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Diagnostic value of super microvascular imaging in differentiating axillary lymph nodes: semi-quantitative and qualitative approach in primary breast cancer and suspicious axillary nodes

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Abstract

Background The evaluation of axillary lymph nodes (ALNs) using ultrasound (US) plays a crucial role in the diagnosis and management of breast cancer. This study aims to assess the diagnostic performance of both quantitative and qualitative features of suspicious ALNs using superb microvascular imaging (SMI). To the best of our knowledge, this is the first prospective study in the literature to evaluate the largest number of suspicious ALNs using SMI and to analyze the combined diagnostic value of these findings.

Methods Our prospective study involved 102 patients with suspicious lymph nodes in the axilla. SMI method was employed individually to assess distribution, appearance, and number of vascular structures. After histopathological or follow-up confirmation, images were re-evaluated. We also examined the diagnostic value of various combinations of these vascular features. Lastly, two radiologists, each with 22 and 4 years of experience, independently reviewed the images, blinded to clinical and pathological data, to assess interobserver agreement.

Results A total of 108 lymph nodes were evaluated in 102 patients, including 67 benign and 41 malignant cases. The diagnostic performance of various combinations in receiver operating characteristic (ROC) analysis revealed that the highest accuracy (78.70%) and area under the curve (AUC) value in ROC analysis were achieved by distribution-appearance combinations (AUC: 0.776, $p < 0.001$). Interobserver agreement was significant for both the SMI and PDUS methods. In patients diagnosed with breast cancer, the diagnostic accuracy for suspicious axillary lymph nodes reached 92.76%, with an AUC value of 0.855.

Conclusion In conclusion, our findings suggest that SMI facilitates more accurate identification of suspicious axillary lymph nodes prior to surgical intervention.

Keywords Breast, Cancer, Axillae, Lymph node, SMI, Ultrasound

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Introduction

Breast cancer is the most common type of cancer in women worldwide, accounting for almost $\frac{1}{4}$ of all cancer cases [1, 2]. The substantial mortality and the adverse effects on both cognitive and physical health associated with breast cancer underline the importance of regular screening [3–9]. Mammography is the main radiological imaging methods for screening but ultrasound is also frequently used as an additional imaging method.

One of the most important prognostic factors in breast cancer is the presence of axillary lymph node metastasis [1, 10]. Demonstration of axillary lymph node involvement in a breast cancer case is an important guide for treatment and prognosis. However, similar imaging findings can be seen in axillary lymph nodes after infections, some granulomatous diseases, and vaccinations, which may cause misinterpretation of benign and malignant pathologies [11–13].

The most reliable methods to demonstrate the involvement are axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) but these may lead to increased morbidity such as nerve/vascular damage, infection, lymphedema, pain, limitation of shoulder movements and weakness in the arm due to their invasive nature and lead to a rise in expenses. As a result of that, radiological imaging methods are important part of diagnosis. Studies have shown that the evaluation of lymph nodes with imaging methods can contribute to the selection of patients who will benefit more from axillary lymph node dissection [14, 15].

US is the first and most important imaging method to evaluate axillary lymph nodes as it is non-invasive, easily accessible, rapid and radiation-free [1, 16]. Many features of lymph nodes can be evaluated with various ultrasonographic methods. It was revealed that in addition to morphological features, vascular findings with Doppler US examination contribute to benign/malignant differentiation [17].

Colour Doppler (CDUS) and Power Doppler (PDUS) methods are commonly used as Doppler methods but the recent method, Superb Microvascular Imaging (SMI), has demonstrated high effectiveness in differentiating between benign and malignant lesions in various medical conditions and reseraches indicate the superiority of SMI over other methods in depicting the vascular features of lesions [16, 18–28].

In this study, we aimed to demonstrate the diagnostic value of SMI in suspicious axillary lymph nodes. To the best of our knowledge, our study is the first in the literature to evaluate the highest number of suspicious axillary lymph nodes using SMI and to assess the combined contribution of quantitative and qualitative data to the diagnosis.

Materials and methods

Patients

The single-center prospective study, approved by the ethics committee of University of Health Sciences, Ankara Training and Research Hospital (E-93471371-514.10), was conducted between April 2021 and April 2022. A total of 139 female patients aged between 18 and 74 years were enrolled in the study. Informed consent was obtained from all individual participants included in the study. All patients have at least one suspicious axillary lymph node and met the inclusion criteria. 13 patients were excluded from the study due to non-diagnostic biopsy results and the absence of a repeat biopsy. Additionally, 20 patients did not attend follow-up visits, and 4 patients were excluded because their ultrasound images were of insufficient diagnostic quality. Among the 3 patients who were initially undiagnosed in the first biopsy, a diagnosis was established in the second biopsy. Consequently, after the exclusion of 37 patients, the study included 108 lymph nodes from 102 patients.

The study excluded individuals under the age of 18, male patients, those who did not provide signed informed consent, individuals with a prior histopathological diagnosis of axillary lymph node metastasis, those with a known history of chemotherapy or radiotherapy to the axillary region, individuals who had undergone axillary lymph node dissection, and patients with active infections in the axillary region. Additionally, patients without pathology results or those who later declined to participate in the research were excluded from the study.

Methods

In our study, suspicious axillary lymph nodes in enrolled patients were evaluated using the Toshiba Aplio A ultrasound (US) device equipped with a 14–18 MHz high-frequency linear probe. Grey-scale US, Power Doppler US (PDUS), and Superb Microvascular Imaging (SMI) images of lymph nodes were captured during examinations. During image acquisition, adjustments were made to the Pulse Repetition Frequency (PRF) and gain settings to minimize artifact formation and maximize signal quality, with these settings maintained consistently across all methods. Additional time, typically 1–2 min per patient, was allocated for routine examination in SMI assessment.

Subsequently, based on clinical suspicion, either a 21G fine-needle aspiration biopsy (FNAB) or core biopsy (16–18G) was performed for histopathological evaluation, or follow-up ultrasound was conducted on the relevant lymph node(s). In cases with multiple suspicious lymph nodes, biopsies were prioritized for the nodes deemed most suspicious. Separate biopsy procedures were conducted for suspicious lymph nodes located in different axillary regions. Follow-up patients underwent ultrasound control every 1–3 months, during which

regressing or disappearing lymph nodes were considered benign. Histopathological sampling was conducted for lymph nodes showing stability or progression.

Patients with non-diagnostic biopsies were recalled for repeat FNAB/core biopsy. Both cytology and pathology samples were evaluated by a pathologist with over 10 years of experience. Prior to histopathological diagnosis, all patients underwent prospective assessment by a blinded radiologist, considering clinical history and examination, and images were obtained. Pathology results were reassessed alongside PDUS and SMI images, and findings were compared.

Finally, two radiologists with 22 and 4 years of experience in breast radiology independently assessed images for predetermined characteristics, without access to patient clinical information or pathology results. Interobserver agreement was evaluated by comparing results.

In our study, during Superb Microvascular Imaging (SMI) and Power Doppler US (PDUS) examinations, the internal vascularity of relevant lymph nodes was assessed in terms of number, distribution (avascular/central/peripheral/mixed), and appearance (normal, dysplastic, avascular). SMI utilized both monochromatic (mSMI) and color (cSMI) images for evaluation.

In the image assessment, if diffuse cortical thickening of the suspicious lymph node was observed in grey-scale US, the evaluation encompassed the entire cortex. For lymph nodes with asymmetric cortical thickening, only the suspicious area was considered. Internal vascularity was quantified by identifying signals located in the cortex and immediately adjacent to it. Regarding vascular distribution, nodes lacking vascular signals in the cortex were categorized as avascular, those exhibiting only peripheral vascular signals were classified as peripheral, those with vascular signals extending from the hilum to the cortex were designated as central, and those displaying vascular signals both in the periphery and the center were termed mixed.

Furthermore, the appearances of vascular signals were considered in the assessment. Nodes with smooth, symmetrical hilar extensions of signals were regarded as normal, nodes with eccentric signals were labeled as dysplastic, and nodes without any signals were evaluated as avascular.

Statistical analysis

In the study, mean $\pm$ standard deviation was employed for continuous variables, while frequency and percentage values were utilized for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to evaluate the homogeneity of patient distribution. Student's *t*-test and Mann-Whitney *U* test were applied for continuous variables, and the chi-square test

or Fisher's exact chi-square test was used to assess categorical features.

For each investigated feature of Doppler methods, the area under the curve (AUC) in receiver operating characteristic (ROC) analysis was separately calculated to evaluate diagnostic performance in distinguishing between benign and malignant lymph nodes, whether used individually or in combination. Logistic regression analysis was employed to determine significance when features were used together. Additionally, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of each method were computed.

To assess interobserver agreement, Cohen's Kappa test was applied for categorical features in both SMI and PDUS. The intraclass correlation coefficient test was used to compare vascular numbers. After consensus, the chi-square test or Fisher's exact chi-square test was utilized to evaluate vascular features between benign and malignant categories.

All statistical analyses were conducted using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA, 2017). A *p*-value < 0.05 was considered statistically significant.

Results

In our study, a total of 108 lymph nodes from 102 patients were evaluated. Among these, 41 lymph nodes in the malignant group were identified cytologically or pathologically as malignant. In the benign group, 55 lymph nodes were classified as benign through cytology or pathology, and an additional 12 lymph nodes were monitored for at least 3 months, totaling 67 benign lymph nodes.

Within the malignant group, diagnoses included lobular carcinoma in 1 patient, ductal carcinoma in 37 patients, and pathological evidence of non-mammary carcinoma metastasis in 3 patients. In the benign group, 21 patients presented with breast malignancies (2 with lobular carcinoma and 19 with ductal carcinoma). Additionally, chronic granulomatous mastitis was observed in 2 patients, one patient had a breast abscess, and another patient, who had one lymph node assessed on each side, was diagnosed with systemic lupus erythematosus.

Among the total of 67 lymph nodes deemed benign, 43 exhibited only suspicious axillary lymph nodes without any pathology in the breast.

The age distribution of patients ranged from 18 to 74 years, with a mean age of 50.64 ± 11.08 . In the malignant group, the mean age was calculated as 54.85, whereas it was 48.06 in the benign group, indicating a statistically significant difference with a higher average age observed in the malignant group ($p = 0.002$).

Among the identified suspicious axillary lymph nodes, 42 (38.9%) were located on the right side and 66 (61.1%)

Table 1 Demographic data according to the pathological results of patients

Features	Benign (n = 67)	Malign (n = 41)	Sum (n = 108)	P
Age	48.06 ± 10.77	54.85 ± 10.39	50.64 ± 11.08	0.002
Axillae				0.08
Right	31(46.3)	11(26.8)	42(38.9)	
Left	36(53.7)	30(73.2)	66(61.1)	

on the left side. The distribution of benign lymph nodes was 31 (46.3%) on the right and 36 (53.7%) on the left, while for malignant lymph nodes, 11 (26.8%) were on the right and 30 (73.2%) on the left. However, the distribution of lymph nodes between axillary regions did not exhibit a significant difference between the groups ($p = 0.08$) (Table 1).

During the examination, the vascular distribution and appearance of lymph nodes were evaluated as categorical variables using PDUS and SMI imaging (Fig. 1). Additionally, the findings were compared both within and between groups. According to the results, there was no significant difference in vascular distribution ($p = 0.574$) and the appearance of vascular structures ($p = 0.434$) between the benign and malignant groups in the PDUS examination. However, in the SMI examination, there was a statistically significant difference between the groups in terms of vascular distribution ($p < 0.001$) and vascular appearance ($p < 0.001$) (Table 2) (Fig. 2).

The groups were assessed via quantitative analysis of countable vascular structures using SMI and PDUS. The results revealed no significant difference between the benign and malignant groups in PDUS ($p = 0.739$).

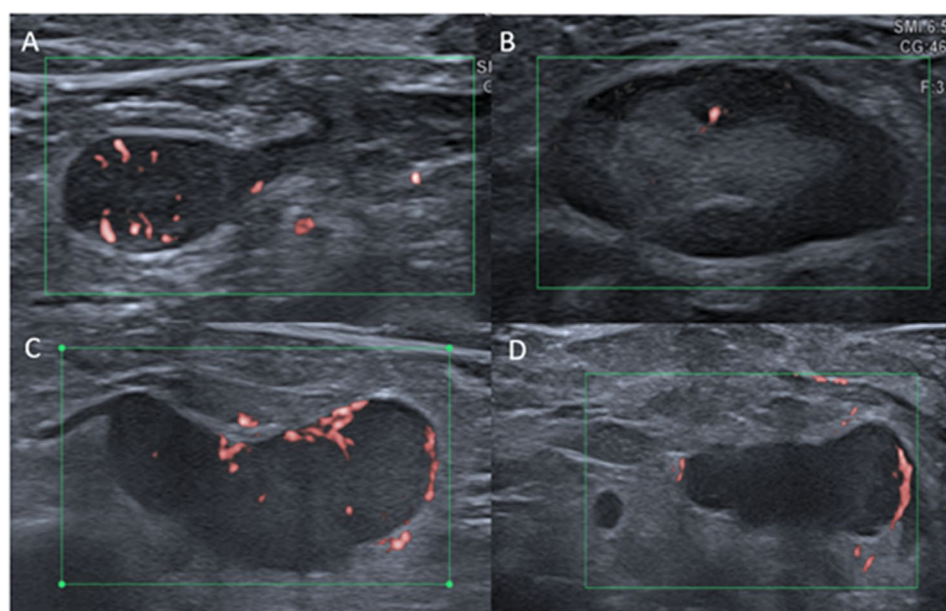


Fig. 1 Suspicious lymph nodes and their vascular distribution characteristics: **A** A lymph node exhibiting asymmetric thickening with mixed-type vascularization in SMI (Fine-needle aspiration biopsy (FNAB) result: Malignant cytology). **B** A lymph node demonstrating diffuse cortical thickening and central vascularization (FNAB result: Benign cytology). **C** A lymph node with diffuse cortical thickening displaying mixed-type vascularization (FNAB result: Malignant cytology). **D** A lymph node with diffuse cortical thickening showing peripheral vascularization (FNAB result: Malignant cytology)

Table 2 Distribution, number, and appearance characteristics of vascular structures according to PDUS and SMI examination findings

Features	Benign	PDUS Malign	P	Benign	SMI Malign	P
Vascular Disturbition			0.574			< 0.001
Central	40 (59.7%)	20 (48.8%)		42 (62.7%)	5 (12.2%)	
Peripheral	4 (6%)	2 (4.9%)		2 (3%)	1 (2.4%)	
Avascular	12 (17.9%)	8 (19.5%)		8 (11.9%)	4 (9.8%)	
Mix	11 (16.4%)	11 (26.8%)		15 (22.4%)	31 (75.6%)	
Vascular Number	2,58 ± 2.27	2,85 ± 2.27	0.739	3,41 ± 2.58	5,85 ± 4.04	< 0.001
Vascular Appareance			0.434			< 0.001
Normal	39 (58.2%)	19 (46.3%)		40 (59.7%)	6 (14.6%)	
Eccentric	16 (23.9%)	14 (34.1%)		19 (28.4%)	31 (75.6%)	
Avasculary	12 (17.9%)	8 (19.5%)		8 (11.9%)	4 (9.8%)	

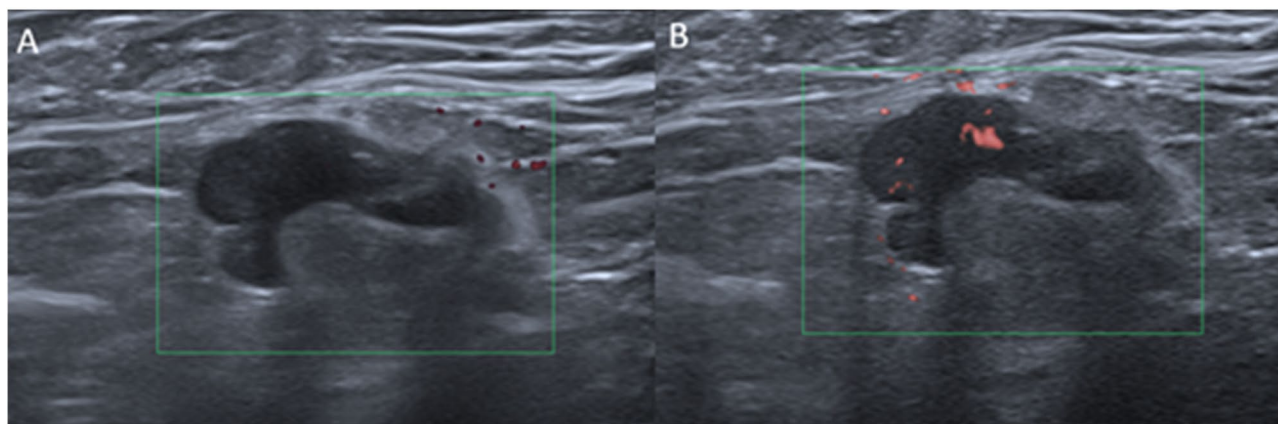


Fig. 2 Comparison of PDUS and SMI. In the axillary lymph node demonstrating diffuse thickening with additional focal asymmetric thickening, **(A)** No vascular flow signal is detected in PDUS. **B** Peripheral-type vascularization with a dysplastic appearance is observed in SMI. (Fine-needle aspiration biopsy (FNAB) result: Malignant cytology)

However, in the SMI examination, a statistically significant difference was observed, with a higher number of vascular structures identified in the malignant group ($p < 0.001$) (Table 2).

In our study, we evaluated the characteristics of central, peripheral, mixed, and avascular distribution in both benign and malignant lymph nodes. In the PDUS assessment, central distribution was the most commonly observed pattern in both groups. Specifically, 40 nodes out of 67 (59.7%) in benign lymph nodes and 20 nodes out of 41 (48.8%) in malignant lymph nodes exhibited central distribution. Conversely, in the SMI assessment, mixed-type distribution was the most frequently observed pattern in malignant lymph nodes, with 31 out of 41 nodes (75.6%) displaying this pattern. In contrast, central distribution was the predominant pattern in benign lymph nodes, with 42 out of 67 nodes (62.7%) demonstrating this distribution (Table 2).

The vascular structures of lymph nodes were analyzed based on their appearances, categorized as normal/central, eccentric, or avascular. According to PDUS, central vascularization was predominantly observed in 39 out of 67 benign nodes (58.2%) and 19 out of 41 malignant nodes (46.3%). In SMI imaging, an eccentric appearance was most common in 31 out of 41 malignant nodes (75.6%), while central vascularization was most prevalent in 40 out of 67 benign nodes (46.7%) (Table 2).

ROC analysis was utilized to assess the significance of the number, appearance, and distribution of vascular vessels in lymph nodes for diagnosis. In our study, the categorical features that exhibited statistical significance and the highest accuracy rate were the mixed-type distribution and eccentric appearance. Regarding the number of vessels, the threshold value was determined as '3.5' for SMI and '4.5' for PDUS.

In the ROC analysis, the AUC values for the evaluation of distribution, number, and appearance features separately with SMI were found to be statistically significantly higher ($p < 0.001$) (Table 3). Regarding diagnostic accuracy, the highest accuracy value, 76.85%, was attained when evaluating distribution features with SMI. Detailed data are provided in Table 3.

Additionally, the contribution of combinations of defined features to the diagnosis was explored. In the study, all combinations in the SMI method were found to be statistically significant, with the highest AUC value obtained with the distribution-appearance combination (AUC: 0.776, $p < 0.001$). The highest accuracy values were achieved with the distribution-appearance and distribution-number-appearance combinations in SMI (78.70%). In contrast, statistically significant differences were not observed with combinations in the PDUS method (Table 4).

Lymph node vascularization was quantitatively assessed, and when the threshold value calculated for SMI was taken as 3.5, it was found to be diagnostically significant when used alone. However, when used in combination with other features in both methods, its contribution to diagnostic accuracy was minimal or non-existent (Table 4).

Statistically, the combination of appearance-distribution had the highest accuracy (78.70%) and AUC (0.776) values, with a sensitivity of 73.17%, specificity of 82.09%, positive predictive value of 71.46%, and negative predictive value of 83.33% (Table 4).

Furthermore, in our study, the axillary lymph nodes of 59 patients diagnosed with breast cancer (56 ductal carcinoma, 3 lobular carcinoma) were analyzed. Metastasis was present in axillary lymph nodes in 38 patients (37 ductal, 1 lobular carcinoma). In the evaluation using combinations of features examined with both PDUS and

Table 3 Diagnostic value of PDUS and SMI methods for discriminating between benign and malignant lymph nodes based on examined features

Features	Sensitivity (%95CI)	Specifity (%95CI)	PPV (%95CI)	NPV (%95CI)	Accuracy (%95CI)	AUC (%95CI)
PDUS						
Distribution*	26.83 (14.22–42.94)	83.58 (72.52–91.51)	50 (32.30–67.70)	65.12 (60.12–69.80)	62.04 (52.19–71.20)	0.552 (0.438–0.666)
Number**	19.51 (8.82–34.87)	83.58 (72.52–91.51)	42.11 (24.19–62.37)	62.92 (58.53–67.11)	59.26 (49.38–68.62)	0.535 (0.422–0.649)
Appearance***	34.15 (20.08–50.59)	74.63 (62.51–84.47)	45.16 (31.32–59.79)	64.94 (58.79–70.62)	59.26 (49.38–68.62)	0.551 (0.438–0.665)
SMI						
Distribution*	75.61 (59.70–87.64)	77.61 (65.78–86.89)	67.39 (56.15–76.93)	83.87 (74.92–90.05)	76.85 (67.75–84.43)	0.766 (0.670–0.862)
Number**	80.49 (65.13–91.18)	55.22 (42.58–67.40)	52.38 (44.76–59.89)	82.22 (70.55–89.93)	64.81 (55.04–73.76)	0.679 (0.576–0.781)
Appearance***	75.61 (59.70–87.64)	71.64 (59.31–81.99)	62.00 (51.78–71.26)	82.76 (73.28–89.36)	73.15 (63.76–81.22)	0.736 (0.638–0.835)

*Abbreviations: AUCArea Under the Curve, PPVPositive Predictive ValueNPVNegative Predictive Value, PDUSPower Doppler UltrasonographySMISuperb Microvascular Imaging

*Due to its statistically more significant nature in the distribution assessment, the 'mixed' distribution feature has been considered

**For the vascular count analysis, the threshold value is 4.5 for PDUS and 3.5 for SMI

***Due to its statistically more significant nature in the appearance assessment, the 'eccentric' appearance feature has been considered

Table 4 Diagnostic value of PDUS and SMI methods according to combinations of examined features for discriminating between benign and malignant lymph nodes

Features	Sensitivity (%95CI)	Specifity (%95CI)	PPV (%95CI)	NPV (%95CI)	Accuracy (%95CI)	AUC (%95CI)
PDUS						
Distribution-Number-Appearance	16.63 (5.57–29.17)	89.55 (79.65–95.70)	46.15 (23.63–70.36)	63.16 (59.58–66.59)	61.11 (51.25–70.34)	0.521 (0.407–0.634)
Distribution- Number	17.07 (7.15–32.06)	89.55 (79.65–95.70)	50.00 (27.43–72.57)	63.83 (60.03–67.46)	62.04 (52.19–71.20)	0.533 (0.419–0.647)
Distribution- Appearance	24.39 (12.36–40.30)	85.07 (74.26–92.60)	50.00 (31.31–68.89)	64.77 (60.07–69.21)	62.04 (52.19–71.20)	0.547 (0.434–0.661)
Appearance -Number	14.63 (5.57–29.17)	88.06 (77.82–94.70)	42.86 (17.66–71.14)	62.77 (52.18–72.52)	60.19 (50.32–96.48)	0.513 (0.400–0.627)
SMI						
Distribution -Number- Appearance	68.29 (51.91–81.92)	85.07 (74.26–92.60)	73.68 (60.37–83.73)	81.43 (73.45–87.42)	78.70 (69.78–86.00)	0.767 (0.669–0.865)
Distribution -Number	70.73 (54.46–83.87)	82.09 (70.80–90.39)	70.73 (58.25–80.71)	82.09 (73.76–88.20)	77.78 (68.76–85.21)	0.764 (0.667–0.862)
Distribution -Appearance	73.17 (57.06–85.78)	82.09 (70.80–90.39)	71.46 (59.21–81.20)	83.33 (74.87–89.35)	78.70 (69.78–86.00)	0.776 (0.681–0.872)
Appearance -Number	70.73 (54.46–83.87)	76.12 (64.14–85.69)	64.44 (53.10–74.37)	80.95 (72.16–87.45)	74.07 (64.75–82.03)	0.722 (0.620–0.824)

*Abbreviations: AUCArea Under the Curve, PPVPositive Predictive Value, NPVNegative Predictive Value, PDUSPower Doppler Ultrasonography, SMISuperb Microvascular Imaging

SMI methods, the highest accuracy rate (92.76%) and AUC value (0.855) were obtained when the distribution and appearance features were analyzed together with SMI. Additionally, the sensitivity, specificity, positive predictive value, and negative predictive value of this evaluation were determined as 71.05%, 100.00%, 91.20%, and 92.76%, respectively (Table 5).

In the evaluation conducted with combinations of the examined features, the highest accuracy rate (92.76%) and an AUC value of 0.855 were achieved when the

distribution and appearance features were assessed together with SMI. Additionally, the sensitivity of this evaluation was found to be 71.05%, the specificity was 100.00%, the positive predictive value (PPV) was 91.20%, and the negative predictive value (NPV) was 92.76%. According to the research results, the vascular features examined with SMI, except for quantitative vascular count measurement, were significantly superior to those from the PDUS method (Table 5).

Table 5 Diagnostic value of PDUS and SMI methods after evaluating the features of axillary lymph nodes in patients diagnosed with breast cancer following the combination of examined features

Features	Sensitivity (%95CI)	Specificity (%95CI)	PPV (%95CI)	NPV (%95CI)	Accuracy (%95CI)	AUC (%95CI)
PDUS						
Distribution-Number-Appearance	10.00 (2.79–23.66)	100.00 (82.35–100.00)	100.00 (39.76–100.00)	76.92 (63.60–87.21)	77.50 (64.76–87.35)	0.553 (0.403–0.703)
Distribution -Number	12.82 (4.30–27.43)	100.00 (83.16–100.00)	100.00 (47.82–100.00)	77.48 (64.07–87.73)	78.21 (65.54–87.90)	0.566 (0.417–0.714)
Distribution -Appearance	21.05 (09.55–37.32)	100.00 (83.89–100.00)	100.00 (63.06–100.00)	79.17 (65.50–89.26)	80.26 (67.85–89.26)	0.605 (0.461–0.749)
Appearance -Number	10.53 (2.94–24.80)	100.00 (83.89–100.00)	100.00 (39.76–100.00)	77.03 (63.71–87.29)	77.63 (64.90–87.45)	0.553 (0.403–0.703)
SMI						
Distribution-Number-Appearance	65.79 (48.65–80.37)	100.00 (83.89–100.00)	100.00 (86.28–100.00)	89.76 (74.49–97.48)	91.45 (81.22–97.15)	0.829 (0.726–0.932)
Distribution -Number	68.42 (51.35–82.50)	95.24 (76.18–99.88)	82.73 (63.36–94.44)	90.05 (74.23–97.76)	88.53 (77.56–95.35)	0.818 (0.709–0.928)
Distribution -Appearance	71.05 (54.10–84.58)	100.00 (83.89–100.00)	100.00 (87.23–100.00)	91.20 (75.73–98.27)	92.76 (82.93–97.88)	0.855 (0.760–0.951)
Appearance -Number	65.79 (48.65–80.37)	100.00 (83.89–100.00)	100.00 (86.28–100.00)	89.76 (74.49–97.48)	91.45 (81.22–97.15)	0.829 (0.726–0.932)

Inter-Observer agreement

Inter-observer agreement was assessed based on findings from two separate radiologists with 4 and 22 years of experience, respectively, who reviewed the images without knowledge of the patients' clinical and pathology results. For PDUS distribution, the kappa value was calculated to be 0.84 (0.61–0.80), and for vascular appearance, the kappa value was 0.82 (0.61–0.80), indicating significant agreement. The intra-class correlation coefficient for vascular count comparison was calculated to be 0.939, signifying an excellent level of reliability ($P < 0.001$).

Regarding SMI, the kappa value for distribution between observers was 0.75 (0.61–0.80), and for vascular appearance, the kappa value was 0.667 (0.61–0.80), demonstrating significant agreement. The intra-class correlation coefficient for vascular count comparison was calculated to be 0.918, indicating an excellent level of reliability ($P < 0.001$).

Discussion

Axillary lymph node involvement in breast cancer holds critical significance for prognosis and treatment strategy. While various invasive and non-invasive methods are available for determining involvement, ultrasonographic evaluation stands as the most commonly utilized approach [29]. Suspicious findings indicative of malignancy have been outlined in the literature for grayscale ultrasonography, encompassing features such as spherical shape, asymmetric cortical thickening, loss of fatty hilum, and alterations in the long/short axis ratio [14, 30]. However, standardized grayscale criteria for axillary lymph node metastasis are lacking, thus emphasizing the

widespread acceptance of evaluating vascular structure for distinguishing lymph nodes [14, 31].

Peripheral vascularity presence suggests the disruption of hilar vascularity and the emergence of new vessel formation, a characteristic often associated with metastatic lymph nodes but can also manifest in infectious processes like tuberculosis lymphadenitis [32]. Moreover, the presence of coarse dysplastic vascular structures has been highlighted as a significant criterion for differentiation [1]. Despite these distinctions, the evaluation of suspicious axillary lymph nodes solely with Doppler ultrasonography may not suffice in discerning some benign/malignant lymph nodes due to overlapping imaging features [12, 33]. In a study conducted by Esen et al., which evaluated axillary lymph nodes based on vascular distribution using PDUS, the sensitivity was reported to be low (50.54%), while specificity was high (97.14%) [17]. Similarly, in our study, PDUS evaluation of vascular distribution showed low sensitivity (26.83%) and high specificity (83.58%).

Recently, Superb Microvascular Imaging has provided a promising approach for diagnosing various diseases by enabling more effective evaluation of lesion vascularity [12, 25, 32, 34]. It has also been demonstrated that SMI holds promise in distinguishing between metastatic lymph nodes and tuberculosis lymphadenitis, as well as differentiating lymphoma from lymphadenitis, with particular relevance to the pediatric population [35]. Additionally, studies have revealed the effectiveness of SMI in differentiating between benign and malignant cervical lymph nodes [12, 28]. While there are existing studies utilizing the SMI method for evaluating breast masses [2, 25, 36, 37], there remains a scarcity of research focused

on assessing suspicious axillary lymph nodes [38, 39]. To our knowledge, our study represents the first comprehensive investigation incorporating the largest patient population and qualitative values for evaluating axillary lymph nodes using SMI.

Uslu et al. demonstrated in their study that the vascular index (VI), a quantitative analysis utilized in SMI, holds potential for distinguishing between benign and malignant axillary lymph nodes, with malignant lymph nodes exhibiting higher VI values [38]. Similarly, in our study, we observed a statistically significant high in vascular number within malignant lymph nodes compared to benign lymph nodes through SMI. Additionally, Kurt et al. conducted an evaluation of suspicious axillary lymph nodes based on VI and reported higher values in the malignant group, aligning closely with the findings of increased vascular number in our study. They also evaluate the vascular distribution and appearance characteristics in suspicious axillary lymph nodes in 52 patients newly diagnosed with breast cancer using both SMI and PDUS. They collectively assessed the vascular distribution and appearance characteristics under the term “vascular pattern,” resulting in PPV, NPV, and diagnostic accuracy values for PDUS of 92%, 70%, and 82%, respectively; and for SMI, 96%, 85%, and 92%, respectively [39]. In our study, similar results were obtained when the distribution and appearance characteristics of lymph nodes in patients diagnosed with breast cancer were evaluated collectively. The PPV, NPV, and diagnostic accuracy for PDUS were calculated as 100%, 79.17%, and 80.26%, respectively; while for SMI, they were 100%, 91.20%, and 92.70%, respectively.

In another study focusing on distinguishing cervical lymph nodes in the pediatric population, which primarily employed SMI and VI, it was observed that VI was elevated in malignant lymph nodes. This observation closely parallels the increased vascularity noted in malignant lymph nodes in our study [35].

Several studies have emphasized additional vascular imaging characteristics that can aid in the differentiation between benign and malignant lymph nodes. According to these studies, hilar vessels and peripherally branching vessels that originate from the hilar vessel and run parallel to the long axis are regarded as characteristic of benign vascularity. Conversely, lymph nodes displaying aberrant peripheral vascularity, subcapsular vascularity, and a dysplastic course despite the presence of hilar vascularity are suggestive of malignant involvement [33, 40–44].

In our study, similar to the study conducted by Sim et al. which evaluated suspicious cervical lymph nodes, a mixed type of distribution, including peripheral vascularity within SMI, was more frequently observed in malignant lymph nodes compared to PDUS (SMI 75.6%, PDUS

26.8%). Conversely, in benign lymph nodes, central vascularity was more commonly observed with both methods, consistent with previous findings (31/41, 62.7% with SMI, and 11/41, 59.7% with PDUS) [12]. Similarly, in the study by Kurt et al., both PDUS and SMI predominantly depicted central vascularity in benign lymph nodes, while in malignant lymph nodes, a high prevalence of mixed vascularity pattern was noted with both imaging methods [39]. However, in our study, only SMI yielded similar findings, and no statistically significant difference in vascular distribution features between the two groups was observed with PDUS.

In their study, Sim and colleagues found that in both methods, the vascular appearance features of suspicious cervical lymph nodes exhibited a more frequent eccentric distribution in both benign and malignant nodules. In contrast, our study revealed differing patterns; a normal vascular distribution characterized by central hilar vascularity was more frequently found in benign lymph nodes with both methods and in malignant lymph nodes with PDUS. However, in SMI examination, an eccentric distribution was more frequent in malignant lymph nodes (75.6%) [12]. Additionally, unlike Sim and colleagues, the combinations of the evaluated features were assessed in our study. It was demonstrated that the diagnostic accuracy increased when the appearance, number, and distribution features of the vascular structures were evaluated together (78.70%).

Finally, similar to studies evaluating cervical and axillary lymph nodes with SMI in the literature, our study also found that SMI is superior to PDUS in distinguishing malignant lymph nodes [12, 28, 38, 39].

The study has several limitations. Firstly, motion-related artifacts were observed in some patients, particularly in those who were unable to cooperate with the doctor regarding their breathing. These artifacts made it challenging to distinguish true vascular signals from motion-induced artifacts. Pre-scan breath-holding exercises with the patient may help minimize the occurrence of such artifacts. Secondly, as the evaluation was based on still images, there may be interobserver variability in assessment of vascularity. In addition, since sonographic evaluation of lymph nodes is not considered the gold standard, the findings were confirmed either by pathology or follow-up. However, it should be noted that micro-metastases may be pathologically missed. Furthermore, validation of the thresholds in independent cohorts is necessary to confirm their reliability and applicability. While our study suggests a favorable effect of SMI on cost and clinical outcomes, its quantitative impact should be supported by larger and more comprehensive future studies. Lastly, vascular index (VI) was not utilized to quantify vascularity, which presents a limitation in the current assessment. Combining qualitative findings with

VI measurements in future studies may enable a more objective and quantifiable evaluation.

Conclusion

Assessing axillary lymph node involvement holds critical importance for the treatment and prognosis of breast cancer. However, it's crucial to be aware of that other etiological factors, such as infections and systemic diseases, can also present with similar findings. SMI has markedly significant diagnostic accuracy of axillary lymph node assessment, particularly when evaluating vascular characteristics in terms of distribution and appearance simultaneously. Consequently, we believe that this advancement will lead to a reduction in the cost and morbidity associated with additional surgical procedures performed for diagnostic purposes.

Abbreviations

ALN	Axillary lymph node
US	Ultrasound
SMI	Superb microvascular imaging
mSMI	Monochrome superb microvascular imaging
cSMI	Color superb microvascular imaging
ALND	Axillary lymph node dissection
SLNB	Sentinel lymph node biopsy
CDUS	Color doppler ultrasound
PDUS	Power doppler ultrasound
PRF	Pulse repetition frequency
FNAB	Fine-needle aspiration biopsy
VI	Vascular index
PPV	Positive predictive value
NPV	Negative predictive value
ROC	Receiver operating characteristic
AUC	Area under the curve

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Authors' contributions

Conceptualization, O.T. and P.S.O.; methodology, O.T.; software, S.A.; validation, O.T., P.S.O. and F.K.; formal analysis, S.A., O.T.; investigation, T.D.; resources, F.K., T.D., P.S.O.; data curation, O.T.; writing—original draft preparation, O.T.; writing—review and editing, O.T. and P.S.O.; visualization, F.K.; supervision, S.A. and P.S.O.; project administration, O.T. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of University of Health Sciences, Ankara Training and Research Hospital approval number [E-93471371-514.10]. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Written informed consent was obtained from patients for publication of this study and any accompanying images.

Competing interests

The authors declare no competing interests.

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