Original Article

Predictive Role of Blood Flow Characteristics in the Detection of Malignant Breast Lesions: A Prospective Study

Malign Meme Lezyonlarının Saptanmasında Kan Akışı Özelliklerinin Prediktif Rolü: Prospektif Bir Çalışma

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ABSTRACT

Introduction: The aim of this study is to investigate the predictive feature of lateral thoracic artery (LTA) and internal thoracic artery (ITA) power doppler ultrasound examination results of patients with malignant breast lesions.

Material and Methods: This is a prospective case-control study in which 47 patients with suspicious lesions detected by ultrasonography and mammography and diagnosed with pathologically invasive breast carcinoma between 2018-2020 were included in a tertiary hospital. The breast with invasive carcinoma and the intact breast of the same patient were evaluated with LTA and ITA by power doppler ultrasonography. Healthy breast was the control group.

Results: In the diagnostic statistical tests; the optimum cut-off value for LTA peak systolic flow (PSF) value is 19.6 cm/s, sensitivity of this value is 81.3% and specificity is 95.8%. The optimal cut-off value for LTA resistive index (RI) value was 0.805, sensitivity of this value was 91.7% and specificity was 95.8%. For the detection of invasive breast carcinoma in the contralateral breast, the sensitivity of ITA peak diastolic flow (PDF) below 8.35 is 77.1% and the specificity is 79.2%.

Conclusion: To the best of our knowledge, this study is the first publication to examine the flow patterns of internal ITA and LTA together. This study presents new quantitative diagnostic tests that can be used to detect breast cancer, are easily accessible, applicable, and have high sensitivity and specificity.

Keywords: Breast Tumors; Blood Flow Velocity, Doppler Ultrasound Imaging, Thoracic Arteries

ÖZET

Giriş: Bu çalışmanın amacı malign meme lezyonu olan hastaların lateral torasik arter (LTA) ve internal torasik arter (İTA) power doppler ultrason inceleme sonuçlarının prediktif özelliğini araştırmaktır.

Gereç ve Yöntemler: Bu çalışma, 2018-2020 yılları arasında ultrasonografi ve mamografi ile şüpheli lezyonları saptanan ve patolojik invaziv meme kanseri tanısı konan 47 hastanın üçüncü basamak bir hastanede dahil edildiği prospektif bir vaka kontrol çalışmasıdır. Aynı hastanın invaziv karsinom tanısı alan memede ve sağlıklı memede power doppler ultrasonografi ile LTA ve İTA ile değerlendirildi. Sağlıklı meme kontrol grubuydu.

Bulgular: Tanısal istatistiksel testlerde; LTA PSF değeri için optimum cut-off değeri 19.6 cm/s, bu değerin duyarlılığı %81.3 ve özgüllüğü %95.8'dir. LTA RI değeri için optimal cut-off değeri 0.805, bu değerin duyarlılığı %91.7 ve özgüllüğü %95.8 idi. Karşı memede invaziv meme kanseri tespiti için ITA PDF'nın 8.35'in altındaki duyarlılığı %77.1, özgüllüğü %79.2'dir.

Sonuç: Bildiğimiz kadarıyla, bu çalışma dahili ITA ve LTA'nın akış modellerini birlikte inceleyen ilk yayındır. Bu çalışma, meme kanserini tespit etmek için kullanılabilecek, kolay erişilebilir, uygulanabilir, yüksek duyarlılık ve özgüllüğe sahip yeni kantitatif tanı testleri sunmaktadır.

Anahtar Kelimeler: Meme tümörleri, Kan Akış Hızı, Doppler Ultrason Görüntüleme, Torasik Arterler

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Introduction

The most common malignancy in women is breast cancer and is the second most common cause of death after lung cancer worldwide [1]. Early diagnosis is the most important factor that increases survival in breast cancer, and the prognosis of the disease is directly related to the stage at the time of diagnosis [2]. Screening with mammography at a rate of 16-40% plays a role in the reduction of breast cancer deaths among women aged 40-74 [3,4]. However, it has been reported that mammography rates decrease as the breast density increases [5]. Screening by mammography alone may be insufficient in these women [6]

For the evaluation of breast lesions, breast ultrasonography is an important imaging method that complements mammography and has high sensitivity and specificity. It is easily possible to evaluate cystic lesions in the breast and to evaluate peripherally located breast lesions with breast ultrasonography [7-9]. However, the quality of ultrasound images for ultrasonographic evaluation is affected by many factors such as contrast and signal to noise ratio, acoustic shadowing and enhancement artifacts. In addition, it is subjective because it depends on the experience and skill levels of the person performing ultrasonography (10). Quantitative ultrasonographic parameters are investigated in order to decrease misdiagnosis in breast ultrasonography and to eliminate this subjective evaluation [11].

Internal thoracic artery (ITA), lateral thoracic artery (LTA) and internal mammarian artery (IMA) play a role in breast feeding. ITA nourishes the breast and anterior chest wall. IMA feeds the breast through the posterior and anterior medial branches and LTA feeds the lateral part of the chest [12,13]. Power doppler ultrasound (PDUS), on the other hand, has a diagnostic value in distinguishing benign and malignant masses of lesions by evaluating the blood flow and vascularization of solid lesions in gray scale ultrasonography (US) findings [14,15]. However, there are not enough studies investigating values such as resistive index (RI), pulsatility index (PI) of ITA and LTA in patients with malignant breast lesions.

The aim of this study is to investigate the predictive feature of LTA and ITA PDUS examination results of patients with malignant breast lesions.

Materials and Methods

Ethic Approval and Patients

This is a prospective case-control study in which 47 patients with suspicious lesions detected by ultrasonography and mammography and diagnosed with pathologically invasive breast carcinoma between 2018-2020 were included in the Adıyaman Training and Research Hospital. Local ethics committee approval was obtained for the study. The study was carried out in accordance with the Declaration of Helsinki, and a signed consent form was obtained from all participants or their legal guardians.

Being 18 years of age or younger, women diagnosed with malignancy at the time of diagnosis or previously, having a history of breast surgery in the last 12 months, receiving radiotherapy and chemotherapy in the last 12 months, infectious diseases such as periductal mastitis and granulomatous mastitis that have been treated in the last 12 months, having illnesses and being in the lactation period were exclusion criteria from the study.

Ultrasonographic examination

The evaluation of the patients was performed on a GE Logiq S8 (GE Healthcare, Milwaukee, WI, USA) ultrasound device using a 12-MHz linear probe.

Patients were evaluated primarily by US examination and B-Mode US examination by two radiologists with 5 years and 15 years of

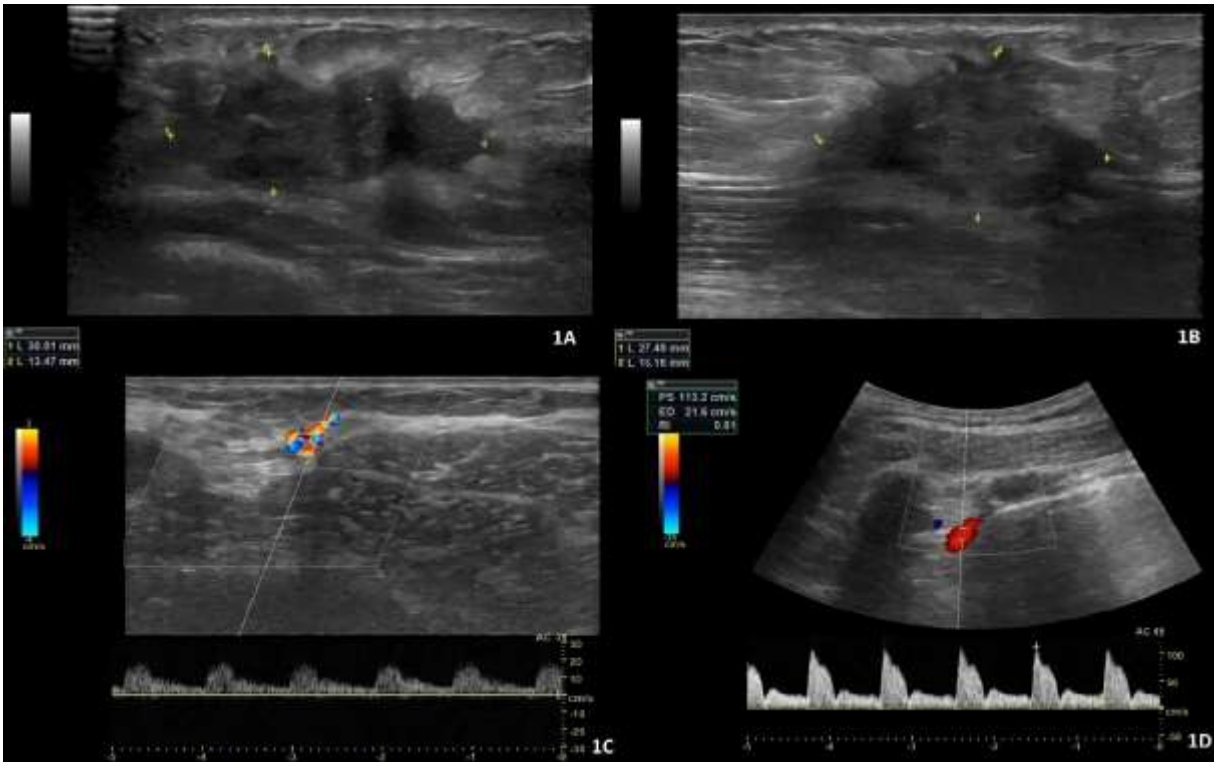

Figure 1:1A-1B An irregular shaped solid mass lesion in the upper outer quadrant of the right breast with a spicule contour, 30x27x15 mm in size, diagnosed as invasive ductal carcinoma. 1C:Evaluation of lateral thoracic artery by power doppler ultrasonography.1D: Evaluation of the internal thoracic artery by power doppler ultrasonography.

experience, and they were characterized using the Breast Imaging Reporting and Data System (BIRADS (American College of Radiology 2013)) classification system. The lesions in BIRADS categories 4 and 5 were lesions with a high probability of malignancy according to this classification. Location, size, lesion shape/margin features and echogenicity of the lesions were noted (Figure 1A-1B).

Biopsy Method

All lesions were sampled by US-guided core biopsy and pathological evaluation results were obtained for all lesions.

PDUS examination

Patients whose pathological examination results were presented as early-stage invasive breast carcinoma and who were decided to have an operation were performed an ultrasound examination before the operation. After the biopsy procedure, PDUS examination was performed 2-4 weeks later to prevent the flow parameter changes that may develop due to the procedure. PDUS imaging and spectral analysis were performed on the patient's ITA and LTA feeding the breast with lesions and the ITA and LTA feeding the healthy breast.

Patients were placed on their back with their hands under their heads and arms in flexion to detect LTA and ITA. The probe was first placed parallel to the edge of the pectoral muscle and LTA was detected with color doppler (Figure 1C). ITA was detected with color doppler by placing a probe in the second intercostal space of both sides (Figure 1D). ITA was located 1-2 cm lateral to the sternal border [16,17]. Spectrum examination in Doppler imaging was measured at the lowest pulse frequency repetition value that did not

Table 1. Patients demographic characteristics and lesion characteristics.

	Number	%
Age		
30-44	23	47,9
45-59	18	37,5
60 and above	7	14,6
Breast Pattern		
B	12	25,0
C	31	64,6
D	5	10,4
Breast Localization		
Right	19	39,6
Left	29	60,4
Lesion Localization		
Lower inner	10	20,8
Upper inner	8	16,7
Upper outer	15	31,3
Lower outer	7	14,6
Upper middle	8	16,7
Lesion Edge		
Spiculation	23	47,9
Angulation	11	22,9
Microlobulation	14	29,2
Lesion Shape		
Irregular	46	95,8
Oval	2	4,2

cause aliasing artifacts, the lowest Doppler inspection window, and a low wall filter (50 Hz). Peak systolic flow (PSF), peak diastolic flow (PDF), resistive index (RI) and Pulsatility index (PI) values were obtained for both arteries.

Statistical Analysis

Statistical analysis of all results was performed using the SPSS software version 22.0 (SPSS Inc., IBM Corp. Armonk, NY).

The Mann-Whitney U test was used for independent binary groups that did not fit the normal distribution. Categorical variables presented as ratio, continuous variables were presented as median (min-max) value and standart deviation (SD). A $p<0.05$ value was considered significant.

We used Reciever Operator Characteristics Curve (ROC) analysis to determine the effectiveness of the PDUS parameters and predict malignant breast lesions. Although the, LTA RI, LTA PSF, ITA PDF and ITA RI values were statistically significant in areas under the curve in the predict of malignant breast lesions and their specificities were high.

Results

The sociodemographic characteristics of the patients and the characteristics of the lesions are given in Table 1.

PSF, PDF, RI and PI values of LTA and ITA values were compared for the breast with the lesion diagnosed as invasive carcinoma and healthy breast.

LTA PSF, LTA RI and ITA RI values were found to be significantly higher in the invasive carcinoma side compared to the healthy side ($p<0.001$), and the ITA PDF value was significantly higher in the healthy side ($p<0.001$) (Table 2).

ROC Analysis Results

In deciding the diagnosis of invasive breast carcinoma, it was found that LTA PSF, LTA RI and ITA RI on the breast side diagnosed with carcinoma and ITA PDF values on the healthy breast side are very good diagnostic tests and the areas under the curve are significant. The values of the area under the curve (AUC) of these measurements are given in Table 3.

It has been determined that these values can be used to decide the distinction between invasive breast carcinoma and healthy breast. It was found that higher LTA PSF, LTA RI and ITA RI values in the breast with invasive breast carcinoma compared to the healthy

Table 2. Comparison of PDUS measurements of breast with malignant lesions and healthy breast*

	Control Breast			Invasive Carcinoma Detected Breast			
Measurement Value	Mean	S.D.	Median	Mean	S.D.	Median	p
LTA PSF	15,95	4,14	15,50	26,91	13,46	22,10	<0.001
LTA PDF	3,73	1,11	3,40	4,49	2,88	3,80	0.204
LTA RI	0,76	0,05	0,78	0,84	0,03	0,84	<0.001
LTA PI	2,03	0,35	2,11	2,11	0,18	2,15	0.323
ITA PSF	49,77	22,01	42,20	48,77	16,49	44,80	0.714
ITA PDF	10,68	3,77	9,40	6,95	3,59	6,40	<0.001
ITA RI	0,76	0,06	0,76	0,86	0,05	0,84	<0.001
ITA PI	3,10	0,57	3,22	2,99	0,55	3,22	0.336

LTA: Lateral thoracic artery, ITA: Internal thoracic artery; PSA: Peak systolic flow;
PDA: Peak diastolic flow; RI: Resistive index; PI: Pulsatility Index; SD: Standart Deviation
* Mann Whitney U

Table 3. ROC characteristics of various parameters

				% 95 Confidence Interval	
Variable	Area	Std. Error	p	Lower Bound	Upper Bound
LTA PSF	0,859	0,042	<0,001	0,777	0,942
LTA RI	0,944	0,027	<0,001	0,891	0,997
ITA PDF	0,784	0,048	<0,001	0,690	0,877
ITA RI	0,883	0,037	<0,001	0,811	0,956

LTA: Lateral thoracic artery, ITA: Internal thoracic artery; PSA: Peak systolic flow; PDA: Peak diastolic flow; RI: Resistive index; PI: Pulsatility Index

Table 4. Cut-off values and validity results

	Cut-off	Sensitivity	Spesifity	J statistic	LR+	LR-
LTA PSF	19,6	81,3	95,8	0,771	19,35	0,20
LTA RI	0,805	91,7	95,8	0,875	21,83	0,08
ITA PDF (low)	8,35	77,1	79,2	0,563	3,70	0,28
ITA RI	0,8	89,6	81,2	0,708	4,76	0,12

LTA: Lateral thoracic artery, ITA: Internal thoracic artery; PSA: Peak systolic flow; PDA: Peak diastolic flow; RI: Resistive index; PI: Pulsatility Index; LR: Likelihood ratio

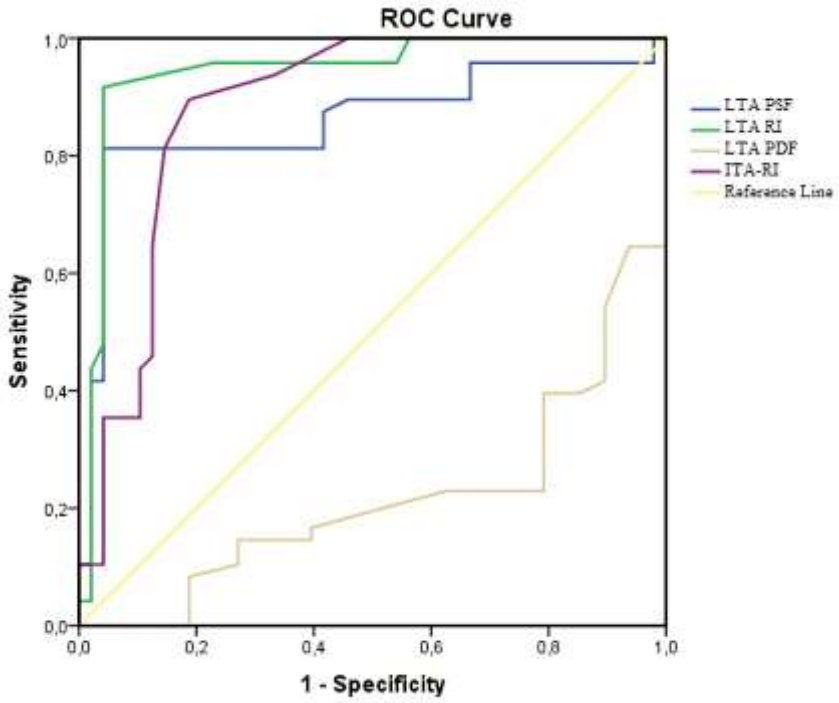

Figure 2: Area under curve in ROC analysis. LTA: Lateral thoracic artery, ITA: Internal thoracic artery; PSA: Peak systolic flow; PDF: Peak diastolic flow; RI: Resistive index; PI: Pulsatility Index

breast can predict the diagnosis of invasive breast carcinoma in the current breast. Low ITA PDF value in the healthy breast compared to the breast with invasive breast carcinoma can predict the diagnosis of invasive carcinoma in the other breast (Figure 2).

The optimal cut-off value for LTA PSF value is 19.6 cm/s, the sensitivity of this value is 81.3% and the specificity is 95.8%. If there are LTA PSF values above this cut-off value, that lesion can be interpreted in favor of a malignant lesion.

The optimal cut off value for LTA RI value was determined as 0.805, the sensitivity of this value was 91.7% and the specificity was 95.8%. The lesion detected at LTA RI values above this cut-off value can be interpreted in favor of invasive breast carcinoma (Table 4).

The sensitivity of the ITA PDF value below 8.35 for the detection of invasive breast carcinoma in the opposite breast is 77.1% and the specificity is 79.2%. Among these measurement values, the diagnostic value with the lowest false positivity and false negativity rates is the LTA RI value. The positive likelihood ratio value of this value is 21.83 and the negative likelihood ratio value is 0.008 (Table 4).

Discussion

According to the results of this study, from the quantitative data obtained in PDUS examinations of LTA and ITA arteries. The cut-off values of LTA PSA, RI and ITA RI values were determined to detect invasive breast carcinoma, and the sensitivity and specificity of these values are quite high.

Angiogenesis plays an important role in both local growth and distant metastases of breast cancer. Breast ultrasonography is an inexpensive diagnostic method that can be easily applied in young women with a family history, in patients admitted to outpatient clinics for reasons such as mastalgia, nipple discharge, and in women with palpable lesions on breast examination without radiation exposure [18]. In addition, it is more sensitive in detecting lesions that cannot be

detected in mammography in dense breasts [19].

The features of the masses detected in the breast such as their shape, contour features, and their location in the breast axis can be easily determined by ultrasonography. The characteristics of the masses can be determined by evaluating the vascularization of the masses with PDUS examination. In recent studies, it has been reported that PDUS examination is very important in increasing blood flow in the tumor and detecting neoangiogenesis and can be used to determine the malignant character of lesions [14,15].

It is known that new vascular structures that do not have a smooth muscle structure are observed among the malignant lesions detected in the breast [20]. Although it has been shown in various studies that the hypervascularity detected in US examination can provide information about the malignant character of the lesions. It has been stated that the RI and PI values detected in the lesions are not good diagnostic tools for lesion characterization [21]. In a recent study, it was shown that the diastolic flow reversed in the flow in the mass detected in the breast and the RI value above 1 was most likely associated with lesion malignancy [21]. However, it has been previously stated that lesion vascularization is not always evident in patients with breast cancer. Accordingly, PDUS evaluation can gain sensitivity when evaluated together with the morphological features of the mass identified in ultrasonography [22]. Although PDUS imaging is thought to be helpful in distinguishing benign and malignant solid masses, it has been stated that it does not have high predictive quantitative values. PDUS imaging can only be used to support the pre-diagnosis of lesions with suspicious morphological features in B-mode US examination [23].

The hypothesis of our study was that vascularization could change in the breast developing malignancy rather than lesion vascularization for malignancy characterization. Therefore, PDUS examination of the main vascular structures feeding the breast was performed and it was aimed to obtain quantitative data. In some previous studies investigating the value of LTA and axillary artery blood flow in determining the lesion characteristics in breast masses, have been conducted. It has been reported that a LTA RI value of 0.67 and above is significant for detecting malignancy in these studies [17,24]. However, even in the healthy breast determined as the control group in our study, LTA values were generally above 0.67. This explains why the sensitivity and specificity values of the values determined in our study are high. In addition, the statistical analyzes made in our study are more comprehensive and powerful. Moreover, as far as we know, there is no current publication where ITA evaluations were made, and in the results of our study, not only LTA RI but also LTA PSA and ITA RI values were obtained with high sensitivity and specificity predicting malignancy. This also supports our hypothesis. In addition, unlike other studies, this study allows for easily calculable evaluations rather than spectral examinations such as negative diastolic flow, which are rare and not always possible to detect.

According to these data, LTA RI, LTA PSF, ITA PDF and ITA RI values may be a new diagnostic method with high sensitivity and specificity that can be used for the detection of invasive breast carcinoma.

The strength of this study is that it is prospective. Another strong feature is that multiple parameters belonging to LTA and ITA arteries work together with their diagnostic features and obtain cut-off values with high sensitivity and specificity values.

This study had some limitations. First of all, the study population was small, because the patients included in this study consisted of

patients who were made surgical preparations immediately after their diagnosis, and patients diagnosed with locally advanced breast cancer who were diagnosed with neoadjuvant chemotherapy in our center were excluded. It was thought that the application of neo-adjuvant chemotherapy would affect breast vascularization, and measurements were not taken from these patients before the operation. Second, the evaluations of the patients were made only for lesions diagnosed with pathologically invasive breast carcinoma. Further studies with larger populations including vascular changes of benign lesions can be conducted.

Conclusion:

In conclusion, this study presents new quantitative diagnostic tests with high sensitivity and specificity, easily accessible, and applicable in detecting breast cancer.

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