering it. Besides, AVS can be used in bilateral breast cancer or patients with mastectomy whereas asymmetrical increased vessels can be used only when a normal contralateral breast exists (Figure 1). Maximum intensity projection (MIP) series constructed from early postcontrast images are best to

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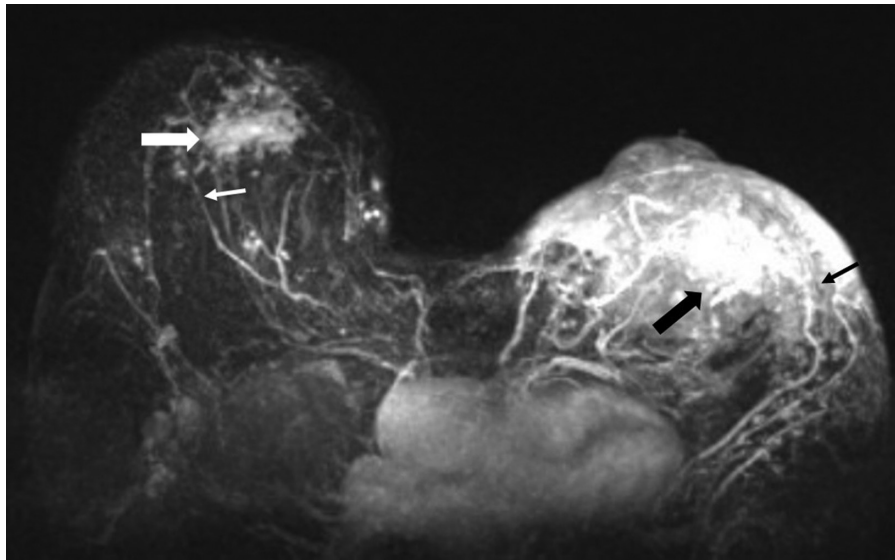


Figure 1. 60-year-old woman with invasive carcinoma of no special type (IC-NST) on the right breast (thick white arrow) and invasive papillary carcinoma on the left breast (thick black arrow), both positive for adjacent vessel sign (AVS) on maximum intensity projection (MIP) imaging (thin arrows). Asymmetrical increased vascularity cannot be used in this case since both breasts bear malignancy. Instead, AVS can be readily utilized.

search for AVS since breast parenchyma is less enhanced (Figure 2). AVS is associated with malignancy.^{4,12,13} Only a few studies about the prognostic value of AVS are found in the literature.^{4,14}

Prognostic factors in breast cancer provide information about the course of the disease before surgery and are irrelevant to neoadjuvant therapy. Patient age, axillary lymph node metastasis, tumor size, type, histopathologic grade, lymphovascular invasion (LVI), tumor proliferation speed (Ki-67), oncogenes (Her-2/neu), tumor suppressor genes (p53), and estrogen and progesterone receptor (ER and PR) are independent classic prognostic factors.¹⁵ Predictive factors show possible response to treatment but

cannot demonstrate the disease course. ER, PR, Ki-67, and HER2 existence or percent are both prognostic and predictive parameters.

In this study, we aimed to assess the relationship between AVS and classical pathological prognostic-predictive parameters and MRI findings in malignant breast tumors.

Methods

Patients

A total of 124 patients with 133 malignant lesions were included in this study. Dynamic breast MRI reports recorded in the hospital local database (PACS) between the years 2012 and 2017 indicating “contrast-enhanced mass” were screened. Among these reports, patients with the histopathological result as malignant breast tumors were included. The final diagnosis was made by core biopsy, excisional biopsy, and partial-total mastectomy. Patients with benign diagnosis, recurrent breast cancer, having received chemotherapy beforehand, and under treatment for another malignancy were excluded. All patients were female with an average age of 49 years (min-max: 21-88). Menopause status and family history of breast cancer were also recorded. Institutional Review Board (IRB) approval was taken (decision number; 7/83, date: November 15, 2016).

MRI evaluation

All breast MRI scans were performed on a 1.5 T system (Siemens, Avanto) in a prone position and by using a bilateral 4-channel dedicated breast coil. Axial fat saturated T2-weighted imaging (T2A) (time to repetition/time to echo [TR/TE]=4560/59 ms; slice thickness 4 mm, matrix 340 × 512), axial T1-weighted imaging (T1A) (TR/TE=571/11 ms; slice thickness 4 mm, matrix 340 × 512), 1 precontrast and 5 post-contrast 3D T1 turbo spin echo (TSE) (TR/TE=5.16.2.38 ms; flip angle 100, slice thickness 1.1 mm, matrix 320 × 512), diffusion-weighted imaging (b values: 0-800 s/mm²) series, Apparent diffusion coefficient (ADC) maps, subtraction, and MIP images were obtained.

Two radiologists (4-20 years of experience) evaluated all the images by Siemens Syngo Via workstation, blinded to clinical data and histopathology results. The first or second MIP series were considered valid since tumor and vessels were brighter while background parenchymal enhancement was low. MIP images were examined by 3600 rotations in every 3 directions in order to evaluate all of the surface and the vessels around the mass (Figures 3 and 4). The readers practiced examining AVS on about 30 lesions together prior to their own separate evaluation. The conventional MRI findings defined by BI-RADS-MR[®] (fifth ed.) atlas and signal intensity curves were also noted by each reader.

Histopathological assessment

Histopathological assessment was examined by a breast pathologist (with an experience of more than 10 years) according to the World Health Organization Breast Cancer Classification 2012.²¹ Time duration between MRI scans and histopathological examination was about 2 months. HER-2 scores of 0 and 1 were counted as negative and 3 as positive whereas those with a score of 2 were classified as suspicious and *in situ* hybridization results were taken into account. For Ki-67, 20% was taken as the cutoff value.¹⁷ Samples with positive staining with a ratio of 1% and more were taken as ER and PR positive.¹⁸ Bloom-Richardson scores were dichotomized as 1-7 to be low and 8-9 as high. Axillary lymph node metastasis was evaluated by fine-needle aspiration, core needle biopsy, or dissection. Cases without histopathological examination for

Main points

- Adjacent vessel sign (AVS) shows poor prognosis since it is related to axillary lymph node metastasis, increased Ki-67 index, lymphovascular invasion, peritumoral edema, rapid early contrast enhancement, increased background enhancement, and skin extension.
- AVS is also associated with T2 hypointensity, non-homogeneous contrast enhancement, irregular lesion shape, and larger tumor size which all point out malignant lesion character.
- AVS is an easily and rapidly applicable sign showing substantial interobserver agreement.

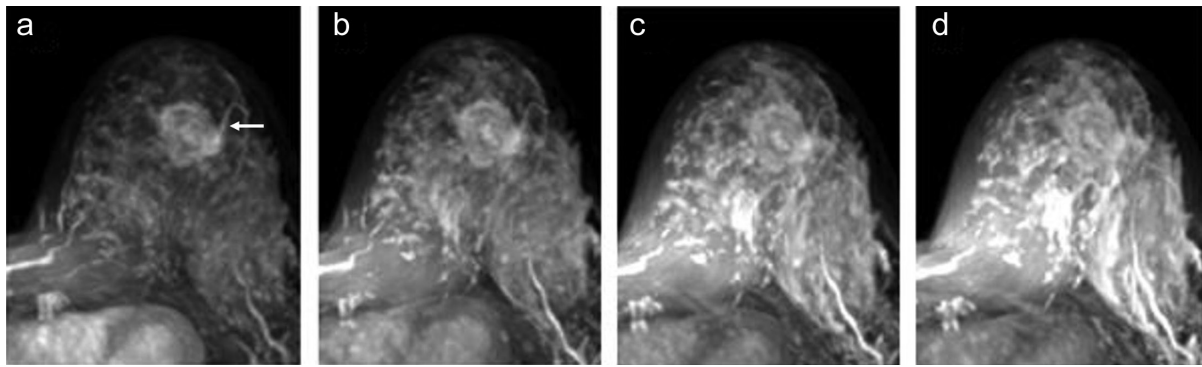


Figure 2. a-d. Early through late MIP images (a-d); AVS appears best at early series (a, arrow).

axilla and positron emission tomography computed tomography (PET-CT) positivity for axillary metastasis were taken into account.

Statistical analysis

All statistical analyses were performed by using Statistical Package for Social Sciences software, Version 20.0 (IBM). The Kappa method was used to search for interobserver agreement and results were grouped as <0, no agreement; 0.01-0.20, none to slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-80, substantial; and 0.81-1.00, almost perfect. Chi-squared

testing was used for categorical values, and Bonferroni adjustment was applied when necessary. The variables were investigated using Kolmogorov-Smirnov test to determine whether or not they are normally distributed. Student t test was used for statistical comparison of groups. A *P* value of < .05 was considered to indicate a statistically significant difference.

Results

The study group consisted of 124 female patients with 133 malignant lesions (mean age 49; range, 21-88 years). AVS was positive in 109 lesions (82%) and

negative in 24 lesions (18%). Interobserver agreement of AVS positivity was substantial ($\kappa=0.64$, $P < .001$). Sixty women were premenopausal and 64 were postmenopausal. A family history of breast cancer was observed in 28 of 99 patients (29.9%). No relation was found between AVS and patient age (compared as over or below 40 years or as decades), menopause status, or family history.

We dichotomized the lesions as smaller or bigger than 2 cm, taking account of the pathology specimens. No relation was found between tumor size and AVS. In consideration of correlation between AVS and histopathological subtypes, no significant difference was found either by comparing each or when dichotomized as invasive carcinoma of no special type (IC-NST) and others (Table 1).

Compared with prognostic and predictive biomarkers, a significant relation was found between AVS and increased Ki-67 values (20 accepted as threshold) ($P=.009$) and axillary lymph node metastasis ($P=.019$) (Figure 5) (Table 2). Besides, no relation was found between AVS and hormone receptors (ER and PR) or HER-2 status.

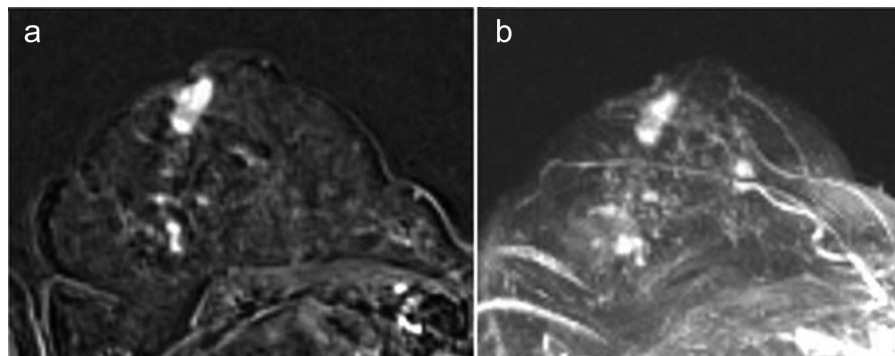


Figure 3. a, b. A 65-year-old patient with IC-NST lesion diagnosed in the right breast (a). Lesion is AVS negative (b).

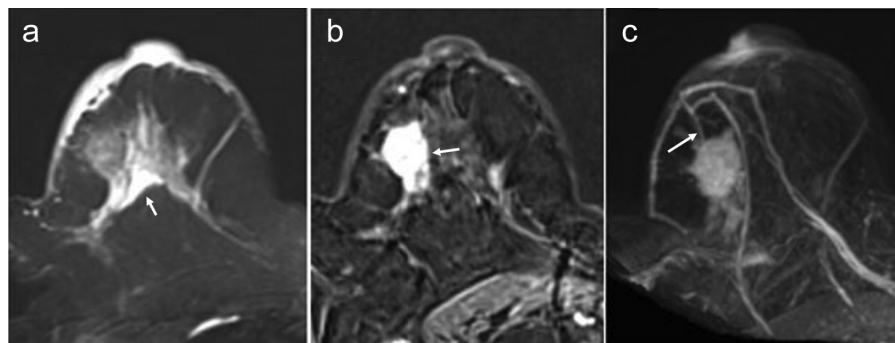


Figure 4. a-c. An 89-year-old patient with IC-NST. A hypointense lesion with peritumoral edema (a, arrow) on TIRM; rapid early contrast-enhanced malignant lesion (b, arrow); AVS is positive on MIP image (c, arrow).

Table 1. Tumor histopathological subtypes		
Histopathological diagnosis	n	%
IC-NST	99	73.8
Invasive lobular carcinoma	9	6.7
Ductal carcinoma <i>in situ</i>	9	6.7
Tubular carcinoma	6	5.2
Mucinous carcinoma	4	2.9
Neuroendocrine differentiated carcinoma	2	1.4
Papillary carcinoma	3	2.2
Cribriform carcinoma	1	0.7

IC-NST, invasive carcinoma of no special type.

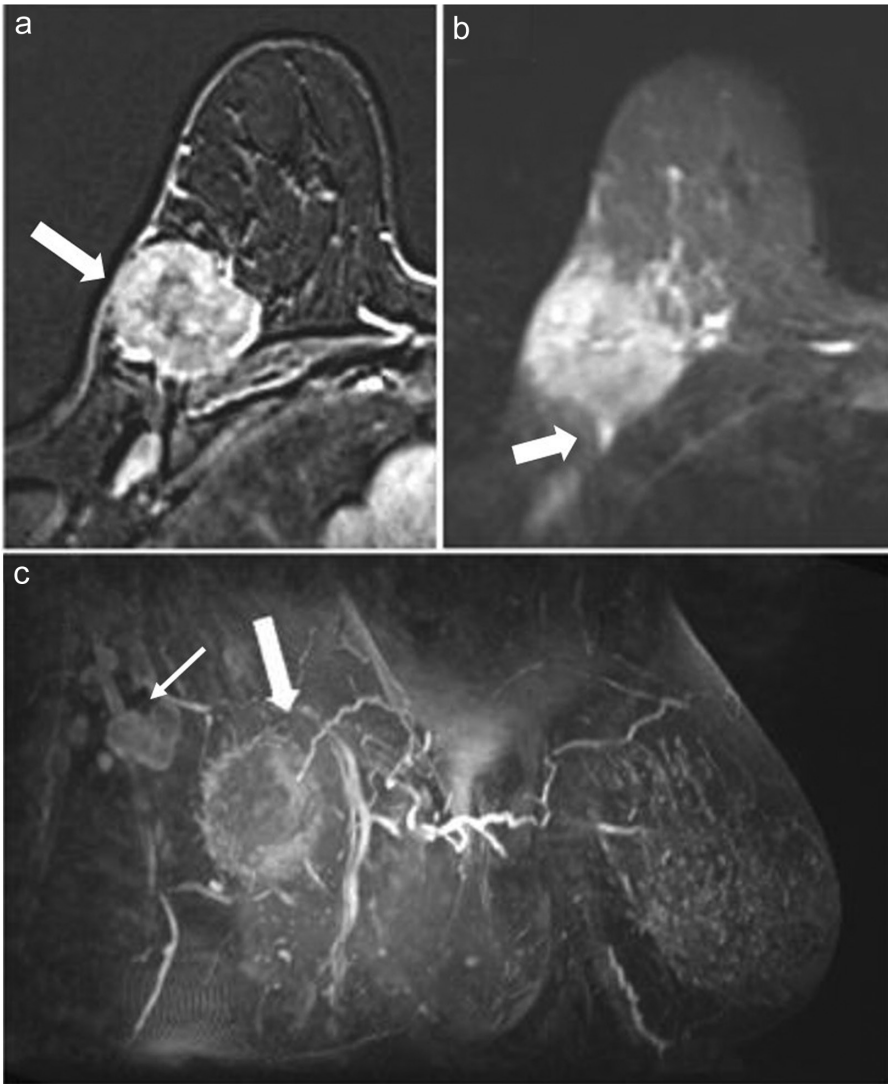


Figure 5. a-c. A 49-year-old patient with invasive carcinoma with squamous differentiation. Malignant lesion with irregular shape and nonhomogeneous enhancement (arrow) (a), peritumoral edema at TIRM images (arrow) (b), AVS positive at MIP imaging (arrow) and axillary lymph node metastasis (thin arrows) (c).

Molecular subtypes varied as 20 luminal A, 81 luminal B, 10 non-luminal, and 12 triple-negative, and no association was found with AVS.

Among histopathological results, only LVI showed a trend toward statistical significance ($P=.076$). No relation was found between AVS and tumor grade.

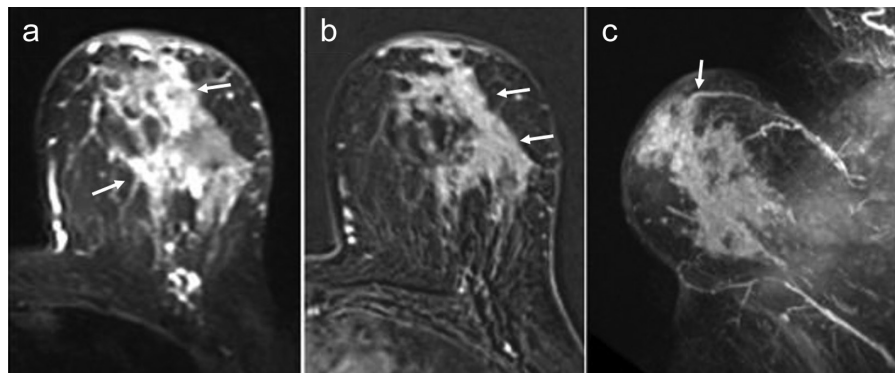


Figure 6. a-c. 57 years, NST-IC, hypointense lesion, and peritumoral edema at TRIM image (arrows) (a), early rapid contrast-enhanced irregular-shaped lesion (arrows) (b), AVS positive at MIP imaging (arrow) (c).

Table 2. Prognostic and predictive markers compared with AVS

	AVS –	AVS +	<i>P</i>
ER (n = 129)			.231
Negative	3 (12.5%)	23 (21.9%)	
Positive	21 (87.5%)	82 (78.1%)	
PR (n = 120)			.476
Negative	10 (43.5%)	39 (40.2%)	
Positive	13 (56.5%)	58 (59.8%)	
HER-2 (n = 124)			.786
Negative	16 (72.7%)	77 (75.5%)	
Positive	6 (27.3%)	25 (24.5%)	
Ki-67 (n = 124)			.009
Low (<20%)	11 (50%)	23 (22.5%)	
High (>20%)	11 (50%)	79 (77.5%)	
Axillary lymph node (n = 109)			.019
Negative	11 (61.1%)	29 (31.9%)	
Positive	7 (38.9%)	62 (68.1%)	

AVS, adjacent vessel sign; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

Considering MRI findings and AVS relation, increased background enhancement, hypointensity at turbo inversion recovery magnitude (TIRM) ($P < .001$) (Figure 6), peritumoral edema ($P < .001$) (Figure 6), irregular shape ($P < .001$), rapid initial enhancement ($P=.021$), axillary lymph node positivity ($P=.012$), larger lesion size (AVS negative mean: 15 ± 7 mm, median: 12.5 mm, min-max: 6-33 mm; AVS positive mean: 36.8 ± 21 mm, median: 31 mm, min-max: 9-123 mm, $P < .001$) and skin extension ($P=.021$) showed statistical significance except increased background enhancement that showed a trend toward statistical significance ($P=.085$) (Table 3).

Discussion

In this study, the prognostic and predictive value of AVS in malignant breast tumors was investigated by comparing classical histopathological prognostic and predictive biomarkers and MRI findings. As angiogenesis plays a major role in tumor liveliness, growth, and metastasis, increased ipsilateral vascularity is seen in malignant breast lesions compared to benign masses. In addition, studies show that it is related to poor prognosis.⁶⁻⁸ Later studies point out AVS to be an indicator of malignancy

Table 3. MRI findings compared with AVS			
	AVS – (n=24)	AVS+ (n=109)	P
Tumor size on MRI	15 ± 7 mm	36.8 ± 21 mm	.000
Breast type			.346
Type 1 and 2	14 (58.3%)	52 (47.7%)	
Type 3 and 4	10 (41.7%)	57 (52.3%)	
Background enhancement			.085
Low (1, 2)	15 (62.5%)	47 (43.1%)	
High (3, 4)	9 (37.5%)	62 (56.9%)	
Side			.435
Right	10 (41.7%)	55 (50.5%)	
Left	14 (58.3%)	54 (49.5%)	
Localization			.437
Inner quadrant	10 (41.7%)	31 (28.4%)	
Outer quadrant	13 (54.2%)	71 (65.1%)	
Inner and outer quadrant (central)	1 (4.2%)	7 (6.4%)	
TIRM signal			.000
Hypointense	9 (39.1%)	87 (79.8%)	
Hyperintense	14 (60.9%)	22 (20.2%)	
Peritumoral edema			.000
No	16 (66.7%)	31 (28.4%)	
Yes	8 (33.3%)	78 (71.6%)	
Shape			.000
Oval-round	13 (51.2%)	18 (16.5%)	
Irregular	11 (45.8%)	91 (83.5%)	
Margin			.580
Smooth	1 (4.2%)	5 (4.6%)	
Irregular	19 (79.2%)	75 (68.8%)	
Spiculated	4 (16.7%)	29 (26.6%)	
Contrast enhancement			.020
Homogeneous	4 (16.7%)	3 (2.8%)	
Non-homogeneous (heterogeneous, rim, dark internal septa)	20 (83.3%)	106 (97.2%)	
Initial enhancement pattern			.021
Slow and medium	6 (25%)	8 (7%)	
Fast	18 (75%)	100 (93%)	
Axillary lymph node metastasis			.012
Yes	4 (17%)	48 (44%)	
No	20 (83%)	60 (56%)	
Skin extension			.021
No	24 (100%)	91 (83.5)	
Yes	0 (0%)	18 (16.5%)	

AVS, adjacent vessel sign; MRI, magnetic resonance imaging; TIRM, turbo inversion recovery magnitude.

There was no difference between lesion size when pathological specimens were divided into 2 groups as smaller or bigger than 2 cm. In this study, an insufficient number of lesions could be the reason for the discrepancy since only 44 lesions were suitable to evaluate lesion size directly from a pathology specimen. However, larger lesions assessed by MRI presented with AVS more often (AVS positive mean: 36.8 ± 21 mm, median: 31 mm, min-max: 9-123 mm; AVS negative mean: 15 ± 7 mm, median: 12.5 mm, min-max: 6-33 mm, $P < .001$). These results are concordant with the literature.^{12,13} In the study of Kul et al.,¹² mean lesion size was 38.2 ± 18.2 mm versus 12.6 ± 5.4 mm (AVS positive vs. negative, respectively).

In our study, IC-NST was the largest group of histopathological types with 73.8% ratio and the number of lesions in each subgroup was insufficient and therefore all of the lesions were dichotomized accordingly. There was no significant difference between the 2 groups regarding AVS. Dietzel et al.¹³ found the same results in a study including 1084 cases, identifying no relationship between AVS and histopathological subtypes.¹³ Also, in their study.

We examined the relationship between AVS and ER, PR, HER-2, Ki-67, and axillary lymph node metastasis. AVS was significantly associated with increased Ki-67 index and axillary lymph node metastasis ($P = .009$ and $P = .019$). No relationship was found between AVS and ER, PR, and HER-2, respectively. Lymph node metastasis is the most important prognostic factor. Ten-year life expectancy was 75% in those with negative axillary lymph nodes, while it was 25%-30% in those with positive axilla.¹⁹ Han et al.⁴ studied 249 patients showing significant association between AVS and axillary lymph node metastasis, ER, and PR ($P < .001$, $P = .007$, and $P = .005$, respectively). Ki-67 was not included in their study. Our study is the first in the literature in this regard as far as we know. Nevertheless, it would be beneficial to perform the study on a larger group of patients to better prove these results. In accordance with previous studies, our study verifies and additionally shows that AVS indicates a poor prognosis.⁴

In comparison with other histopathological results, there was a trend toward a higher prevalence of AVS in lesions with LVI ($P = .076$). LVI is an independent prognostic factor in breast cancers that

for breast tumors, and only a few studies examined the prognostic significance of this sign.^{4,12-14}

In this study, 133 malignant lesions of 124 patients were examined; 24 lesions

(%18) were AVS negative and 109 (%82) were positive. Interobserver agreement was substantial ($\kappa = 0.64$). Han et al.⁴ assessed 249 breast cancer patients and interobserver agreement was poor ($\kappa = 0.44$).

are node-negative or smaller than 2 cm. Besides, it increases the risk of axillary lymph node metastases. Blood vessel invasion is related to unfavorable clinical outcome.¹⁹ Cheon et al.²⁰ performed a study with 389 patients and found a significant relationship between AVS and LVI. To the best of our knowledge, ours is the second study in the literature. Although its relationship with AVS is unclear, neoangiogenesis occurring at the early stages of cancer may explain this finding, as stated in previous studies.²¹

In our study, we detected no significant relationship between tumor grade and AVS. Han et al.'s⁴ study states that AVS is significantly associated with distant metastasis and nuclear grade presenting in 243 patients ($P=.011$ and $P=.023$, respectively), whereas Dietzel et al.'s¹³ study puts forth no relationship between AVS and tumor grade examined on 532 patients. Consistent with this study, we also identified no relationship between tumor grade and AVS which we could examine in only 41 patients. Neovascularization in the early stages of invasive breast carcinomas is considered to be the reason for this status.¹³ These results show that AVS can be used in malignant breast tumors irrespective of tumor grade.

In the comparison of AVS with MRI findings, no significant difference was found regarding fibroglandular tissue amount, left- or right-sidedness, and localization within the breast. These results lead to the conclusion that AVS can be used to evaluate lesions in all areas regardless of localization. On the other hand, there was a trend of higher parenchymal enhancement of the background in the cancer-bearing breast with AVS ($P=.085$). In the literature, increased background parenchymal enhancement is defined as an independent cancer risk factor in terms of late recurrence and decreased disease-free survival.²² Hereby, AVS can indicate a poor prognosis again. Long-term studies with more patients, in which they are monitored directly for survival and recurrence, might prove this claim.

As commonly known, malignant breast lesions are mostly T2 hypointense with some exceptions such as mucinous carcinoma or cancer with necrosis.^{23,24} Likewise, malignant lesions are more often associated with AVS as stated repeatedly in previous studies.^{12,13,25} We found a significant relationship between T2 hypointensity and

AVS as expected. To the best of our knowledge, this study is the first one in the literature to present this relationship.

AVS and peritumoral edema point out a significant association ($P < .001$). Studies show peritumoral edema to be related to increased risk of axillary lymph nodes, distant metastasis, and decreased metastasis-free survival. Moreover, lack of peritumoral edema is found to be associated with complete response to neoadjuvant chemotherapy and disease-free survival.²⁶ Consequently, AVS can be considered a bad prognostic sign since it is highly related to peritumoral edema which implies a poor prognosis from many perspectives. Further prospective studies with longer follow time are needed in order to better understand the direct effect of AVS on survival.

We found a significant relationship between AVS and irregular lesion shape as the lesions were dichotomized as irregular and others ($P < .001$). When the lesions were divided as non-homogeneous and homogeneous contrast-enhancing, AVS was found to be related to non-homogeneous contrast enhancement ($P=.020$). In the literature, we did not encounter any study investigating these characteristics. Considering the irregular shape and non-homogeneous enhancement pattern showing malignancy, it is not surprising to find them related to AVS which is also known to be a malignancy marker.

When evaluating kinetic curves of lesions in 2 groups, slow (slow and medium) and rapid speed, we found a statistically significant association between AVS and rapid early contrast enhancement ($P=.021$). Early contrast enhancement is known to be associated with invasive carcinoma rather than benign tumors. Furthermore, there are studies showing a correlation of rapid early contrast enhancement with poor prognosis such as decreased disease-free survival and overall survival.^{27,28} Skin infiltration also showed significant relation with AVS ($P=.021$). Skin invasion raises the tumor stage to T4, leading to poor prognosis.²⁹ These results show that AVS is related to poor prognosis and higher stages of cancer. We did not encounter a prior study analyzing the relationship between kinetic-morphologic MRI parameters and AVS in the literature.

There were some limitations to this study. The number of patients without

presurgical treatment was limited and therefore evaluation of pathological results such as histological grade, tumor staging, and axillary lymph node status was suboptimal. In order to overcome this obstacle regarding axillary lymph nodes status, PET-CT evaluation was used to determine axillary metastasis. The numerical range of histopathological or molecular subtypes of the lesions was unequally distributed, making adequate comparison impossible.

AVS does not discriminate artery or vein which might show different resistance to invasion. Further examinations by advanced imaging techniques to differentiate between artery and vein might give more detailed information about tumor development, progression, and course of the disease. In this study, the prognostic value of AVS was analyzed via classical prognostic-predictive pathological biomarkers and MRI findings. To find the actual prognostic value of AVS determined by long-term follow-up of survival and recurrence rates with larger patient groups should be performed. Another limitation of our study was the lack of distance metastasis status which also influences prognosis considerably. The reason was that the number of patients with PET CT was insufficient. AVS relation with distant metastasis can be a subject for another study.

In conclusion, AVS is related to axillary lymph node metastasis, increased Ki-67 index, LVI, T2 hypointensity, nonhomogeneous contrast enhancement, larger lesion size, peritumoral edema, and irregular lesion shape. Considering these results, AVS can be used as a poor prognostic marker and can indicate malignancy.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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